AETC AIDS Education & Training Center Program Northeast/Caribbean

Treatment & Prevention of Syphilis in People with HIV

June 4, 2026

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Disclosures

- None

Objectives

- At the end of this presentation, participants will be able to:
  - Recognize the clinical manifestations of syphilis and its complications among adults with HIV
  - Describe approaches to managing clinical and serological complications
  - Characterize the implications of doxycycline use as post-exposure prophylaxis for syphilis
  - Identify the limitations of new diagnostics for syphilis

Natural History of Syphilis

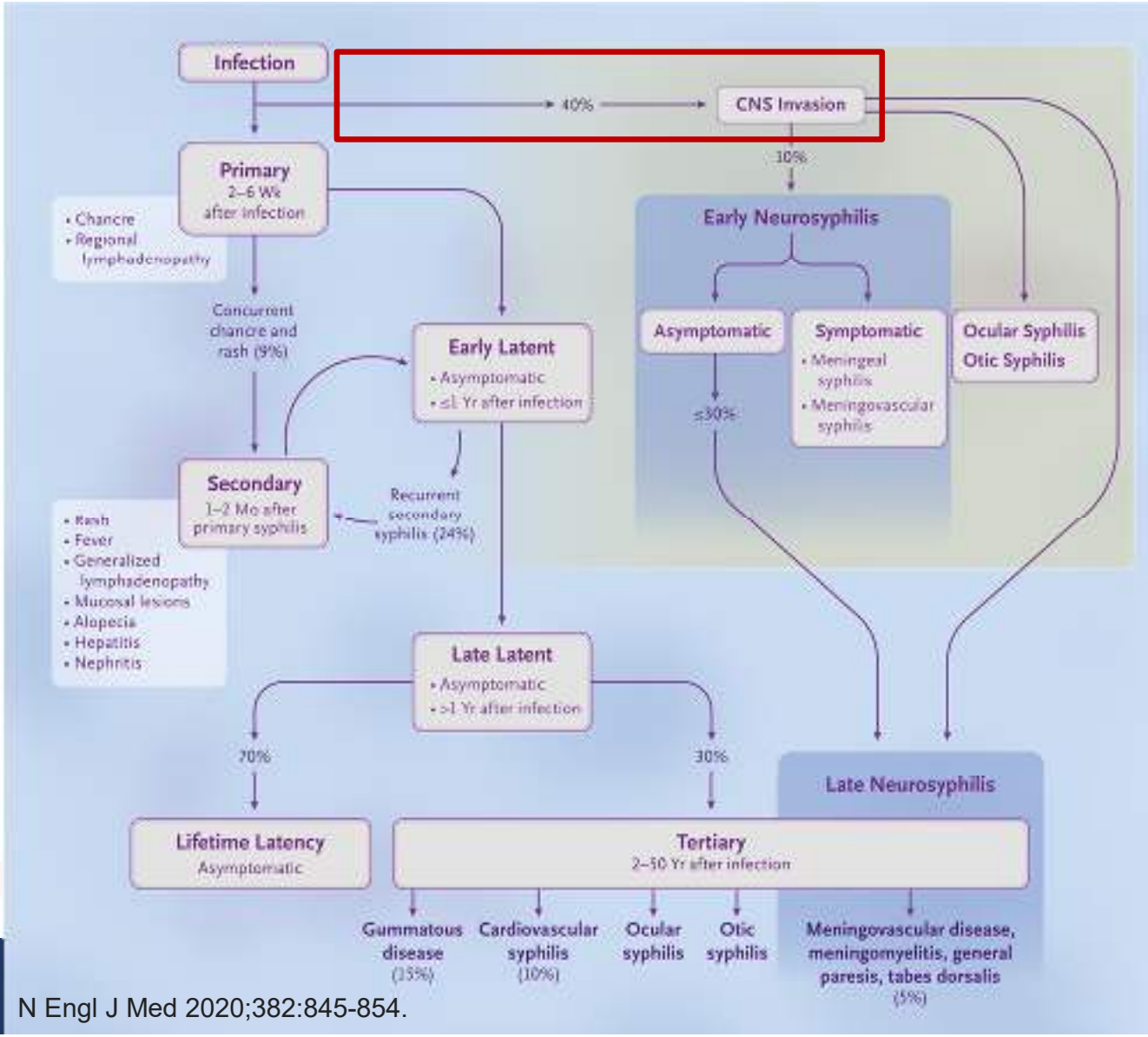
Sexual transmission (only occurs in early stages)

- Risk of infection after 1 exposure: 40%
- Index patient is most contagious during 1° and 2° stage, less so in early latent stage

Vertical transmission (may occur during any stage)

- ~80% transmission in the early stages
- ~10% transmission in the late stages

Rarely, transmission may occur through **blood transfusions** and **organ transplantations**

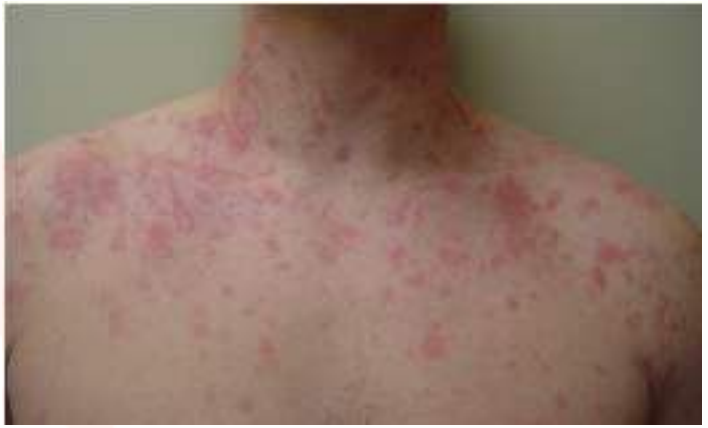


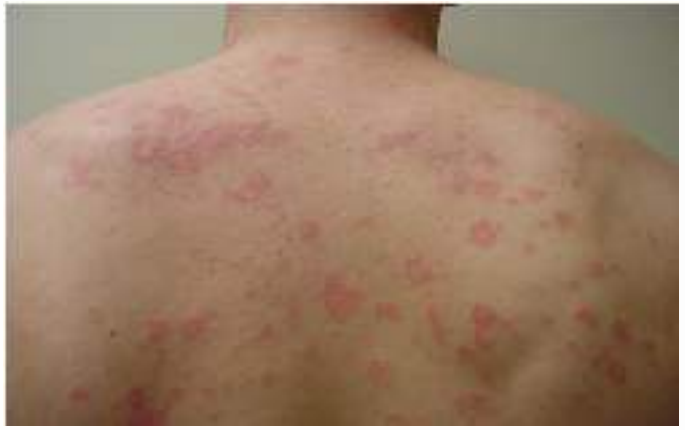
N Engl J Med 2020;382:845-854.

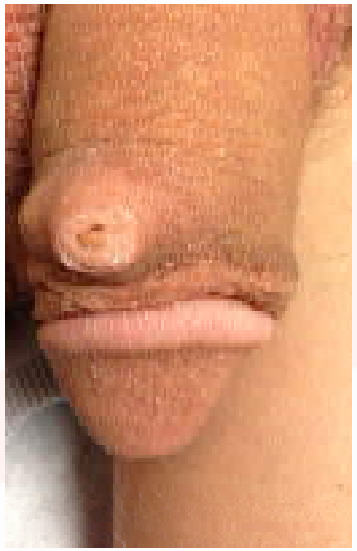
Patient 1

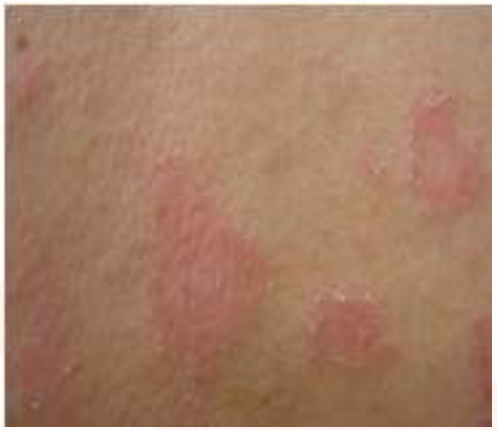
Patient Encounter 1

- **HPI:** 38-year-old man with HIV (on BIKTARVY CD4 800 cells/mm^3) presents with low-grade fevers and a rash for 3 days. He noticed a painless ulcer that appeared on his penis a week earlier and severe rectal pain associated with defecation.
- **PMHx:** (1) Chlamydia proctitis
  (2) Gonorrhea X3 (pharyngeal X1)
- **Social:** No tobacco; drugs; 3 male sex partners in the last 3 months (all PWH); inconsistent condom use
- **PE:** Diffuse rash and penile ulcer (see next slide); exquisite tenderness on DRE; no lesions noted around the anus or any other mucosal site









