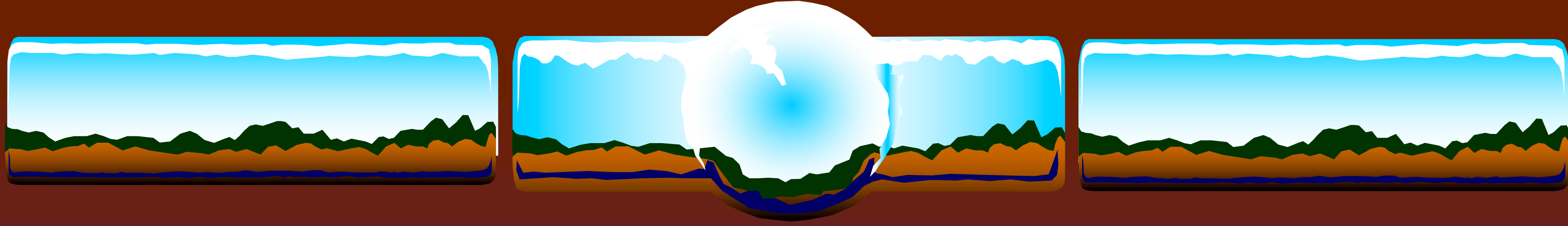


Syphilis 101: Diagnosis, Treatment and Elimination

Jonathan Vilasier Iralu, MD, MACP, FIDSA

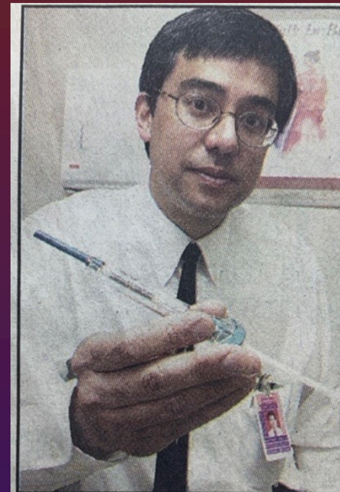
Indian Health Service

Chief Clinical Consultant for

Infectious Diseases

Disclosures

I hate syphilis!



DOUGLAS TESNER
THE ASSOCIATED PRESS

DISEASE FIGHTER: Dr. Jonathan Iralu, of the Gallup Indian Medical Center, holds a syringe of penicillin used to treat syphilis, a disease that is sharply increasing on the Navajo Reservation.

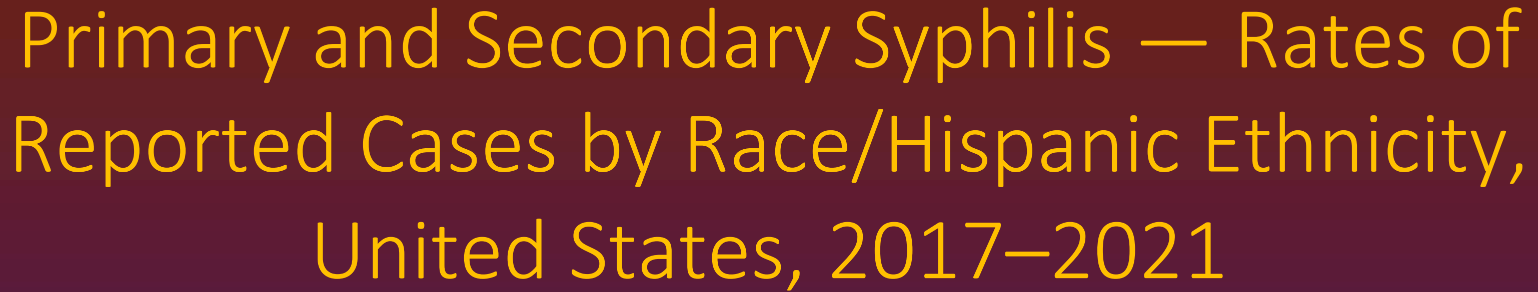
ABQ Journal
June 2003

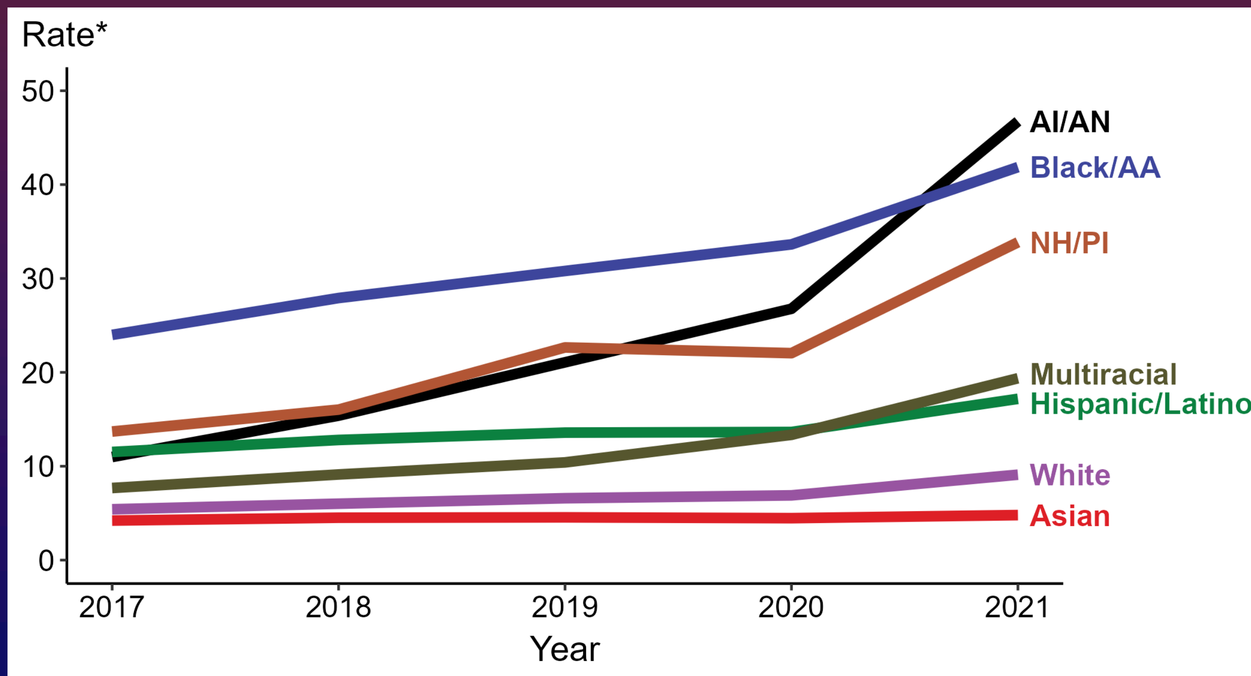
At the end of this presentation, participants will be able to:

1. Examine the epidemiologic trends of syphilis in Indian Country.
2. Identify and stage syphilis cases (primary, secondary, early latent, late latent).
3. Provide the proper treatment for syphilis in accordance with current CDC guidelines.
4. Understand STI elimination best practices in the IHS

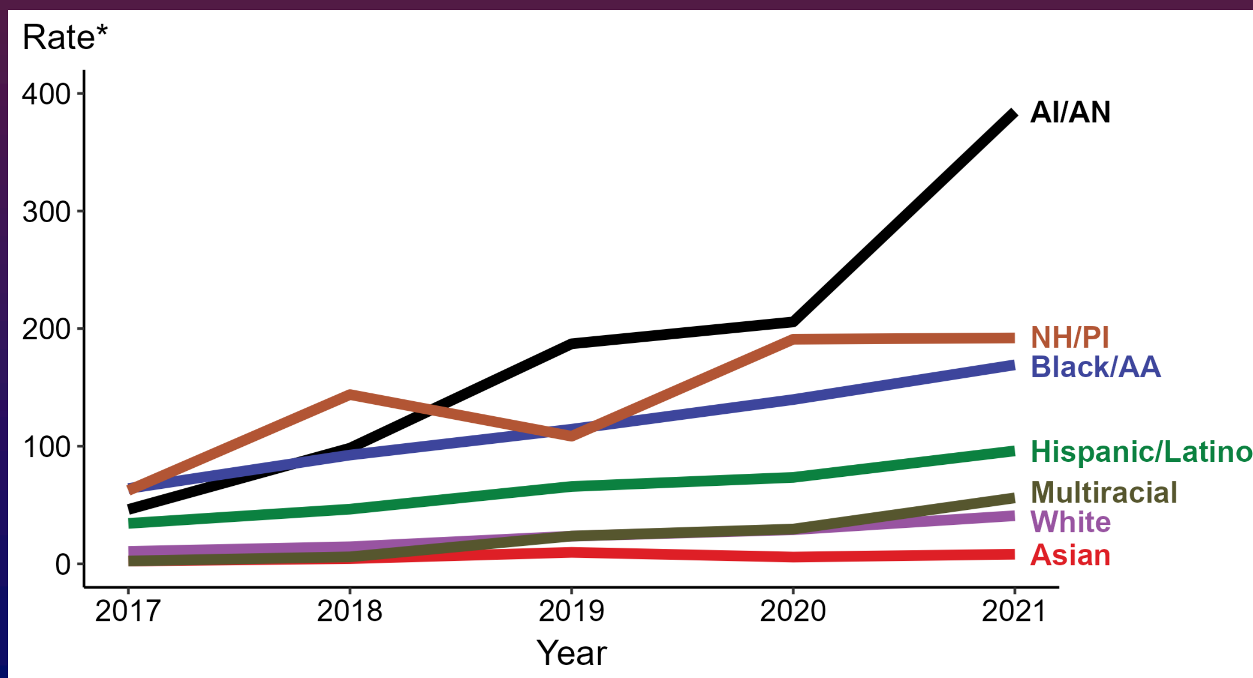
Case Presentation

- A 26 year-old woman walks in to the OB-GYN clinic to request pregnancy testing. She is asymptomatic with no complaints. Physical exam is completely normal including eye, skin, neurologic and pelvic examination. She opted in for HIV and STI testing as part of the prenatal bundle. The tests come back negative except for a positive screening syphilis EIA and a reflex RPR titer of 1:16 dilutions.

