

Diagnosis and Management of Syphilis

WRHA STBBI Conference

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A syphilis primer- outline

- The organism
- Epidemiology
- Clinical manifestations
- Syphilis in HIV infected individuals
- Principles of diagnosis
- Pitfalls and controversies in diagnosis
- Management

The organism

- Caused by *Treponema pallidum*.
- The genus *Treponema* (order Spirochaetales; family Spirochaetaceae), all very closely related with indistinguishable morphology and >95% DNA homology
- Includes four species of human pathogens
- *Treponema pallidum* includes three pathogens: *T. pallidum* subsp. *pallidum*; subsp. *endemicum* (endemic syphilis); subsp. *pertenue* (yaws)
- *Treponema carateum* (pinta) is a separate species

The organism

- *T. pallidum* is 0.18 μ in diameter and 6-20 μ long
- Move by rapid rotation around the axis-corkscrew motility
- Can be seen on darkfield microscopy

The organism

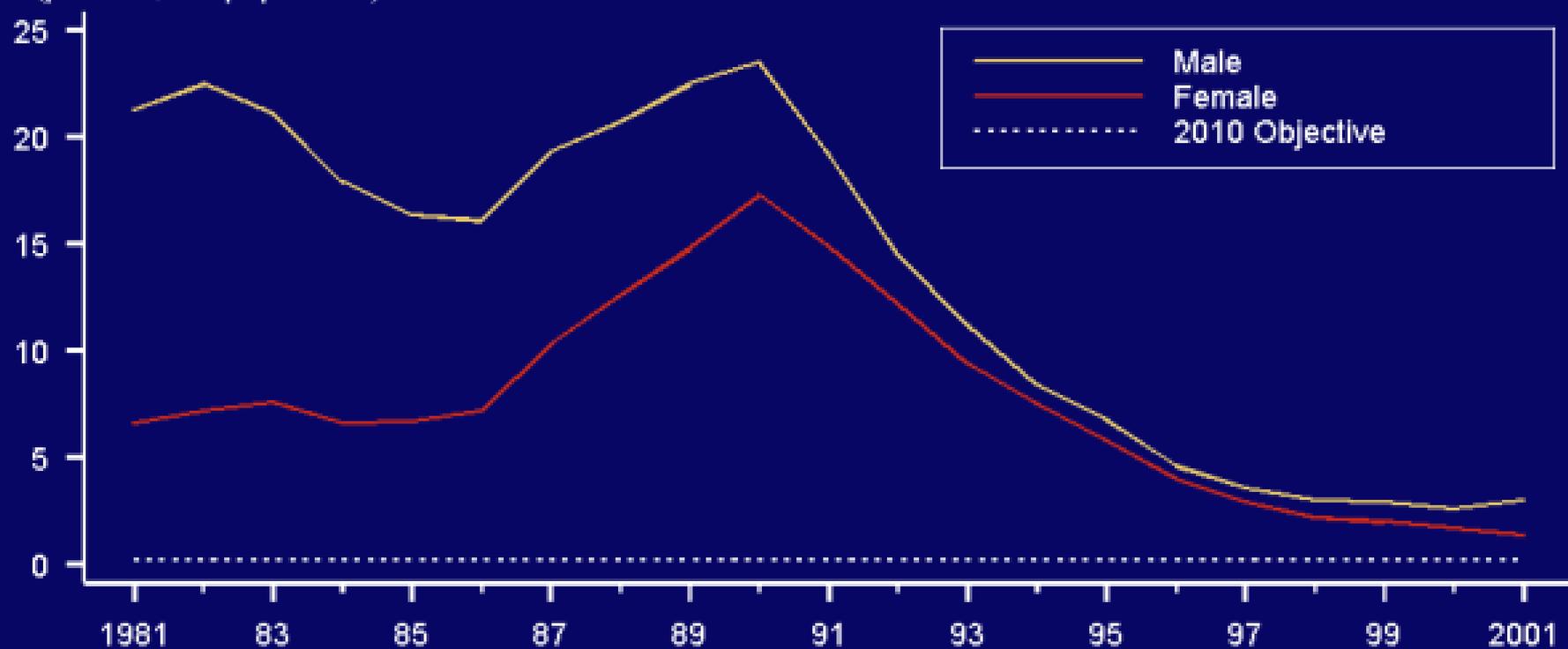
- Transmission: sexual; maternal-fetal, and rarely by other means
- Related organisms cause non venereal disease: transmitted by skin contact

Epidemiology

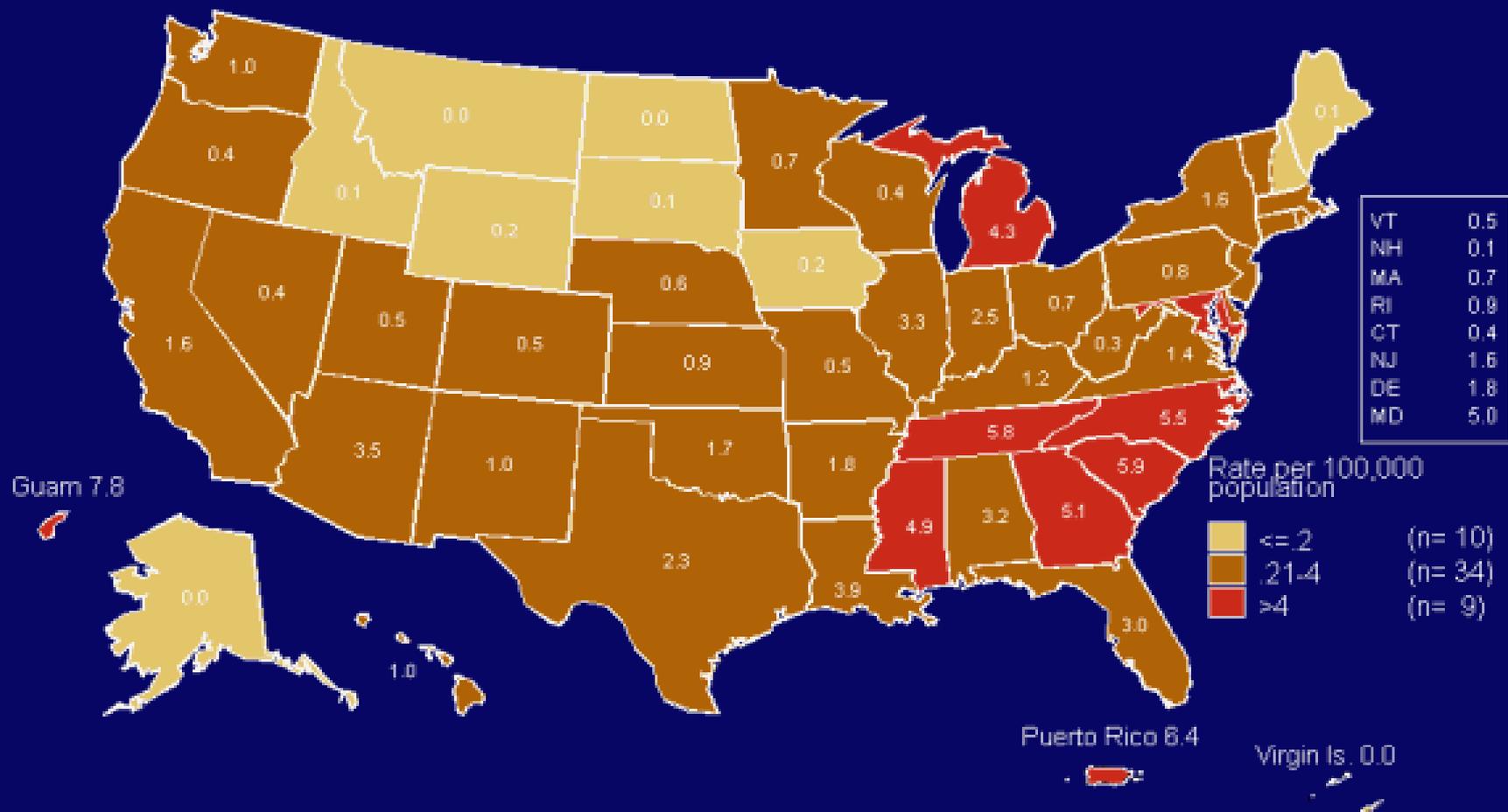
- WHO estimates >12 million cases worldwide
- The rates of syphilis decreased to reach a nadir in 2000 (US).
- National plan in the US was to eliminate syphilis with a target of 0.2/100,000 cases
- However, increased rates have been reported for the past decade
- The increase is mainly among men, with nearly 2/3 being among MSM.
- Male to female ratio increased from 1.6 to 5.3 between 1999 and 2003
- 20% of individuals are co-infected with HIV in the US.

