AETC AIDS Education & Training Center Program Mountain West

OI Guidelines and Pregnancy Considerations: Updates on Tuberculosis, Syphilis, and Mpox

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Project ECHO

Disclosures

Research funding to my institution from Merck (C19 in pregnancy)
Royalties from UpToDate (TB infection in pregnancy topic)

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Disclaimer

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TB Project ECHO®

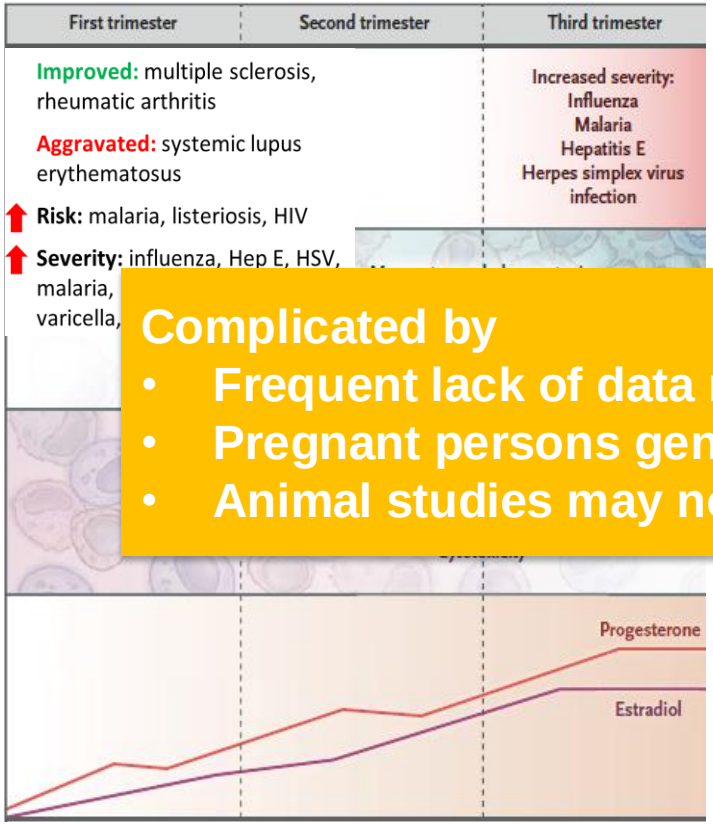
Tuesdays 12:30-1:30 PT

https://doh.wa.gov/you-and-your-family/illness-and-disease-z/tuberculosis-tb/public-health-professionals/tb-echo

Outline

- **Background**
  - OI guidelines: Pregnancy considerations
- **Tuberculosis**
- **Syphilis**
- **Mpox (if time)**

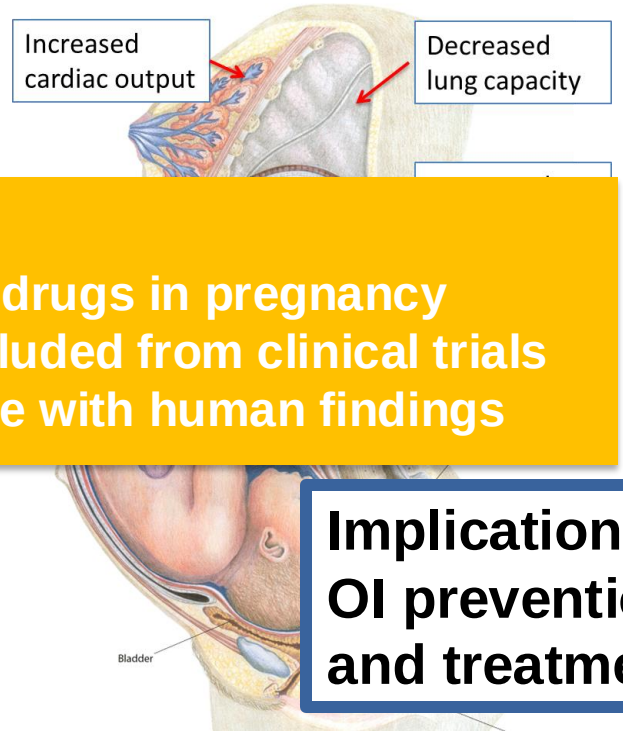
Pregnancy-related immunologic and physiologic changes



Kourtis NEJM 2014

albumin

body fat, total body weight



Frederiksen Sem Perinatol 2001, Anderson Clin PK 2005

Complicated by

- **Frequent lack of data regarding drugs in pregnancy**
- **Pregnant persons generally excluded from clinical trials**
- **Animal studies may not correlate with human findings**

Implications for OI prevention and treatment

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Have you used the HHS OI guidelines for recommendations regarding OI prevention or treatment in pregnant PWH?