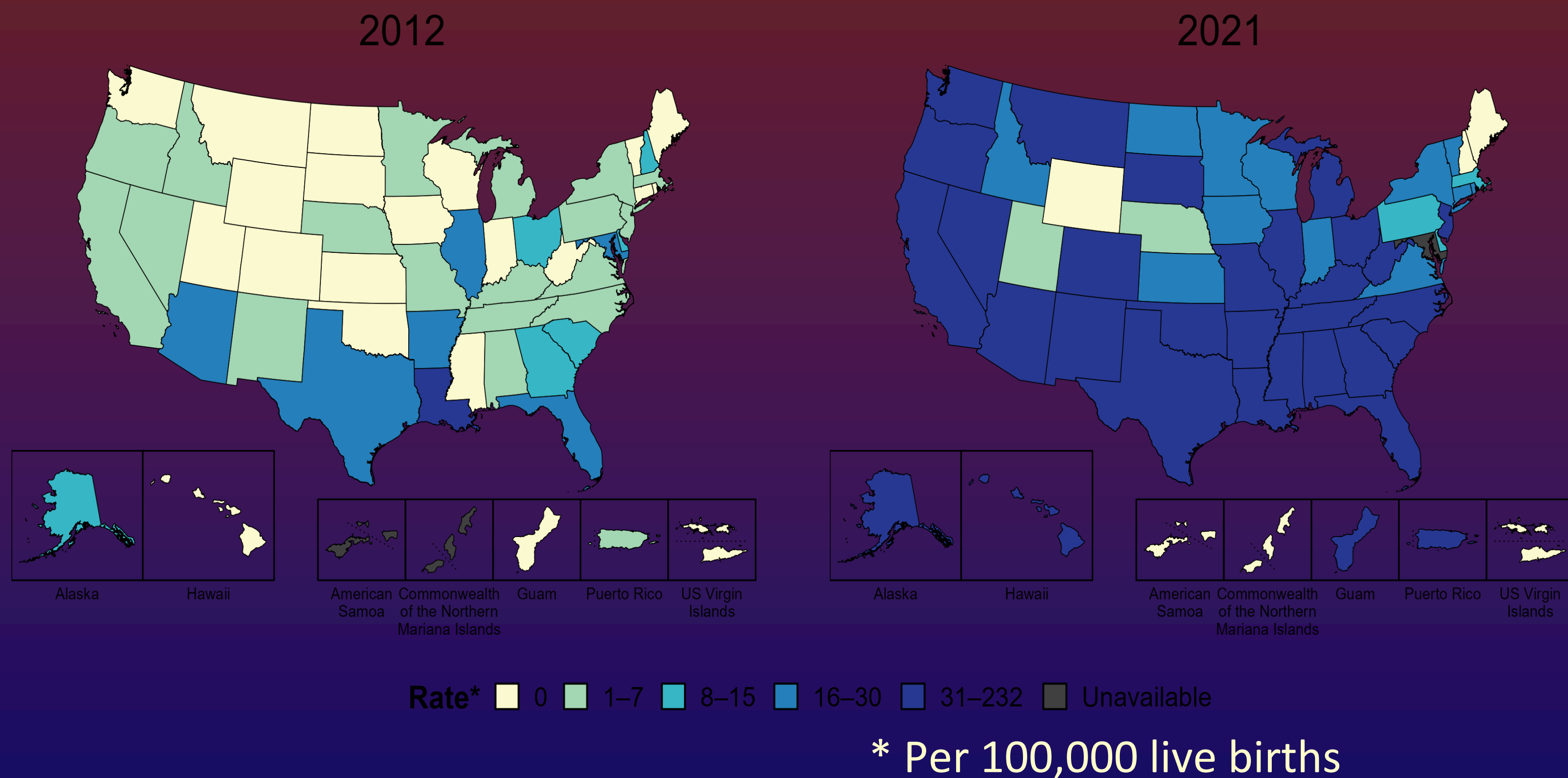

Primary and Secondary Syphilis — Rates of
Reported Cases by Race/Hispanic Ethnicity,
United States, 2017–2021


Rate*
50
40
30
20
10
0
2017
2018
2019
2020
2021
Year
AI/AN
Black/AA
NH/PI
Multiracial
Hispanic/Latino
White
Asian

Congenital Syphilis — Rates of Reported Cases by Year of Birth, Race/Hispanic Ethnicity of Mother, United States, 2017–2021



Congenital Syphilis — Rates of Reported Cases by Year of Birth and State, United States and Territories, 2012 and 2021



* Per 100,000 live births

Syphilis Overview

- Sexually transmitted disease
- Caused by *Treponema pallidum,* a microaerophillic, corkscrew shaped bacteria

Syphilis Transmission

- Transmission by
  - Sexual contact
  - Passage through placenta
  - Kissing or other contact with active lesion
  - Transfusion of blood
  - Accidental direct inoculation

Syphilis Pathophysiology

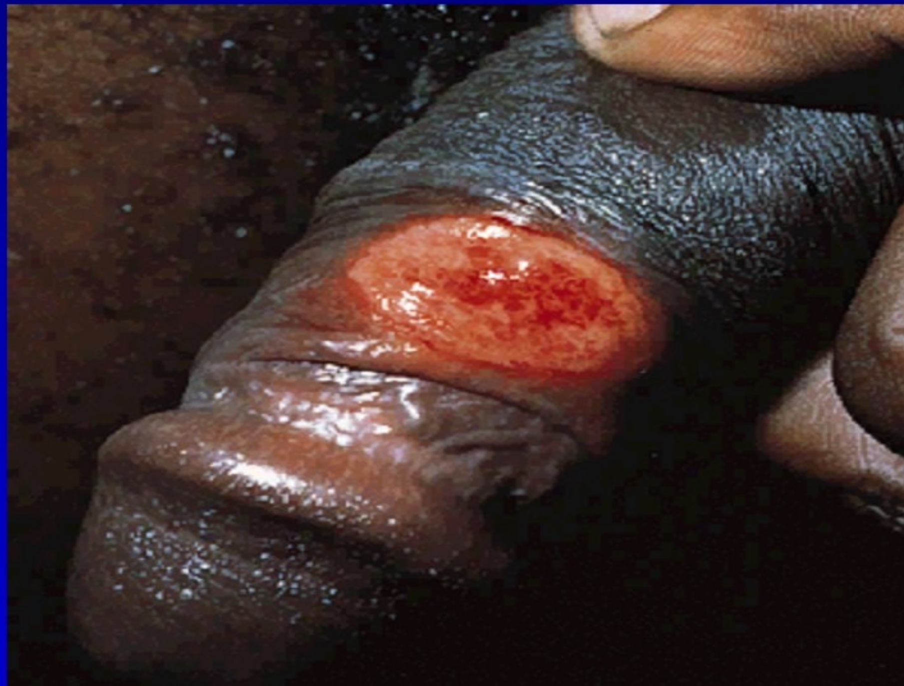
- *T pallidum* divides every 30 to 33 hours
- Invades locally but disseminates widely
  - 30% of 58 patients with early syphilis in one study had organisms isolatable from CSF
- Local lesions are marked by plasma cell, lymphocyte and histiocyte infiltration first then capillary proliferation and finally, necrosis with ulceration.

