Treatment of Latent Tuberculosis Infection (LTBI)

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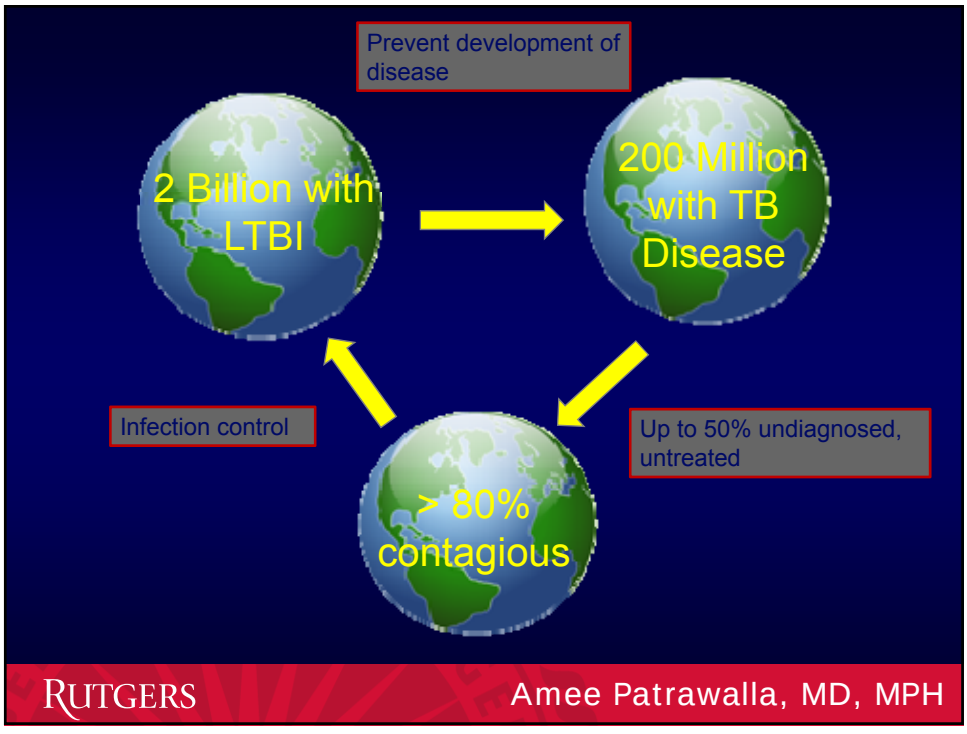

Why is There Debate About Treating LTBI?

Hypertension	Latent TB infection
• Asymptomatic condition	• Asymptomatic condition
• Very serious complications – Death – Major disability	• Very serious complications – Death, – Major disability – AND transmission
• Treatment is for years – Expensive medications – Potential serious side effects – Requires close monitoring and follow up	• Treatment is max 9 months – Cheap medications – Potential serious side effects – Requires close monitoring and follow up
• BUT – no debate about Treating	• WHY the debate about Treating??

Menzies et al., *Indian Journal of Medical Research*, 2011

Treatment of LTBI – Milestones

1965: ATS recommends treatment of LTBI
1967: Recommendations expanded to include all TST ≥ 10 mm
1974: Guidelines established for screening to decrease risk of INH hepatitis; Treatment recommended for persons ≤ 35 y/o
1983: ~~Laboratory monitoring recommended of persons ≥ 35 y/o~~
1998: ~~2 months RIF plus PZA as an option for HIV-infected patients~~
2000: 9 months INH preferred; ~~2 month RIF plus PZA~~ or 4 months RIF recommended as options
2001: Liver injury and death associated with 2-month regimen of RIF plus PZA, use of this option de-emphasized
2003: 2 month regimen of RIF and PZA not recommended
2011: 12 doses INH plus RPT (DOT) recommended for adults
2018: INH plus RPT recommended for ages 2-17, SAT acceptable

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Case

- A 24 year old man needs medical evaluation for pre-employment
- PMH: healthy; no previous TB testing
- TST is 12 mm
- Patient denies fever, cough, weight loss or other systemic symptoms
- CXR is normal

Case

- Is there any further evaluation required to rule out active tuberculosis?
- What if the CXR shows RUL changes?

