How long is too long to wait to see a doctor?!

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Case

26 yo male decides to self-test for STIs using on-line testing

Past Hx

- **Penicillin allergy (hives)**

Social Hx

- Bisexual, 6 partners in past 6 mths, insertive/receptive anal and oral sex
- Last sex 1 mth ago
- Uses Grindr to meet partners
- No condom use
- 2019 gonorrhea dx + tx
- Uses marijuana w/e's

November 2020*

Noticed rash on stomach and waistline, lasted ~2 wks

Also had sore throat, swollen glands, mucous patches on tongue

Spotty hair loss since

December 2020*

Left eye flashes evolved to black spots, then diagonal blurry slash

Saw ophthalmologist, "no concerns"

Visual symptoms persist

March 2021*

Diagonal slash also seen in right eye

Self-tests for STI using on-line testing for privacy reasons and because he has no primary care or health insurance

March 2021: public health department directly notified of syphilis testing: trep EIA positive, RPR 1:128

*Outpatient clinics open throughout this time period (COVID prevalence down, PPE available)

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Questions for Learning Collaborative

- Has self-testing for STIs taken hold in your region?
- How urgent is the concern re: ocular syphilis?
- What are some possible next steps?

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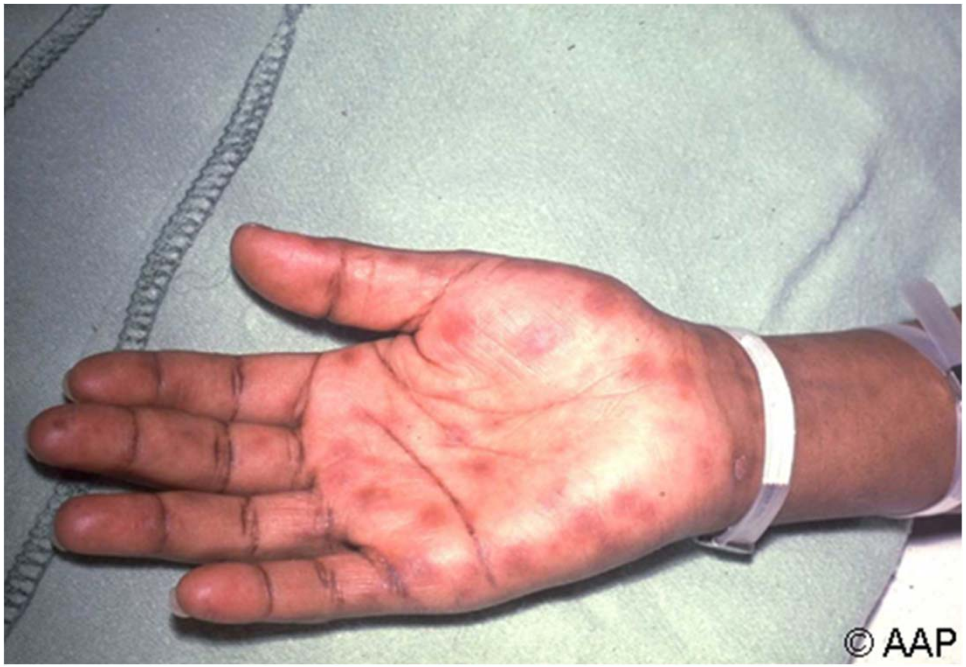
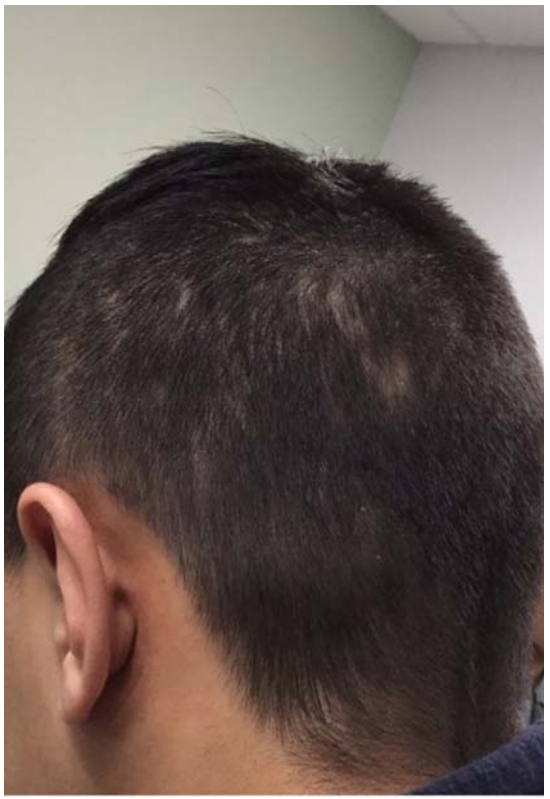
Physical Exam