- Primary Syphilis **(21 day incubation)**
  - Chancre (heals 3-6 weeks)
  - Regional lymphadenopathy (starts 1 wk. later)
  - RPR/VDRL positive in 78% (74-87% range)
  - Treponemal EIA is 54-100% sensitive for this stage

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7312216/

  - This is an eyeball diagnosis, not a lab diagnosis

Syphilis
Primary Chancre, Penile Shaft

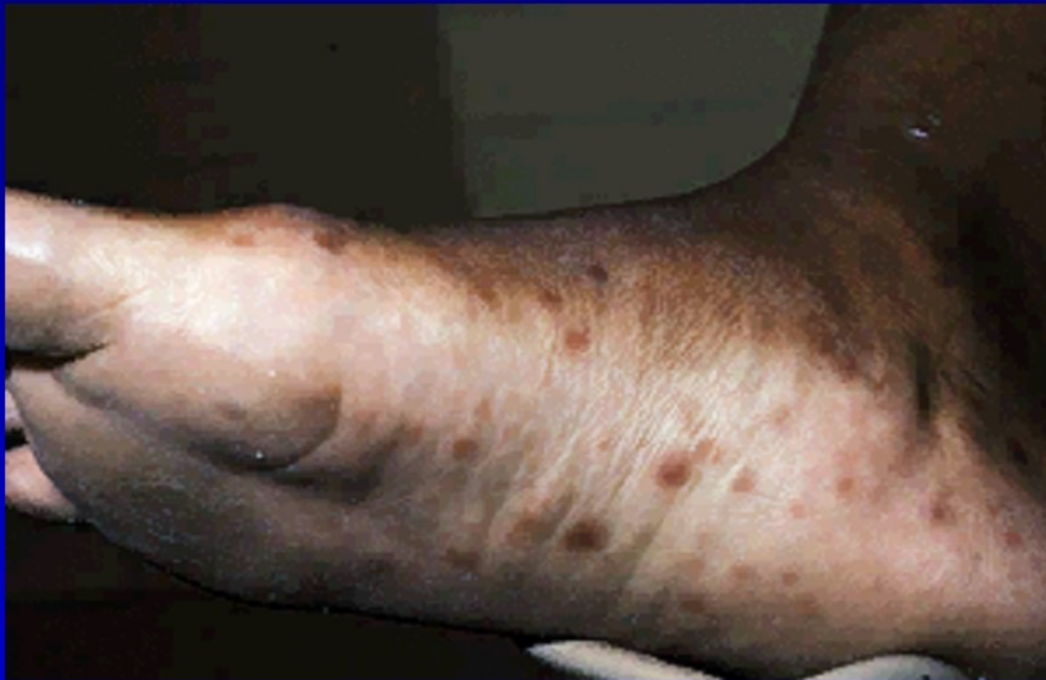


Mosby *STD Atlas, 1997*

Syphilis Clinical Stages

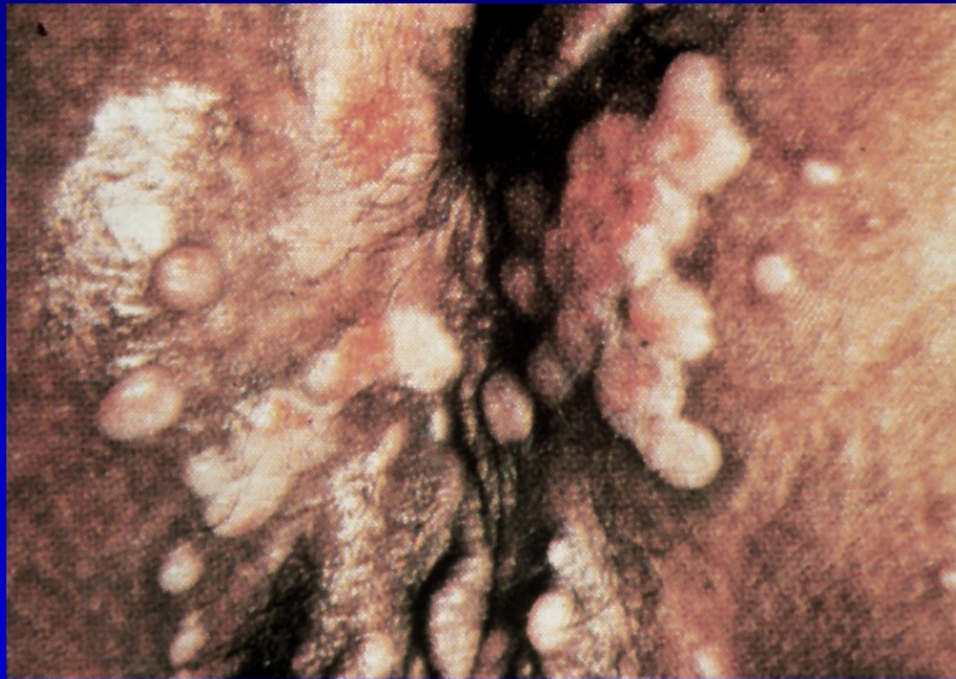
- Secondary Syphilis (2-8 weeks post chancre)
  - palmar/plantar rash
    - macular, papulosquamous, pustular syphilides
  - condylomata lata/mucous patches
  - Patchy alopecia (moth eaten appearance)
  - Pharyngitis, epitrochlear adenopathy, myalgia, weight loss, aseptic meningitis 1-2%, proteinuria, hepatitis, uveitis
  - RPR/VDRL and Treponemal EIAs are all 100% sensitive in this stage

Rash of Secondary Syphilis Papular Form



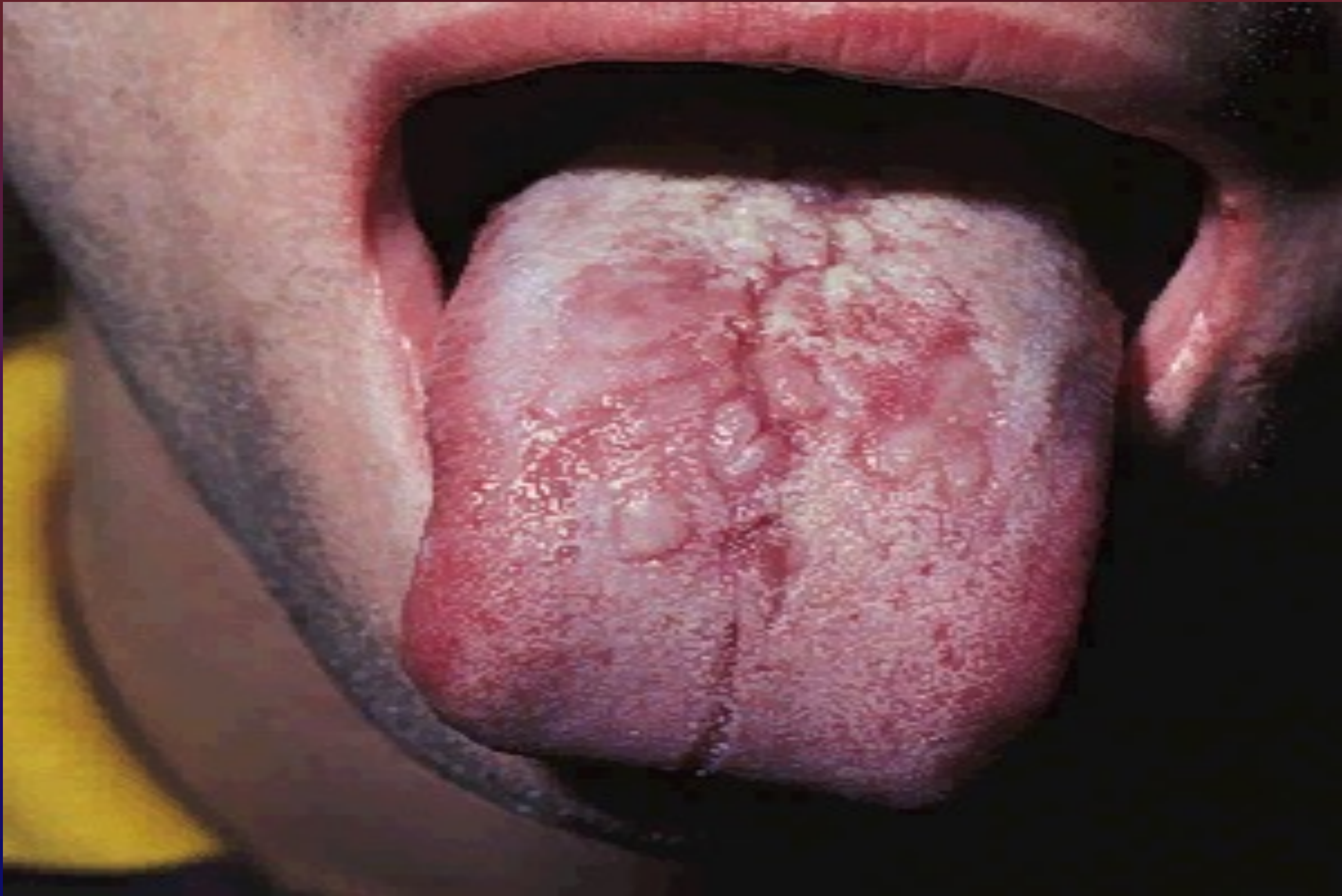
CALIFORNIA STD/HIV PREVENTION TRAINING CENTER

