Treatment of Latent TB Infection (LTBI)

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Pre-Treatment Evaluation

Before initiating treatment for LTBI:

- **Rule out TB disease**
  - Wait for culture result if specimen obtained
  - Assess/evaluate for symptoms
- **Determine prior history of treatment for LTBI or TB disease**
- **Assess risks and benefits of treatment**
  - Active liver disease
- **Ascertain current and previous drug therapy and side effects**

Initiating Treatment: Patient Education

- Counsel and educate patient
  - Discuss patient's risk for progressing to TB disease
  - Emphasize benefits of treatment
  - Assess whether patient willing to be treated for full treatment period
- Review common side effects
- Establish treatment plan

Baseline Medical Evaluation

- **Medical history**
  - History of TB or HIV treatment
  - TB exposure
  - Risks for drug toxicity
    - e.g., alcoholism, liver disease, pregnancy
  - Complete medication list
- **Chest x-ray**
  - Rule out TB disease
- **Laboratory tests**
  - CBC and chemistry panel, if indicated
  - 3 sputum samples for AFB smear, culture, & DST if TB symptoms or findings on chest x-ray

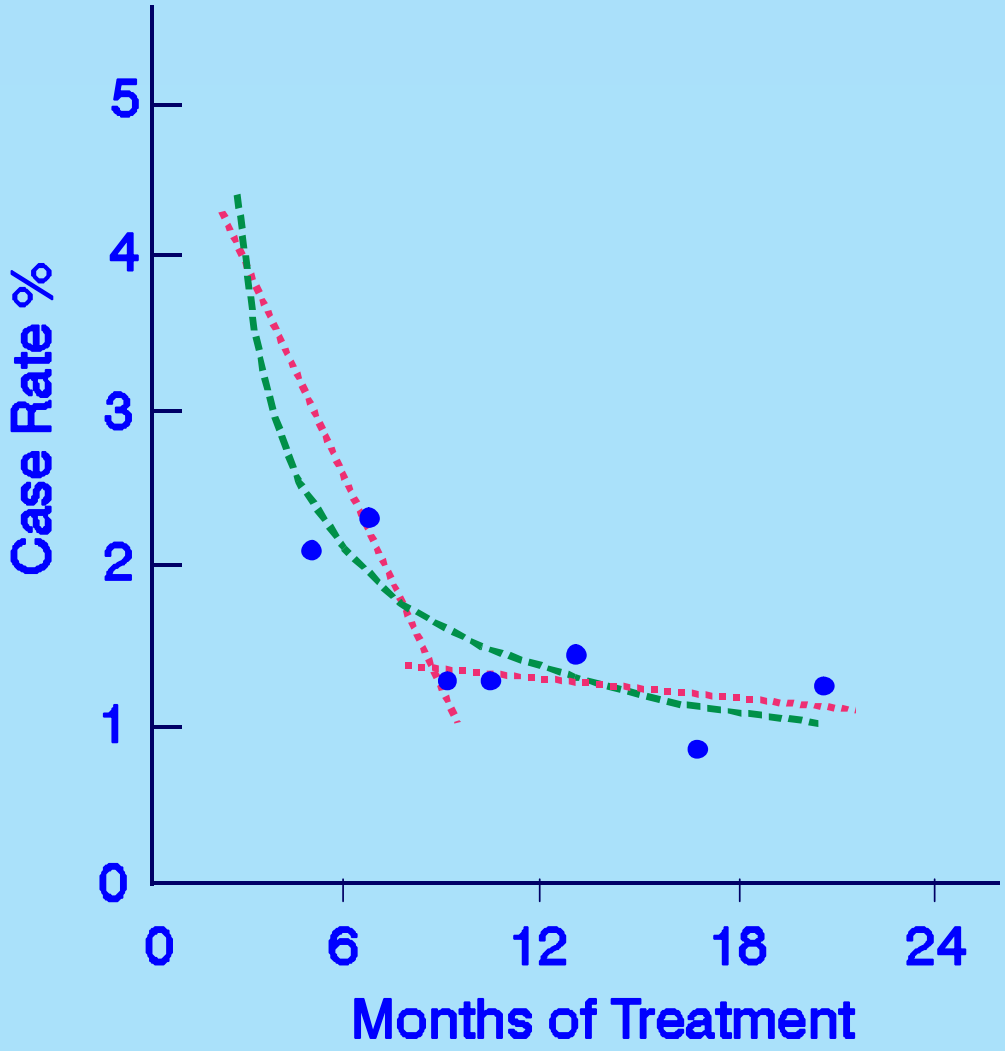
Treatment Regimens for LTBI

Drugs	Months of Duration	Interval	Minimum Doses
INH	9*	Daily	270
		2x wkly**	76
INH	6	Daily	180
		2x wkly**	52
RIF	4	Daily	120

*Preferred ** Intermittent treatment only with DOT

INH=isoniazid; RIF=rifampin

How Much INH Needed for Prevention of TB?



- **Longer duration corresponded to lower TB rates if took 0 – 9 mos.**
- **No extra increase in protection if took > 9 mos.**

Comstock GW, Int. J Tuberc Lung Dis 1999; 3:847-50

Isoniazid Regimens

Regimen	Doses	Ideal Duration	Complete Within	
Daily	**270**	**9 months**	**12 months**	
Twice weekly*	**76**	**9 months**	**12 months**	
Daily	**180**	**6 months**	**9 months**	**Avoid: HIV infected, fibrotic lesion on CXR, children**
Twice weekly*	**52**	**6 months**	**9 months**	

via Directly Observed Therapy

Rifampin Regimens

- **Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible**
  - INH resistant or intolerant
  - Patient unlikely to be adherent for longer treatment period
- **In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted**
- **Children should receive 6 months**
- ~~**RIF + PZA for 2 months**~~