Laboratory Results

- Treponemal CIA: **Reactive**
- Serum RPR: **Reactive 1:32**
- Rectal/pharyngeal gonorrhea and chlamydia NAATs negative
- Rectal HSV PCR negative

Clinical Course

- The patient was treated with 1 dose of 2.4 MU IM BPG
  - Pre-treatment serology: 1:32
  - Follow-up serology @ 3 m: 1:16
  - Follow-up serology @ 6 m: 1:16
  - Follow-up serology @ 12 m: 1:16
- Now what?

Options

A. Wait & continue to follow
B. Treat with 3 doses of BPG empirically
C. Perform a CSF examination

Syphilis Serologies

- **Nontreponemal (lipoidal) tests: RPR and VDRL**
  - Nonreactive in 30% of persons with primary syphilis
  - False positives occur (older age; autoimmune diseases; HIV & other infections)
  - **May become nonreactive over time with or without treatment**
- **Treponemal tests: (EIA, CIA, FTA-ABS, TPPA, etc.)**
  - Nonreactive in 30% of persons with primary syphilis
  - False positives occur (non-syphilitic treponematoses; severe gingivitis)
  - **Once reactive always reactive-independent of treatment history**

Table 1. Traditional and Reverse-Sequence Algorithms for Serologic Testing.*

Algorithm	NTT	TT	Confirmatory TT†	Interpretation‡
Traditional	Nonreactive			No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Treated or long-standing untreated syphilis
Traditional	Reactive	Nonreactive		Biologic false positive NTT§
Traditional and reverse sequence	Reactive	Reactive		Untreated syphilis (likely) Treated syphilis (likely) Endemic treponematoses
Reverse-sequence	Nonreactive	Reactive	Nonreactive	Biologic false positive TT¶
Reverse-sequence	Nonreactive	Reactive	Reactive	Treated syphilis (most likely) Long-standing untreated syphilis Early primary syphilis (before NTT has turned positive) Prozone reaction (more common with VDRL test than with RPR test)
Reverse-sequence		Nonreactive		No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Long-standing treated syphilis if TT shows seroreversion

* The traditional algorithm starts with a nontreponemal test (NTT) followed, if reactive, by a confirmatory treponemal test (TT). The reverse-sequence algorithm starts with a TT (e.g., fluorescent treponemal-antibody absorption test, *Treponema pallidum* particle agglutination test, or automated enzyme or chemiluminescence immunoassay), followed, if reactive, by an NTT. RPR denotes rapid plasma reagin, and VDRL Venereal Disease Reference Laboratory.

† The confirmatory TT should be different from the TT performed initially.

‡ The likely or most likely interpretation of test results is noted for each algorithm.

§ Causes of a biologic false positive NTT include older age, autoimmune diseases, infections (e.g., human immunodeficiency virus infection), and drug use; pregnancy as a cause is controversial.

¶ Causes of a biologic false positive TT include infections (e.g., Lyme disease), autoimmune diseases, and older age.

NEJM 2020 382(9):845-854

Serological Non-Response

Based on the 2021 CDC STI Treatment Guidelines

Are there any neurological, ocular, or otic signs or symptoms?

Yes → **Manage accordingly**

No ↓

Did you wait long enough for the titers to decline?

No → **Keep following**

Yes ↓

Did the patient get reinfected or is the patient pregnant?

Yes → **Re-treat**

No ↓

Is the titer >=1:64?

Yes → **Consider CSF examination**

Cai *Scientific Reports* 2017

No ↓

Keep following the titers

5 observational studies show no difference in intermediate-term outcomes between treatment and watchful waiting. If you feel better re-treating, do so, <u>but only once</u>!

Reviewed by Hamill *CID* 2023

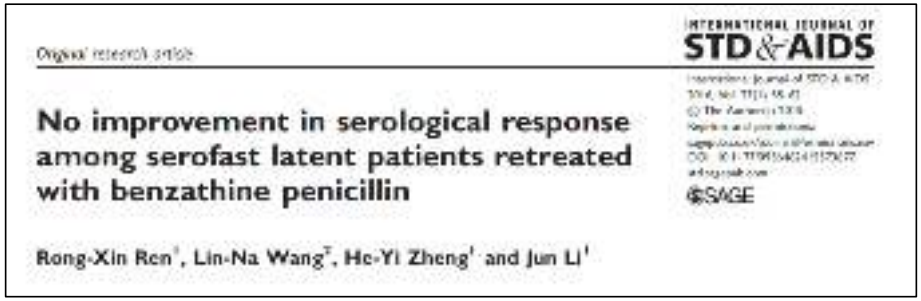
RPR titers that are <=1:4 may not decline fourfold- leave them be

Additional Treatment vs. Observation?


Journal of Antimicrobial Chemotherapy

Serological response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin

Zhong-Shuai Wang, Xiao-Ke Liu and Jun Li*


INTERNATIONAL JOURNAL OF STD & AIDS

Original research article

No improvement in serological response among serofast latent patients retreated with benzathine penicillin

Rong-Xin Ren[1], Lin-Na Wang[2], He-Yi Zheng[1] and Jun Li[1]

SAGE


Response to Therapy Following Retreatment of Serofast Early Syphilis Patients With Benzathine Penicillin

Arlene C. Seña,[1] Mark Wolff,[2] Frieda Behets,[1,3] Kathleen Van Damme,[3] David H. Martin,[4] Peter Leone,[1] Linda McNeil,[5] and Edward W. Hook[6]


Outcomes From Re-Treatment and Cerebrospinal Fluid Analyses in Patients With Syphilis Who Had Serological Nonresponse or Lack of Seroreversion After Initial Therapy

Yuanhua Zhang, MD,* Andrea Shaham, MD, PhD,*† Li-Gang Yang, MD, MSc,* Yaohua Xue, PhD,* Linyuan Wang, MD,* Bin Yang, MD, PhD,* Heping Zheng, PhD,* Jane S. Chen, MSPH,† Justin D. Radolf, MD,‡ and Arlene C. Seña, MD, MPH*


EXPERIMENTAL AND THERAPEUTIC MEDICINE

Is repeated retreatment necessary for HIV-negative serofast early syphilis patients?

YONG LIU[1-4], QUEQIAO BIAN[1-4], SHUHUAN ZHANG[1-4], JUN WANG[1-4], ZHENMING WANG[2,5] and JUNYUE LI[2-4]

In summary, these observational studies suggest that additional antibiotics in persons whose titers do not decline fourfold does not appear to confer short-term benefits. Whether additional treatment confers long-term benefits is not known.

Additional Treatment vs. Observation?

- What do I do?
  - I will only re-treat if the patient is pregnant or if I suspect that the patient will be lost to follow-up
  - If you elect to re-treat, then use:
    - 2.4 MU of IM BPG X3 (because in these cases, you waited **at least** a full year, so you are theoretically treating late latent syphilis)

What to do with RPR Titers that Increase Four-fold

- You must determine whether this is a serological failure or a reinfection. Approach the patient in a manner that decreases the risk of social desirability bias

Based on the 2021 CDC STI Treatment Guidelines

Serological Failure

Four-fold increase in titers

Are there any neurological, ocular, or otic signs or symptoms?

Yes → **Manage accordingly**

No ↓

Did you repeat the titers 2-weeks later?

No → **Repeat the titers**

Yes ↓

Are the titers still elevated?