Mosby *STD Atlas, 1997*



CALIFORNIA STD/HIV
PREVENTION TRAINING CENTER

Mucous Patches of Secondary Syphilis



Latent Syphilis

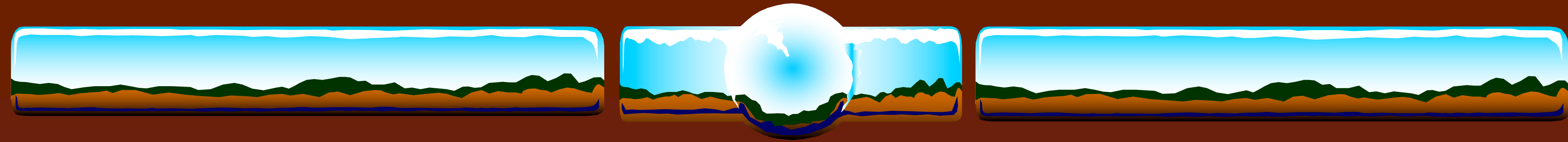
Latent syphilis = positive serology with no symptoms or signs

- **Early Latent Syphilis:**
  - **Seroconversion** within the last year
  - **primary or secondary** syphilis within 1 year
  - **Contact** of a primary, secondary or early latent case
- **Late Latent Syphilis:** present > 1 year
- **Latent Syphilis of Unknown Duration:** No prior serology in chart

Neurosyphilis happens at any stage

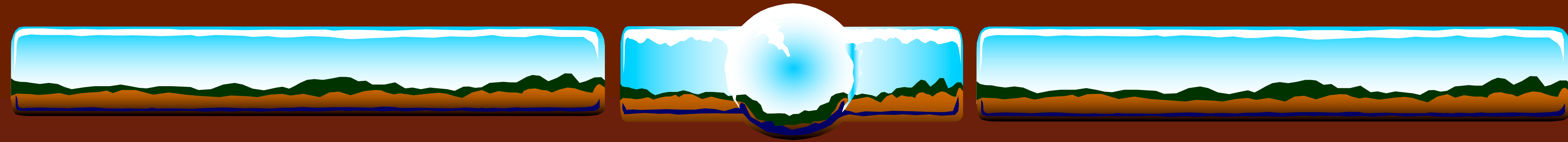
- **Meningovascular** (infarction)
  - **Stroke syndromes** (aphasia, hemiparesis, seizures)

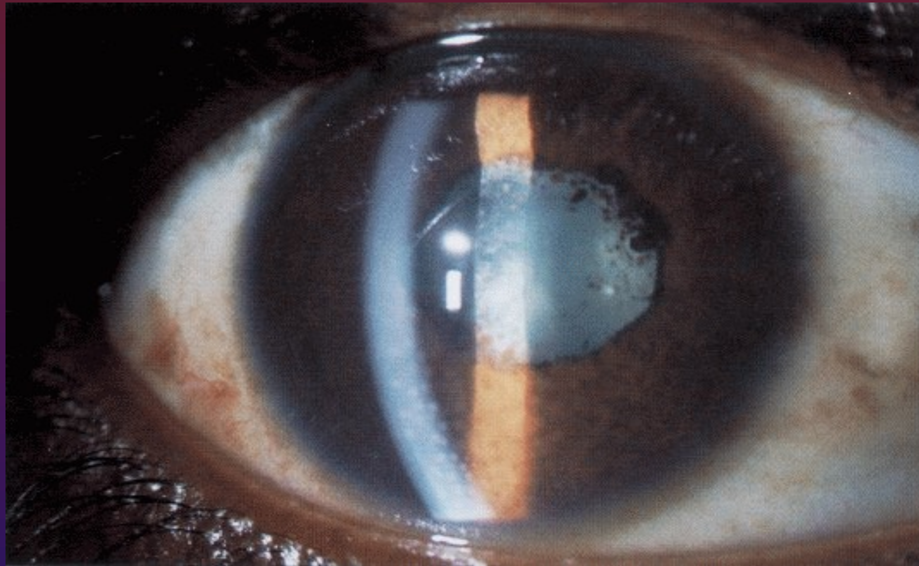
- **Parenchymal** (neuron destruction)
  - **Tabes dorsalis** (foot slap, wide based gait, lightning pains, (+) Romberg, Charcot Joints)
  - **General paresis** (Personality, Affect, Reflexes, Eye, Sensorium, Intellect, Speech)
  - **Other:** Gunbarrel sight (optic atrophy), uveitis, CN VII and VIII palsy, syphilitic otitis (deafness and tinnitus)

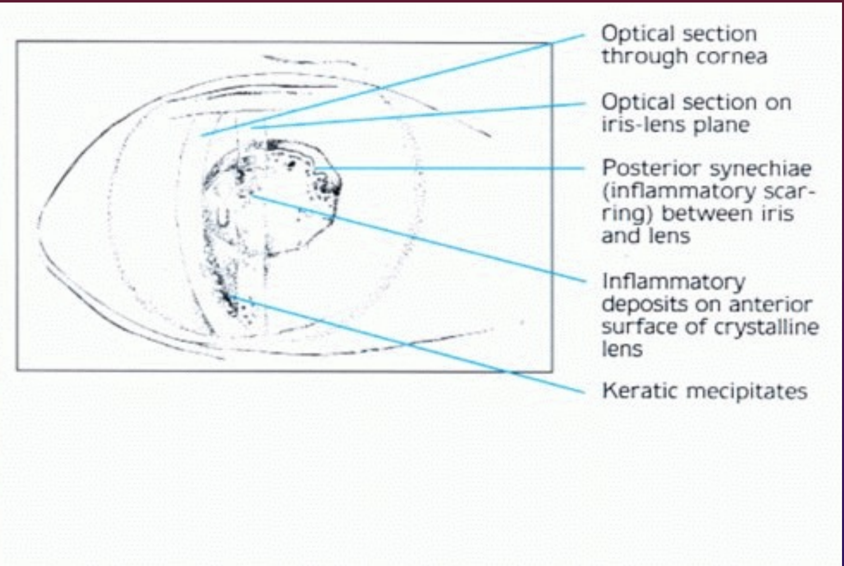


Ocular syphilis

- Quite common in the current outbreak
- Can involve any part of the eye
  - Keratitis of the cornea
  - Flare (white cells) in the anterior chamber
  - Iritis
  - Vitritis
  - Retinitis
  - Optic neuritis
- Argyll-Robertson pupils are a marker for neurosyphilis, not ocular
  - Irregular pupil
  - React to accommodation, not light.





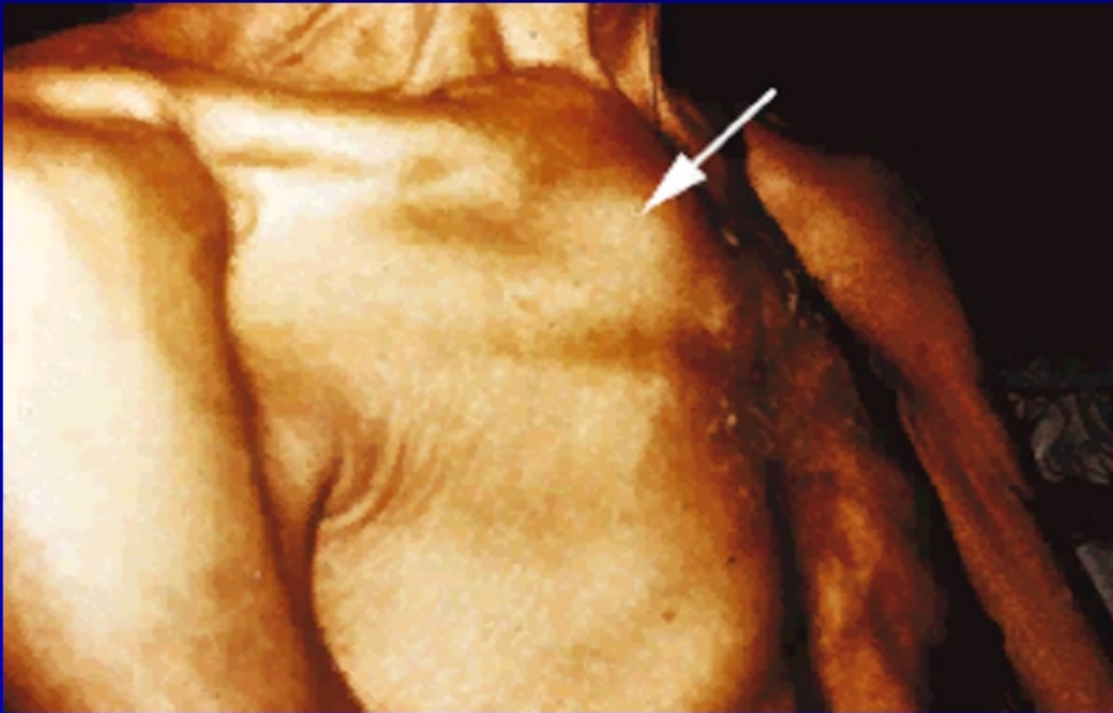

Optical section
through cornea
Optical section on
iris-lens plane
Posterior synechiae
(inflammatory scar-
ring) between iris
and lens
Inflammatory
deposits on anterior
surface of crystalline
lens
Keratic mecipitates

Other Tertiary Syphilis Dx

- **Cardiac Syphilis**
  - Aortitis-endarteritis obliterans of vasa vasorum
    - **Saccular aortic aneurysm**
  - Secondary aortic insufficiency due to expanding aortic root

- **Benign Gummatous Syphilis**
  - Develop in 10 years if HIV negative
  - ***Develop in months if HIV positive***