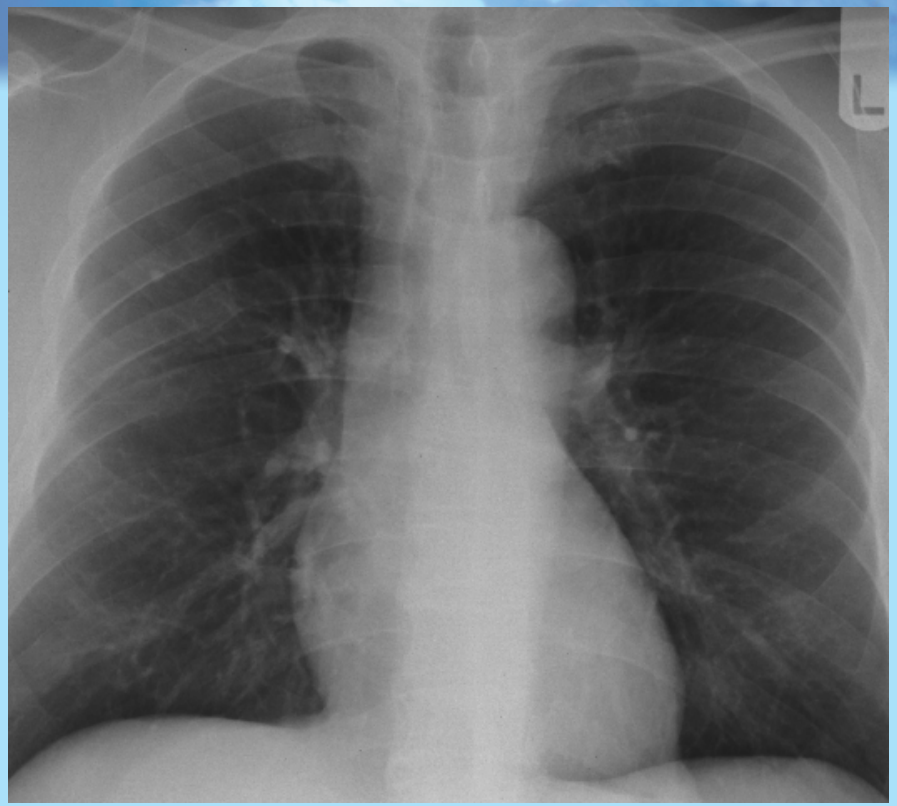
Special Situations – 1

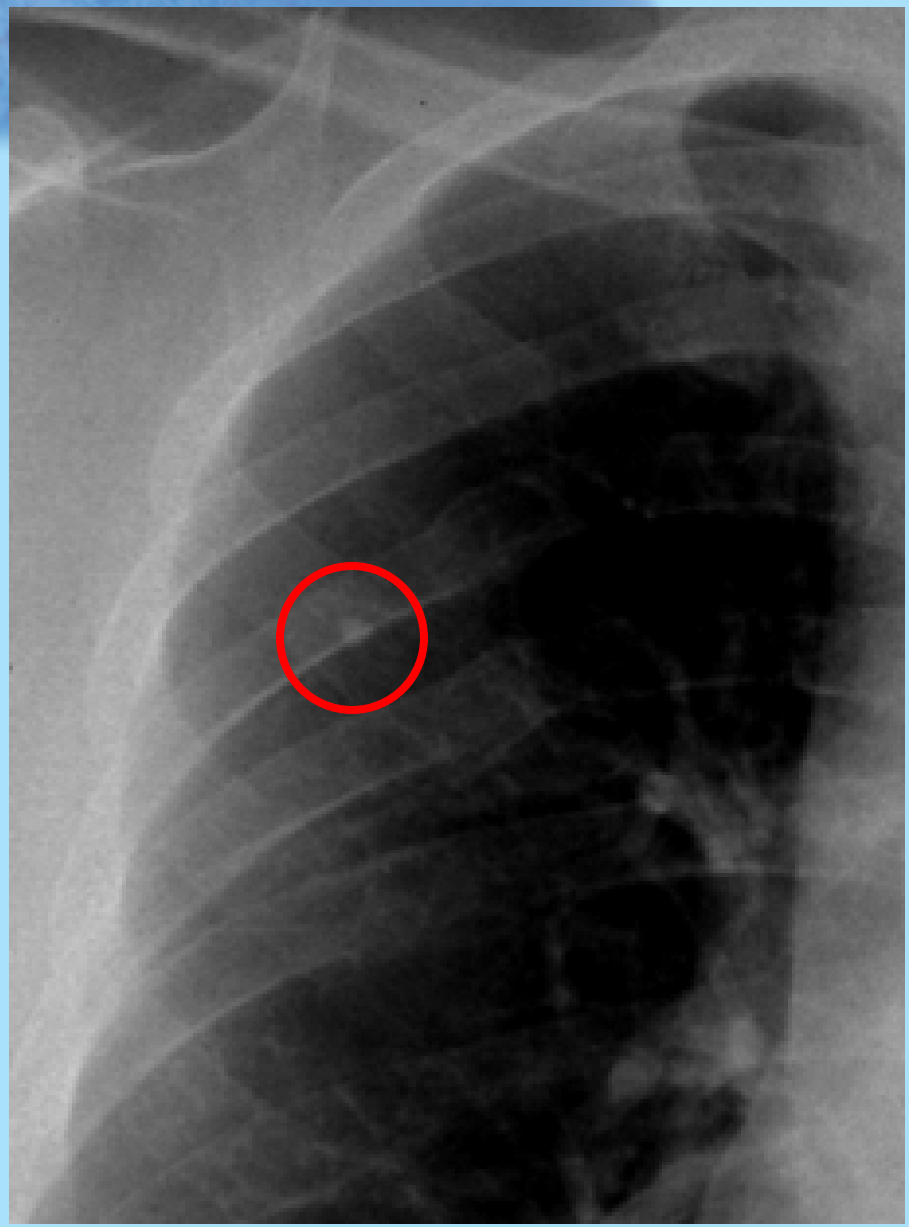
- **Children and adolescents (<18 years old):**
  - 9 mo INH
  - 6 mo RIF
- **Pregnant women:**
  - INH preferred
  - May defer past the early post-partum period, except for HIV-infected women & recently infected with *M. tb*

