TUBERCULOSIS SCREENING AND TREATMENT IN PREGNANCY

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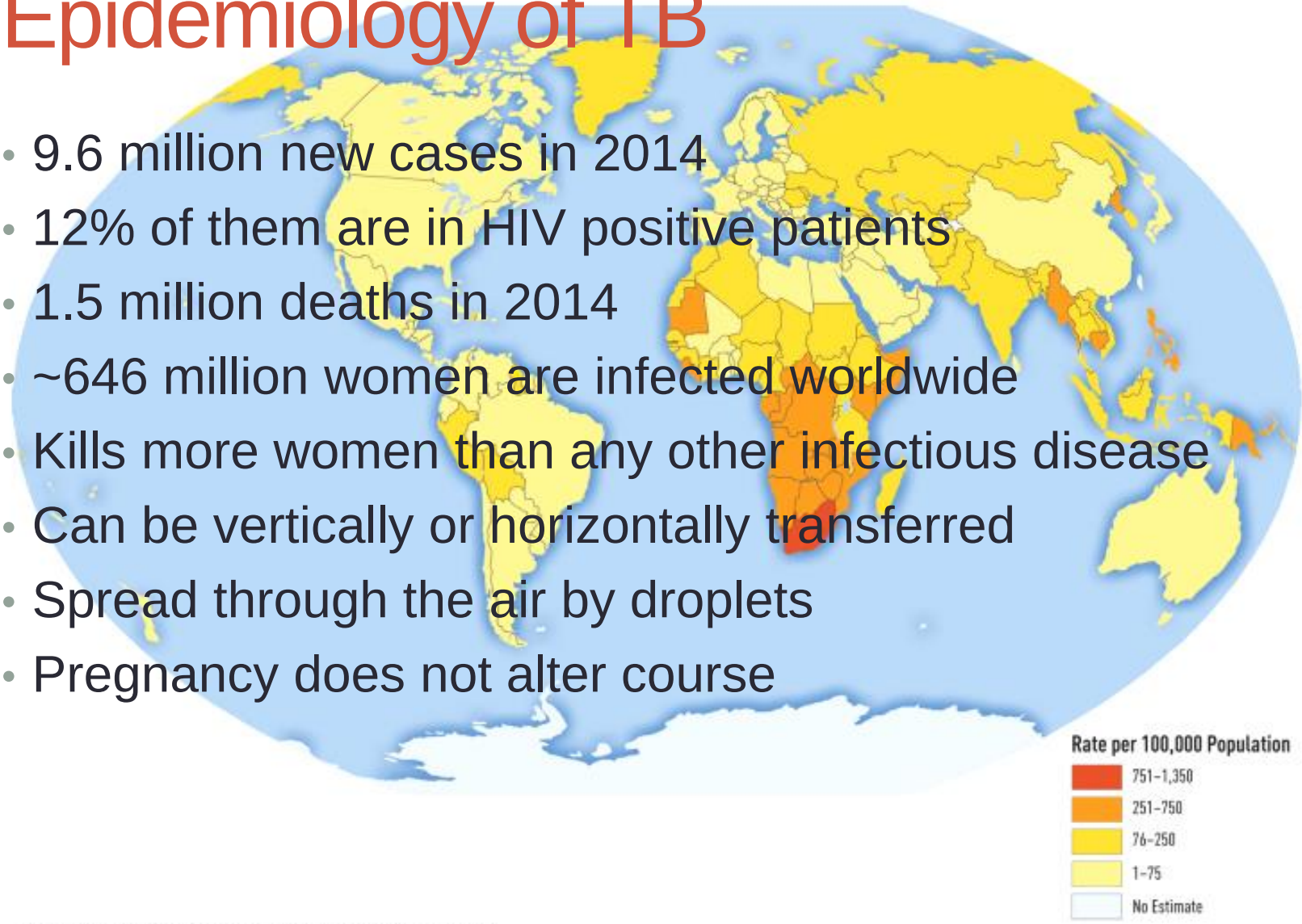
Epidemiology of TB

- 9.6 million new cases in 2014
- 12% of them are in HIV positive patients
- 1.5 million deaths in 2014
- ~646 million women are infected worldwide
- Kills more women than any other infectious disease
- Can be vertically or horizontally transferred
- Spread through the air by droplets
- Pregnancy does not alter course



MAP 3-13. ESTIMATED TUBERCULOSIS INCIDENCE RATES[1]

[1] Disease data source: World Health Organization. "Global Tuberculosis Report 2013" at http://www.who.int/tb/country/data/download/en/. Accessed June 23, 2014.