No → **Nothing more to do; continue routine monitoring**

Yes ↓

Reinfection? [minimize social desirability bias]

Yes → **Re-treat**

No ↓

Consider a CSF examination; if CSF examination is normal consider re-treatment w/BPG (but only once)

→ **There are no data comparing outcomes for patients who undergo a CSF examination vs. empiric re-treatment with 3 doses of BPG without a CSF examination; the CDC Guidelines recommend clinicians consider a CSF examination**

Patient

- Should you prescribe DoxyPEP?

Trials on Doxycycline as PEP

Study	Design and Intervention	Sample Size and Population	Results: STI Rate or Outcome — Doxycycline	Results: STI Rate or Outcome — No Doxycycline	Relative Risk Reduction
Completed Studies					
Bolan (Los Angeles, CA, USA; 2011–2012) [3]	Open-label RCT, randomized 1:1 to daily doxy-PrEP (doxycycline hyclate 100-mg tablet) and standard of care Primary Endpoint: diagnosis of a bacterial STI	30 MSM living with HIV infection; 2 or more treated syphilis diagnoses since HIV diagnosis	6 total STIs	15 total STIs	73% OR, 0.27 (.09–.93, $P = .02$)
ANRS IPERGAY, Molins (France; 2015–2016) [4]	Open-label RCT, randomized 1:1 to doxy-PEP (doxycycline hyclate 200-mg tablet 24–72 h post-condomless sexual encounter[a]) and no prophylaxis Primary Endpoint: occurrence of a first STI (NG, CT, or syphilis)	232 MSM and TGW on HIV PrEP having condomless sex with men	37.7 per 100 person-years[b] 28 total STIs	69.7 per 100 person-years[b] 45 total STIs	47%[b] HR, 0.53 (.33–.85, $P = .008$)
DoxyPEP, Luetkemeyer (Seattle, WA and San Francisco, CA, USA; 2020–2022) [5]	Open-label RCT, randomized 2:1 to doxy-PEP (doxycycline hyclate 200 mg within 72 h after condomless sex) and standard of care Primary Endpoint: incidence of at least 1 STI per follow-up quarter	501 MSM and TGW with HIV or on HIV PrEP with NG, CT, or syphilis in the past year — HIV (n = 174), PrEP (n = 327)	11.8% visits with STI per quarter 10.7% visits with STI per quarter	30.5% visit with STI per quarter 31.9% visits with STI per quarter	62% RR, 0.39 (.24 to .60; $P < .001$) NNT[c]: 5.3 66% RR, 0.34 (.24 to .46; $P < .001$) NNT[c]: 4.7
DOXYVAC, Molins (France; 2021–2022) [6][d]	RCT open-label; 2 × 2 factorial design, randomized 2:1 to doxy-PEP (doxycycline monohydrate 200 mg taken orally within 24–72 h after condomless sexual encounters) or no PEP Primary Endpoint: time to first syphilis or chlamydia infection	502 MSM on HIV PrEP with a bacterial STI in the past 12 mo; 332 randomized to doxy-PEP versus 170 to no PEP	5.6 per 100 person-years[b]	35.4 per 100 person-years[b]	84%[b] aHR, 0.16 (.08 to .30, $P < .0001$)[b] 51% decrease in GC infection: aHR, 0.49 (.32 to .76, $P < .001$)
dPEP, Stewart (Kenya; 2020–2022) [7]	Open-label RCT, randomized 1:1 to doxy-PEP (doxycycline hyclate 200 mg taken within 72 h of sex) and standard of care Primary Endpoint: any incident CT, NG, or syphilis infection	449 cisgender women on HIV PrEP, ages 18–30 y; 224 randomized to doxy- PEP; 225 to standard of care	50 GC/CT infections	59 GC/CT infections	12% RR, 0.88 (.60–1.29, $P = .51$)
DuDHS, Grennan (Canada; 2018–2019) [8, 9]	RCT, randomized 1:1 to doxy-PrEP (daily doxycycline 100 mg) and delayed doxy-PrEP Primary Endpoints: incidence of syphilis, GC, and CT infection and proportion of individuals reporting adverse events	52 MSM and TGW on HIV PrEP with prior syphilis	4 STIs (all NG)	19 STIs (1 syphilis, 10 CT, 9 NG)	82% OR, 0.18 (.05–.69, $P = .011$)

DoxyPEP: The Ecological Data

JAMA Internal Medicine | Original Investigation

Doxycycline Postexposure Prophylaxis and Sexually Transmitted Infection Trends

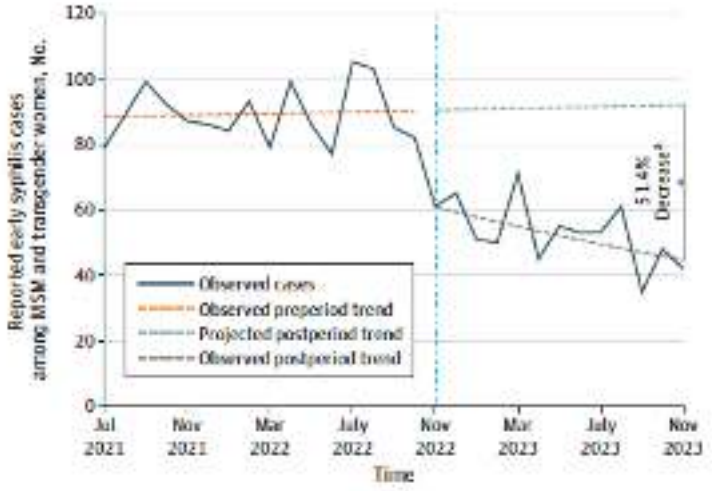
Madeline Sankaran, MPH; David V. Glidden, PhD; Robert P. Kohn, MPH; Trang Q. Nguyen, PhD; Oliver Bacon, MD; Susan P. Buchbinder, MD; Monica Gandhi, MD; Diana V. Hardt, MD; Courtney Liebl, MPP; Annie I. Luetkemeyer, MD; Janet Q. Nguyen, MPH; Jorge Roman, MSN; Hyman Scott, MD; Thiago S. Torres, PhD; Stephanie E. Cohen, MD

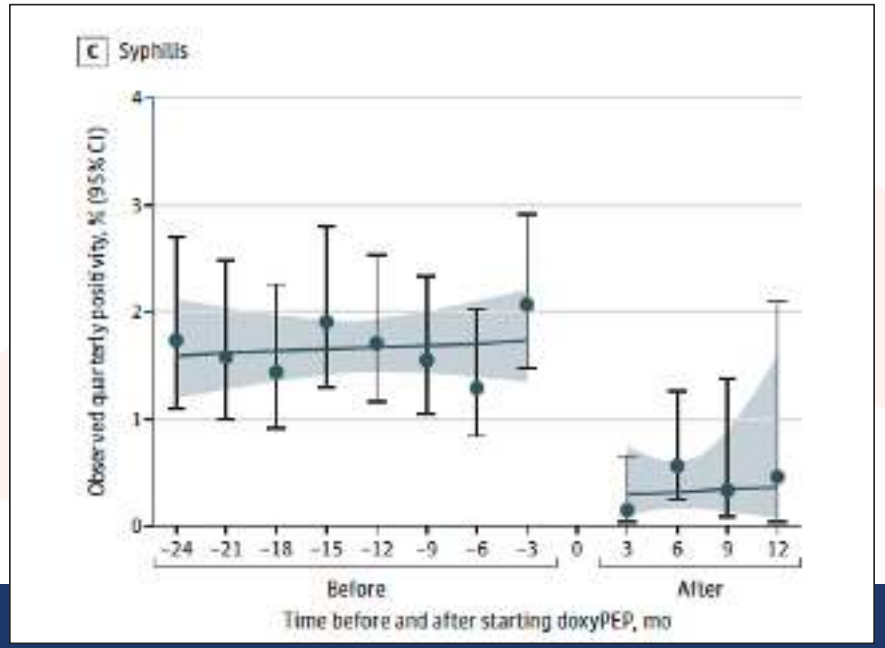
JAMA Internal Medicine | Original Investigation