Case One

- What would you recommend for this pt who has none of the TB risk factors?
- What would you recommend if the pt has a TB risk factor?

TST Cutoff 5 mm

- HIV
- Other significant immunosuppression
- Recent contact to TB
- CXR shows changes c/w prior TB

TST Cutoff 10 mm

- Diabetes
- Carcinoma of head or neck
- IVDA without HIV
- Dialysis or ESRD
- Silicosis
- Jejunoileal bypass
- Gastrectomy

TST Cutoff 10 mm

- Converter: increase in TST ≥ 10 mm in past 2 yrs (no age limit)
- Weight < 90% IBW
- Children < 4 y/o
- Employees/residents in high risk setting
- Immigrant within past 5 yrs

TST Cutoff 15 mm

- No risk factors for TB
- Usually seen in an individual being hired to a position in health care setting
- Treatment?

Before Initiating Treatment for LTBI:

- Rule out TB disease by history, physical examination, chest radiography and, when indicated, bacteriologic studies
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment

Treatment Regimens for LTBI

Drug(s)	Duration	Interval	Minimum Doses
Isoniazid (INH)	9 months	Daily	270
		Twice weekly	76
	6 months	Daily	180
		Twice weekly	52
Rifampin (RIF)	4 months	Daily	120
Isoniazid & Rifapentine (INH + RPT)	3 months	Once weekly	12

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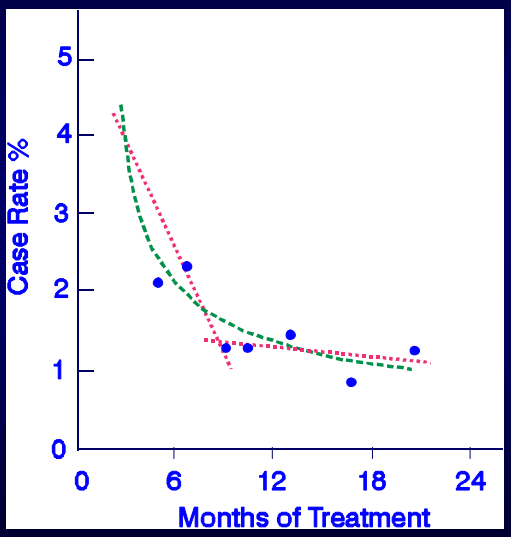
How Much INH Needed for Prevention of TB?



- Longer duration corresponded to lower TB rates if took 0 – 9 mos.
- No extra increase in protection if took > 9-10 mos.

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

LTBI Treatment Regimens: INH

- 9-month regimen of INH is one of the preferred regimens
- 6-month regimen is accepted (with exceptions) but may be used if unable to complete 9 months
- May be given daily or intermittently (twice weekly)
- Directly observed therapy (DOT) recommended for intermittent regimen

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LTBI Treatment Regimens: INH

- INH daily for 9 months - 270 doses within 12 months
- INH twice/week for 9 months - 76 doses within 12 months
- INH daily for 6 months - 180 doses within 9 months
- INH twice/week for 6 months - 52 doses within 9 months

- Restart treatment if longer gap in therapy occurs

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LTBI Treatment Regimens: RIF

- RIF given daily for 4 months is another acceptable alternative
- May be preferred to INH (emerging data)
- Drug interactions may be problematic
- Rifabutin may be substituted, when necessary (e.g., patients on protease inhibitors)
- RIF - 120 doses within 6 months

Efficacy of 4RIF versus 9INH

- Multicenter RCT of > 6000 adults

Rx	INH	RIF
Tx completion*	57.8%	70.7%
Active TB	1	1
Adverse events	4.8%	2.2%

Menzies, et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. N Engl J Med 2018;379:440-53.