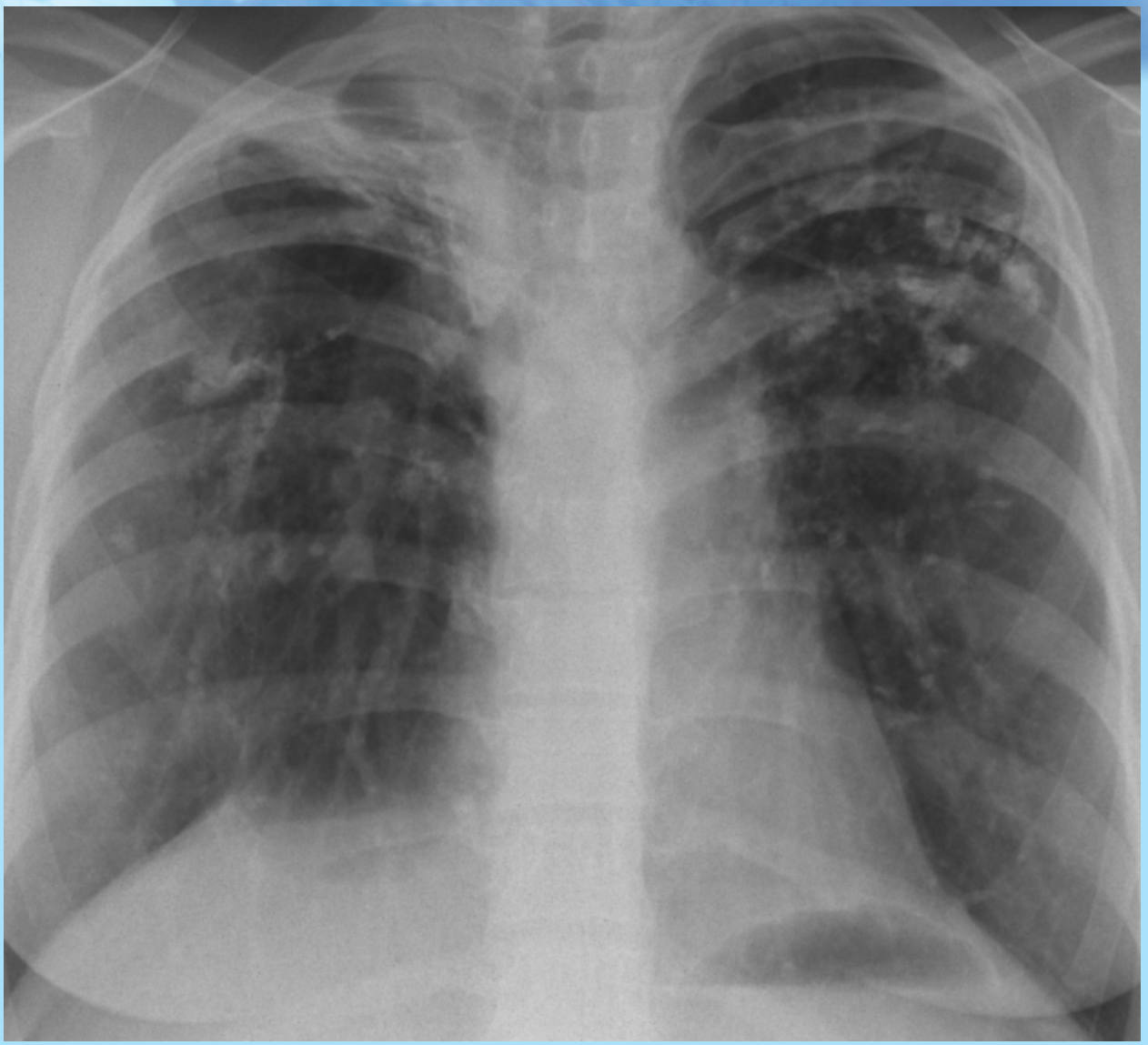
See lecture on pediatric TB

Special Situations – 2

- **CXR consistent with old TB:**
  - i.e. Fibrotic lesion consistent with untreated TB disease
  - TST reaction 5mm or greater
  - In addition to standard LTBI regimens, some prefer INH + RIF for 4 months, after ruling out active disease
- **CXR with evidence of old healed primary TB:**
  - i.e. Calcified solitary pulmonary nodule, apical pleural capping, calcified hilar lymph node
  - Not at increased risk of developing TB disease
  - Use other risk factors and appropriate TST size to determine treatment with standard regimen







Special Situations – 3

- **Persons exposed to INH-resistant TB:**
  - 4 mo RIF - adults
  - 6 mo RIF - children
- **Persons likely infected with multidrug-resistant TB:**
  - 6-12 mo PZA and EMB, or PZA and quinolone (i.e., ≥ 2 drugs to which organism is susceptible)

See lecture on MDR-TB

LTBI Treatment for HIV-Positive Individuals

- **HIV-positive patients in close contact to infectious TB should receive treatment for LTBI regardless of age, TST results or history of previous treatment for LTBI**
- **If Rifampin contraindicated (i.e. protease inhibitor), should receive Rifabutin**

See lecture on TB/HIV co-infection

LTBI and Tumor Necrosis Factor-alpha Inhibitors

- **TNF alpha is a pro-inflammatory cytokine, often implicated in autoimmune diseases**
- **Necessary for host response to mycobacterial infections**