Tertiary Syphilis
Aortic Aneurysm



Mosby *STD Atlas, 1997*

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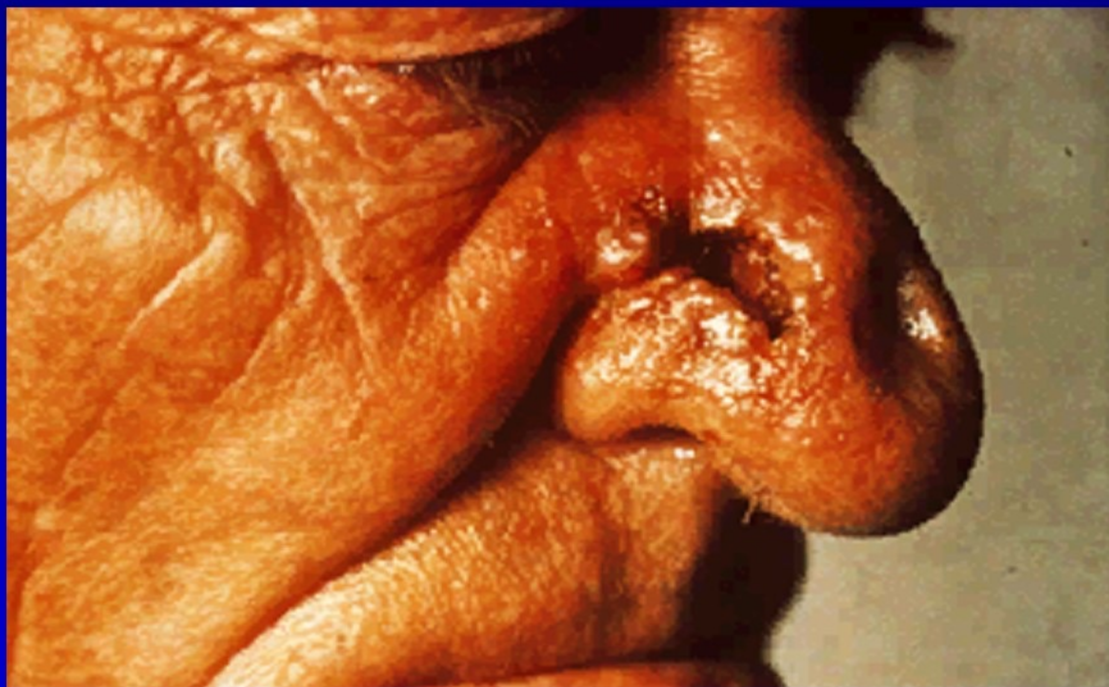
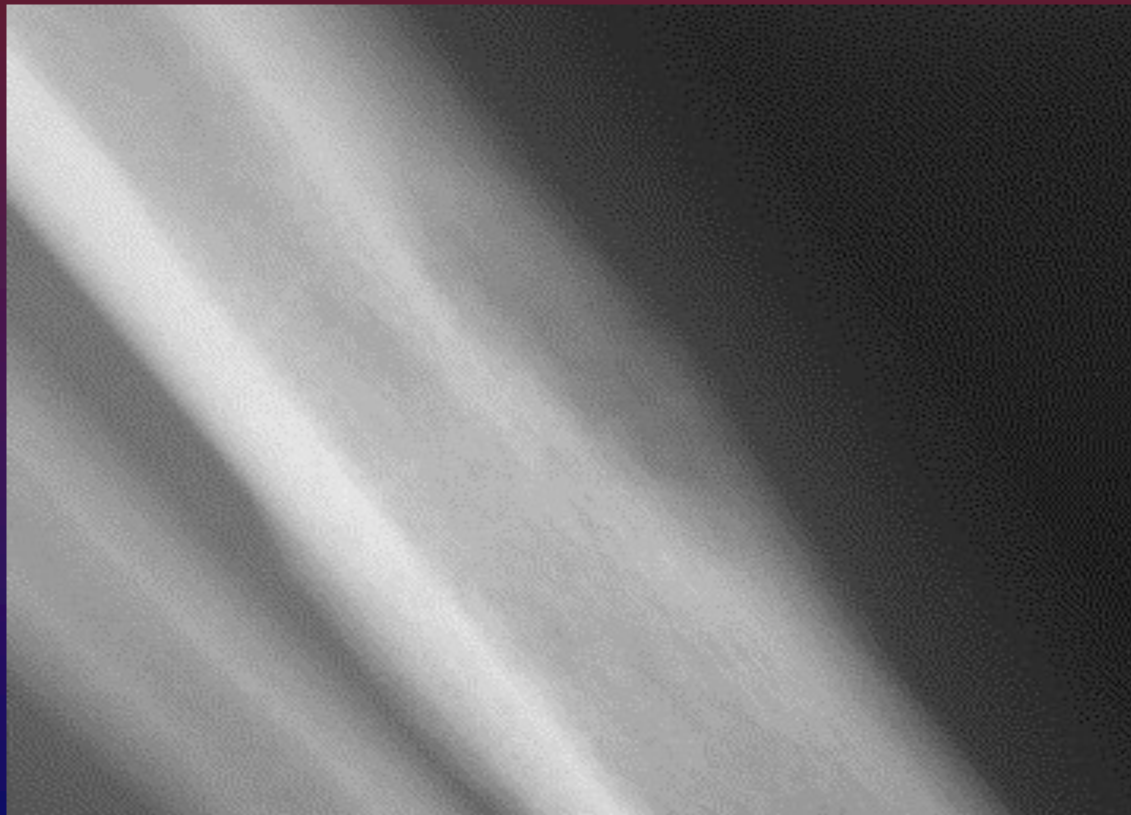
Tertiary Syphilis
Ulcerating Facial Gumma