Primary and secondary syphilis — Rates by sex: United States, 1981–2001 and the Healthy People year 2010 objective

Rate (per 100,000 population)



Primary and secondary syphilis — Rates by state: United States and outlying areas, 2001



Note: The total rate of primary and secondary syphilis for the United States and outlying areas (including Guam, Puerto Rico and Virgin Islands) was 2.2 per 100,000 population. The Healthy People year 2010 objective is 0.2 per 100,000 population.

Epidemiology-Canada

(Health Canada Jan 2010)

- Infectious syphilis (primary, secondary and early latent stages) is the least common of the three nationally reportable bacterial sexually transmitted infections (STIs)
- Similar to US data, after achieving rates of 0.4–0.6/100,000 from 1994 to 2000, rates of infectious syphilis started to rise. The projected figures for 2008 show a reported rate of 4.0/100,000.
- The rate of infectious syphilis is increasing in both males and females, but more so in males.

Epidemiology-Canada

(Health Canada Jan 2010)

- In recent years, localized outbreaks of infectious syphilis have been reported in a number of locations worldwide and in Canada, including Vancouver, Yukon, Calgary, Edmonton, Northwest Territories, **Winnipeg**, Toronto, Ottawa, Montreal and Halifax.
- Most of the outbreaks in men who have sex with men (MSM) and other outbreaks related to commercial sex (Some large outbreaks among MSM primarily in the United States have been associated with the acquisition of anonymous sex partners through the Internet). Similar reports from Alberta.

Epidemiology-Canada (Health Canada Jan 2010)

- In British Columbia (B.C.), Alberta and Yukon, Aboriginal people are disproportionately affected by STIs.
- Nationally, 2 congenital cases or less a year were reported in the decade before 2005. No cases of congenital syphilis were reported in Canada in 2003 and 2004.
- In 2005 there were 8 cases (5 from Alberta, 3 from B.C.), in 2006 there were 7 cases (Alberta, B.C., Ontario) and in 2007, there were 8 reported cases (Alberta, B.C., Ontario).

Five P's: Partners, Prevention of Pregnancy, Protection from STDs, Practices, and Past History of STDs

1. Partners

- “Do you have sex with men, women, or both?”
- “In the past 2 months, how many partners have you had sex with?”
- “In the past 12 months, how many partners have you had sex with?”
- “Is it possible that any of your sex partners in the past 12 months had sex with someone else while they were still in a sexual relationship with you?”

2. Prevention of pregnancy

- “What are you doing to prevent pregnancy?”

3. Protection from STDs

- “What do you do to protect yourself from STDs and HIV?”

4. Practices

- “To understand your risks for STDs, I need to understand the kind of sex you have had recently.”
- “Have you had vaginal sex, meaning ‘penis in vagina sex’?” If yes, “Do you use condoms: never, sometimes, or always?”
- “Have you had anal sex, meaning ‘penis in rectum/anus sex’?” If yes, “Do you use condoms: never, sometimes, or always?”
- “Have you had oral sex, meaning ‘mouth on penis/vagina’?”
- For condom answers:
- If “never:” “Why don’t you use condoms?”
- If “sometimes:” “In what situations (or with whom) do you not use condoms?”

5. Past history of STDs

- “Have you ever had an STD?”
- “Have any of your partners had an STD?”
- Additional questions to identify HIV and viral hepatitis risk include:
- “Have you or any of your partners ever injected drugs?”
- “Have any of your partners exchanged money or drugs for sex?”
- “Is there anything else about your sexual practices that I need to know about?”

Stage	Clinical Manifestations	Incubation period
Primary	Chancre, regional lymphadenopathy	3 weeks (3–90 days)
Secondary	Rash, fever, malaise, lymphadenopathy, mucus lesions, condyloma lata, patchy or diffuse alopecia, meningitis, headaches, uveitis, retinitis	2–12 weeks (2 wks–6 mo)
Latent	Asymptomatic	Early: <1 year Late: ≥1 year

Stage	Clinical Manifestations	Incubation period
<i>Tertiary</i> Cardiovascular syphilis Neurosyphilis Gumma	Aortic aneurysm, aortic regurgitation, coronary artery ostial stenosis Ranges from asymptomatic to symptomatic: headaches, vertigo, personality changes, dementia, ataxia, presence of Argyll Robertson pupil Tissue destruction of any organ; manifestations	10–30 years <2 years–20 years 1–46 years
Congenital Early Late	2/3 may be asymptomatic Fulminant disseminated infection, mucocutaneous lesions, osteochondritis, anemia, hepatosplenomegaly, neurosyphilis Interstitial keratitis, lymphadenopathy, hepatosplenomegaly, bone involvement, anemia, Hutchinson’s teeth, neurosyphilis	Onset <2 years Persistence >2 years after birth

Clinical manifestations

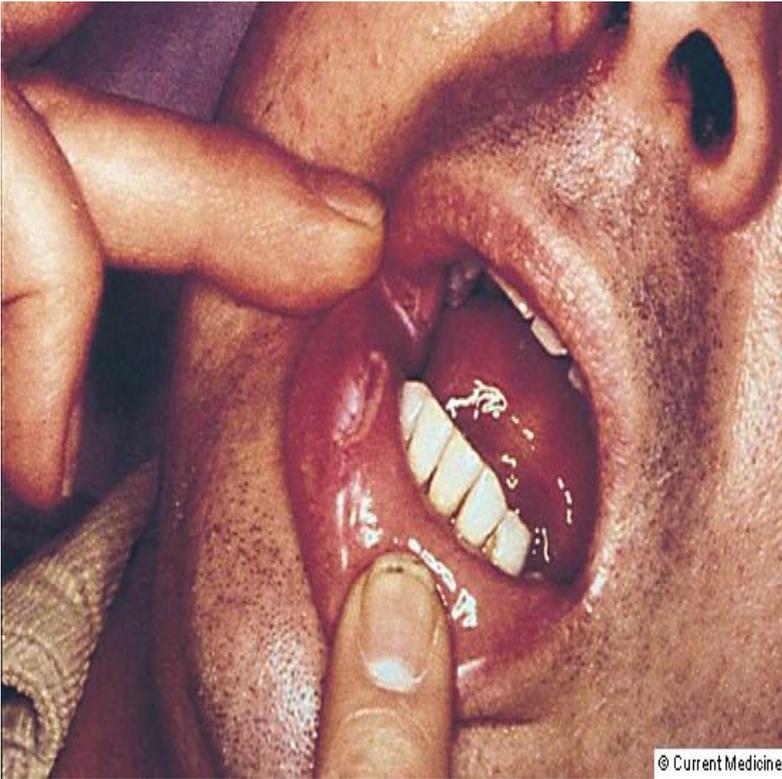
- Syphilis is a systemic disease caused by *Treponema pallidum*
- On the basis of clinical findings, the disease has been divided into a series stages, these may overlap but are useful for guiding treatment and follow-up
- primary infection: chancre at the infection site
- secondary infection: manifestations include a skin rash, mucocutaneous lesions, and lymphadenopathy, neurologic infection (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities, which might occur through the natural history of untreated infection)