Doxycycline Postexposure Prophylaxis and Bacterial Sexually Transmitted Infections Among Individuals Using HIV Preexposure Prophylaxis

Michael W. Traeger, PhD, MSc; Wendy A. Leyden, MPH; Jonathan E. Volk, MD; Michael J. Silverberg, PhD; Michael A. Horberg, MD; Toankese L. Davis, PhD; Kenneth H. Mayer, MD; Douglas S. Krakower, MD; Jessica G. Young, PhD; Samuel M. Jenness, PhD; Julia L. Marcus, PhD

Figure 2. San Francisco Early Syphilis Cases Among Men Who Have Sex With Men (MSM) and Transgender Women Before and After Doxycycline Postexposure Prophylaxis Guideline Implementation





Doxy PEP: What We Don't Fully Understand

- Impact on the development of resistance in both STI-related bacterial pathogens and non-STI pathogens
- Impact on the structure, composition, and function of the human microbiome
- Impact on syphilis serologies and clinical manifestations
- Impact on the risk of early neurosyphilis

The Impact of DoxyPEP on Syphilis Clinical Presentation and Serologies

- 1777 patients on HIV PrEP in Seattle (91% male, 52% white, 36% DoxyPEP use; 25% prior history of syphilis)
- 59 syphilis cases in 56 patients (24% on DoxyPEP)
- **CLINICAL:** Higher proportion of symptomatic P&S syphilis among non DoxyPEP users (88%) than DoxyPEP users (12%)
- **SEROLOGICAL**: Median RPR titer of DoxyPEP users is 1:8 vs. 1:32 in non DoxyPEP users

These preliminary data suggest that DoxyPEP significantly impacts early clinical and serological manifestations of syphilis

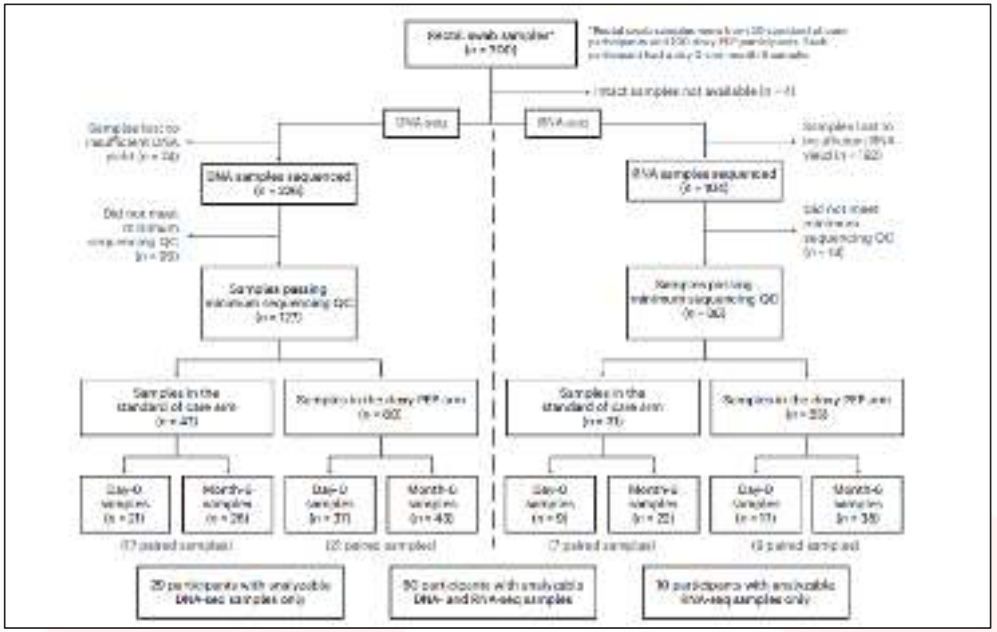
Cannon et al. ISSTDR July 2025 Montreal, Canada: Evaluation of RPR Titer Differences at Early Syphilis Diagnosis in DoxyPEP Users vs. Non-Users

Doxycycline & the Microbiome

nature medicine

Article

Impact of doxycycline post-exposure prophylaxis for sexually transmitted infections on the gut microbiome and antimicrobial resistome



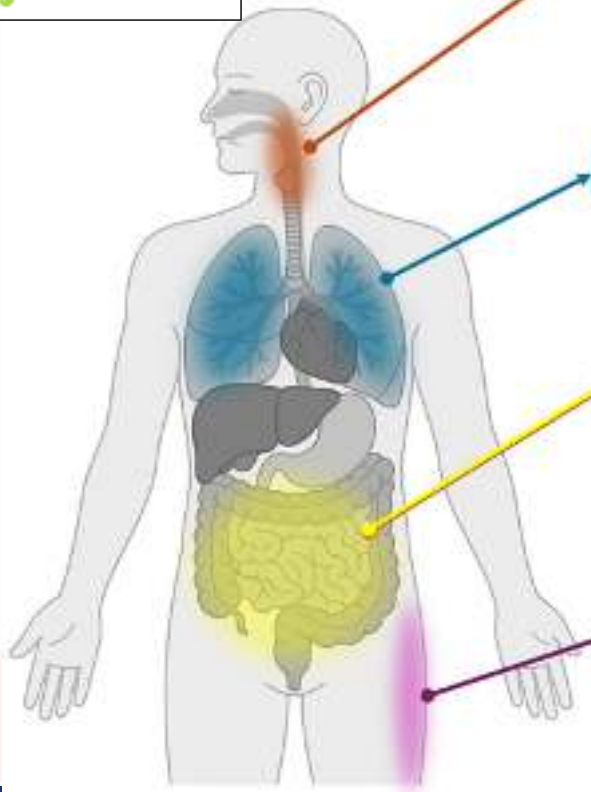
"Doxy-PEP use increased both the relative proportion and expression of tetracycline antimicrobial resistance genes while minimally impacting the ecology of the gut microbiome" (as measured by alpha and beta-diversity indices).

Infect Dis Ther (2026) 15:57–84
https://doi.org/10.1007/s40121-025-01270-8

REVIEW

A Review of Doxycycline Post-Exposure Prophylaxis and Its Implications for Antimicrobial Resistance and the Human Microbiome

Ruben Fernandez-Ibanez · Santiago Moreno · Moises Fernandez



Oropharynx

- **Taxonomic:** No significant effect on diversity or bacterial load; only transient shifts in anaerobes, and occasional *E. coli* or Gram-positive increases.
- **Functional:** Resistance gene proportion and expression consistently increase, mainly via ribosomal protection and efflux.
- **Clinical:** Not observed. Theoretical risks of HGT and resistome expansion.

Respiratory

- **Taxonomic:** Reduced *Cutibacterium acnes* and increased Gram-negative and Gram-positive opportunists such as *Staphylococcus* and *Corynebacterium*.
- **Functional:** Increase in the abundance of resistance genes (*tet(K)* and *tet(L)*).
- **Clinical:** Clinical significance unclear.

Gut

- **Taxonomic:** No major shifts; transient increases in *Streptococcus*, *Prevotella*, and *Veillonella*, with full recovery over time.
- **Functional:** Temporary rise in resistance genes (*tet(M)*, *tet(W)*, *tet(Q)*, *tet(K)*), with no sustained MIC elevation; some gene transfer events detected.
- **Clinical:** Resistance generally declined over months; concerns include increased colonization by resistant strains and potential for horizontal gene transfer.

Skin and mucosal surfaces

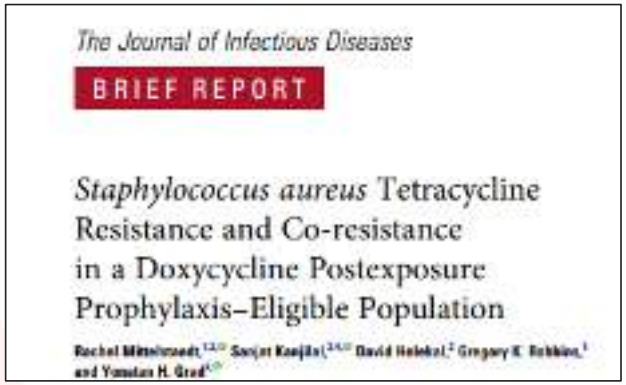
- **Taxonomic:** Does not alter overall *S. aureus* carriage rates but promotes the acquisition and expansion of doxycycline-resistant *S. aureus*. Increased *Streptococcus* and *Veillonella*; shifts in community structure.
- **Functional:** Functional impact not directly assessed at the community level; ecological disruption inferred. Potential co-selection of resistance traits in *S. aureus*.
- **Clinical:** Effects unclear; likely varies by host, with no defined resistance profile. No associated increase in the prevalence of MRSA.