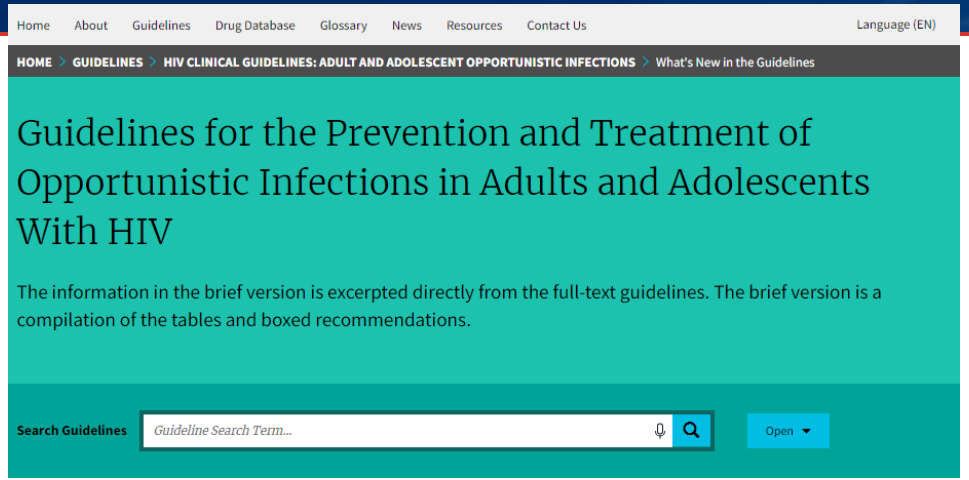
A. Yes

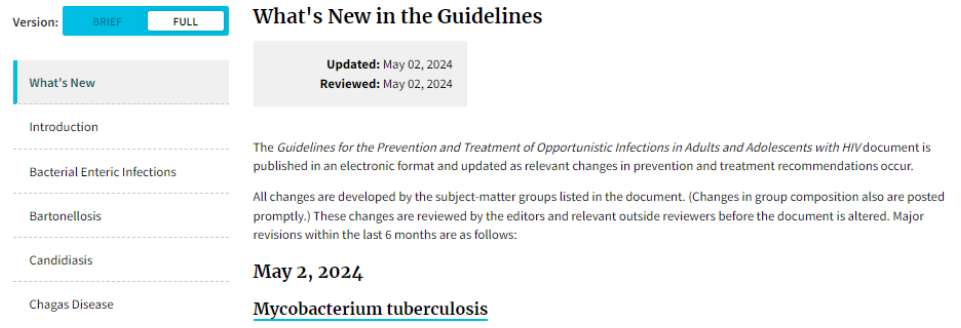
B. No

C. Wait, the HHS OI guidelines include pregnancy considerations?

(Hint: there is no right answer!)

HHS OI guidelines: Pregnancy Considerations





Treatment of TB for Pregnant People

- TB therapy should not be withheld because of pregnancy **(AIII).**
- Treatment of TB disease for pregnant people should be the same as for nonpregnant people, but with attention to the following considerations **(AIII):**
  - Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(BIII).**
  - If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy with isoniazid, rifampin, and ethambutol should be 9 months for drug-susceptible TB **(AII).** The decision regarding whether to include pyrazinamide in treatment regimens for a pregnant person should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.
  - Fluoroquinolones are typically not recommended for pregnant people because arthropathy has been noted in immature animals exposed to fluoroquinolones *in utero* **(CIII).** Fluoroquinolones can, however, be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(BII).**
  - Based on data derived from studies of streptomycin and kanamycin, and the theoretical risk of ototoxicity with *in utero* exposure to amikacin, aminoglycosides should be avoided during pregnancy, if possible (AIII).

TB

Pregnancy Considerations

- Tecovirimat can be used as a first-line antiviral for people who are pregnant, recently pregnant, or breastfeeding **(BIII).**
- In animal studies, cidofovir and brincidofovir have been shown to be teratogenic; therefore, these agents are not recommended for use in pregnancy **(AIII).**

Mpox

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new

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Latent TB infection (LTBI) screening, and treatment for LTBI and TB treatment in pregnant PWH

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Which of the following is **false** regarding TB and pregnant PWH?

A. Isoniazid (INH) given for 6 or 9 months (6H or 9H) is recommended as first line treatment of latent TB infection in pregnant PWH

B. If pyrazinamide is not included, treatment for drug susceptible TB with isoniazid, rifampin, and ethambutol is extended from 6 to 9 months

C. Shorter course regimens to prevent TB disease including 3 months weekly isoniazid and rifapentine (3HP) or 1 month of daily isoniazid and rifapentine (1HP) are recommended for pregnant PWH due to improved tolerability and adherence

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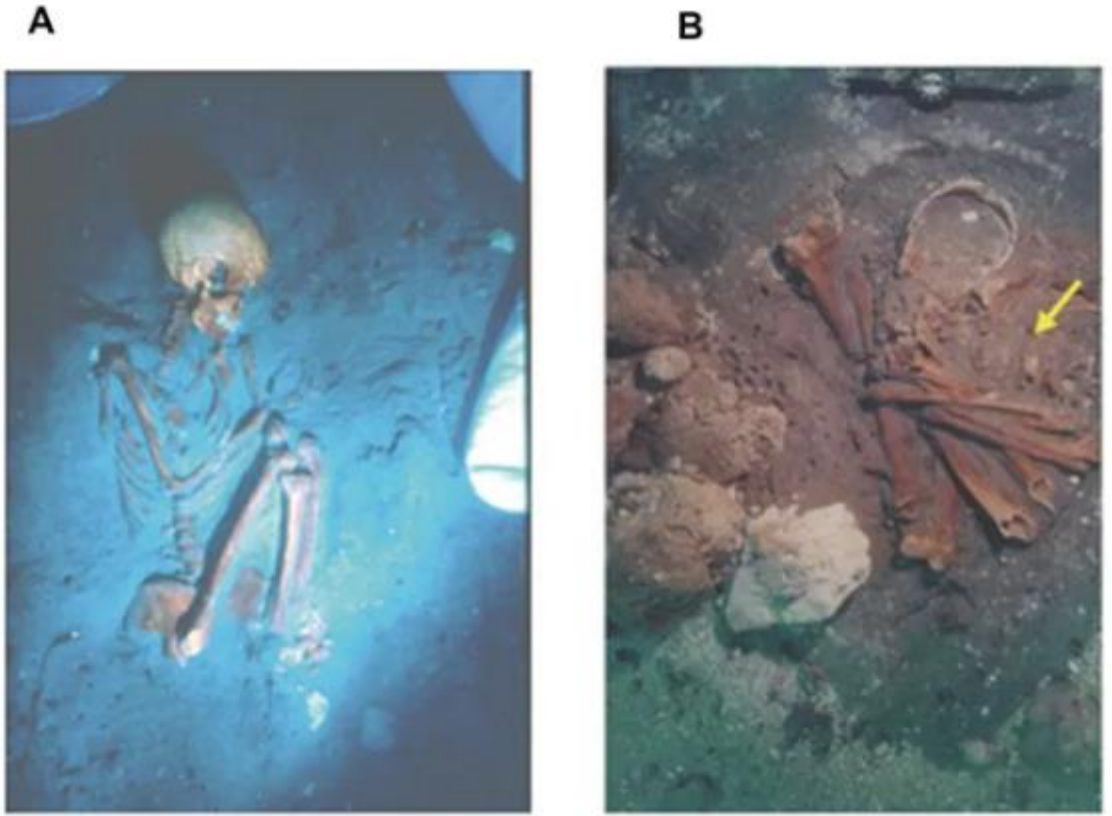
OPEN ACCESS Freely available online