Clinical manifestations

- tertiary infection ; cardiac or gummatous lesions
- Latent infections: **asymptomatic**, detected by serologic testing.
- Divided to early latent syphilis- acquired within the last year; all other cases of latent syphilis are either late latent syphilis or latent syphilis of unknown duration.
- Treatment for both late latent syphilis and tertiary syphilis requires a longer duration of therapy

PRIMARY SYPHILIS

- Incubation period 9-90 days, usually around 3 weeks.
- Develops at site of contact/inoculation.
- Classically: single, painless, clean-based, indurated ulcer, with firm, raised borders. Atypical presentations may occur.
- Mostly anogenital, but may occur at any site (tongue, pharynx, lips, fingers, nipples, etc...)
- Accompanied by non-tender regional adenopathy.
- Highly infectious.
- May be darkfield positive but serologically negative.
- Untreated, heals in several weeks, leaving a faint scar.



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Primary syphilis lesions

Differential diagnosis of genital ulcer

- Genital Herpes- grouped vesicles on erythematous base, last 2-3 weeks, very painful, recurrences
- Chancroid- rare, tender, painful, undermined edges, satellite ulcers
- Lymphogranuloma venereum- papulovesicular, heals rapidly, enlarging regional lymph nodes
- Drug reactions
- Bowen's disease; malignancy
- Behcet's disease; Reactive arthritis with mucosal involvement

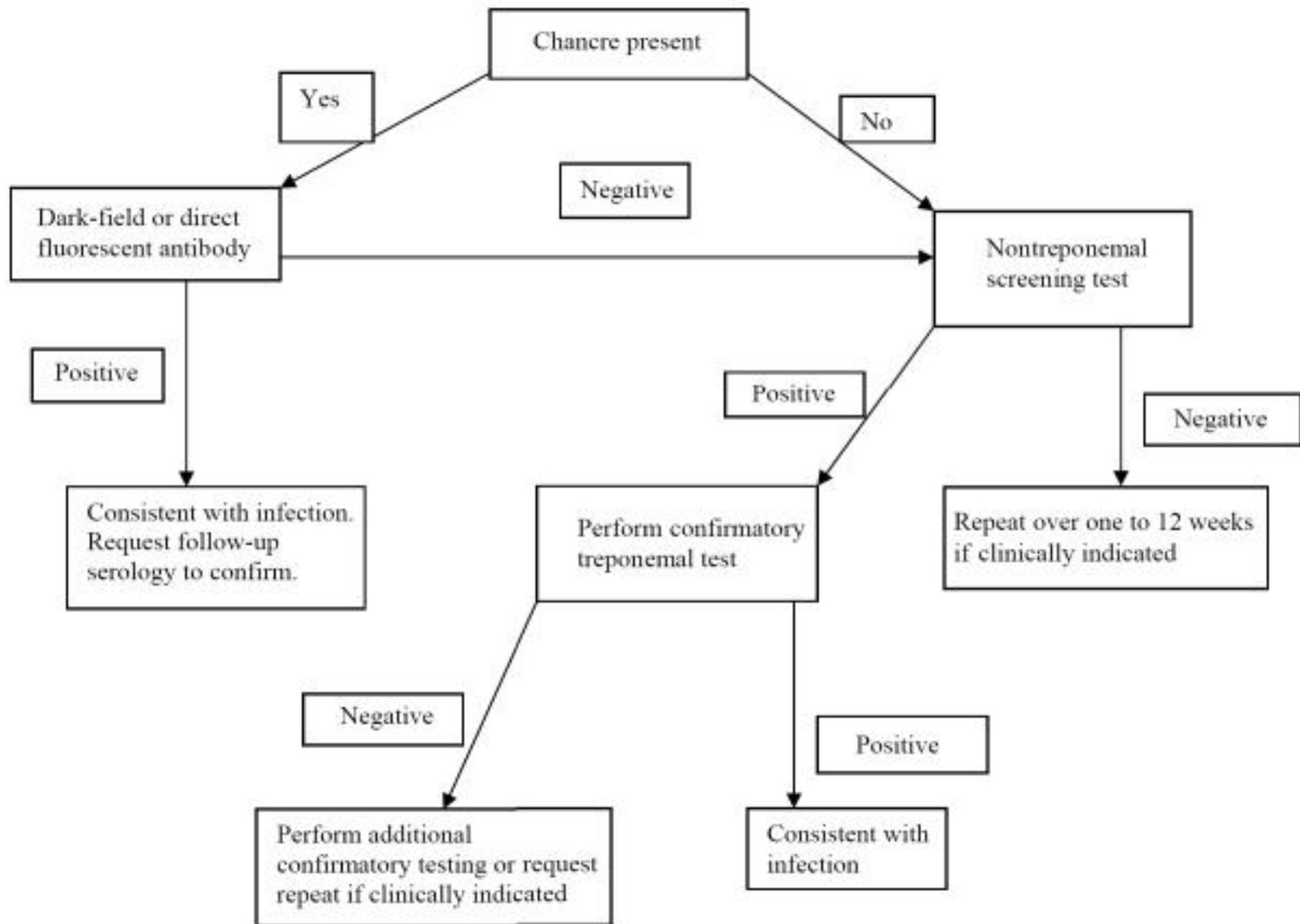


TABLE 2

The application and limitations of diagnostic tests in different stages of syphilis

Stage	Recommended tests	Comments
Primary syphilis	Direct examination, Nontreponemal tests, Treponemal tests	Detection of <i>Treponema pallidum</i> in lesions is definitive evidence of syphilis but a negative result does not rule out syphilis. PCR-based tests have a high reliability. In the first two to three weeks, serology may not be positive in most cases, and in early primary syphilis, treponemal tests are recommended. The presence of a genital ulcer and a positive nontreponemal test may not indicate primary syphilis. Repeat serology over a two to 12 week period to rule out syphilis
Secondary syphilis	Direct examination, Nontreponemal tests, Treponemal tests	<i>T pallidum</i> can be detected in skin and mucosal lesions, and PCR-based tests may be useful in atypical lesions. Serological tests have nearly 100% sensitivity. In persons with a history of syphilis, a fourfold increase in titre

SECONDARY SYPHILIS

- Seen 6 wks to 6 mos after primary chancre
- Usually presents with diffuse non-pruritic, indurated rash, involving palms & soles.
- May be accompanied by systemic symptoms and signs:
 - Fever, malaise, headache, sore throat, myalgia, arthralgia, generalized lymphadenopathy
 - Hepatitis (10%)
 - Renal: an immune complex type of nephropathy with transient nephrotic syndrome
 - Ocular involvement: Iritis or anterior uveitis
 - Bone: periostitis
 - CSF pleocytosis in 10 - 30% (symptomatic meningitis is seen in <1%)

SECONDARY SYPHILIS

- **The skin rash:**
 - Diffuse, often with a superficial scale (papulosquamous).
 - May leave residual pigmentation or depigmentation.
- **Condylomata Lata:**
 - Formed by coalescence of large, pale, flat-topped papules.
 - Occur in moist areas such as the perineum.
 - Highly infectious.
- **Mucosal lesions:**
 - ~ 30% of secondary syphilis patients develop mucous patch (slightly raised, oval area covered by a grayish white membrane, with a pink base that does not bleed).
 - Highly infectious.