TB in the United States

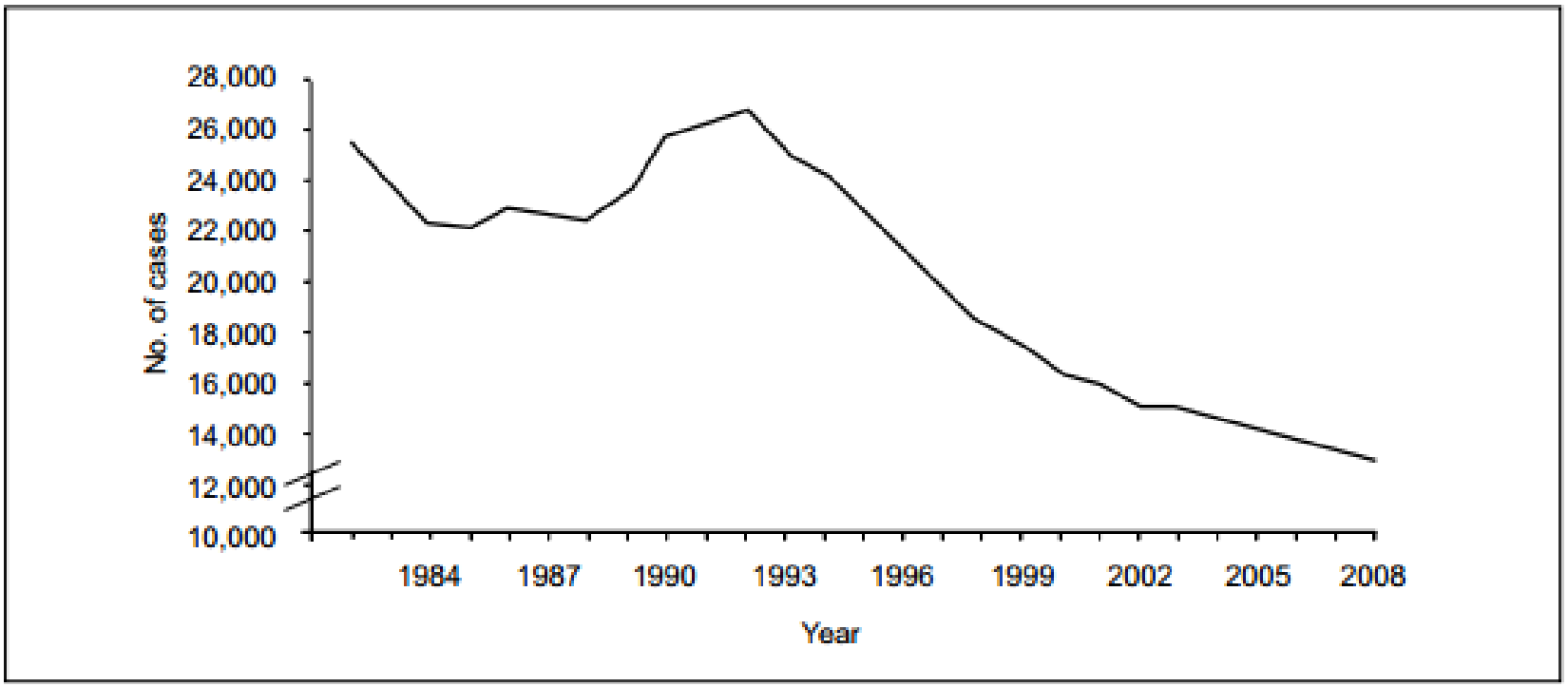


Figure 1 Reported TB cases in the USA for 1982–2008[9]

Who is at risk?