- **TNF alpha blockers increasingly used for Rheumatoid Arthritis, Inflammatory Bowel Disease, Psoriatic arthritis, Ankylosing Spondylitis**
- **One of the major complications is reactivation of *M.tb***

LTBI and TNF alpha inhibitor: Management

- **Rigorous screening for TB risk factors (e.g. country of origin, exposure, radiographic evidence of prior TB) prior to TNF alpha blocker**
- **Can use multiple modalities to increase sensitivity of recognizing LTBI (TST, IGRA, CXR)**
- **LTBI treatment is effective**
- **Concurrent LTBI treatment and TNF alpha inhibitor initiation is generally accepted**
- **Consider periodic re-testing**

Prioritizing treatment based on reactivation risk

Table 1. Annual Risk of Reactivation Tuberculosis.*

Size of Induration on Tuberculin Skin Test	Age				
	0–5 Yr	6–15 Yr	16–35 Yr	36–55 Yr	≥56 Yr
	percent (95 percent confidence interval)				
Persons with nonconversion positive result					
5–9 mm	0.06 (0.03–0.11)	0.04 (0.03–0.06)	0.12 (0.05–0.32)	0.07 (0.03–0.19)	0.07 (0.03–0.16)
10–14 mm	0.19 (0.12–0.28)	0.08 (0.06–0.11)	0.15 (0.08 –0.29)	0.10 (0.05–0.19)	0.10 (0.06–0.17)
≥15 mm	0.24 (0.19–0.30)	0.14 (0.12–0.17)	0.19 (0.10–0.34)	0.12 (0.07–0.21)	0.12 (0.08–0.20)
Persons with recent conversion or contacts of patients with active tuberculosis					
5–9 mm	0.29 (0.08–0.74)	0.06 (0.02–0.18)	0.30 (0.18–0.50)	0.23 (0.10–0.44)	0.12 (0.02–0.44)
10–14 mm	0.37 (0.16–0.71)	0.12 (0.05–0.25)	0.37 (0.26–0.53)	0.28 (0.17–0.45)	0.15 (0.04–0.39)
≥15 mm	0.54 (0.27–0.95)	0.12 (0.07–0.23)	0.56 (0.41–0.76)	0.42 (0.28–0.62)	0.17 (0.05–0.42)