SECONDARY SYPHILIS

- Very versatile rashes with broad differential diagnosis; macular rashes can mimic drug reactions; rubella; measles and pityriasis rosea
- Papular rash can mimic psoriasis, seborrheic dermatitis and lichen planus
- **Not pruritic**
- **Not vesicular**



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Condylomata lata of secondary syphilis Reproduced with permission from: Begovac, J, Lukas, D. Images in clinical medicine. Condylomata lata of secondary syphilis. N Engl J Med 2005; 352:708. Copyright ©2005 Massachusetts Medical Society.



Seattle STD/HIV Prevention Training Center Source: Connie Celum, Walter Stamm

LATENT SYPHILIS

Positive syphilis serology without clinical signs of syphilis

- It begins with the resolution of secondary syphilis and may last for a lifetime.
 - Pt may or may not experienced primary or secondary syphilis.
 - *Many conditions capable of causing occasional false-positive nontreponemal test reactions for syphilis, such as systemic lupus erythematosus (SLE), and congenital syphilis must be excluded before the diagnosis of latent syphilis can be made.*
- Is divided into early and late latency: Early: <1 year; Late: ≥1 year. Many cases of Latent infection are of undetermined duration.

Natural history

- 25% of latent syphilis relapse to active secondary syphilis, usually in the first 2 years
- Untreated about a third will develop tertiary syphilis 2-30 years later:

Benign- 15-17%- gummas or parenchymal involvement

Neurosyphilis-8%; Cardiovascular-8%

A 27 years old with rash

- Presented 9/2010 with Rash covering chest, back, abdomen, arms and legs
- Reports fatigue, headache, no fever or weight loss
- HIV diagnosed 1 year ago, not on therapy, recently moved to MB from ON

27 years old,
HIV+, not on
ART, CD4
109/mm³



- #Reports a penile lesion several weeks prior to presentation
- #Lesion has now completely healed with scarring
- #One 2.4MU Benzathine penicillin administered
- #Rash, feeling unwell, no fever documented
- #MSM, several partners, inconsistent condom usage

What is your diagnostic plan?

HIV Syphilis interaction

- Syphilis is 8 times more common among HIV+ individuals
- Syphilis can increase HIV transmission- multiple mechanisms- 2-9 fold increase
- Syphilis co-infection decreases CD4 counts and increases HIV viral loads at least transiently
- More frequent presentation with secondary syphilis
- Higher rate of CNS involvement
- High false positive non-treponemal serology in HIV infection
- Slower rates of decline of non-treponemal tests
- False negative non-treponemal tests due to Prozone phenomena

Studies of serological response

First Author Year (Ref.)	Inclusion Period, Country	Design	No. Syphilis Cases With Available Serologic Follow-Up		Key Demographic and Clinical Features	Primary Endpoint	Main Result
			HIV+	HIV-			
Ghanem, 2007 (12)	1992–2000, USA	R cohort study	129	168	Early syphilis, late latent (or unknown duration) syphilis and neurosyphilis	Serologic failure: 4-fold rise at 30–400 d or lack of 4-drop decrease in RPR titer at 270–400 d	22/129 in HIV+ vs. 5/168 in HIV- patients ($p < 0.001$)
Goeman, 1995 (14)	?, Zaire	P cohort study	47	73	Women only	Serologic failure: lack of 4-fold decrease in RPR titer at months 6, 12, and 24	Similar evolution of RPR titers across HIV status groups
Gourevitch, 1993 (18)	1985–1991, USA	R cohort study	26	17	All syphilis stages; IVDU only	Serologic failure: lack of 4-fold decrease in RPR titer at months 3 (if primary or secondary syphilis) and 6 (if early latent syphilis)	0/26 in HIV+ vs. 1/17 in HIV- patients (NS)
Hutchinson, 1994 (20)	1990–1991, USA	R case-control study	28	78	Early syphilis	Serologic failure: lack of 4-fold decrease in RPR titer at months 3 (if primary or secondary syphilis) and 6 (if early latent syphilis)	5/28 in HIV+ vs. 11/78 in HIV- patients ($p = 0.76$)
Janier, 1999 (21)	1986–1993, France	P case-control study	49	29	Primary, secondary, and latent syphilis; male only	Lack of VDRL seroreversion	18/49 in HIV+ vs. 14/29 in HIV- patients, (log-rank $p = 0.053$)
Kingston, 2004 (22)	1999–2002, UK	R cohort study	31, 20, and 12*	23, 17, and 11*	Early syphilis	Mean RPR titers decrease (coded as a quantitative parametric variable) at months 3, 6, and 12	No significant difference according to HIV status
Long, 2006 (26)	May–June 2003, Peru	P cohort study	11	65	Latent syphilis	Serologic failure: lack of 4-fold decrease in RPR titer at month 12	1/11 in HIV+ vs. 4/65 in HIV- patients (NS)
Manavi, 2007 (27)	2003–2005, UK	R cohort study	100	161	Early syphilis and syphilis of unknown duration	Serologic failure: lack of 4-fold decrease in VDRL titer within 6–12 months	No significant difference according to the HIV status
Riedner, 2005 (31)	2000–2003, Tanzania	P RCT	171	157	Early syphilis	Serologic failure: lack of 4-fold decrease in RPR titer within 9 months	94.7% in HIV+ vs. 98.4% in HIV- patients ($p > 0.50$)
Roßi, 1997 (32)	1991–1994, USA	P RCT	75, 69, and 61*	285, 257, and 218*	Early syphilis	Serologic failure: lack of 4-fold decrease in RPR titer at months 3, 6, and 12	In multivariate analysis, at month 6, HIV was significantly associated with serologic failure in primary (but not in secondary) syphilis.
Telzak, 1991 (35)	1987–1988, USA	R case-control study	69	462	Primary and secondary syphilis	Serologic failure: lack of 4-fold decrease in RPR titer at month 6	At month 6, HIV was significantly associated with serologic failure in primary (but not in secondary) syphilis.
Yinnon, 1996 (39)	1989–1991, USA	R case-control study	52	52	All syphilis stages	Serologic failure: lack of 4-fold decrease in RPR titer at months 6 and 12	No significant difference according to the HIV status

Abbreviations: IVDU = intravenous drug user; NS = not statistically significant; P = prospective; R = retrospective; RCT = randomized controlled trial.

*At 3, 6, and 12 mo, respectively.

Clinical and Serologic Baseline and Follow-Up Features of Syphilis According to HIV Status in the Post-HAART Era.

Farhi, David; Benhaddou, Nadjet;
Grange, Philippe; Zizi, Nada;
Deleuze, Jean; Morini, Jean-
Pierre; Gerhardt, Philippe;
Krivine, Anne; Avril, Marie-
Francoise; Dupin, Nicolas; MD,
PhD

Medicine. 88(6):331-340,
November 2009.