- HIV positive patients
- Close contact with persons known or suspected to have tuberculosis
- Medical risk factors known to increase risk for disease if infected
  - E.g. Immunocompromised, on TNF blockers
- Recent immigrants from TB endemic areas
- Low income
- IV Drug Use
- Alcohol addiction
- Residency in a long-term care facility (e.g. correctional institution, mental institution, nursing home)
- Health professionals working in high-risk health care facilities

Signs/Symptoms of Active TB

- Cough (74%)
- Weight loss (41%)
- Fever (30%)
- Malaise and fatigue (30%)
- Hemoptysis (19%)
- Abnormal CXR
  - Adenopathy
  - Multinodular infiltrates
  - Cavitation
  - Loss of volume in upper lobes
  - Upper medial retraction of hilar markings
  - **HIV infected patients can have normal CXR**

Extrapulmonary TB

- Occurs in 16% of cases
- Occurs in up to 60 to70% of AIDS patients with TB
- Can affect
  - Lymph nodes
  - Bone
  - Kidneys
  - Intestine
  - Meninges
  - Breasts
  - Endometrium
- Rare in pregnancy

Latent TB

- Positive PPD or blood test
- Asymptomatic
- Not infectious
- Negative CXR
- Negative Sputum Cultures
- Without treatment only 5 to 10% of HIV negative patients will progress to active disease (most likely to occur within 2 years of infection)
- 50% of HIV positive patients develop active disease within 2 years of infection
- 5-10% of patients with TB who acquire HIV will develop active disease each year

Screening Tests

- PPD (Mantoux Tuberculin Skin test)
- Interferon-Gamma Release Assays (IGRAs)
  - QuantiFERON® – TB Gold In-Tube test (QFT–GIT)
  - SPOT® TB test (T–Spot)

PPD (Tuberculin Skin Test)

www.mayomedicallaboratories.com

- Tuberculin injected subcutaneously
- Delayed hypersensitivity reaction
- Must be read 48 to 72 hours later
- Requires two visits
- Measure induration (not erythema)
- Positive test is induration >5 to 15 mm depending on population

Cutoffs for Positive PPD

≥ 5mm	≥ 10 mm	≥ 15 mm
HIV positive individuals	Recent immigrants (< 5 years) from high-prevalence countries	Considered positive in anyone
Recent contact of a person with active TB	Injection drug users	
Fibrotic changes on CXR consistent with prior TB	Residents and employees of high-risk congregate settings	
Patients with organ transplants	Mycobacteriology laboratory personnel	
Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-a antagonists)	Persons with clinical conditions that place them at high risk	
	Children < 4 years of age	
	Infants, children, and adolescents exposed to adults in high-risk categories	

Causes of False Positive or Negative PPD

False Positive	False Negative
Infection with non tuberculosis mycobacterium	Weakened immune system and impaired cellular reactivity
Previous BCG Vaccination	Recent TB infection within 8 to 10 weeks of exposure
Technical Factors • Improper Storage • Improper placement • Improper Interpretation	Very old TB infection
	Very young age < 6 months
	Recent live virus immunization
	Overwhelming TB disease
	Some Viral illnesses
	Technical Factors

Modified from: http://www.mayomedicallaboratories.com/articles/communique/2010/01.html

Interferon Gamma Release Assays

- QuantiFERON® – TB Gold In-Tube test (QFT–GIT)
- SPOT® TB test (T–Spot)
- Measure immune reactivity to *M. tuberculosis*
- Interferon gamma released from white blood cells in patients with *M. Tuberculosis* infection when mixed with *M. tuberculosis* antigens
- Advantages
  - Single blood draw
  - Does not require second visit for interpretation
  - Results available in 24 hours
  - Prior BCG does not affect results
- Disadvantages
  - Expensive
  - Blood samples must be processed within 8-30 hours after collection while white blood cells are still viable
  - Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRA

	Specificity (%)	Sensitivity(%)	Affected by BCG Vaccine	Mechanism
PPD	97*	77**	Yes	Measures amount of skin induration based on cutaneous delayed-type hypersensitivity response to purified protein derivative
T-SPot	93ŧ	90ŧ	No	Measures the number of IFN_{γ} producing T cells in reaction to the antigens ESAT-6 and CFP-10 produced by MTB and not in the BCG vaccine
QFT–GIT	96ŧ	70ŧ	No	Measures the IFN_{γ} produced by T cells in reaction to the antigens ESAT-6 and CFP-10 produced by MTB, and not in the BCG vaccine

BCG, Bacille Calmette-Guerin; ESAT-6, early secretory antien target-6; CFP-10, culture filtrate protein 10; MTB, *Mycobacterium tuberculosis*; IFN, interferon
*in non-BCG vaccinated individuals **From Pai et al. ŧFrom Lalvani et al

Which Test to Choose

- PPD
  - Children < 5 years old
- IGRA
  - Prior BCG Vaccine
  - Patient who is unlikely to return for PPD reading