The Impact of DoxyPEP on GC Antimicrobial Resistance

- In a follow-up study nested within the DOXYVAC trial: MSM on HIV PrEP randomized to DoxyPEP (n= 362) or no-PEP (n=183) arms were tested for GC at baseline and every three months thereafter, by culture (N=78) and NAAT (N=233)
  - **Increase in rate of high-level tetracycline GC resistance in the DoxyPEP arm** than in the no-PEP arm (35.5 vs. 12.5%, p=0.043)
  - **Decreased susceptibility to cefixime more frequent in the DoxyPEP arm** than the no-PEP arm (32.3% vs 10.0%, p=0.033)
  - The MICs of ceftriaxone, fluoroquinolones and azithromycin were similarly distributed in the DoxyPEP and no-PEP arms

Bercot B, et al. Clinical Infectious Diseases, 2025 (in press)

The Impact of DoxyPEP on *S aureus* Antimicrobial Resistance



The Journal of Infectious Diseases

BRIEF REPORT

Staphylococcus aureus Tetracycline Resistance and Co-resistance in a Doxycycline Postexposure Prophylaxis–Eligible Population

Rachel Mitchell,[1,2] Sanjat Kanjilal,[3,4] David Heinzel,[2] Gregory K. Robbins,[1] and Yonatan H. Grad[4,5]

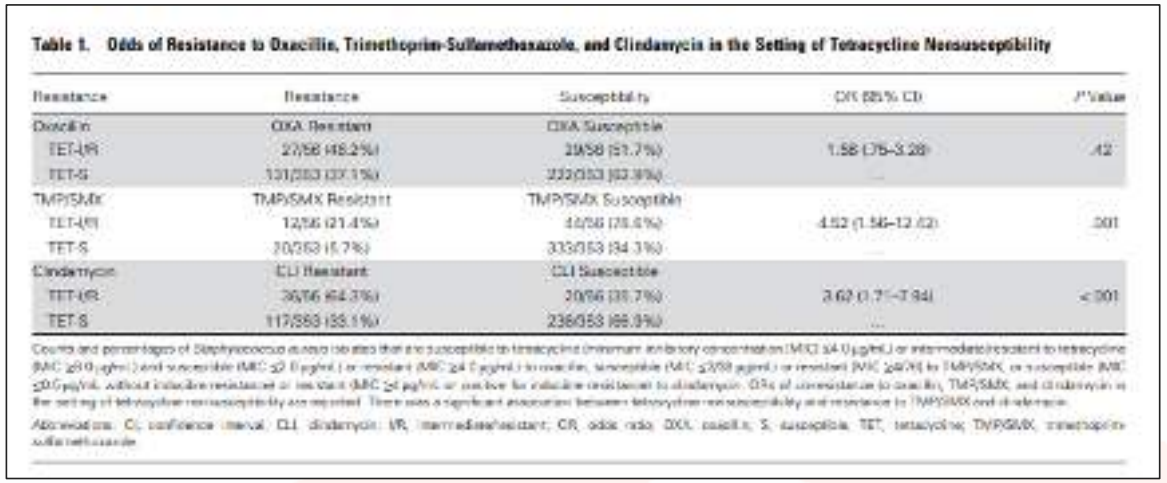


Table 1. Odds of Resistance to Oxacillin, Trimethoprim-Sulfamethoxazole, and Clindamycin in the Setting of Tetracycline Nonsusceptibility

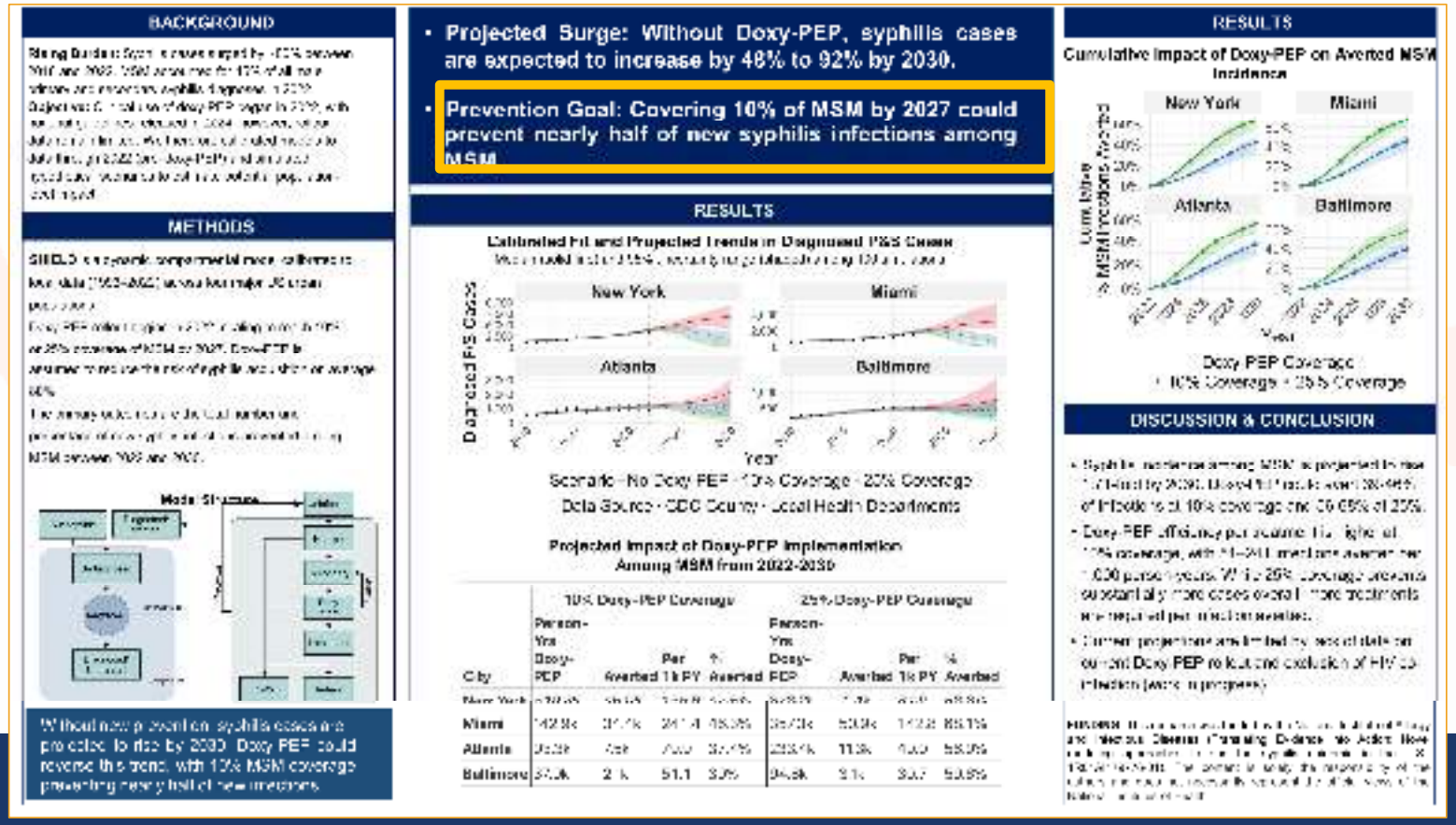
Resistance	Resistance	Susceptibility	OR (95% CI)	*P* Value
Oxacillin	OXA Resistant	OXA Susceptible		
TET-IR	27/56 (48.2%)	29/56 (51.7%)	1.58 (.76–3.28)	.12
TET-S	131/353 (37.1%)	222/353 (62.9%)		
TMP/SMX	TMP/SMX Resistant	TMP/SMX Susceptible		
TET-IR	12/56 (21.4%)	44/56 (78.6%)	4.52 (1.56–12.62)	.001
TET-S	20/353 (5.7%)	333/353 (94.3%)		
Clindamycin	CLI Resistant	CLI Susceptible		
TET-IR	36/56 (64.3%)	20/56 (35.7%)	3.62 (1.71–7.94)	< .001
TET-S	117/353 (33.1%)	236/353 (66.9%)		