Diagnostic tests

Recent changes in how syphilis is diagnosed and monitored:

- the use of EIA or Chemiluminescent Immunoassay (CLIA) for the serologic screening of syphilis is increasing and has been incorporated to the protocol of Ontario
- the order of screening and confirmatory tests may be reversed in settings these tests are available
- Traditionally screening used a non-treponemal test, RPR or Venereal Disease Research Laboratory (VDRL)-CPL does RPR
- Confirmation using *T. pallidum* particle agglutination (TP-PA) or another treponemal test

Diagnostic tests

Nontreponemal Tests:

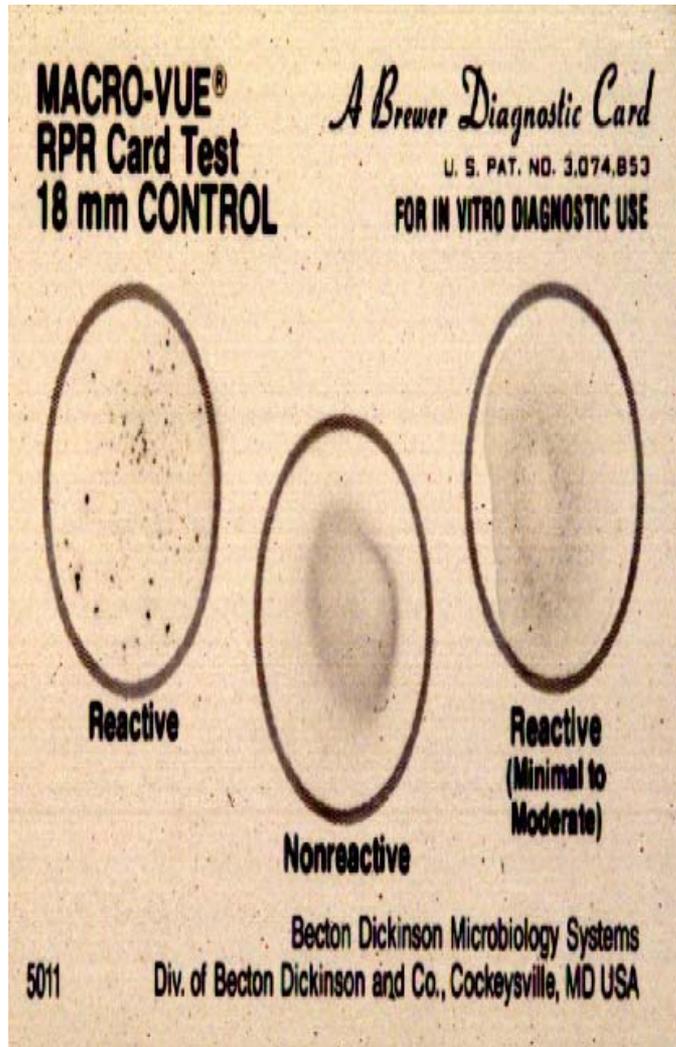
- The nontreponemal tests, VDRL and RPR, target antibodies to cardiolipin-lecithin-cholesterol antigen and are not specific to *T. pallidum*
- These tests are quantitative, providing a measurement of titer and are used to monitor treatment response
- A reactive RPR suggests active infection or recently treated infection, RPR titer decreases with treatment and time; it is most useful for assessing acute disease and for monitoring treatment

Diagnostic tests

Nontreponemal Tests:

- The same test should be used in a given patient for follow up, rather than switching between RPR and VDRL
- RPR often produces titers 1-2 times higher than the VDRL

Diagnostic tests- non treponemal



False positive non-treponemal

Infectious

- Lyme disease
- Leptospirosis
- Leprosy
- Tuberculosis
- SBE
- Rickettsial disease
- Malaria
- Hepatitis
- Vaccinia (vaccination)

Noninfectious

- Drug addiction
- Any connective tissue disease
- Rheumatoid heart disease
- Transfusions (multiple)
- Pregnancy
- “Old age”
- Chronic liver disease

Diagnostic tests

Treponemal Tests

- TP-PA and the fluorescent treponemal antibody absorption test (FTA-ABS)- used in CPL
- EIA or the CLIA are being used in their place
- if these tests are used for screening, a non-treponemal test should be performed to quantify the titer
- The EIA and CLIA tests have been cleared by the US Food and Drug Administration (FDA) for clinical use

Diagnostic tests

- Both immunoglobulin G and immunoglobulin M (IgM) tests are available, although the IgM test has no clinical value in early syphilis. These assays are highly automated, less costly, and require less labour
- Chemiluminescent Microparticle Immunoassay:
- ARCHITECT Syphilis TP is a two-step immunoassay for the qualitative detection of IgG or IgM in human serum or plasma using chemiluminescent microparticle immunoassay (CMIA) technology

Diagnostic tests

- In the first step, sample microparticles coated with recombinant TP (TpN15, TpN17, and TpN47) and diluent are combined
- Anti-TP antibodies present in the sample bind to the coated microparticles After washing, acridinium-labelled anti-human IgG and IgM conjugate is added in the second step
- The resulting chemiluminescent reaction is measured as relative light units (RLUs)

Diagnostic tests

- If the RPR and TP.PA results are non-reactive or indeterminate, the Fluorescent Treponemal Antibody Absorbance (FTA-Abs) test may be included
- The FTA-Abs is a third test that detects IgG and IgM treponemal antibodies.

	Primary	Secondary	Latent	Tertiary
VDRL	78	100	95	71
RPR	86	100	98	73
FTA-ABS	84	100	100	96
TP-PA	88	100	100	96
Syphilis IgG	97	97	97	97

Diagnostic tests- Ontario Public Health

Screening Test	Confirmation Testing			
CMIA	RPR	TP.PA	FTA-Abs	INTERPRETATIONS
Non-reactive	Not tested	Not tested	Not tested	No serological evidence of current or past infection If primary syphilis is suspected a repeat sample is suggested in ~ 4 weeks
Reactive	Reactive (high titre, RPR _≥ 16)	Reactive	Not tested	Most likely interpretations include: <ul style="list-style-type: none"> Active infectious syphilis (primary, secondary or early latent) Latent or treated syphilis
Reactive	Reactive (low titre, RPR ≤ 8)	Reactive	Not tested	Most likely interpretations include: <ul style="list-style-type: none"> Active infectious syphilis (primary, secondary or early latent) Latent or treated syphilis
Reactive	Non- reactive	Reactive	Not tested	Most likely interpretations include: <ul style="list-style-type: none"> Treated syphilis Early primary syphilis Latent syphilis
Reactive	Non-reactive	Non- Reactive	Non- reactive	Most likely interpretations include: <ul style="list-style-type: none"> Early syphilis Previously treated syphilis Biological false positive
Reactive	Non- reactive	Non- Reactive	Indeterminate	Suggest: Repeat serology in 2 to 4 weeks. If no change with repeat serology, likely biological false positive
Reactive	Non- reactive	Indeterminate	Non- reactive	
Reactive	Non - reactive	Indeterminate	Indeterminate	