Diagnostic Tests

- Culture for M. Tuberculosis
  - Sputum
  - Bronchoaveolar lavage
  - Gastric lavage
  - CSF
  - Urine
- Tissue biopsy
- Must be performed by experienced lab
- Negative test does not rule out infection
- Can take up to 6 to 8 weeks to get results

BCG Vaccine

- Bacille Calmette-Guerin
- Vaccine for TB
- Live vaccine made from mycobacterium bovis
- Used to prevent childhood tuberculous meningitis and miliary disease
- Has variable effectiveness against pulmonary TB
- Recommended for children in endemic areas
- Recommended for children exposed to active TB

BCG Vaccine and Screening Tests

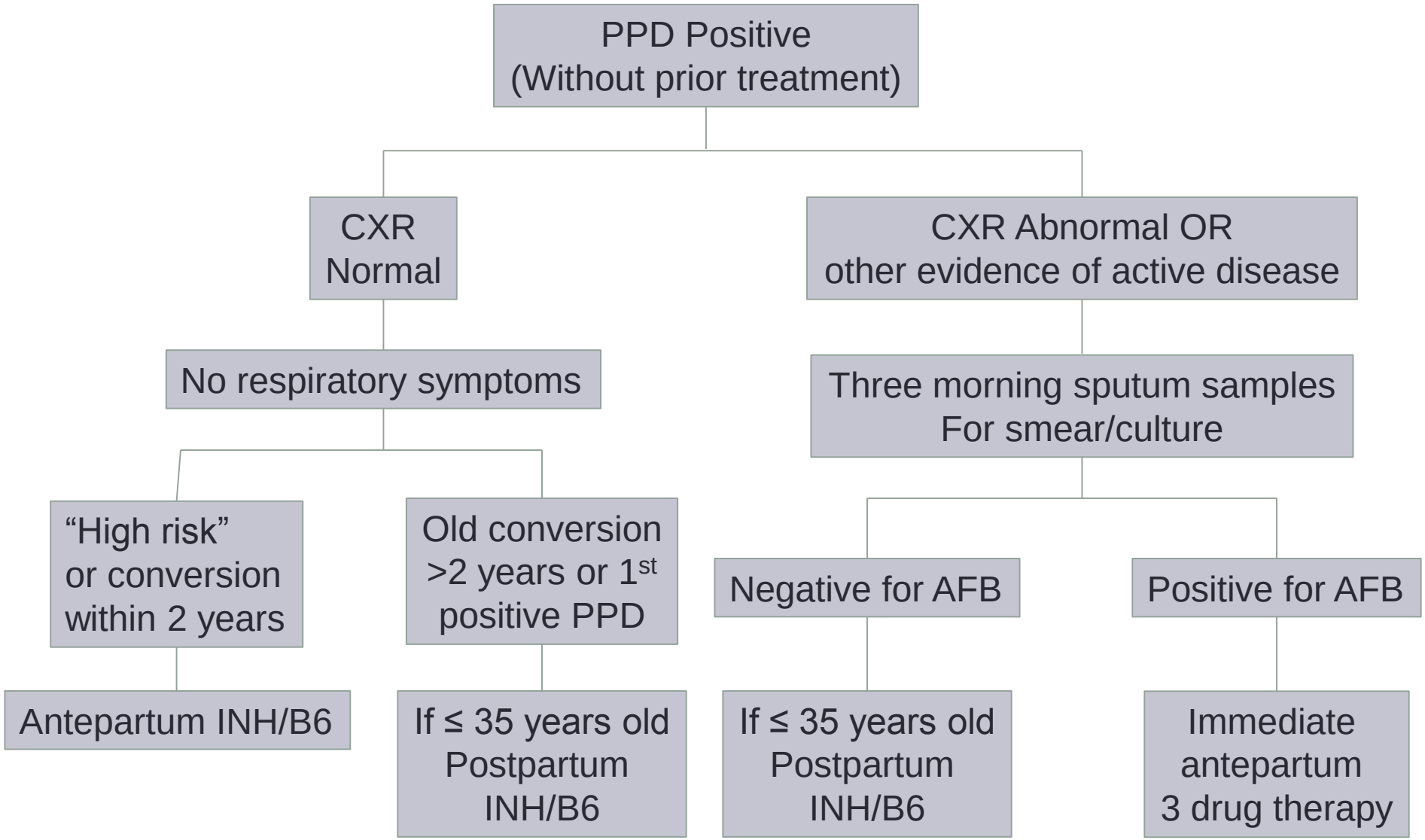
- CAN still screen with PPD
  - Can cause false positive, most likely in those recently immunized
  - If >10 years since BCG vaccine assume infected with TB if positive PPD
- QuantiFERON® – TB Gold In-Tube test (QFT–GIT)
  - Not affected by BCG vaccine
- SPOT® TB test (T–Spot)
  - Not affected by BCG vaccine