PLOS one

Detection and Molecular Characterization of 9000-Year-Old *Mycobacterium tuberculosis* from a Neolithic Settlement in the Eastern Mediterranean

Israel Hershkovitz[1☯], Helen D. Donoghue[2☯*], David E. Minnikin[3], Gurdyal S. Besra[3], Oona Y-C. Lee[3], Angela M. Gernaey[4¤a], Ehud Galili[5], Vered Eshed[1], Charles L. Greenblatt[6], Eshetu Lemma[6¤b], Gila Kahila Bar-Gal[7], Mark Spigelman[2,6]



An excavated skeleton of a Neolithic woman and an infant buried with her shown underwater. A study revealed signs of tuberculosis on the bones, making them the oldest known TB cases confirmed with DNA, researchers at Tel-Aviv University and University College London say. (Image credit: Tel-Aviv University)

Hershkovitz, PloS One 2008

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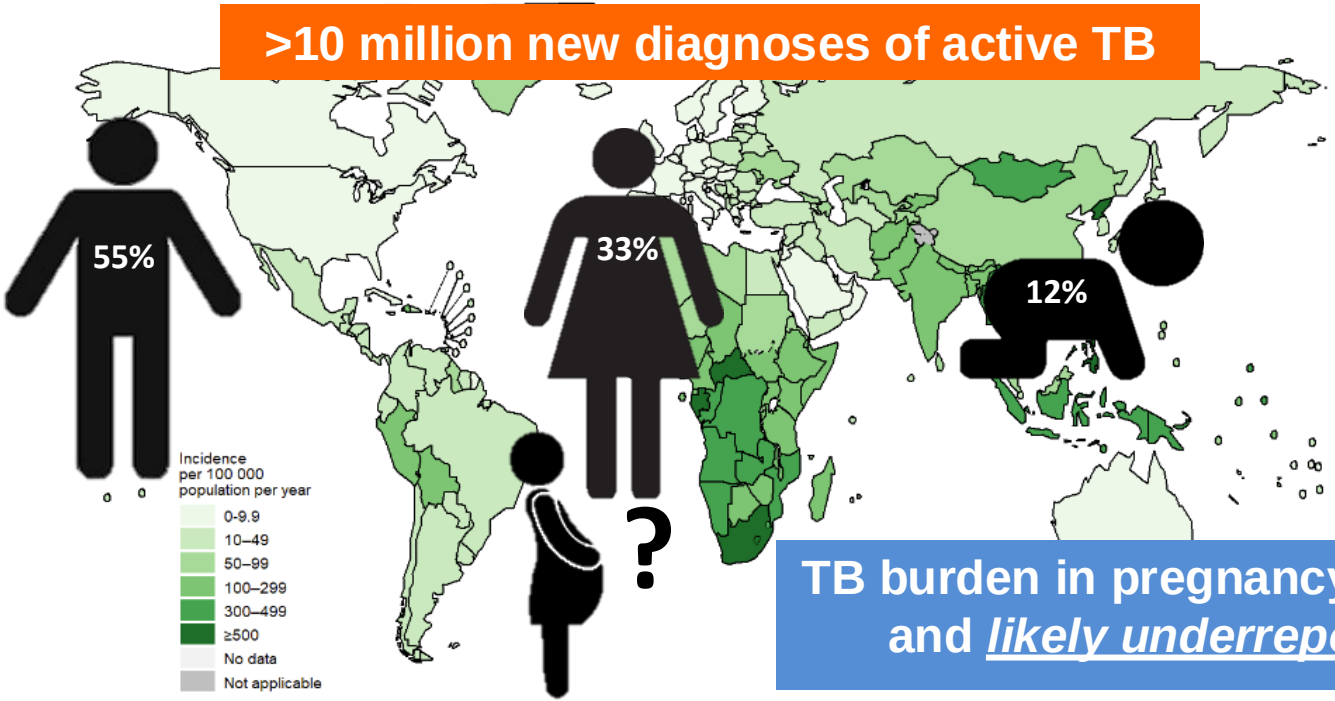
Global TB burden

Estimated TB incidence rates, 2022

>10 million new diagnoses of active TB



TB burden in pregnancy is high, and *likely underreported*

200K per year?