Counts and percentages of *Staphylococcus aureus* isolates that are susceptible to tetracycline (minimum inhibitory concentration [MIC] ≤4.0 μg/mL) or intermediate/resistant to tetracycline (MIC ≥8.0 μg/mL) and susceptible (MIC ≤2.0 μg/mL) or resistant (MIC ≥4.0 μg/mL) to oxacillin, susceptible (MIC ≤2/38 μg/mL) or resistant (MIC ≥4/76) to TMP/SMX, or susceptible (MIC ≤0.5 μg/mL without inducible resistance) or resistant (MIC ≥1 μg/mL) or positive for inducible resistance to clindamycin. ORs of co-resistance to oxacillin, TMP/SMX, and clindamycin in the setting of tetracycline nonsusceptibility are reported. There was a significant association between tetracycline nonsusceptibility and resistance to TMP/SMX and clindamycin.

Abbreviations: CI, confidence interval; CLI, clindamycin; IR, intermediate/resistant; OR, odds ratio; OXA, oxacillin; S, susceptible; TET, tetracycline; TMP/SMX, trimethoprim-sulfamethoxazole.

"Use of doxy-PEP in this population may select for strains of *S aureus* that carry resistance not only to tetracyclines, but also to other common anti-staphylococcal antibiotics (TMP/SMX & clindamycin). The extent to which doxy-PEP will select for these strains and the efficiency with which resistant strains will be transmitted is unknown."

How Much DoxyPEP Uptake is Necessary to Impact Syphilis Rates?



Parastu Kasaie

Unpublished data; CROI 2026 Abstract 1020

Summary: DoxyPEP

Every antimicrobial prescription carries trade-offs, and DoxyPEP is no different. Its impact can be considerable **but directing it to those most likely to benefit** is essential to optimize outcomes and reduce risks; this approach may still provide significant public health benefits.

Patient 2

Patient

- 56-year-old woman with HIV (HIV RNA 23 copies/ml; last CD4 716 cells/mm^3, on BIC/TAF/FTC) who presents with bilateral eye pain, redness, photosensitivity, vision loss, and bilateral tinnitus
  - First developed a **rash** over her legs, palms, and soles about a month earlier, and noticed (at the same time)some **flat painless lesions on her genitals**.
  - The gradual development of right **eye pain**, **redness, photophobia,** and **blurry vision** with subsequent involvement of the left eye.
    - She was seen in the ED initially and was diagnosed with “conjunctivitis” and sent home
  - She then noted **tinnitus** in both her ears but no hearing loss.

Patient

- She was seen by ophthalmology and diagnosed with **anterior uveitis**
- Laboratory tests:
  - HgB 12.4; platelets 437K; ESR 78; **alkaline phosphatase 602; AST 53; ALT 143**
  - **RPR 1:64; CIA Reactive**

Diagnoses

- **Early syphilis** (secondary lesions one month earlier)
- **Ocular syphilis** (bilateral redness and decreased vision)
- **Otic syphilis** (tinnitus)
- **Syphilitic hepatitis** (elevated alkaline phosphatase; mildly elevated AST/ALT)

FYI-Clinical Manifestations of Syphilis

Altered Clinical Presentation of Early Syphilis in Patients with Human Immunodeficiency Virus Infection

Catherine M. Hutchinson, MD; Edward W. Hook, 3d, MD; Mary Shepherd, MS; Janice Verley, MD; and Anne M. Rompalo, MD, ScM

■ ***Conclusions:*** **The clinical presentation of syphilis in patients with HIV infection differs from that of patients without HIV infection in that patients with HIV infection present more often in the secondary stage and those with secondary syphilis are more likely to have chancres.**

Hutchinson et al. 1994 Ann Int Med

Painful and multiple anogenital lesions are common in men with *Treponema pallidum* PCR-positive primary syphilis without herpes simplex virus coinfection: a cross-sectional clinic-based study

Janet M Towns,[1] David E Leslie,[2] Ian Denham,[1] Francesca Azzato,[2] Christopher K Fairley,[1,3] Marcus Chen[1,3]

Results 183 men with *T. pallidum* PCR-positive primary anogenital lesions were included. 89% were men who have sex with men, and 10.9% were heterosexual. 38 men (20.8%) were HIV positive. Anal lesions were more common in HIV-positive men (34.2%) than in HIV-negative men (11.6%). Primary lesions were frequently painful (49.2%) or multiple (37.7%), and infrequently associated with HSV (2.7%). Of 37 men with both painful and multiple primary lesions, only 8% had concurrent HSV. Presentation was not significantly altered by HIV status.

Towns et al. 2016 STI

FYI-Syphilitic Hepatitis

- Involvement of the liver in late stages of the disease as fibrosis, gumma, and hepar lobatum well documented in the pre-antibiotic era
- Early-stage asymptomatic involvement, usually as a **disproportionally elevated alkaline phosphatase** in the setting of secondary syphilis, is a more recent observation- but is not universal
  - **Clinical: Association with rash and anorectal lesions**
  - Histology: pericholangiolar inflammation; **mild** (proliferation of sinus endothelial cells and Kupffer cells, eosinophils, and lymphocytes) to **severe** (diffuse necrosis, especially in the periportal region and central vein)
  - In half of the cases, spirochetes were found in the necrotic foci, walls of sinusoids, and the endothelial cells
- Incidence of LFT abnormalities in both immunocompetent and HIV-infected persons in secondary syphilis noted in up to 38% -but the majority are asymptomatic
- The rare occurrence of abscesses in the liver

West J Med. 1978;128(1):64-7 Int J STD AIDS. 2012;23(8):e4-6 Lancet. 1975;2(7941):896-9
Am J Surg Pathol 2014; 38 (12):1636-43 Int J STD AIDS. 2009;20(4):278-84

Otic and Ocular Syphilis Take-Home Points

Otosyphilis

- **Clinical manifestations**: cochleovestibular dysfunction and syphilis infection without an alternate diagnosis; ~50% bilateral
  - Symptoms: **Hearing loss, vertigo, and/or tinnitus** (ringing in the ears)
  - Diagnosis is presumptive; **CSF examination is normal in at least 40% of cases and is NOT recommended if patient only has otic signs and symptoms**
- **Therapy**: IV penicillin (+ corticosteroids)
- **Prognosis**: 23% experience improvement in hearing; up to 80% experience improvement in tinnitus and vertigo

Ocular Syphilis

- Clinical manifestations: any portion of the eye; any ocular manifestation; **immediate ophthalmological examination**
  - Symptoms: Redness, pain, floaters, flashing lights, visual acuity loss
  - Diagnosis is presumptive; **CSF examination is normal in up to 40% of cases and is NOT recommended if patient only has ocular signs and symptoms**
- **Therapy**: IV penicillin (+ corticosteroids)

N Engl J Med 2020;382:845-854.

Questions

- Does this patient need a CSF examination?
  - Will the CSF examination change management?
  - If so, how?