* Completed >80% of doses within allowed time

Safety and Efficacy of RIF in Children

- Multicenter RCT of 829 children

Rx	INH	RIF
Tx completion*	76.4%	85.3%
Active TB	2	0
Adverse events	12.8%	4.7%

Diallo, et al. Safety and Side Effects of Rifampin versus Isoniazid for in Children. N Engl J Med 2018;379:454-63.

* Completed >80% of doses within allowed time

LTBI Treatment Regimens: INH plus RPT

- Originally only recommended for healthy people
  - Age 12 years or older
  - Risk factor for developing active TB (recent contact, TST/IGRA conversion, or abnormal CXR)
- Dosing

Isoniazid
15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum

Rifapentine

10.0–14.0 kg	300 mg
14.1–25.0 kg	450 mg
25.1–32.0 kg	600 mg
32.1–49.9 kg	750 mg
≥50.0 kg	900 mg maximum

Recommendations for Use of an INH-RPT Regimen with DOT to Treat LTBI. *MMWR* December 9, 2011 / Vol. 60 / No. 48

3HP DOT vs. Self Administered (SAT) vs. Self Administered with Text Message Reminder (eSAT): iAdhere Study

- Treatment Completion:

	All	US group
DOT	87.2%	85.4%
SAT	74%	77.9%
eSAT	76.4%	76.7%

Non-inferior

- Self administered once weekly 3HP in the US may be acceptable

Belknap et al., *Annals of Internal Medicine*, 2017

RUTGERS Amee Patrawalla, MD, MPH

LTBI in HIV-Infected Persons

- Consult an expert in managing HIV and TB
- INH daily for 9-mo, rather than 6-mo, is optimal: 270 doses within 12 months
- RIF is generally contraindicated for persons taking protease inhibitors
- Rifabutin with dose adjustments can sometimes be substituted for RIF
- ~~INH/RPT regimen not recommended for HIV-infected people taking antiretroviral therapy~~

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LTBI Treatment Regimens: Fibrotic Lesions on CXR

- Should be treated for LTBI if they have:
  - A positive TST reaction (at least 5 mm) or +IGRA result
  - No symptoms of infectious TB disease
  - No history of treatment for TB disease
- Treat for LTBI only after active disease excluded
- Acceptable regimens include
  - 9 months of INH
  - 4 months of RIF (with or without INH)
  - 3 months of INH and RPT (12-dose regimen)

LTBI Treatment Regimens: Multidrug-Resistant TB

- Consider risk for progressing to MDR disease before recommending LTBI treatment
- When prescribing treatment for these contacts, consult an MDR TB expert
- Optimal agent(s) depend on source susceptibilities

LTBI Treatment Regimens: Pregnancy or Breast-feeding

- 9 months of INH daily or twice weekly; give with vitamin B6
- If cannot take INH, consult with TB expert regarding risk-benefit ratio
- Women at high risk for progression to TB disease should not delay LTBI treatment; monitor carefully
- Breast-feeding not contraindicated while on INH

Management of Patient Who Miss Doses

- Extend or re-start treatment depending on duration of interruptions
- When treatment has been interrupted for more than 2 months, patient should be re-evaluated to rule out development of active TB disease
- Recommend and arrange for DOT as needed

Adverse Effects of Treatment: INH

- Asymptomatic LFT elevation in 10-20% on INH
  - Generally return to normal even if medication continued
- Clinical hepatitis – 0.1-1% on INH
  - Increased risk with increasing age, substance abuse, pre-existing liver disease
  - Severe (even fatal) reactions very rare but have been reported
- Peripheral neuropathy <0.2%
- Common mild side effects include nausea, lethargy

Adverse Effects of Treatment: Rifamycins

- Asymptomatic hyperbilirubinemia 0.6%
- Risk for hepatitis increases when INH combined with rifapentine
- Cutaneous – up to 6% of people, usually self limited
- Hypersensitivity reactions – rare
- Common mild side effects include nausea, diarrhea

Clinical Monitoring - Instruct Patients to Report

- Fever
- Headache
- Rash
- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet

Clinical Monitoring - Monthly Visits to Review

- Rationale for treatment
- Adherence with therapy
- Symptoms of adverse drug reactions
- Plans to continue treatment

Laboratory Monitoring

Baseline liver tests are not necessary except for patients with risk factors:

- HIV infection
- History of liver disease
- Regular alcohol use
- Pregnancy or in early postpartum period

Laboratory Monitoring

Laboratory monitoring during therapy indicated:

- Abnormal baseline results
- Current or recent pregnancy
- High risk for adverse reactions
- Symptoms of adverse reaction
- Liver enlargement or tenderness during examination

Management of Abnormal LFTs

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually normalize after completion of therapy
- Discontinue treatment if transaminase level exceeds:
  - 3 times the upper limit of normal if patient has symptoms of hepatoxicity
  - 5 times the upper limit of normal if patient is asymptomatic

Case Study A (1)

- 47 year old Hispanic male
- Moved to U.S. from Bolivia 4 years ago
- Known contact of infectious TB case
- TST = 5 mm of induration
- 3 months later TST = 23 mm of induration
- No symptoms of TB disease
- Normal CXR, CBC, AST, and bilirubin

Case Study A (2)

Questions

1. What are this patient's risk factors for TB infection or disease?
2. What errors in management of this patient to date?

Case Study A (3)

Discussion of risk factors

- Patient is a contact of an infectious TB case
- Recent immigrant to the US from a country with a high prevalence of TB
- If the patient had not been a contact, the recency of his immigration (less than 5 years) would have made him a candidate for TB testing, but the 5-mm reaction would not be considered positive

Case Study A (4)

Discussion of risk factors

- Persons who immigrate from TB-endemic countries have increased rates of TB
- Rates of TB approach those of their countries of origin for 5 years after arrival in the US
- These increased rates most likely result from recent *M. tuberculosis* infection in their native country

Case Study A (5)

Discussion of management

- As a contact of an active TB case, 5 mm of induration is considered positive
- This patient should have been treated for LTBI immediately after the first TST
- Repeating TST was not indicated

Case Study B (1)

- 24 year old Asian female
- Moved to US from Philippines > 5 years ago
- Plans to work in a correctional facility
- TST result negative (0 mm) 1 year ago
- TST for pre-employment physical = 26 mm of induration
- CXR normal
- No symptoms of TB disease
- No known contact with a TB patient

Case Study B (2)

Questions

1. What are this patient's risk factors for TB infection or disease?
2. What is the appropriate management for this patient?

Case Study B (3)

Discussion of risk factors

- Patient's TST converted from negative to positive (within a 2-year period)
- TST conversion increases risk for progressing from LTBI to TB disease
- Foreign-born status is less of a risk factor, i.e., she immigrated more than 5 years ago

Case Study B (4)

Discussion of management

- Patient is a recent converter and, as such, is a candidate for treatment of LTBI with INH
- History of BCG should not be a factor in interpreting TST results
- IGRA testing favored over TST in patients with a history of BCG

Case Study C (1)

- 28 year old Asian male
- Moved to US from China < 5 years ago
- Received BCG vaccine in China as a child
- QFT-GIT result = Positive
- CXR normal
- No symptoms of TB disease
- Known contact with a TB patient

Case Study C (2)

Questions

1. What are this patient's risk factors for TB infection or disease?
2. What is the appropriate management for this patient?

Case Study C (3)

Discussion of risk factors

- Positive QFT-GIT result suggests that *M. tuberculosis* infection is likely (result is not affected by prior BCG)
- Recent immigrant to the US from a country with a high prevalence of TB
- Foreign-born status is a risk factor, i.e., he immigrated < 5 years ago
- Known contact with a TB patient

Case Study C (4)

Discussion of management

- Positive QFT-GIT result indicative of LTBI (after ruling out active TB disease)
- Known contact with a TB patient may or may not have been source of infection
- Should be treated for LTBI

Questions?