Slide adapted from Jyoti Mathad, Cornell

WHO 2023, Sugarman Lancet Global Health 2014

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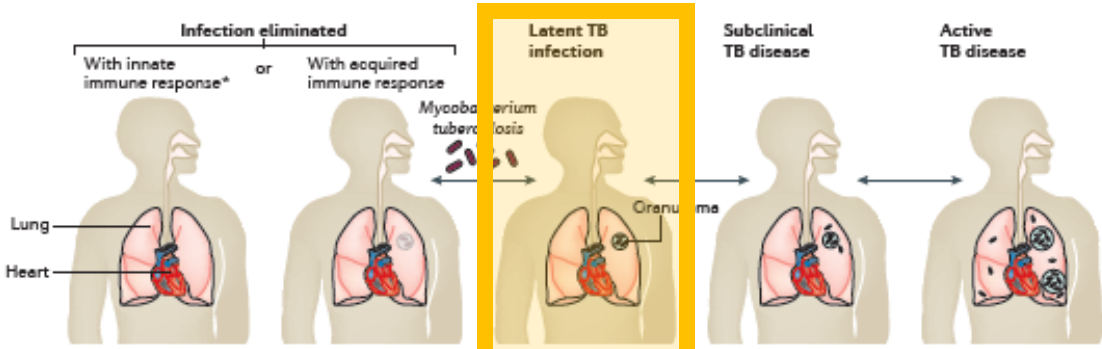
Latent TB infection: persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically active TB

- **No symptoms**
- **Not infectious**

Spectrum of TB
Latent TB infection (LTBI)



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai, Nature Reviews, 2016
Drain, Clin Micro Reviews, 2019

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TB disease:

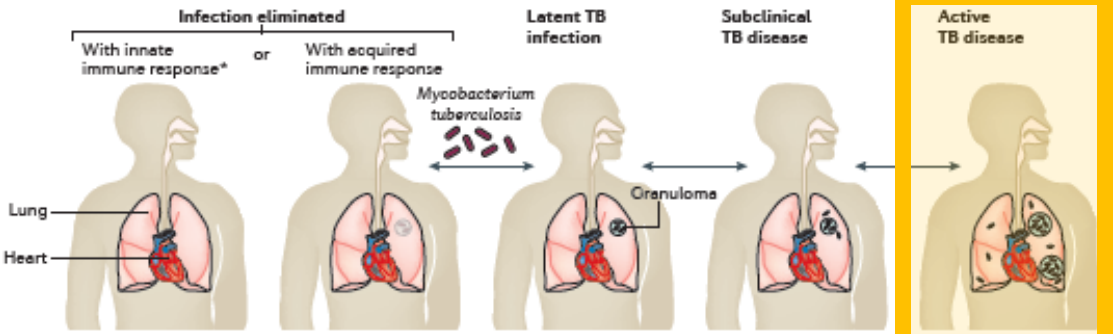
+ symptoms such as cough, fever and weight loss

+ infectious

+ diagnosis often confirmed with sputum smear, culture and molecular tests

Spectrum of TB

TB disease



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Drain, Clin Micro Reviews, 2019
Pai, Nature Reviews, 2016

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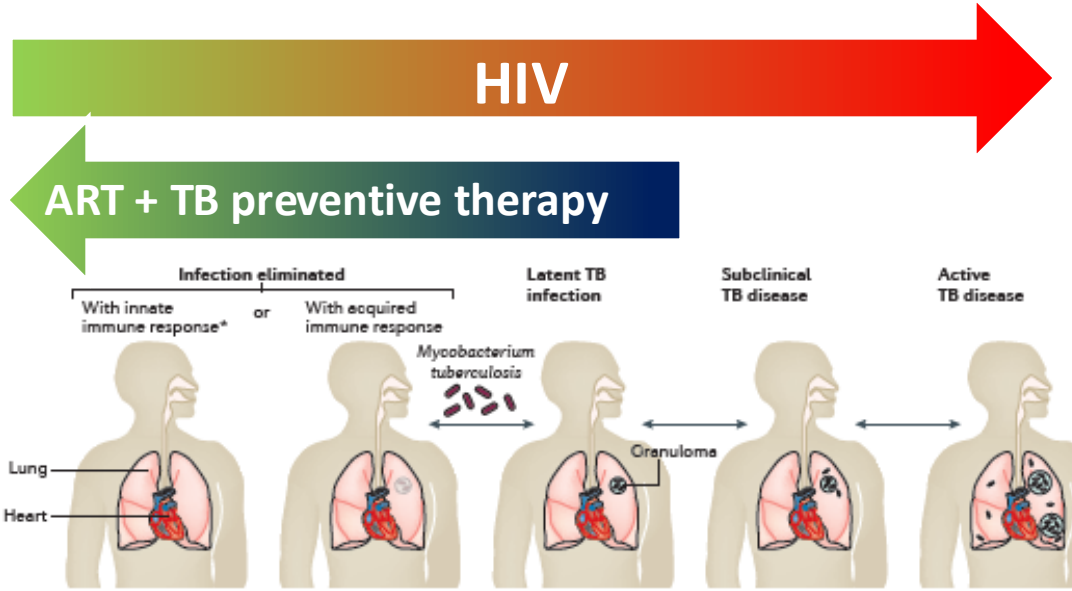
HIV increases risk of progression to TB disease

Both ART and TB preventive therapy reduce progression to TB and mortality



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Mtb = *Mycobacterium tuberculosis*