Diagnostic Algorithms

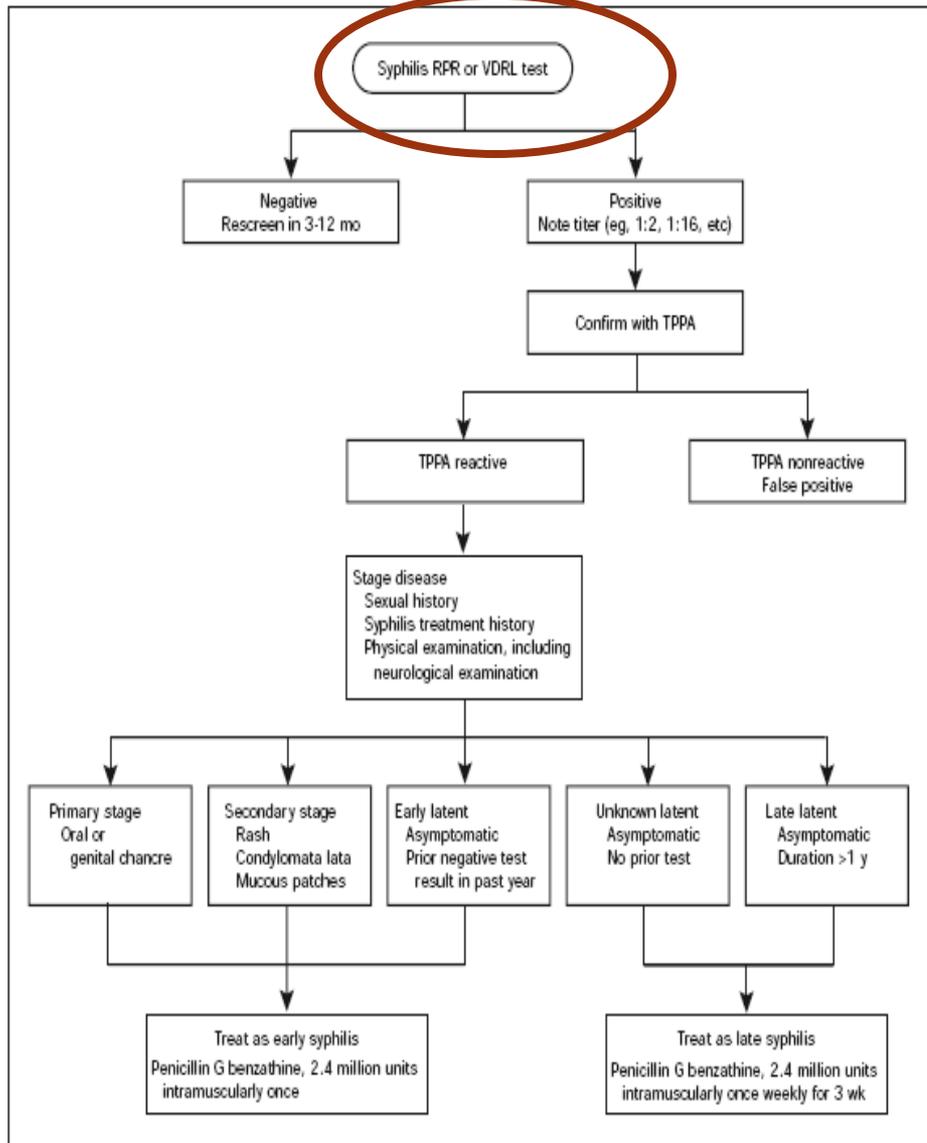
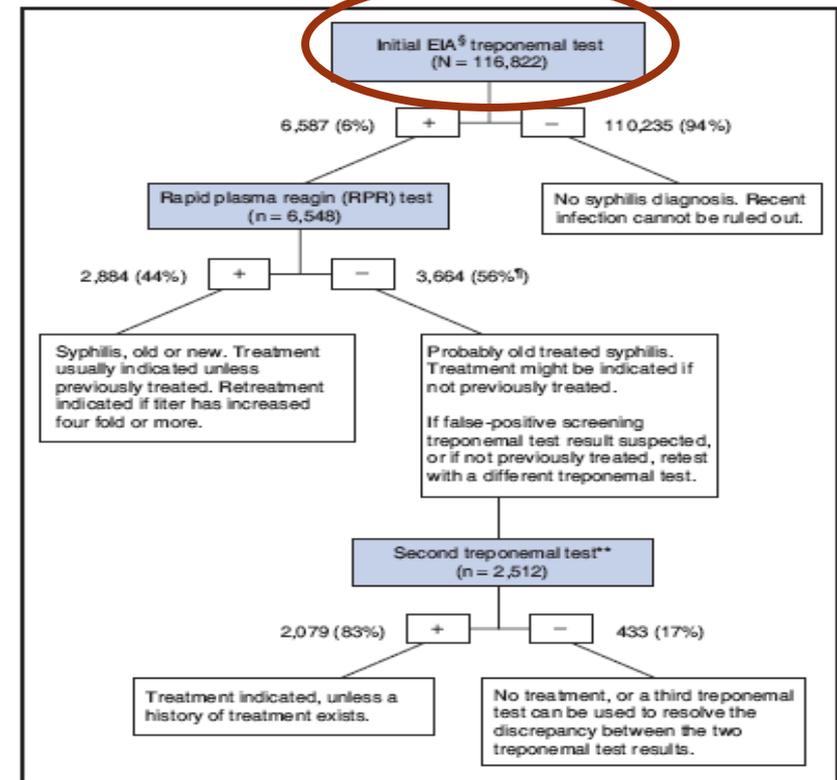


FIGURE. Composite results of syphilis testing algorithms using treponemal tests for initial screening and likely interpretations* — four laboratories, New York City, October 1, 2005–December 1, 2006†



* One laboratory provided limited interpretation of the test results; the other three summarized the results without interpretation. No formal recommendations exist regarding the interpretation of results derived from testing algorithms using treponemal tests as the initial test.

† Using a convenience sample of 116,822 specimens. The four laboratories used different testing algorithms. Data shown are a composite of results from all four laboratories.

§ Enzyme immunoassay.

¶ Reactive with EIA treponemal test but nonreactive with RPR test.

** Using *Treponema pallidum* particle agglutination or fluorescent treponemal antibody tests.

Assessment of the sens/spec of the different algorithms:

The Architect CLIA has a sensitivity of 98.4%; significantly higher than the sensitivity of the murex immune capture enzyme (ICE) immunoassay (86%), the IgM enzyme immunoassay (EIA) (86.8) and the VDRL (83.7%)

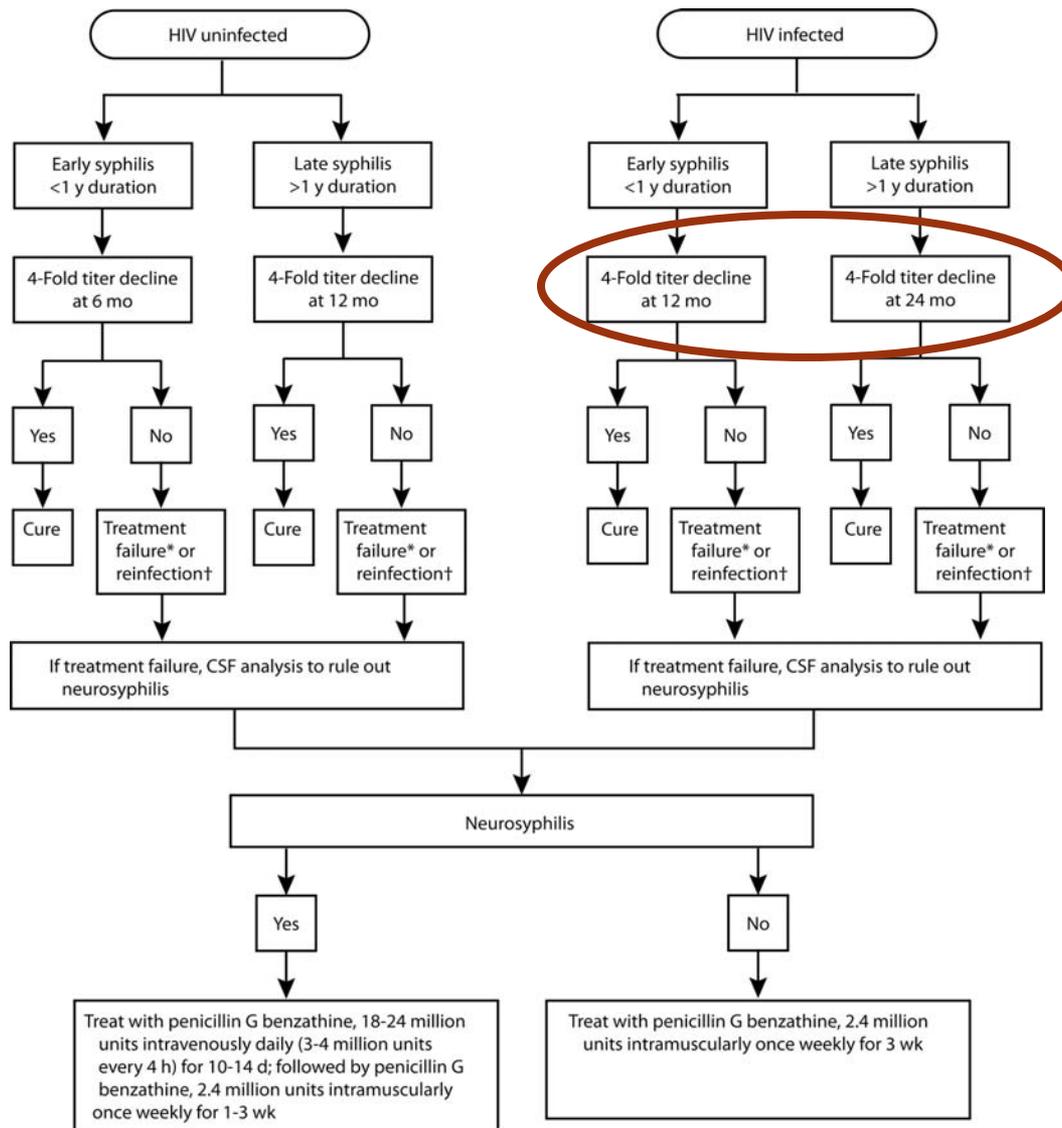
The difference in the sensitivity of the Architect other assays was due to primary stage syphilis (97.5% vs 77.2%) Specificity 99.1%