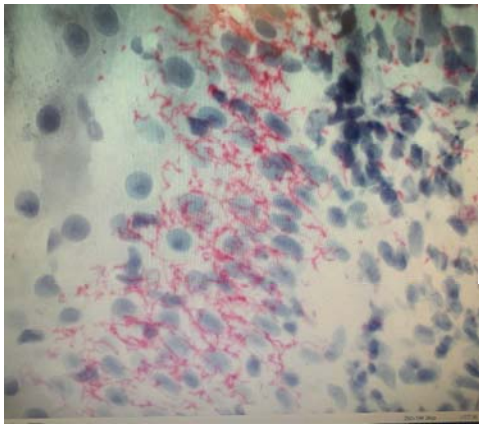
- Afebrile, vital signs stable
- Maculopapular rash over body, including palms
- Alopecia
- Diffuse lymphadenopathy

- Ophthalmologic exam
  - Visual acuity 20/20 bilaterally
  - Left eye “anterior uveitis”
  - Right eye normal

Rash* and Alopecia*







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*Not this specific patient, but similar

Questions for Learning Collaborative

- Is a lumbar puncture indicated at this point (would you delay treatment to get a pre-treatment LP)?
  - Group: No – isolated ocular symptoms mean LP is not critical to do – getting him on treatment *sooner* is goal

- How do you screen for physical signs/symptoms of neurosyphilis, including ocular and otic syphilis?

2021 Update: Otic and Ocular Syphilis

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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 90% of cases and is NOT recommended if patient only has otic signs and symptoms**
- **Immediate referral for evaluation**
- **Therapy**: IV penicillin (+/- corticosteroids)

Ocular Syphilis

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

Slide courtesy of Khalil Ghanem

Screening Questions for Neurosyphilis (Including Ocular and Otosyphilis)

Questions	
Symptoms of Otosyphilis	
1) Have you recently had new trouble hearing?	☐ Yes – refer to ENT ☐ No
2) Do you have ringing in your ears?	☐ Yes – refer to ENT ☐ No
Symptoms of Ocular syphilis	
3) Have you recently had a change in vision?	☐ Yes – refer to ophthalmology ☐ No
4) Do you see flashing lights?	☐ Yes – refer to ophthalmology ☐ No
5) Do you see spots that move or float by in your vision?	☐ Yes – refer to ophthalmology ☐ No
6) Have you had any blurring of your vision?	☐ Yes – refer to ophthalmology ☐ No
Symptoms of neurosyphilis	
7) Are you having headaches?	☐ Yes ☐ No
8) Have you recently been confused?	☐ Yes ☐ No
9) Has your memory recently gotten worse?	☐ Yes ☐ No
10) Do you have trouble concentrating?	☐ Yes ☐ No
11) Do you feel that your personality has recently changed?	☐ Yes ☐ No
12) Are you having a new problem walking?	☐ Yes ☐ No
13) Do you have weakness or numbness in your legs?	☐ Yes ☐ No

http://www.kingcounty.gov/healthservices/health/communicable/hiv.aspx

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Laboratory Data

April 2021: seen urgently by ID through ED consult

- Repeat RPR 1:128
- CSF
  - RBC 0 cells/mm^3
  - WBC 5 cells/mm^3, 88% lymphs
  - Glucose 53 mg/dL (normal 50 – 80 mg/dL)
  - Protein 36 mg/dL (normal 15 – 60 mg/dL)
  - VDRL negative
- Gonorrhea and chlamydia testing (pharyngeal, urine, rectal): negative
- HIV testing negative

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Consider HIV PrEP

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*Tenofovir/emtricitabine now licensed for HIV PrEP in adolescents weighing ≥35kg

Treatment for Neurosyphilis

Neurosyphilis (includes otic or ocular)	Aqueous crystalline penicillin G 3-4 MU IV q4h or continuous infusion x 10-14 days OR Procaine penicillin 2.4 MU IM daily + probenecid 500 mg PO qid x 10-14 days

Questions for Learning Collaborative

- This individual is penicillin-allergic: what would you recommend for him?
  - Group: ceftriaxone! Or densensitize then treat with penicillin!

- Would you use systemic steroids as adjunctive therapy?