Drain, Clin Micro Reviews, 2019
Pai, Nature Reviews, 2016

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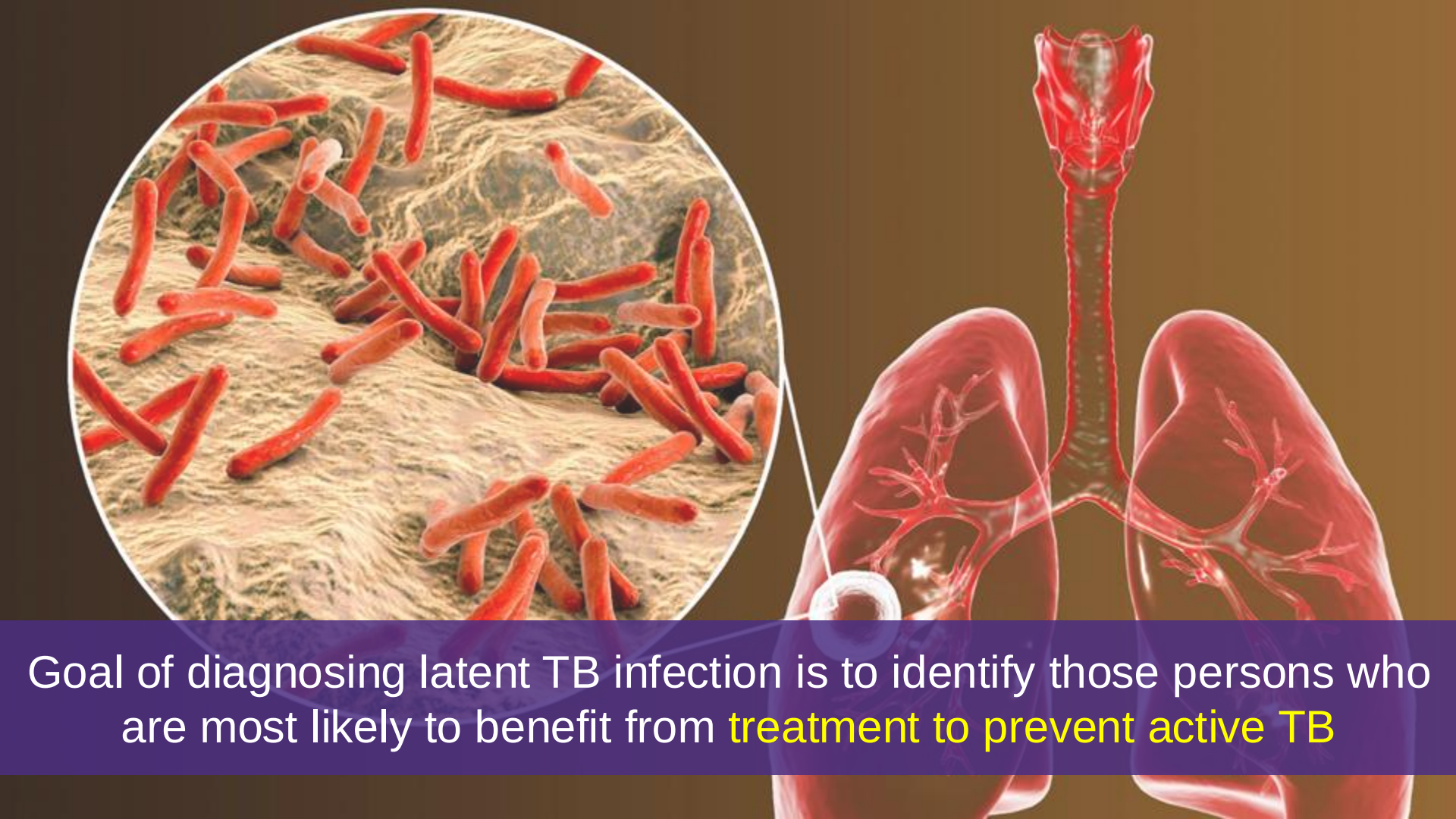

Goal of diagnosing latent TB infection is to identify those persons who are most likely to benefit from treatment to prevent active TB

Screening for LTBI in PWH

Tuberculin Skin Test

Source: CDC

Interferon-Gamma Release Assay

Source: Oxford Immunotec

Pregnancy itself not an indication for screening, though antenatal care may provide opportunity to do so

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Timing of LTBI treatment/TB prevention for pregnant PWH

High burden settings

Pregnant PWH unknown/positive TB infection test (TST/IGRA) treat now regardless of recent TB exposure or TB infection test conversion

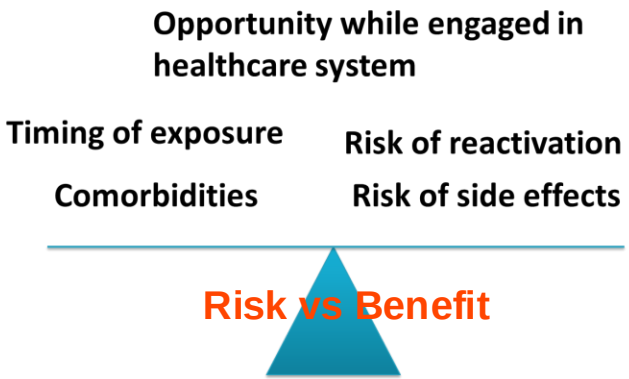
WHO

Low burden settings

Higher risk: recent converter, recent TB contact treat now even 1st trimester

Lower risk: consider waiting after delivery or 2-3 months postpartum

HHS OI guidelines



Source: HHS. Opportunistic Infections Guidelines. *Mycobacterium tuberculosis* Infection and Disease. May 2, 2024.