Young H et al. Sex Transm Infect 2009

TABLE 1. Sensitivity of Serologic Testing Strategies in Detecting Dark-Field-Confirmed Primary Syphilis

Testing Strategy	Total (N = 106)		HIV-Negative (N = 65)		HIV-Positive (N = 29)		P*
	No. Cases Diagnosed	Sensitivity (95% CI)	No. Cases Diagnosed	Sensitivity (95% CI)	No. Cases Diagnosed	Sensitivity (95% CI)	
VDRL confirmed by TP-PA	75	70.8% (61.1, 79.2)	50	76.9% (64.4, 88.5)	18	55.2% (35.7, 73.8)	0.05
TP-PA as first-line test	91	85.9% (77.7, 91.8)	57	87.7% (77.2, 94.5)	24	82.8% (64.2, 94.2)	0.53

Creegan et al STD 2007



Zetola N M et al. Mayo Clin Proc. 2007;82:1091-1102

Diagnostic tests-False positive non-treponemal tests

- False-positive nontreponemal tests occur in 1%-2% of the U.S. population
- Conditions associated with FP test: pregnancy; HIV infection; intravenous drug use; tuberculosis; rickettsial infection; spirochetal infection other than syphilis; infective endocarditis; disorders of immunoglobulin production
- False negative- early infection and during late infection

Diagnostic tests-summary

A presumptive diagnosis is possible with the use of two types of serologic tests:

- 1) nontreponemal tests Venereal Disease Research Laboratory [VDRL] and RPR
- 2) treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] and *T. pallidum* particle agglutination [TP-PA])

The use of only one type of serologic test **is insufficient for diagnosis** because false-positive nontreponemal test results associated with various medical conditions

Neurosyphilis

- No single test can be used to diagnose neurosyphilis (NS).
- VDRL-cerebrospinal fluid (CSF) is highly specific, but insensitive (99% and 70-75% respectively)
- The majority of other tests are both insensitive and nonspecific and must be interpreted in relation to other test results and the clinical assessment
- Diagnosis is based on: reactive serologic test results, CSF cell count or protein, or a reactive VDRL-CSF with or without clinical manifestations
- The CSF leukocyte count is usually elevated (>5 BC/mm³) in patients with neurosyphilis; also is a sensitive measure of the effectiveness of therapy

Neurosyphilis

- The VDRL-CSF is the standard serologic test for CSF, when reactive in the absence of contamination with blood, it is considered diagnostic of neurosyphilis.
- VDRL-CSF might be nonreactive even when neurosyphilis is present- not sensitive
- The CSF FTA-ABS is less specific (i.e., yields more false-positive results) for neurosyphilis than the VDRL-CSF, but the test is highly sensitive- hence recommended by some experts to rule out NS.

Management

- All patients who have syphilis should be tested for other STI's and for HIV infection
- In geographic areas in which the prevalence of HIV is high, patients who have primary syphilis should be **retested for HIV after 3 months** if the first HIV test result was negative (MSM?)
- Quantitative non-treponemal serologic tests should be repeated at 6, 12, and 24 months
- Patients with normal CSF examination should be re-treated for latent syphilis if 1) titers increase fourfold, 2) an initially high titer ($>1:32$) fails to decline at least fourfold (i.e., two dilutions) within 12–24 months of therapy, or 3) signs or symptoms attributable to syphilis develop

Management

- **Primary:** Benzathine penicillin G 2.4 million units IM in a single dose
- **Early Latent Syphilis** Benzathine penicillin G 2.4 million units IM in a single dose
- **Late Latent Syphilis or Latent Syphilis of Unknown Duration** Benzathine penicillin G 7.2 million units total, administered as 3x 2.4 million units IM each at 1-week intervals
- **Neurosyphilis-** Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days

Treatment

- **Primary and secondary syphilis**

- **Benzathine penicillin G 2.4 million units IM in a single dose**
- **Pen allergy:** Doxycycline 100 mg orally twice daily for 14 days or tetracycline (500 mg four times daily for 14 days) are regimens that have been used for many years.
- *ceftriaxone (1 g daily either IM or IV for 10–14 days) is probably effective for treating early syphilis, the optimal dose and duration of ceftriaxone therapy have not been well studied*
- *Azithromycin as a single 2-g oral dose is effective for treating early syphilis, but resistance is emerging in some regions*