Please submit advice to the chat

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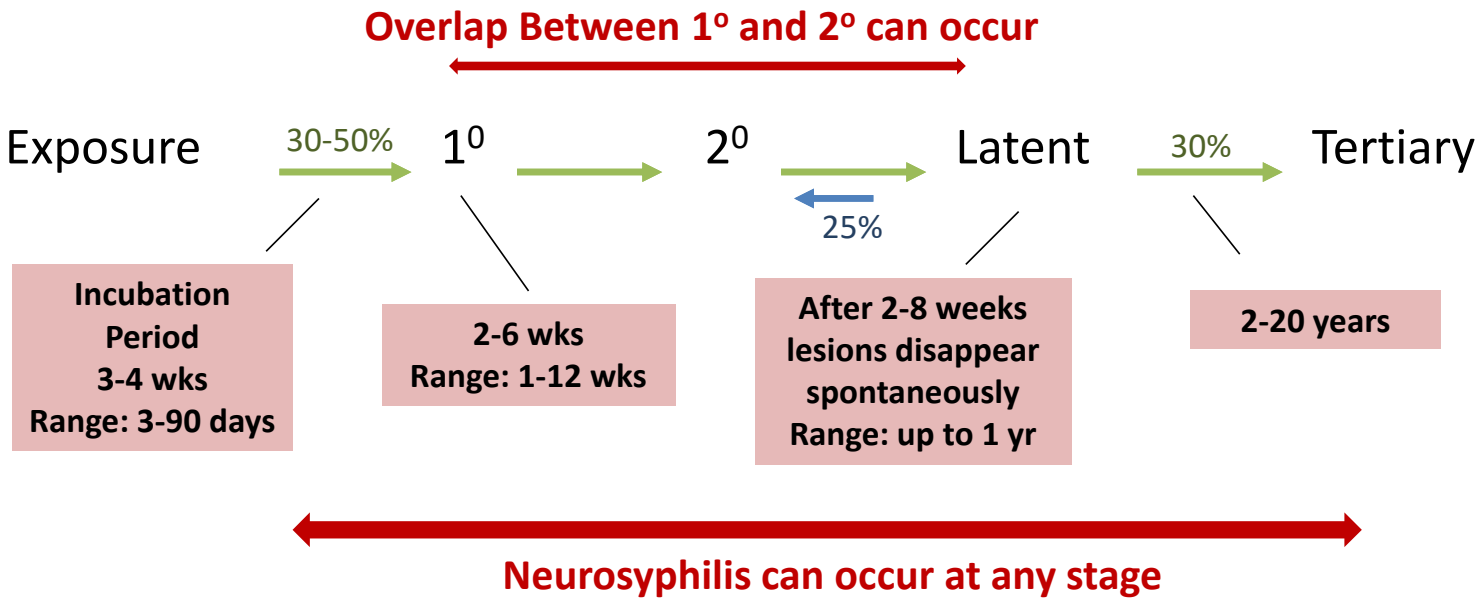
Back to the Case ...

Neurosyphilis (includes otic or ocular)	Alternative Regimen: **Ceftriaxone 2 g IV daily x 14 days (CDC)** OR Additional BASHH Guideline Alternatives: • Doxycycline 200 mg PO bid for 28 days OR • Amoxicillin 2 g PO tid plus probenecid 500 mg PO qid for 28 days “Steroids should be given with all anti-treponemal antibiotics for neurosyphilis; 40–60 mg prednisolone OD for three days starting 24 h before the antibiotics.”

May 2021

- Signs of secondary syphilis resolved
  - Lymphadenopathy gone
  - Reversal of hair loss
  - Visual changes are largely the same with 2 diagonal "streaks" in his vision (“not bothersome”)
- Repeat RPR (1 mth later) 1:32
- No indication to repeat LP (normal at start of tx)

Syphilis Natural History



More rapid progression or severe disease (multiple deep ulcers, simultaneous primary &secondary manifestations, lues maligna, neurologic involvement occurring at any stage) mostly described in HIV-infected persons with advanced immunosuppression

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Courtesy: Susan Philip, SF DPH
And M. Urban, URochester

Questions for Learning Collaborative

Is it necessary to treat syphilis for longer in persons infected with HIV?