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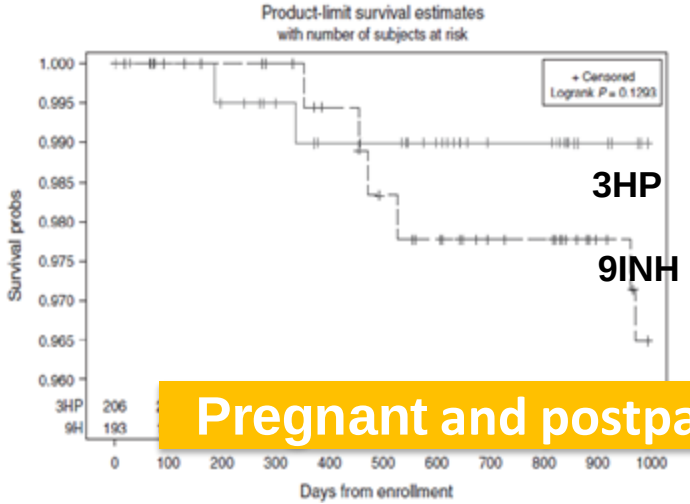
Shorter course regimens for TB prevention for PWH

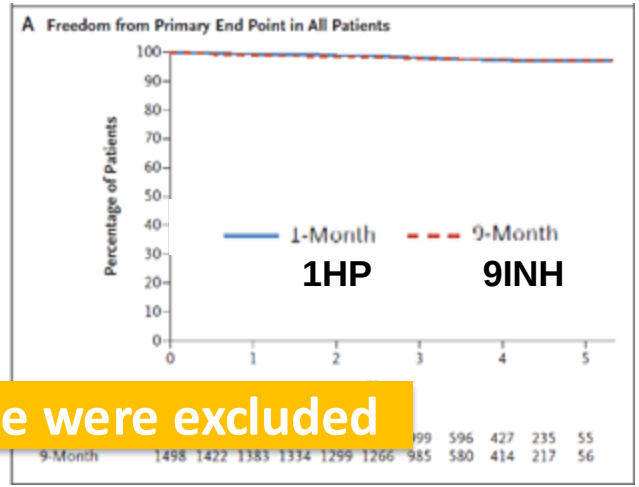
Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV-coinfected persons

AIDS 2016, 30:1607–1615



One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

N ENGL J MED 380;11 NEJM.ORG MARCH 14, 2019



Pregnant and postpartum people were excluded

Both 3HP and 1HP: ↑completion rates, ↓ discontinuation due to side effects

Sterling, AIDS 2016
Swindells, NEJM 2019

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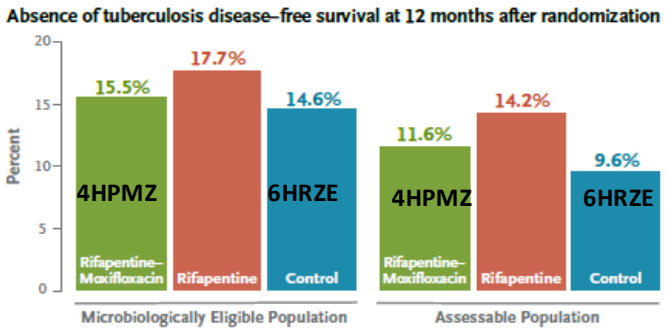
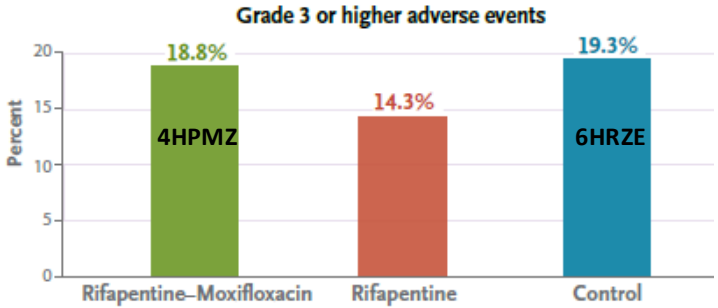
Shorter course regimens for TB treatment including PWH

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis





CONCLUSIONS

A 4-month regimen containing rifapentine and moxifloxacin was noninferior in efficacy and similar in safety and premature discontinuation to a standard 6-month antimicrobial regimen for the treatment of tuberculosis.

CDC and WHO recommend 4HPMZ as an option for adults and adolescents with DS-PTB, including non-pregnant PWH with CD4+ ≥ 100 on EFV ART

Pregnant and postpartum people were excluded

Dorman NEJM 2021, Pettit Clin Infect Dis 2023, Carr MMWR Morb Mortal Wkly Rep. 2022, WHO 2022

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LTBI and TB treatment in pregnant PWH

Latent TB infection treatment

Preferred therapy
6H or 9H (daily x 6 or 9 months)

Alternative therapy
4R (daily x 4 months)
3HR (daily x 3 months)

TB disease treatment

6HRZE (6 months)
Intensive phase: HRZE (x 2 months)
Continuation phase: HR (x 4 months)
or
9HRE (9 months) if pyrazinamide not included

H=isoniazid (INH) R=rifampin/rifabutin Z=pyrazinamide E=ethambutol

Data on rifapentine limited, therefore ***neither 3HP or 1HP are currently recommended for pregnant PWH***

*If **pyrazinamide is not included**, minimum duration of TB therapy with isoniazid, rifampin, and ethambutol should be **9 months for drug-susceptible TB***

Data on rifapentine limited, therefore ***4HPMZ not currently recommended***

Pyridoxine is given with isoniazid to prevent isoniazid-related neuropathy
Dose adjustment or substitution of ART may be needed with rifampin

Source: HHS. Opportunistic Infections Guidelines. *Mycobacterium tuberculosis* Infection and Disease. May 2, 2024.

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Syphilis screening, diagnosis and treatment in pregnant PWH

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Which of the following is **false** regarding screening and treatment for syphilis screening in pregnancy?