- **Latent syphilis**

- Early Latent Syphilis

- **Benzathine penicillin G 2.4 million units IM in a single dose**

- Late Latent Syphilis or Latent Syphilis of Unknown Duration

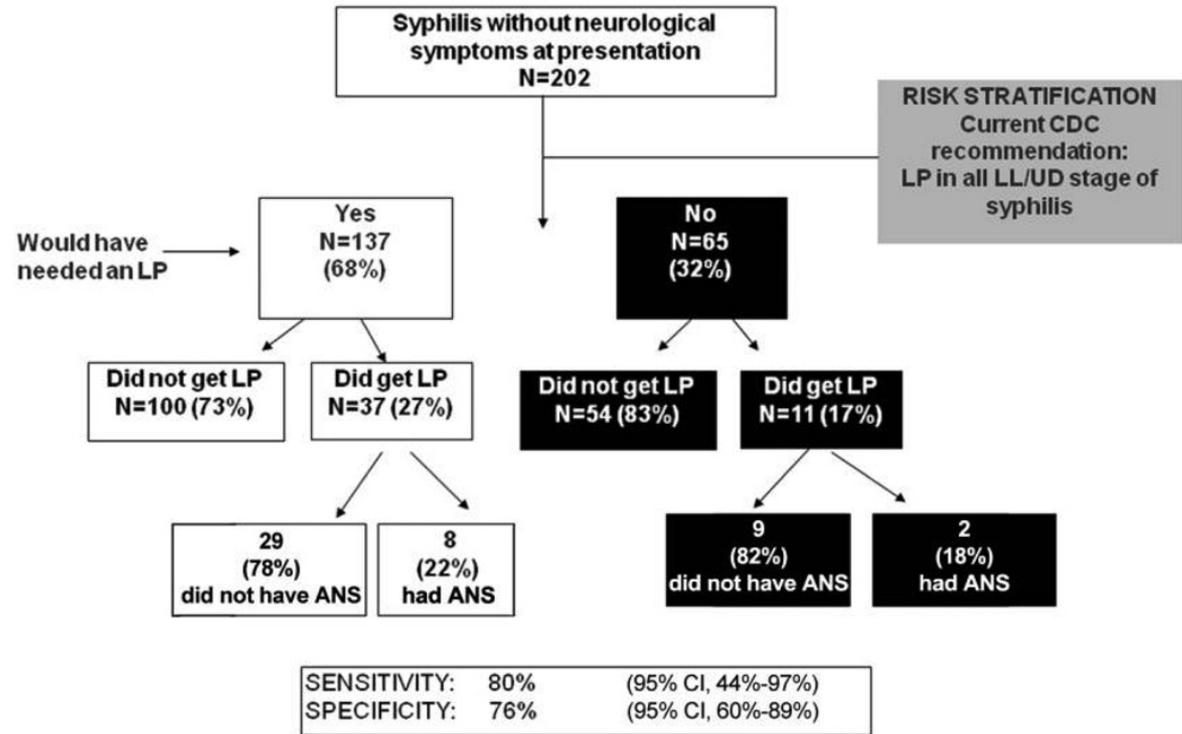
- **Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals**

Treatment

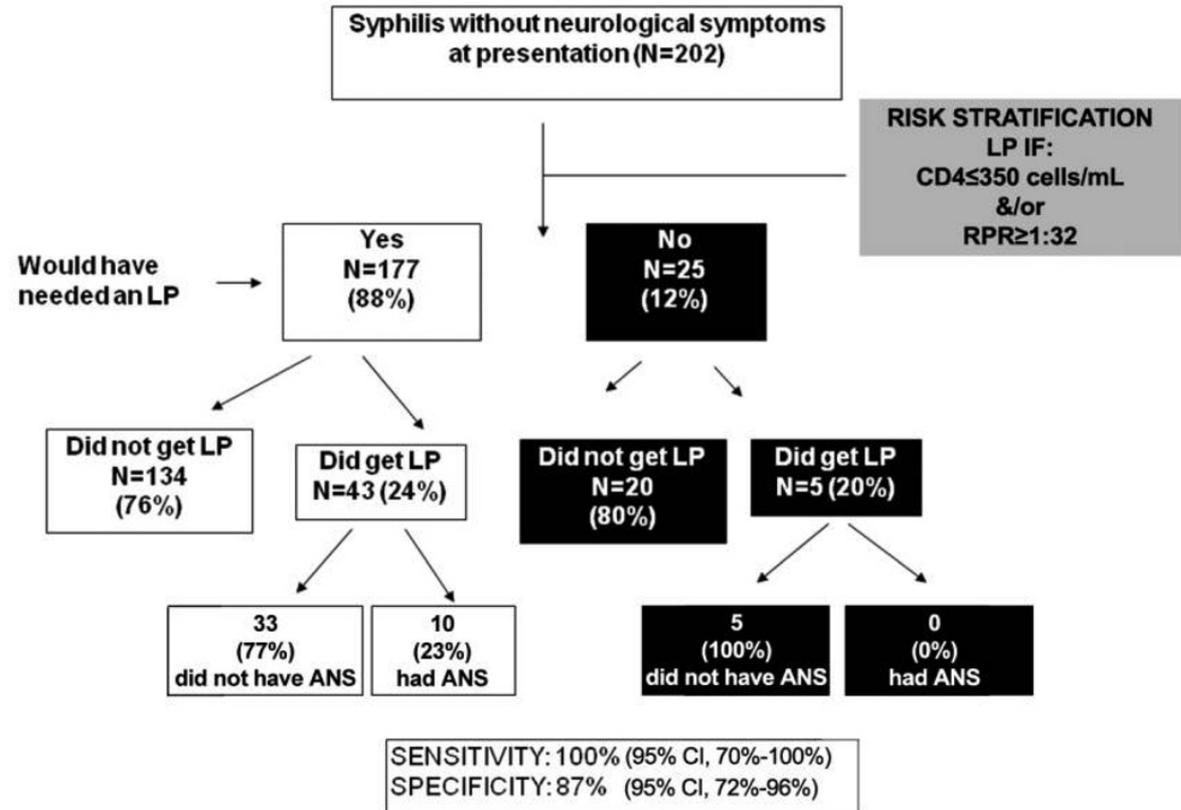
Latent syphilis, Pen allergy:

- The alternatives to penicillin for the treatment of latent syphilis have not been adequately documented
- Non-pregnant patients allergic to penicillin who have clearly defined early latent syphilis should respond to therapies recommended as alternatives to penicillin for the treatment of primary and secondary syphilis
- For late or unknown duration of latecncy: only acceptable alternatives are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), both for 28 days
- Ceftriaxone seems to be effective but formal studies are lacking
- For pregnant women desensitization is the only option

Management-when to LP an HIV- syphilis co-infected?



Management-when to LP an HIV- syphilis co-infected?



“In patients with concurrent HIV infection and syphilis, the use of criteria based on rapid plasma reagin titer and CD4 cell count, instead of stage-based criteria, improved the ability to identify ANS”

Management of syphilis in HIV infected individuals

- From CDC 2010 guidelines:
 - “Most HIV-infected persons respond appropriately to standard benzathine penicillin for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in HIV-infected persons, even in those without neurologic symptoms, although the clinical and prognostic significance of such CSF abnormalities with primary and secondary syphilis is unknown”
 - “Several studies have demonstrated that among persons infected with both HIV and syphilis, clinical and CSF abnormalities consistent with neurosyphilis are associated with a CD4 count of ≤ 350 cells/mL and/or an RPR titer of $\geq 1:32$
- Caveat: however, unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.*
- The use of antiretroviral therapy as per current guidelines might improve clinical outcomes in HIV-infected persons with syphilis



27 yo female HIV+

On ARV

CD4 374

- RPR- Weakly reactive
- VDRL- Non-reactive
- TP PA +4 Reactive
- TP Antibody IFA +4 reactive

What is your interpretation of the results?

Summary

- Syphilis is important to diagnose and treat to prevent transmission and late consequences
- After a nadir in the late 1990's a resurgence of syphilis seen in developed countries
- In many urban settings driven by an increase among MSM
- Prevention is also important as syphilis increases risk for HIV transmission and progression
- Latent syphilis is the most common presentation, hence familiarity with serologic tests is important

Summary

- Among HIV infected individuals differences in disease progression and maybe in rates of serological response to therapy
- Although higher false positive non-treponemal false positivity and higher rates of abnormalities on LP- diagnostic testing should probably follow similar flow charts
- Reversal to treponemal test for initial screening (CMIA)??!!!
- 2010 Guidelines no longer separate HIV+ from HIV-
- LP- neuro sign/symptoms ; $CD4 < 350$ and/or $RPR > 1:32$; or in cases where the titres do not decrease after therapy

Suggested reading

1. Ghanem KG. *Current Infect Dis Rep* 2010 12;140-146.
Evaluation and management of syphilis in the HIV infected patient
2. CDC Guidelines: *MMWR* Vol. 59 / RR-12 December 17, 2010
3. www.phac-aspc.gc.ca/std-mts/sti-its/pdf/510syphilis-eng.pdf revised Jan 2010 Health Canada