No

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Treatment for Neurosyphilis

Neurosyphilis (includes otic or ocular)	Aqueous crystalline penicillin G 3-4 MU IV q4h or continuous infusion x 10-14 days OR Procaine penicillin 2.4 MU IM daily + probenecid 500 mg PO qid x 10-14 days

Equivalent outcomes (CSF parameters) among 150 patients who received either regimen, regardless of HIV status

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2021 CDC STI Guidelines
Dunaway *et al*, CID 2020

Treatment of STI in Persons Infected with HIV

- Most STD treatment guidelines (e.g. U.S. CDC Guidelines) highlight specific regimens for HIV-infected persons when appropriate

- In general, treatment guidelines are similar between HIV-infected and non-infected patients
  - Bacterial STIs: no treatment differences
  - Viral/protozoan STIs: treat with higher doses and/or longer

www.cdc.gov/std/treatment

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RECOMMENDED SYPHILIS TITER FOLLOW-UP IS MORE FREQUENT IN PERSONS WITH HIV, BUT TREATMENT IS THE SAME

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SYPHILIS - TREATMENT

PENICILLIN

Primary, secondary and early latent syphilis
Benzathine PCN 2.4 million units IM x 1 dose
(Jarisch-Herxheimer reaction can occur during tx of secondary syphilis)

PCN allergy – If compliance can't be assured, desensitize, treat with PCN
(instructions in 2021 CDC STI Guidelines, under Management of Persons Who Have a History of Penicillin Allergy)
- Doxycycline or tetracycline for 14 days
- Ceftriaxone 1 g daily for 10-14 days
- Azithromycin 2 g, one dose (but failures/resistance reported – therefore do not use with MSM or pregnant women)

Late latent disease
Benzathine PCN 2.4 million units IM once a week x 3 doses

Neurologic/ocular syphilis
LP, ocular slit-lamp exam, and formal ophthal/otologic eval indicated if related clinical symptoms exist (cognitive dysfunction, motor or sensory deficits, opthal or auditory symptoms, cranial nerve palsies, or meningitis)
Aqueous crystalline penicillin G 18–24 million units per day for 10–14 days
Consider benzathine PCN 2.4 million units IM once a week for up to 3 weeks as chaser

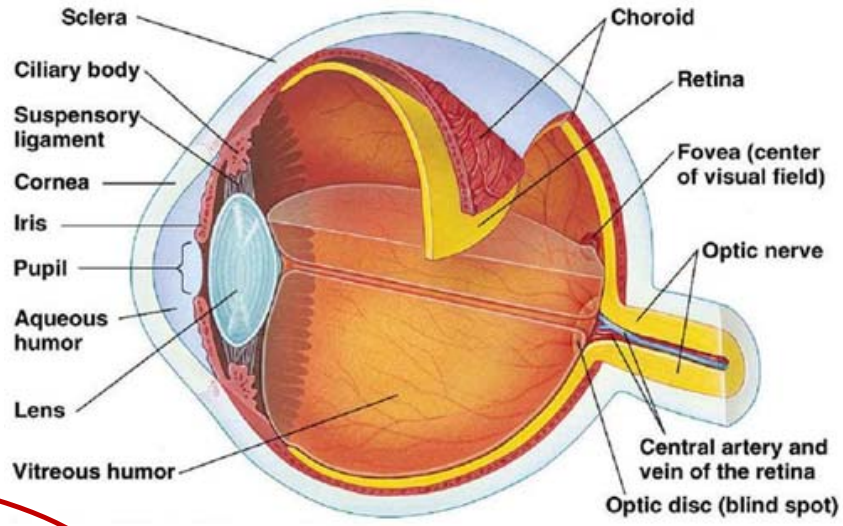
Follow titers q3 mths for a year

SYPHILIS – FOLLOW-UP IN HIV+

- **Quantitative non-treponemal serologic tests should be repeated MORE FREQUENTLY**
  - **3**, 6, **9**, 12, and 24 months after primary and secondary syphilis
  - 6, 12, **18**, and 24 months after latent syphilis
- Neurosyphilis - LP should be repeated q6mths if CSF pleiocytosis was present initially, until cell count normalizes
  - If not decreased after 6 mths or if CSF not normal after 2 yrs, re-tx should be considered
  - Changes in CSF VDRL or CSF protein occur more slowly, persistent abnormalities may be less clinically important
- Re-treat for syphilis (and re-consider neurosyphilis) if
  - Titers increase four-fold during this time
  - Titer fails to decline at least 4-fold within 6-12 months of tx for early syphilis, or 12-24 months of tx for late syphilis
  - New signs or symptoms of syphilis appear

Ocular Syphilis

Manifestations:
- Conjunctivitis, scleritis, and episcleritis
- **Uveitis**: anterior and/or posterior
- Elevated intraocular pressure
- **Chorioretinitis**, retinitis
- Vasculitis



Symptoms:
- Redness
- Eye pain
- Floaters
- Flashing lights
- Visual acuity loss
- Blindness

Diagnosis:
- Ophthalmologic exam
- Serologies: RPR (if negative, rule out prozone, VDRL, treponemal tests
- Lumbar puncture

Slide courtesy of Sarah Lewis, MD

Wender, JD et al. How to Recognize Ocular Syphilis. Review of Ophthalmology. 2008.