A. All pregnant people: screen at the first prenatal encounter with repeat screening at 28 weeks

B. Pregnant person at high risk of infection: repeat screening at 28 weeks and at delivery

C. Any pregnant person who gives birth to a stillborn after 20 weeks of gestation: screen at delivery

D. In the setting of PCN shortage or allergy, doxycycline is recommended to treat syphilis in pregnancy

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Maternal and congenital syphilis rates are significantly increasing

Figure 1. Maternal syphilis rate: United States, 2016–2022

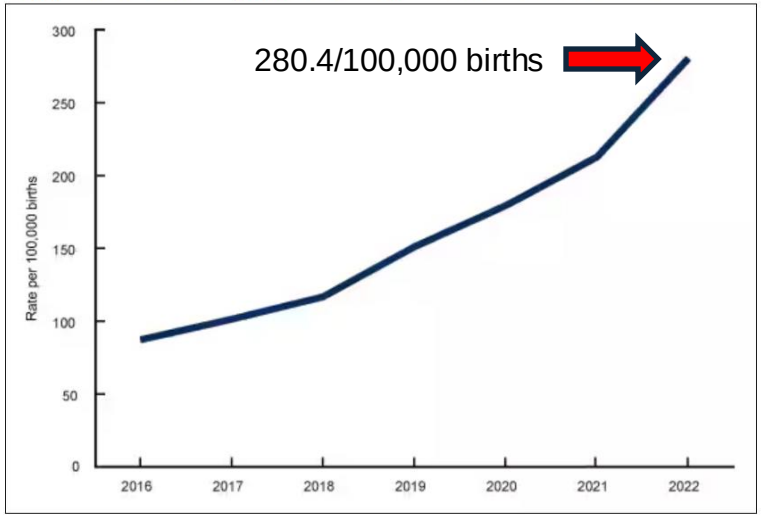
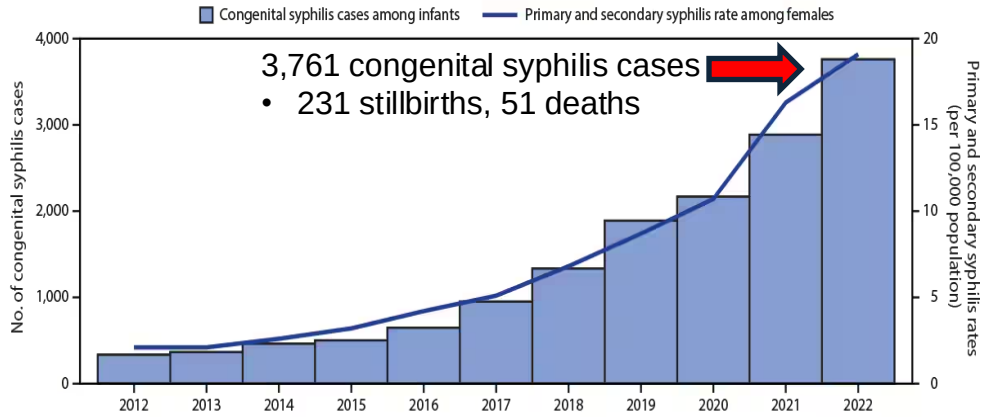


FIGURE 1. Reported number of cases of congenital syphilis among infants, by year of birth, and rates* of reported cases of primary and secondary syphilis† among females aged 15–44 years, by year — United States, 2012–2022



* Cases per 100,000 population.

Syphilis among pregnant people giving birth in US more than tripled 2016-2022

755% increase in US congenital syphilis cases 2012–2021

Source: CDC. NCHS Data Brief No. 496, February 2024. CDC. Vital Signs November 2024

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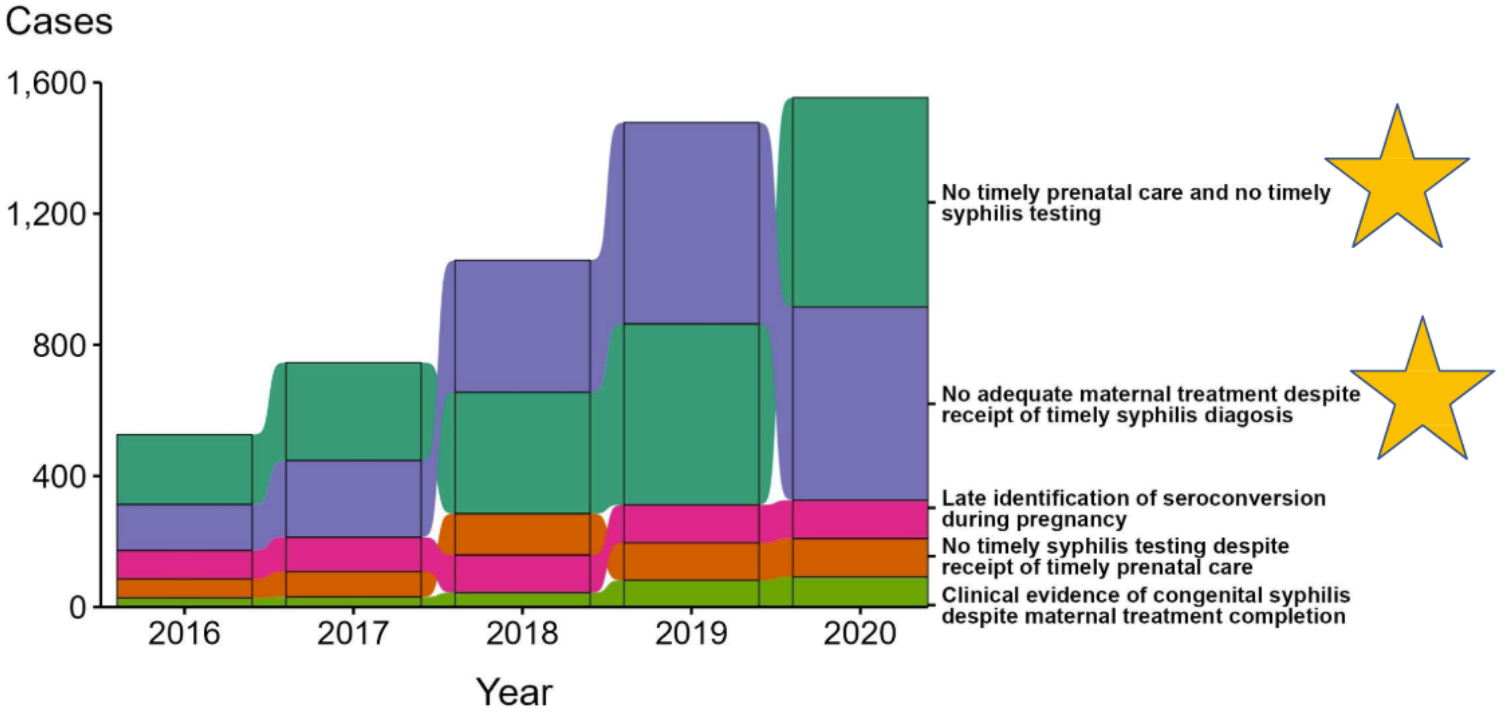
Congenital Syphilis — Missed Prevention Opportunities among Mothers Delivering Infants with Congenital Syphilis, United States, 2016–2020