NEJM 2004;350:2060-7

Table 3. Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis*.*

Condition	Study	Relative Risk (95% CI)
Advanced HIV infection	Pablos-Mendez et al.[27] Moss et al.[26]	9.9 (8.7–11.3)† 9.4 (3.5–25.1)
Old, healed tuberculosis	Ferebee,[13] Ferebee et al.[20]	5.2 (3.4–8.0)
Chronic renal failure	Pablos-Mendez et al.[27]	2.4 (2.1–2.8)†
Infliximab therapy	Keane et al.[28]	2.0 (0.7–5.5)†
Poorly controlled diabetes	Pablos-Mendez et al.[27]	1.7 (1.5–2.2)†
Silicosis	Cowie[29] Corbett et al.[30] Kleinschmidt and Churchyard[31]	1.7 (1.3–2.1)† 1.3 (1.1–1.7)† 1.2 (1.0–1.5)†
Underweight (≤10 percent below normal)	Palmer et al.,[22] Edwards et al.[23]	1.6 (1.1–2.2)
Gastrectomy	Thorn et al.[32] Steiger et al.[33]	1.4 (1.1–1.9)† 1.3 (1.2–1.4)†

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Vitamin B_6 Supplementation

- **Uremia**
- **Malnutrition**
- **Alcoholism**
- **Diabetes**
- **Seizure disorder**
- **HIV infection**
- **Pregnancy**

Baseline Laboratory Evaluation

- **Not indicated routinely**
- **Is indicated in:**
  - Persons with HIV infection
  - Pregnant & postpartum women (up to 2-3 mos. after delivery)
  - History/risk of liver disease
    - Heavy alcohol use
    - Chronic hepatitis
    - History of injection drug use
    - On two or more meds
    - On medications for other medical conditions

Adverse Effects on Liver

- **Incidence of hepatitis in persons taking INH is lower than previously thought (0.1 to 0.15%)**
- **Hepatitis risk increases with age**
  - Uncommon in persons < 20 years old
  - Nearly 2% in persons 50 to 64 years old
- **Risk increased with underlying liver disease or heavy alcohol consumption**
- **Abnormal laboratory results should be further investigated prior to medication initiation**

See lecture on Managing Adverse Drug Effects

Adverse Effects on Liver

- **Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH**
  - Levels usually return to normal after completion of treatment
- **Some experts recommend withholding INH if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic**

See lecture on Medication Side Effects

Monthly Monitoring During Therapy for Latent TB Infection – 1

- **Reinforce patient's understanding of LTBI and its treatment**
- **Evaluate for signs and symptoms of active TB and drug reactions**
- **Monitor adherence to prescribed regimen**
- **Educate patient about signs and symptoms of hepatotoxicity**
- **Review all medications and assess for potential drug interactions**

Monthly Monitoring During Therapy for Latent TB Infection – 2

- Repeat liver function tests for
  - Patients with abnormal baseline
  - Persons with HIV infection
  - Pregnant and post-partum women
  - History/risk of liver disease
    - Heavy alcohol ingestion
    - Chronic hepatitis
    - History of injection drug use
    - On two or more meds

Management of Patient Who Missed Doses

- **Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion within recommended time frame**
- **When treatment has been interrupted for more than 2 months, patient should be examined to rule out TB disease**
- **Recommend and arrange for DOT as needed**
- **Completion of therapy is based on the total number of doses administered, not on duration alone**

Retreatment of LTBI

- **Re-infection can occur and is especially of concern in immunocompromised individuals**
- **Retreatment should be considered based on underlying medical conditions, severity of exposure and age**

Summary

- **Rule out TB disease**
- **Choose treatment regimen based on individualized evaluation of each patient**
- **Importance of monthly clinical assessments and ongoing patient education**
- **Use DOT for high-priority patients**