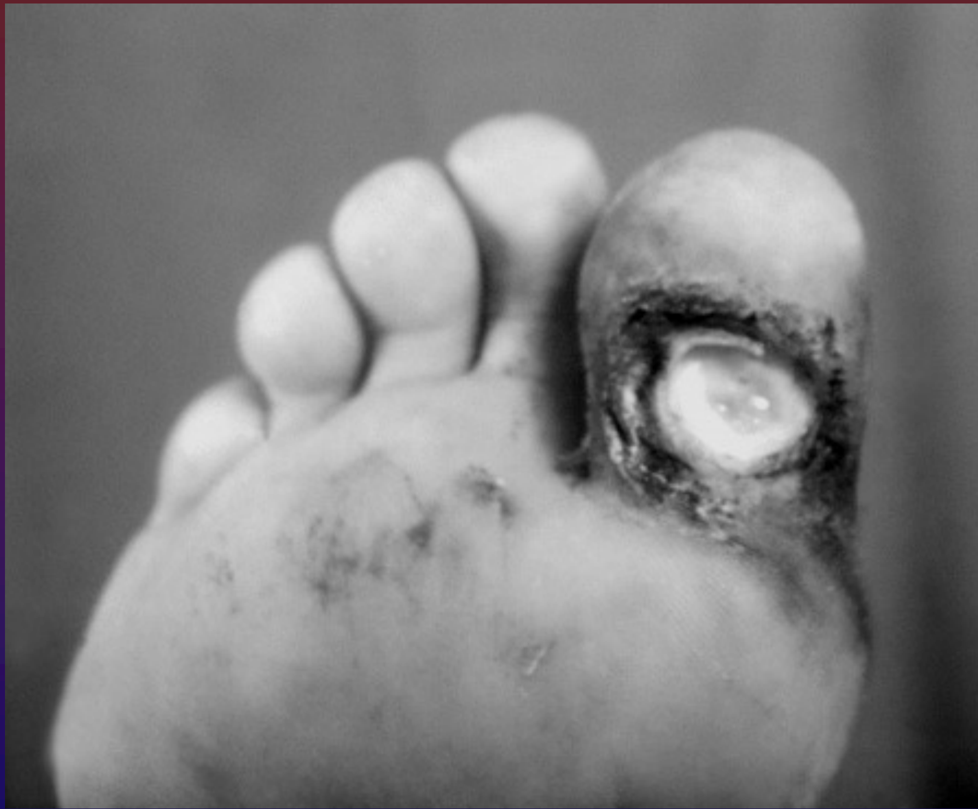
Mosby *STD Atlas, 1997*

CALIFORNIA STD/HIV PREVENTION TRAINING CENTER

Syphilitic periostitis



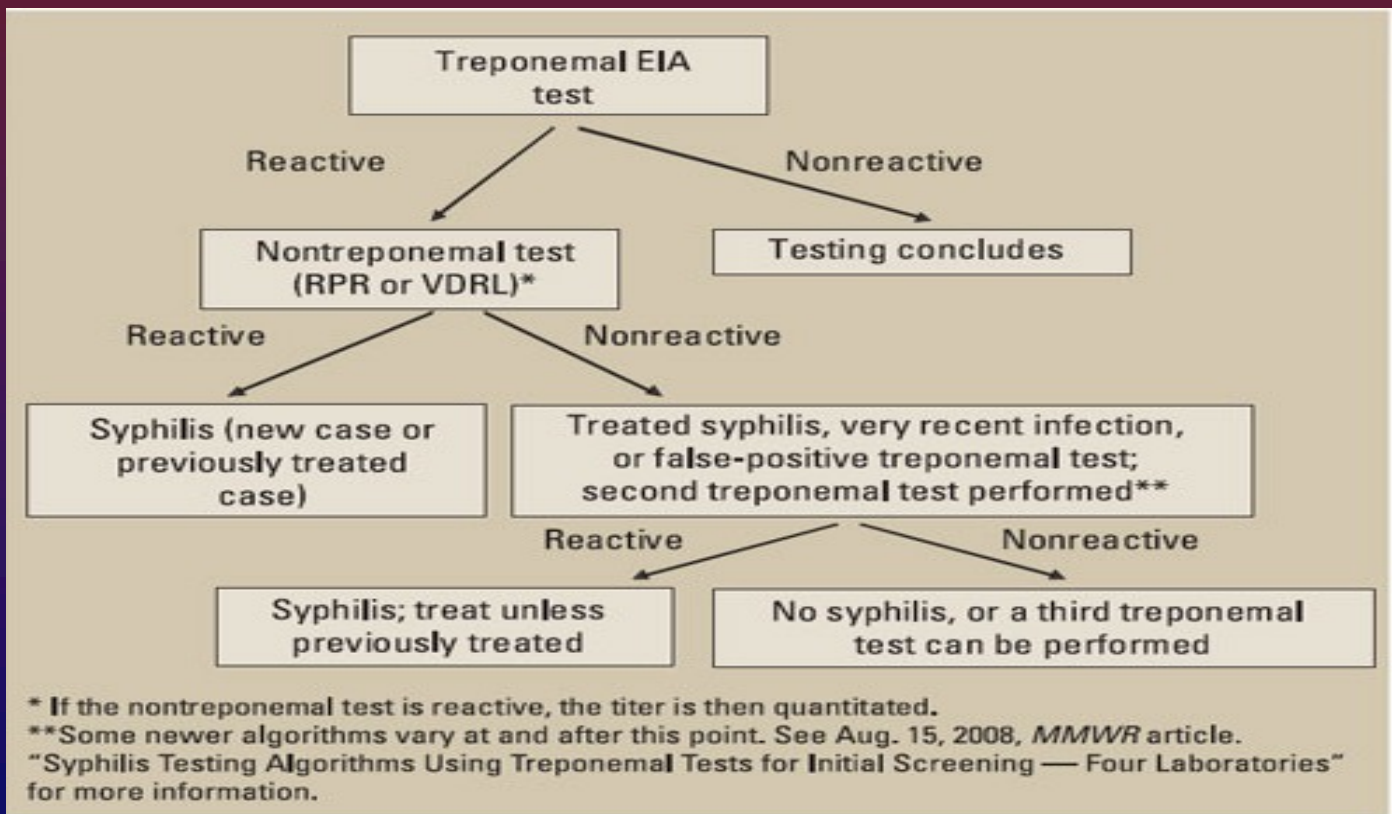
Tabes dorsalis



Syphilis Diagnosis

- We used to do RPRs first the reflex to confirmatory TPPA
- Many labs now do an EIA first, then RPR
  - A four-fold titer change is significant
- Doing EIA first saves money and is quicker
- What to do if RPR is negative?

Syphilis diagnosis reverse algorithm



Syphilis Management

- <u>Primary and Secondary Syphilis</u>
  - Dark-field exam of skin lesions if available
  - Draw Syphilis and HIV serology
  - Administer Benzathine penicillin 2.4 mU IM x 1
    - >>>>> Consider giving a second dose 1 week later if pregnant <<<<<
  - R/O optic/neurosyphilis if symptomatic
  - Check RPR at 6 and 12 months-
    - **if < 4-fold drop at 12 months:**
      - **Do a careful neurologic examination → Lumbar puncture only if abnormal**
      - **Re-check HIV serology**
      - **Re-treat with three weekly doses of Benzathine PCN**

Syphilis Management

- Latent Syphilis
  - Check RPR (reflex MHA TP) and HIV test
  - Careful skin and ano- genital exam
  - LP if symptomatic, tertiary lesion, treatment failure
  - Give Benzathine PCN 2.4 mU IM
    - Treat once if early latent (consider second dose in a week if pregnant)
    - Treat weekly x3 if late latent or latent syphilis of unknown duration.
      - Dose interval can be as long as 10-14 days if not pregnant, 9 days if pregnant

Syphilis Management

- Latent syphilis follow-up
  - Check RPR at 6, 12 and 24 months
  - **if < 4-fold drop at 24 months:**
    - **Do a careful neurologic examination → Lumbar puncture if abnormal**
    - **Re-check HIV serology**
    - **Follow RPR titer serially**
    - **Re-treat with three weekly doses of Benzathine PCN and consider LP especially**
      - **If follow up cannot be ensured**
      - **If initial titer was > 1:32**

Syphilis Management

- Neurosyphilis:
  - PCN G 18-24 mU IV/day for 10-14 days
  - Procaine 2.4 mU IM/day plus Probenecid 500 mg po QID for 10-24 days.
  - Lumbar Puncture is no longer required if the RPR titer is falling over the next 2 years and there is no progression of disease
- Cardiac or Gummatous syphilis
  - Benzathine PCN 2.4 mU IM q wk x 3

Congenital Syphilis

- <u>Pregnancy</u>
  - Treat as appropriate for stage with ***<u>penicillin</u>***
  - Consider Giving a second dose for early syphilis
  - For late syphilis, dosing intervals > 9 days require a restart of the series
  - Fetal Ultrasound and HIV test
  - Beware Jarisch-Herxheimer reaction during second half of pregnancy
    - Old Estimates were 40% incidence; in a recent study incidence was 1.7% *
    - Advise patient of need to come for fever, contractions or decreased fetal movement

*Dhaliwal et al: https://jammi.utpjournals.press/doi/full/10.3138/jammi-2021-0001

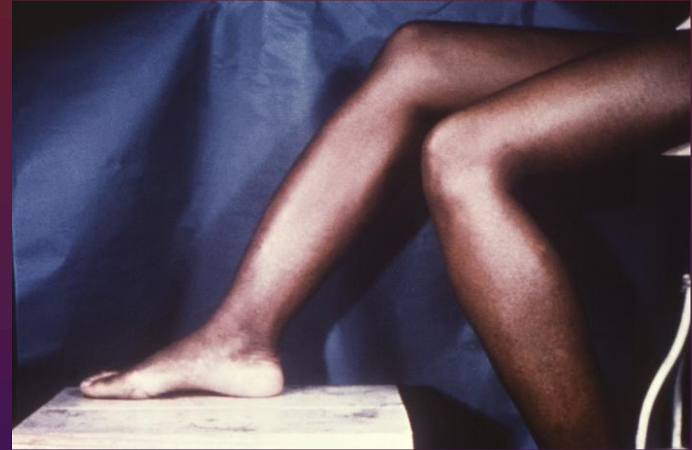
Congenital Syphilis

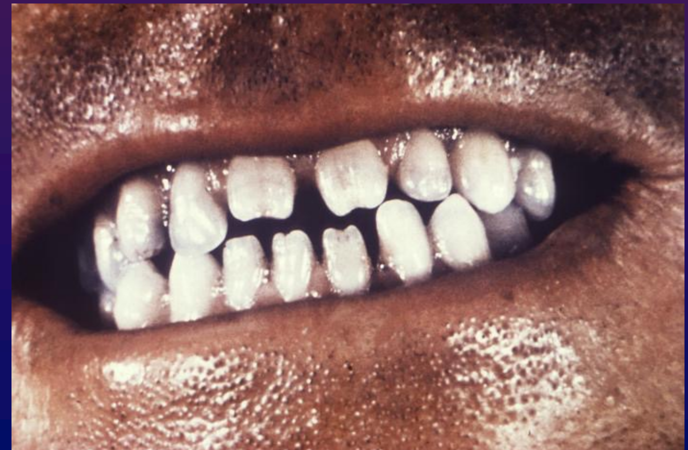
- If diagnosed at or before 24 weeks
  - Don’t check titer before 8 weeks (week 32)
  - Do check titer at delivery
  - Recheck titer sooner if reinfection is suspected
- If diagnosed after 24 weeks, check serology at delivery
- Most women will not achieve a four-fold decrease in titer before delivery
- A four-fold increase sustained > 2 week = reinfection or treatment failure

Congenital Syphilis

- Inadequate Treatment is likely if:
  - Delivery occurs within 30 days of therapy
  - Clinical signs of infection are present at delivery
  - Maternal antibody titer at delivery is four-fold higher than pretreatment titer

Congenital Syphilis Manifestations





Congenital syphilis evaluation and treatment

- See Dr McAuley’s excellent Indian Country ID ECHO talk:
  - https://www.indiancountryecho.org/resources/clinical-overview-of-congenital-syphilis-march-16-2023/

- The goal is to treat with Benzathine PCN with the right number of doses at least 30 days before delivery to avoid the “Possible CS” work up and treatment