NOTE: Of the 6,928 congenital syphilis cases reported during 2016 to 2020, 1,566 (22.6%) were not able to have the primary missed prevention opportunity identified due to insufficient information provided to CDC related to maternal prenatal care, testing, or treatment.

Source: CDC. NCHS Data Brief No. 496, February 2024.
CDC. Vital Signs November 2024

Indication for syphilis screening in pregnant PWH

- **All pregnant people**
  - screen at the first prenatal encounter
  - repeat screening at 28 weeks

ACOG recommends universal screening at delivery

- **Pregnant people at high risk for infection** or who have not yet been screened in pregnancy: screen at delivery
- **People who give birth to a still born after 20 weeks gestation**

All pregnant people including PWH should be screened for syphilis

Source: HHS. Opportunistic Infections Guidelines. *Syphilis*. January 2024.
ACOG. Opportunistic Infections Guidelines. *Screening for Syphilis in Pregnancy*. April 2024.

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Preferred treatment of syphilis in pregnant PWH

Penicillin G is the preferred treatment for syphilis in pregnant people including PWH

Pregnant people with penicillin allergy including PWH should be offered desensitization and treated with penicillin G

Source: HHS. Opportunistic Infections Guidelines. *Syphilis*. January 2024.

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Preferred treatment of syphilis in pregnant PWH

Stage	Treatment
Primary, Secondary, and Early Latent Syphilis (<1 year)*	**Benzathine penicillin G** 2.4 million units IM x 1 dose **2nd dose of benzathine penicillin G 2.4 million units IM 1 week after the single dose treatment may be of benefit for congenital syphilis prevention*
Late Latent (>1 year) or Latent of Unknown Duration	**Benzathine penicillin G** 2.4 million units IM weekly x 3 doses
Neurosyphilis (including otic or ocular syphilis)	**Aqueous crystalline penicillin G** 18–24 million units per day: • 3-4 million units IV every 4 hours or • Continuous IV infusion for 10–14 days +/- followed by benzathine penicillin G 2.4 million units IM x 1 dose
Post-exposure prophylaxis**	**Benzathine penicillin G** 2.4 million units IM x 1 dose

Tetracyclines (ex. doxycycline) not generally recommended in pregnancy, especially in 2nd/3rd trimester

** not mentioned in the OI guidelines, but recommended by expert opinion

Source: HHS. Opportunistic Infections Guidelines. *Syphilis*. January 2024.

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Limited role of nonpenicillin regimens to treat syphilis in pregnant PWH (WHO regimens)

Stage*	Treatment
Early syph Secondary Latent (<2	likely)
Late syphil unknown d	

CORRESPONDENCE

Near-Universal Resistance to Macrolides of *Treponema pallidum* in North America

Published June 12, 2024 | N Engl J Med 2024;390:2127-2128 | DOI: 10.1056/NEJMc2314441 | VOL. 390 NO. 22

Neither erythromycin nor azithromycin cross the placenta barrier efficiently and therefore newborn infant treatment is required

*WHO definition

Source: WHO. WHO guidelines for the treatment of Treponema pallidum (syphilis). 2016.
WHO. Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations. 2022.

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Summary recommendations for pregnant PWH

	Tuberculosis	Syphilis
Screening	Universal at HIV care initiation Repeat once CD4 ≥200 **Risk based screening**	**Universal screening in pregnancy** **Targeted screening at delivery**
Treatment	TB infection: **INH preferred for pregnant PWH** TB disease: **if PZA not used as part of HRZE, treatment is extended from 6 to 9 months** *WHO recommends PZA*	**PCN G benzathine preferred** ->Desensitize if allergy • Duration and regimen depends on stage *Limited role for non-PCN where desensitization not possible (WHO)*
Treatment timing	TB infection: risk of progression to disease? • Higher risk: **Recent TBI test conversion or TB contact *treat now*** • Lower risk: **Can consider waiting until *after delivery or 2-3 postpartum*** *High burden settings: Treat now for pregnant PWH unknown/positive TB infection test (WHO)* **TB disease: Do not delay treatment**	**Do not delay treatment**

Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of award 1 TR7HA53202-01-00 totaling $2,982,063 with 0% financed with non-governmental sources.

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