A Few Important Concepts to Remember Related to Neurosyphilis, Ocular Syphilis, and Otic Syphilis

A normal CSF examination rules out neurosyphilis, but it does not rule out ocular or otic syphilis

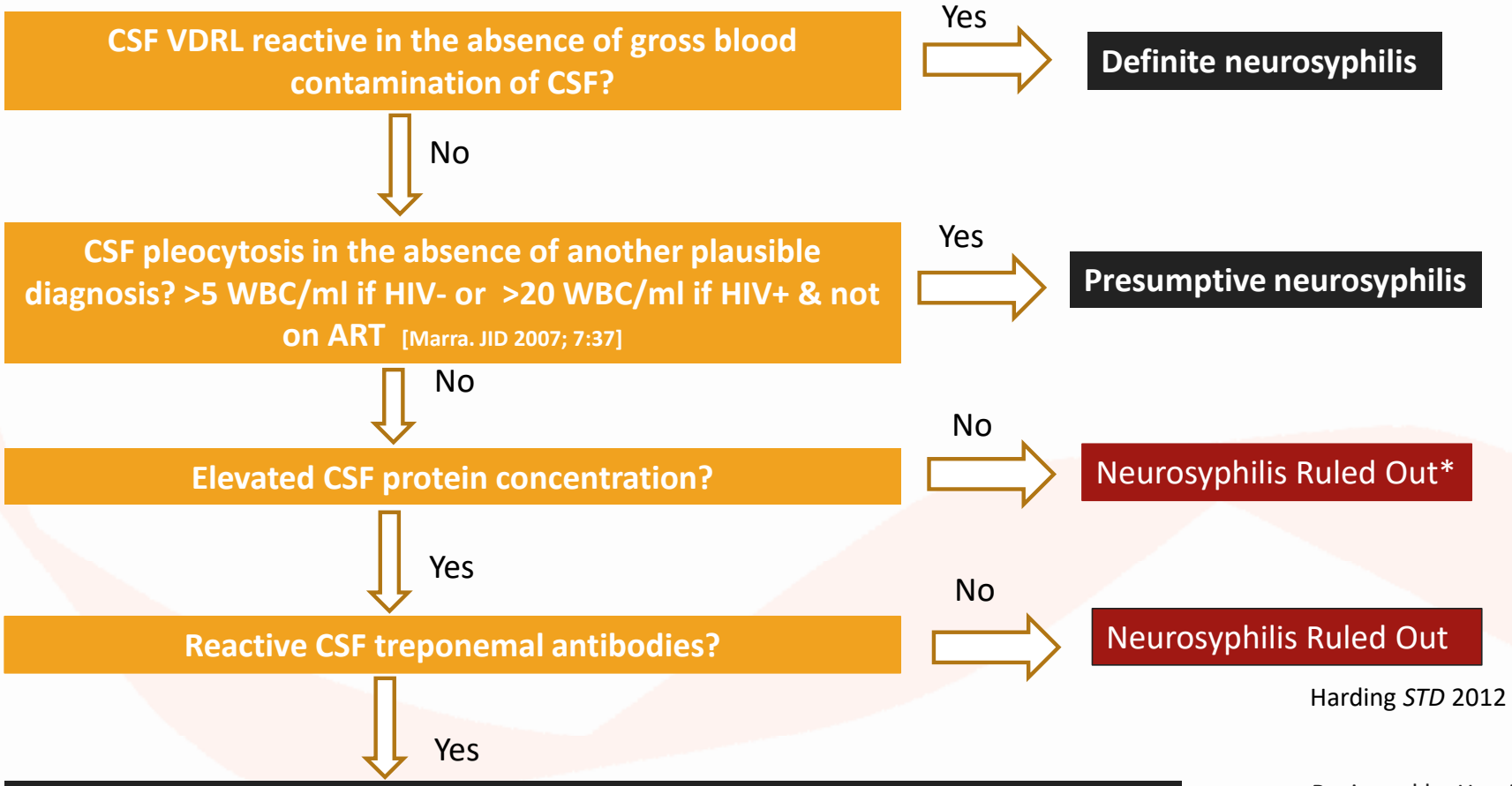
A patient with ocular only or otic only signs and/or symptoms does not need a CSF examination. An immediate thorough clinical evaluation is warranted and if the clinical picture is consistent with ocular or otic syphilis, start antibiotic therapy

A patient with both neurological signs/symptoms and ocular or otic signs/symptoms should undergo a CSF examination. While it may not impact the treatment decision, it may impact diagnostic considerations [patients may have neurological manifestations due to something other than syphilis- you don't want to delay the diagnosis]

Syphilis: CSF Examination

- Perform a lumbar puncture (LP) in persons who:
  - **Have neurological signs and symptoms**
  - Are diagnosed with tertiary syphilis (cardiovascular, gummas)
  - Consider in those who are asymptomatic but whose serological titers increase four-fold after stage-appropriate therapy in the absence of reinfection
  - Consider in those who are asymptomatic but whose titers fail to decrease fourfold if the titers are >=1:64 in the absence of reinfection
- There are no data to support routine LP in asymptomatic PWH

Making a Diagnosis of Neurosyphilis



Harding *STD* 2012

Reviewed by Hamill *CID* 2024

*10% of persons with tabes dorsalis may have a normal CSF formula ("burnt out tabes")

As a Reminder: Diagnosis of Neurosyphilis

The diagnosis of neurosyphilis is based on a combination of clinical and laboratory findings:

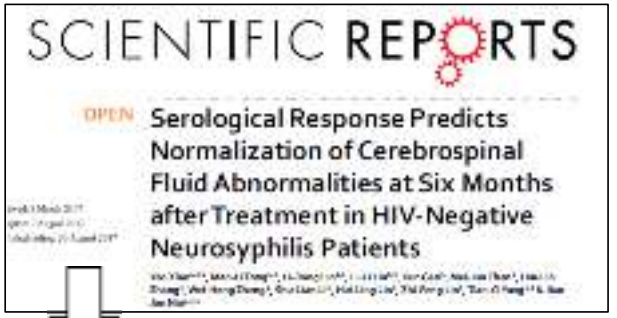
- **Serological evidence of syphilis**
  - Up to 25% of patients with tertiary neurosyphilis may have **non-reactive** serum non-treponemal tests
- **A positive CSF VDRL**
  - ~50% sensitivity & very high specificity in the absence of blood contamination; **most specific parameter**
  - CSF RPR is not sensitive [Marra. *STD* 2012;39(6):453-7]
  - **CSF treponemal tests** (particularly FTA-ABS): high sensitivity but lower specificity; high negative predictive value when the pre-test probability for neurosyphilis is moderate to low [Harding. *STD* 2012; 39(4):291-7]
- **CSF Pleocytosis**
  - >5 WBC/ml if HIV-; >20 WBC/ml if HIV+ & not on ART [Marra. JID 2007; 7:37]
  - **Most sensitive parameter**
- **Elevated CSF protein concentration [>50mg/dl]**
  - Least specific parameter
  - (personally, I don't use this parameter unless it is very high)

Are follow-up CSF Exams Necessary in Persons Treated Appropriately for Neurosyphilis?


Normalization of Serum Rapid Plasma Reagin Titer Predicts Normalization of Cerebrospinal Fluid and Clinical Abnormalities after Treatment of Neurosyphilis

Christina M. Marra,[1,2] Clare L. Maxwell,[1] Lauren C. Tantalo,[1] Sharon K. Sahi,[1] and Sheila A. Lukehart[3]

- In 110 patients with NS normalization of serum RPR titer predicted normalization of other CSF and clinical abnormalities in >80% of patients at 4 months, >85% at 7 months, and >90% at 13 months
- Normalization of serum RPR titer was consistently less accurate in predicting treatment success in human immunodeficiency virus–infected patients who were not receiving antiretroviral therapy


SCIENTIFIC REPORTS

OPEN Serological Response Predicts Normalization of Cerebrospinal Fluid Abnormalities at Six Months after Treatment in HIV-Negative Neurosyphilis Patients

- 58 of 123 HIV- with NS agreed to a CSF examination 6 months after appropriate treatment
- 91.3% of those showing serological response of RPR test achieved CSF normalization; in persons with ≥8-fold decreases in the serum RPR titer (N=8), all CSF parameters had normalized

No need for follow-up LP 6 months after the diagnosis and treatment of neurosyphilis in HIV uninfected or PWH who are on ART if they improve clinically, and their serological titers are responding appropriately

Patient

- You decide to wait and follow…

Patient 3

Patient Encounter

A patient is referred to the Infectious Diseases Clinic by a local obstetrician. She is a 24-year-old woman with HIV doing well on ART, G0P1, currently at 10 weeks' gestation. The referral is for management of reactive syphilis serologies: **her EIA is reactive and her RPR titer is 1:8**, with results obtained three days prior to presentation.