How to handle Syphilis contacts

- Each index case needs a minimum of 2 interviews
- Named contacts need
  - Complete STI bundle testing
    - Syphilis EUA with reflex RPR same day as epi treatment
    - HIV serology
    - Gonorrhea (urine, throat, rectum)
    - Pregnancy test
    - Viral hepatitis test
  - Treatment
    - Benzathine PCN x 1 if less than 90 days → EPI TREATMENT
    - Benzazthine PCN x 1 if over 90 days if Syphilis test is positive or f/u not ensured

Other Considerations for syphilis patients

- Screen with the complete STI bundle
  - HIV
  - GC/CT genital and extragenital
  - Viral hepatitis
  - Pregnancy

- **Offer HIV PrEP to every patient!**

- Offer Mpox JYNNEOS vaccine PrEP to every patient

Doxy PEP is our new tool!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections

Anne F. Luetkemeyer, M.D., Deborah Donnell, Ph.D., Julia C. Dombrowski, M.D., M.P.H., Stephanie Cohen, M.D., M.P.H., Cole Grabow, M.P.H., Clare E. Brown, Ph.D., Cheryl Malinski, B.S., Rodney Perkins, R.N., M.P.H., Melody Nasser, B.A., Carolina Lopez, B.A., Eric Vittinghoff, Ph.D., Susan P. Buchbinder, M.D., Hyman Scott, M.D., M.P.H., Edwin D. Charlebois, Ph.D., M.P.H., Diane V. Havlir, M.D., Olusegun O. Soge, Ph.D., and Connie Celum, M.D., M.P.H., for the DoxyPEP Study Team*

Luetkemeyer et al NEJM, 4/6/2023

- Recruited 501 MSM and transgender women on PrEP or ART
- Offered Doxycycline 200 mg within 72 hours of condomless sex
- Relative risk for infection

	PrEP	ART
Gonorrhea	0.45	0.43
Chlamydia	0.12	0.26
Syphilis	0.13	0.23

- Adverse events: None serious

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2211934?articleTools=true

Doxycycline Post Exposure Prophylaxis

New IHS guideline!

- Patients with STI risk can be offered 200 mg doxycycline within 24-72 hours of sex
  - MSM
  - Bisexual
  - Transgender women
- Indicated for
  - Bacterial STI within the last year
  - No recent STI but attending an event at elevated risk

https://www.cdc.gov/std/treatment/guidelines-for-doxycycline.htm

What about Penicillin allergy?

- PALACE study (Copaescu et al, JAMA Int Med, 9/1/2023)
  - Randomized 382 persons with a low PEN-FAST to skin testing vs automatic penicillin challenge. Scores less than 3 are considered low risk.
  - PEN-FAST: https://www.mdcalc.com/calc/10422/penicillin-allergy-decision-rule-pen-fast
    - Five years since last reaction? If yes, 2 points
    - Anaphylaxis or Severe ADR? If yes, 2 points
    - Treatment required for reaction? If yes, 1 point
    - Most patients had a PEN-Fast score of 0-1 (5% risk of ADR)
  - Persons with PEN-FAST score< 3 or negative skin tests got low dose Amoxicillin or PCN VK 250mg and were observed 60 minutes

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2806976

What about Penicillin allergy?

- Only 1 person in each arm had a reaction to challenge (0.5%)!
- There were no serious ADRs during follow-up

- Take home message: If the PEN-FAST score is < 3, do an amoxicillin challenge and de-label the allergy in the chart if negative

- Priority tiers:
  1. Pregnant and HIV-infected patients and their partners : ALWAYS
  2. Early Syphilis and partners: when supplies are adequate otherwise use doxycycline for 14 days
     1. Primary
     2. Secondary
     3. Early Latent
  3. Late latent syphilis and Latent Syphilis Uncertain Duration: Benzathine PCN when supplies are not limited otherwise use doxycycline for 28 days
     1. Requires PHN/DIS calls or visits during the 28 days to ensure adherence

Components of of a good Indian Country Syphilis Program:

- Screening
  - EHR Clinical Reminders
  - Emergency Department/Urgent Care enhanced screening
  - Express STI testing
  - PHN field outreach with rapid testing for syphilis and HIV
    - Community outreach
    - Homes
    - Other interesting places
- Treatment
  - Hospital and Clinics
  - Field based Penicillin treatment

Screening tools

- EHR alerts
  - Look at the annual syphilis reminder to see if syphilis testing is due
  - Use the EHR Syphilis pop-up function
    - Document the diagnosis and reason for the pop-up
      - Stage of Syphilis
      - Need for Treatment recommended dose
      - Need for follow-up testing

EHR front page reminders are pretty good ….

Allergies/Adverse Reactions

Agent	Type	Reaction	Status	InAct Date
AMOXICILLIN	Drug	HIVES	Verified	
CLINDAMYCIN	Drug	URTICARIA	Verified	
CODEINE	Drug	ANAPHYLA...	Nonverified	
DIGOXIN	Drug	SWELLING ...	Nonverified	
DILAUDID	Drug	RESPIRAT...	Verified	
IBUPROFEN	Drug	ANAPHYLA...	Verified	
MORPHINE	Drug	ANAPHYLA...	Verified	
SYNTHROID	Drug	DIARRHEA	Verified	

Status: All / Active

Medications

Medication	Status	Issue Date
PENICILLIN VK 250MG	ACTIVE*	21-Aug-2009
DOCUSATE SODIUM ...	ACTIVE	

Status: All / Active
Inpatient/Outpatient: All / Out / In

Alerts/Warnings/Directives/Flags

Crisis Alert
DNR/DNI
FALL RISK CLINICAL WARNING

Reminders

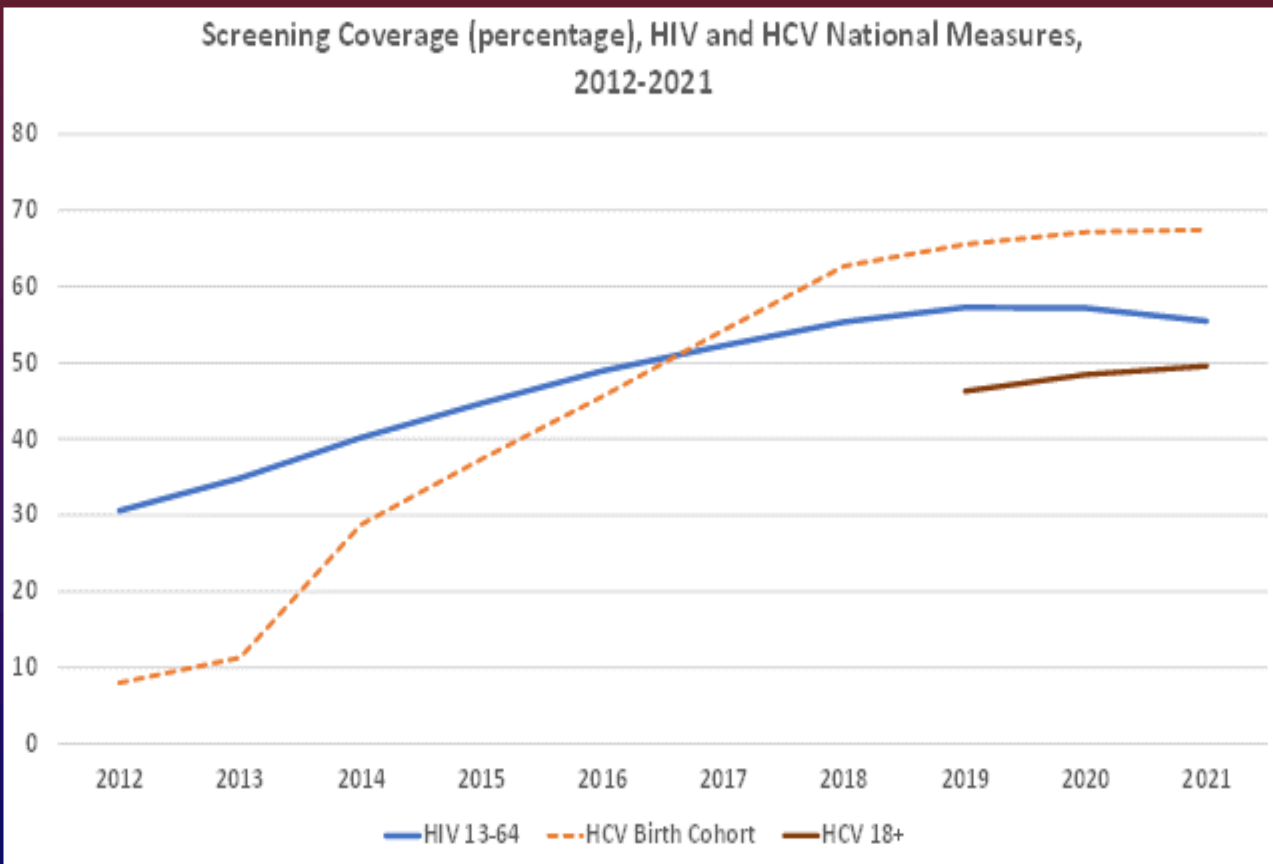
Reminder	Date
Chlamydia Screening	DUE NOW
Dental Visit	11-Feb-2017
DM Eye Exam	18-Aug-2016 11:39
DM Foot Exam	11-Sep-2014 09:22
DM HgbA1c	19-Jan-2013 11:36
DM Nephropathy Screen	DUE NOW
HepB Adult Immunization	DUE NOW
HIV Screen	DUE NOW
Lipid Profile Male	DUE NOW
Med Rec Education	09-Oct-2014 08:52
Tobacco Screen	11-Feb-2017