Who to Screen (ACOG)

- **ONLY screen women at high risk of tuberculosis**
- Known HIV infection
- Close contact with individuals known or suspected to have TB
- Medical risk factors known to increase risk of disease if infected
  - Diabetes
  - Lupus
  - Cancer
  - Alcoholism
  - Drug Addiction
- Birth in or emigration from high-prevalence countries
- Medically underserved
- Homelessness
- Living or working in long term care facilities such as correctional institutions, mental health institutions and nursing homes

Positive Result—Now what?

- Suspect active TB
  - Chest X-ray
  - Sputum culture x3
  - If evidence of active TB treat during pregnancy
- Suspect latent TB
  - Chest X-Ray
  - Consider treatment during pregnancy in those at high risk for conversion
  - When to treat controversial in those not at high risk for conversion



Modified from Creasy & Resnik

Standard Treatment Active TB

- CDC
  - Isoniazid (10mg/kg daily, up to 300mg)*
  - Rifampin (10mg/kg daily, up to 600 mg)
  - Ethambutol (15mg/kg daily, up to 2.5 grams)
  - 3 Drug regimen x 2 months followed by INH and Rifampin x 7 months
- WHO
  - Isoniazid (10mg/kg daily, up to 300mg)*
  - Rifampin (10mg/kg daily, up to 600 mg)
  - Pyrazinamide (15-30mg/kg, up to 2 grams)
  - Ethambutol (15mg/kg daily, up to 2.5 grams)
  - 4 Drug regimen x 2 months followed by INH and Rifampin x 4 months

*Pyridoxine 25 to 50mg daily should be given with INH

Treatment for Latent TB

Treatment	Dosing
Isoniazid (INH) + B6	300mg INH Daily + 50 mg B6 x 9 months (Preferred) 300mg INH Daily + 50mg B6 x 6 months 900mg INH Twice weekly + 50mg B6 x 9 months* 900mg INH Twice weekly + 50mg B6 x 6 months*
Rifampin	600mg daily x 4 months

*Twice weekly therapy should be given as directly observed therapy
B6 (25mg to 50mg daily) given to prevent peripheral neuropathy, should be given to infants of breastfeeding mothers
Modified from UptoDate

Drug Toxicity

- Isoniazid
  - Hepatitis
  - LFT's should be checked prior to starting therapy
  - Monitor LFT's during treatment
  - Pregnancy increases risk of hepatotoxicity
  - Screen for other Hep B, C and HIV
  - Stop treatment if asymptomatic and LFT's 5x normal
  - Stop treatment if symptomatic and LFT's 3 x normal
  - Other side effects include rash and neuropsychiatric symptoms
  - Peripheral neuropathy (Supplement with B6)
- Rifampin
  - Orange discoloration of secretions and urine
  - Hepatitis, Nausea, vomiting

Drug Toxicity (Continued)

- Ethambutol
  - Optic neuritis
  - Rash
- Pyrazinamide
  - Hepatotoxicity
  - Hyperuricemia
  - Arthralgias
  - Rash

Contraindicated Drugs in Pregnancy

- Streptomycin
  - Causes ototoxicity
- Kanamycin
  - Auditory, vestibular and nephrotoxicity
- Amikacin
  - Concern for ototoxicity and nephrotoxicity
- Capreomycin
  - Teratogenic in animals
  - No human data
- Fluoroquinolones
  - Affects cartilage development

Multidrug Resistant TB (MDR TB)
Extensively Drug Resistant TB (XDR TB)

- MDR TB
  - Resistant to INH
  - Resistant to Rifampin
- XDR TB
  - Resistant to INH
  - Resistant to Rifampin
  - Resistant to a fluoroquinalone
  - Resistant to amikacin, kanamycin or capreomycin

Breastfeeding

- Not contraindicated if mother is being treated
- Infant of mother receiving INH should receive B6 supplementation
- Breastfeeding not recommended if on Rifabutin or fluoroquinalones

QUESTIONS?

References

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  - http://www.cdc.gov/tb/publications/ltbi/treatment.htm
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  - http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf
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