She was diagnosed with syphilis 11 months earlier at her primary care physician's office after presenting with a rash. Diagnosis was made using a point-of-care test, and she was treated with 2.4 million units of intramuscular benzathine penicillin G. Her partner at that time was also treated. The diagnosis of syphilis immediately led to the dissolution of that relationship.

Shortly thereafter, the patient entered a monogamous relationship with her current partner.

She reports no symptoms, and physical examination is unremarkable.

What is the most appropriate next step in the management of this patient?

Point of Care & At-Home Testing

- 2 FDA cleared POC tests and 1 at-home (or 'self') test all detect the presence of **treponemal antibodies** with excellent performance characteristics

NOWDiagnostics First To Know® Syphilis Test Receives FDA De Novo Marketing Authorization for Over-the-Counter Use

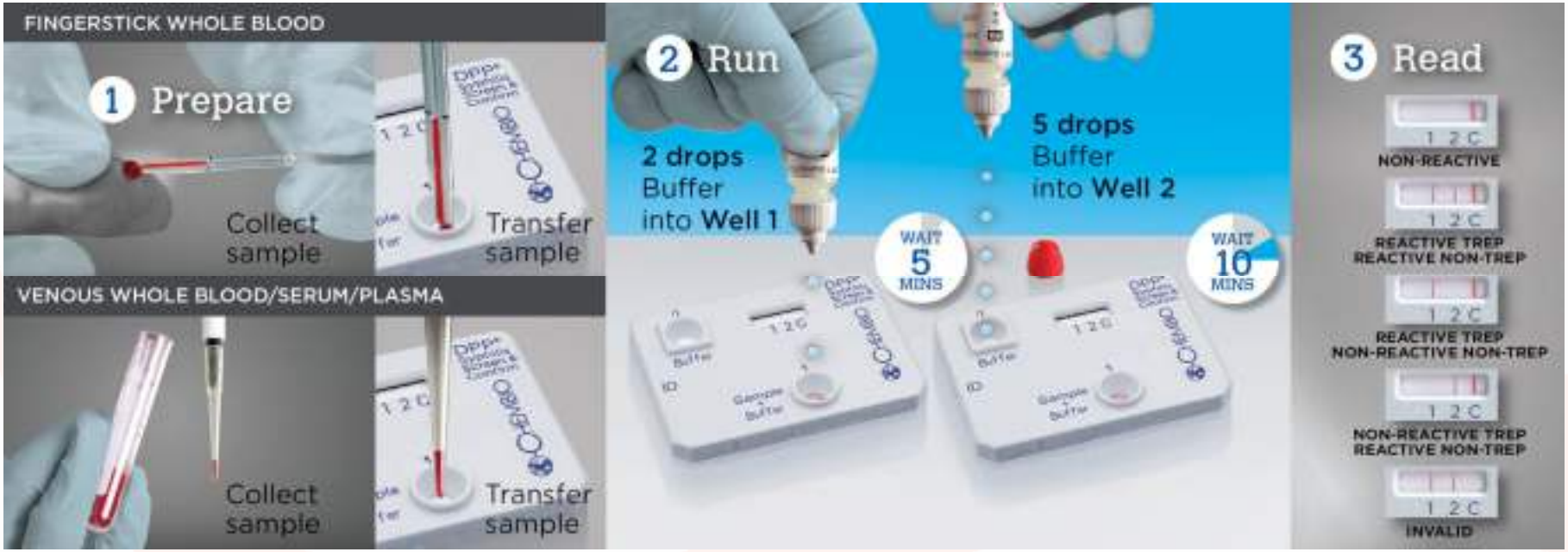
First and only rapid syphilis test with in-home results in minutes, addressing growing epidemic

On 8/16/24, the U.S. Food and Drug Administration granted marketing authorization to NOWDiagnostics for the First To Know Syphilis Test.

The First To Know® Syphilis Test is a qualitative rapid membrane immunochromatographic assay for the detection of *Treponema pallidum* (syphilis) antibodies in human whole blood (capillary). This test is intended for over the counter (OTC) consumer use in individuals suspected of syphilis. Positive test results with the First To Know® Syphilis Test alone are not sufficient to diagnose syphilis infection and must be followed by additional laboratory testing through a health care provider to confirm a diagnosis of syphilis.

Trep/NonTrep (Qualitative) Combined POC Diagnostic

CE-marked but not FDA-cleared



DPP® Syphilis Screen & Confirm

Patient Encounter

A patient is referred to the Infectious Diseases Clinic by a local obstetrician. She is a healthy 24-year-old woman, G0P1, currently at 12 weeks' gestation. The referral is for management of reactive syphilis serologies: **her EIA is reactive and her RPR titer is 1:8**, with results obtained three days prior to presentation.

She was diagnosed with syphilis 11 months earlier at her primary care physician's office after presenting with a rash. Diagnosis was made using a point-of-care test, and she was treated with 2.4 million units of intramuscular benzathine penicillin G.

She reports no symptoms, and physical examination is unremarkable.

The patient is treated with a dose of IM BPG.

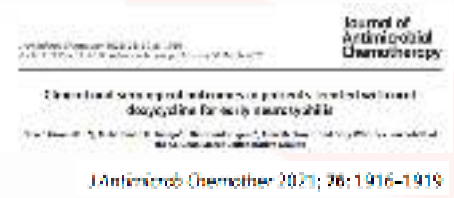
- 3 months later, her titer is 1:8.
- Six months later (at the time of delivery), her titer is still 1:8

What work-up would you recommend for the infant?

WHAT IF THE PATIENT WERE ALLERGIC TO PENICILLIN?

Therapy for Syphilis

- Parenteral penicillin G is the drug of choice for all stages of syphilis
- It is the ONLY therapy with documented efficacy for neurosyphilis or for syphilis during pregnancy
- Data on doxycycline are more limited but suggest excellent efficacy in adults who are not pregnant with early and late latent infections
- High-dose oral doxycycline for neurosyphilis is being investigated



J Antimicrob Chemother 2021; 76: 1916–1919

N Engl J Med 2020;382:845-854.

For primary and secondary syphilis in nonpregnant adults, including HIV-infected adults:
Penicillin G benzathine, 2.4 million units in a single IM dose
Doxycycline, 100 mg orally twice a day for 14 days (first alternative)
Ceftriaxone, 1–2 g daily, IM or IV, for 10–14 days (second alternative)

For latent syphilis in nonpregnant adults, including HIV-infected adults:
Early latent: penicillin G benzathine, 2.4 million units in a single IM dose
Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-week intervals
Doxycycline, 100 mg orally twice a day for 28 days (alternative)

For late syphilis (gummas and cardiovascular manifestations) but not neurosyphilis:
Penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-wk intervals

For neurosyphilis and ocular syphilis:
Aqueous crystalline penicillin G, 18–24 million units per day, administered in IV doses of 3–4 million units every 4 hr or as a continuous infusion, for 10–14 days
Penicillin G procaine, 2.4 million units in a single IM dose daily, plus probenecid, 500 mg administered orally four times a day, both for 10–14 days (alternative)

For primary and secondary syphilis in pregnancy:
Penicillin G benzathine, 2.4 million units in a single IM dose†

For latent syphilis in pregnancy:
Early latent: penicillin G benzathine, 2.4 million units in a single IM dose
Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-wk intervals

* Treatment guidelines are from the Centers for Disease Control and Prevention (Workowski and Bolan[14]). IM denotes intramuscular, and IV intravenous.
† Some experts recommend an additional IM dose of 2.4 million units of penicillin G benzathine, given 1 week later.

Alternatives to Penicillin in Pregnancy

THE REAL WORLD OF STD PREVENTION

ASTDA Position Paper: Alternatives to Benzathine Penicillin G for the Treatment of Syphilis During Pregnancy

Teresa Batteiger, MD, Eloine Liu, PharmD,† Jeanne Sheffield, MD,‡ Hilary Reno, MD, PhD,§ Zoon Wangu, MD,¶|| Khalil G. Ghanem, MD, PhD,‡ and Susan Tuddenham, MD, MHS‡*

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Thank you

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