Lab Orders

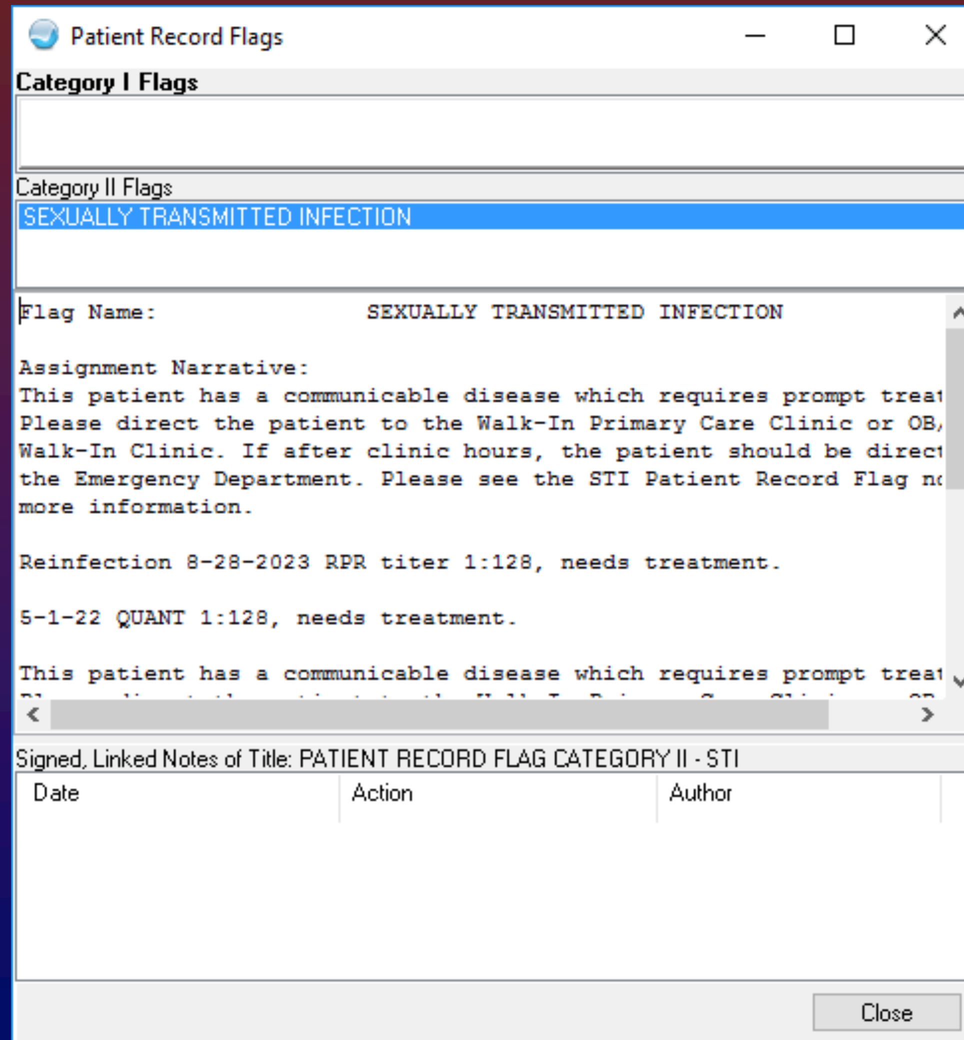
No Lab Orders Found

Triage Summary

…but are not the be all and end all!

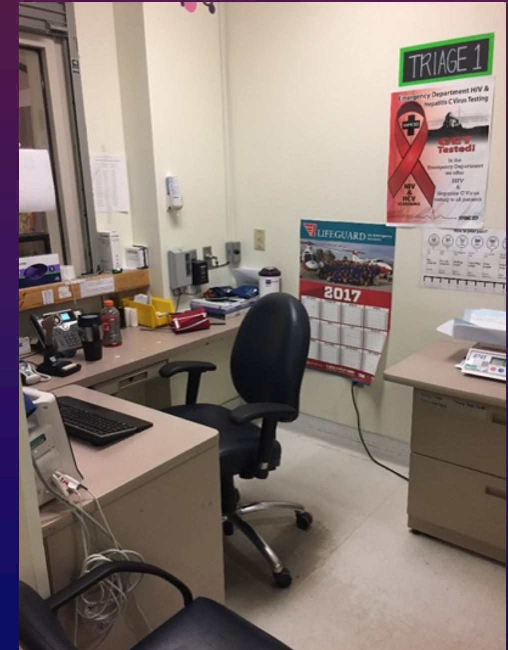


These POP-UP reminders are WAY better!



Screening for STIs outside the office:

- Screen every admission to the hospital, especially the obstetrics ward
- ED/Urgent Care based testing has the highest yield
  - Universal screening is best but challenging
  - Risk-based screening is critical
  - Include the STI bundle into the order templates for
    - Substance use disorder
    - Pregnancy
    - Gastrointestinal bleeding
    - Trauma
    - Mental health crisis
    - STD



Express STI/HIV Testing:

On demand, no provider visit required

1. Lab-based, never see a clinician or nurse
   1. Patients walk directly into lab and request testing
   2. Public Health team follows up on results and treatment

2. Urgent Care testing with no provider visit
   1. Patient signs in to Urgent Care for lab visit only
   2. Telemedicine appointment made to discuss results in 7 days
   3. Patient called in sooner for positive tests to arrange treatment

Testing the community for Syphilis and HIV

- Rapid testing by finger stick assay is optimal off campus
  - Events: Tribal fair, soup kitchens, community pantry, shelters, jails, detox
  - Street Medicine Outreach
  - Partner testing during visits for Field Penicillin treatments for Syphilis
- Getting the word out is the big challenge
  - Advertise on geospatial dating apps
  - Tribal radio and newspapers
  - Social Media

Waiting for business…

Chembio procedure

Test for HIV & Syphilis in 3 Easy Steps with DPP®

FINGERSTICK WHOLE BLOOD

1 Prepare

VENOUS BLOOD

1 Prepare

SNAP!

2 Run

2 drops Sample + Buffer to Well 1

WAIT 5 MINS

4 drops Running Buffer to Well 2

WAIT 10 MINS

3 Read

HIV NON-REACTIVE

HIV REACTIVE

T. pallidum NON-REACTIVE

T. pallidum REACTIVE

INVALID

Read results using the DPP® Micro Reader

Field PCN Injection for patients who can’t or won’t come in for Rx is our IHS standard of care:

- Safe to give at home, at a shelter or jail, on the streets
- Directly Observed Therapy, DOT, is always best and ideal for:
  - Persons experiencing homelessness or substance use disorders
  - Persons who are incarcerated
  - Persons with transportation or adherence issues
  - Pregnant persons
  - Partners of cases

- Make sure you have cell service before giving injection
- Use incentives if available
- OK to give Ceftriaxone for gonorrhea

Take home messages

- Staging is everything in syphilis diagnosis
- Use penicillin whenever possible
- Screen outside the box in innovative places
- Get the penicillin to the patient, not the patient to the penicillin

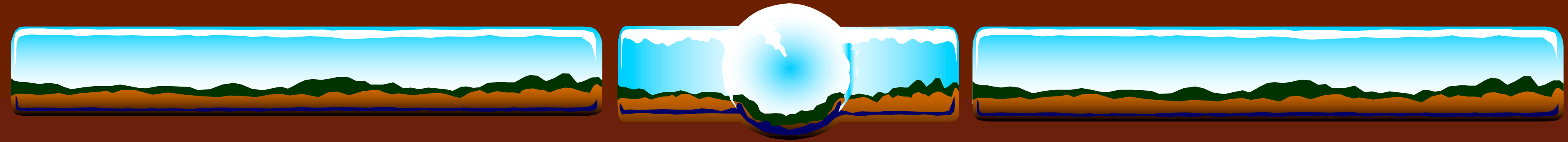
Where to learn more…

- CDC 2021 Treatment Guidelines
  - https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf
- CDC STI App/Wall Chart/quick reference:
  - https://www.cdc.gov/std/treatment-guidelines/provider-resources.htm#MobileApp
- National STI Curriculum (Free CNE)
  - https://www.std.uw.edu

Where to learn more…

- 2023-2024 IHS STI guidance:
  - https://www.ihs.gov/sites/nptc/themes/responsive2017/display_objects/documents/sti/IHS-STI-Guidance.pdf
- IHS Ending the Syndemic Webinar series (IT focused)
  - https://www.ihs.gov/rpms/training/recording-and-material-library/

Thank you IHS PHNs!



Stomp Out Syphilis!!