Review

Ocular syphilis among HIV-infected patients: a systematic analysis of the literature

Joseph D Tucker,[1] Jonathan Z Li,[2] Gregory K Robbins,[1] Benjamin T Davis,[1] Ann-Marie Lobo,[3] Jan Kunkel,[4] George N Papaliodis,[3] Marlene L Durand,[1] Donna Felsenstein[1]

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ABSTRACT

Background Ocular syphilis among HIV-infected patients continues to be a problem in the highly active antiretroviral therapy (HAART) era. However, outside of case reports or small case series, little is known about the clinical, laboratory, and treatment outcomes of these patients.

Objective To examine the literature on HIV-infected patients and determine the results of treatment.

Methods Systematic review of cases series and case reports among HIV-infected individuals with ocular syphilis. Reviews, languages other than English and pre-1980 reports were excluded. The effect of CD4 count and virological suppression on clinical manifestations and diagnostic laboratory values was evaluated.

Results A total of 101 HIV-infected individuals in case series and case reports were identified. Ocular syphilis led to the HIV diagnosis in 52% of cases, including patients with CD4 count >200 cells/mm^3. Posterior uveitis was significantly more common in individuals with CD4 count <200 cells/mm^3 (p=0.002). Three patients with confirmed ocular syphilis had negative non-treponemal tests. Ninety-seven per cent of patients with visual impairment improved following intravenous penicillin or ceftriaxone.

Conclusions Non-treponemal tests may be negative in HIV-infected patients with ocular syphilis. Ocular syphilis remains an important clinical manifestation that can lead to initial HIV diagnosis.

including the following: papulosquamous lesions of the skin of the lids, temporary loss of eyebrows, diffuse papillary conjunctivitis, scleroconjunctivitis, interstitial keratitis, iritis, chorioretinitis and optic neuritis. Studies of ocular syphilis among HIV-negative individuals have found frequent cerebrospinal fluid (CSF) abnormalities that are consistent with neurosyphilis,[21–23] and no substantial differences in CSF characteristics between HIV-infected and uninfected individuals.[22 23]

This systematic review analysed the clinical manifestations, immunological status, and treatment response of patients with HIV with ocular syphilis. The goal of this study is to better understand the clinical picture and laboratory findings of ocular syphilis in the HIV era, focusing on the effects of CD4 count and antiretroviral therapy.

METHODS

We followed PRISMA guidelines for the search strategy, study selection, data abstraction, analysis and presentation (figure 1). PubMed, Science Direct and NLM Gateway online databases were searched using the following terms: ('syphilis' OR 'Treponema pallidum') AND ('HIV' OR 'AIDS') AND ('eye' OR 'ocular', 'iridocyclitis', 'chorioretinitis', 'uveitis', 'retinitis', 'optic neuritis', OR 'conjunctivitis.') PubMed was searched by titles while Science Direct and NLM Gateway were searched by

Key Findings – ART Era

- Diagnosis of ocular syphilis often led to diagnosis of HIV
- Posterior uveitis with central chorioretinal lesions and optic neuritis have worst outcomes (anterior uveitis and other syndromes do better)
- Risk for posterior uveitis correlated with lower CD4 count
- Appropriate IV treatment associated with excellent outcomes

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Tucker et al., *STI* 2011

Clinical Take Home Points: Ocular Syphilis

- Screen all syphilis patients for signs/symptoms of neurosyphilis, including ocular and otic syphilis
  - Sexual history-taking is relevant for our ophthalmology colleagues!
- Treat neurosyphilis in patients with HIV with same regimens as patients who are HIV-negative, and follow closely
  - Few alternatives exist for penicillin-allergic patients, but there are anecdotal case series using ceftriaxone or doxycycline
- Outcomes depend on level of immunocompromise, initial exam findings (posterior eye findings correlate with poorer outcomes), and speed of treatment initiation (as with any bacterial disease)
  - Appropriate treatment associated with good visual prognosis
  - **Treatment delays are NOT always associated with visual loss**

Public Health Take Home Points: Ocular Syphilis

- Asking clinicians practicing in the area can lead to better choices of how to facilitate dx and tx
  - Different systems have different ways of getting patients on outpatient IV therapy quickly
- Averting permanent disability from syphilis complications and assuring a high standard of care for neuro/ocular/otic syphilis is public health muscle we can flex

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Final thoughts?

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