LTBI Treatment: Focus on New LTBI Regimen

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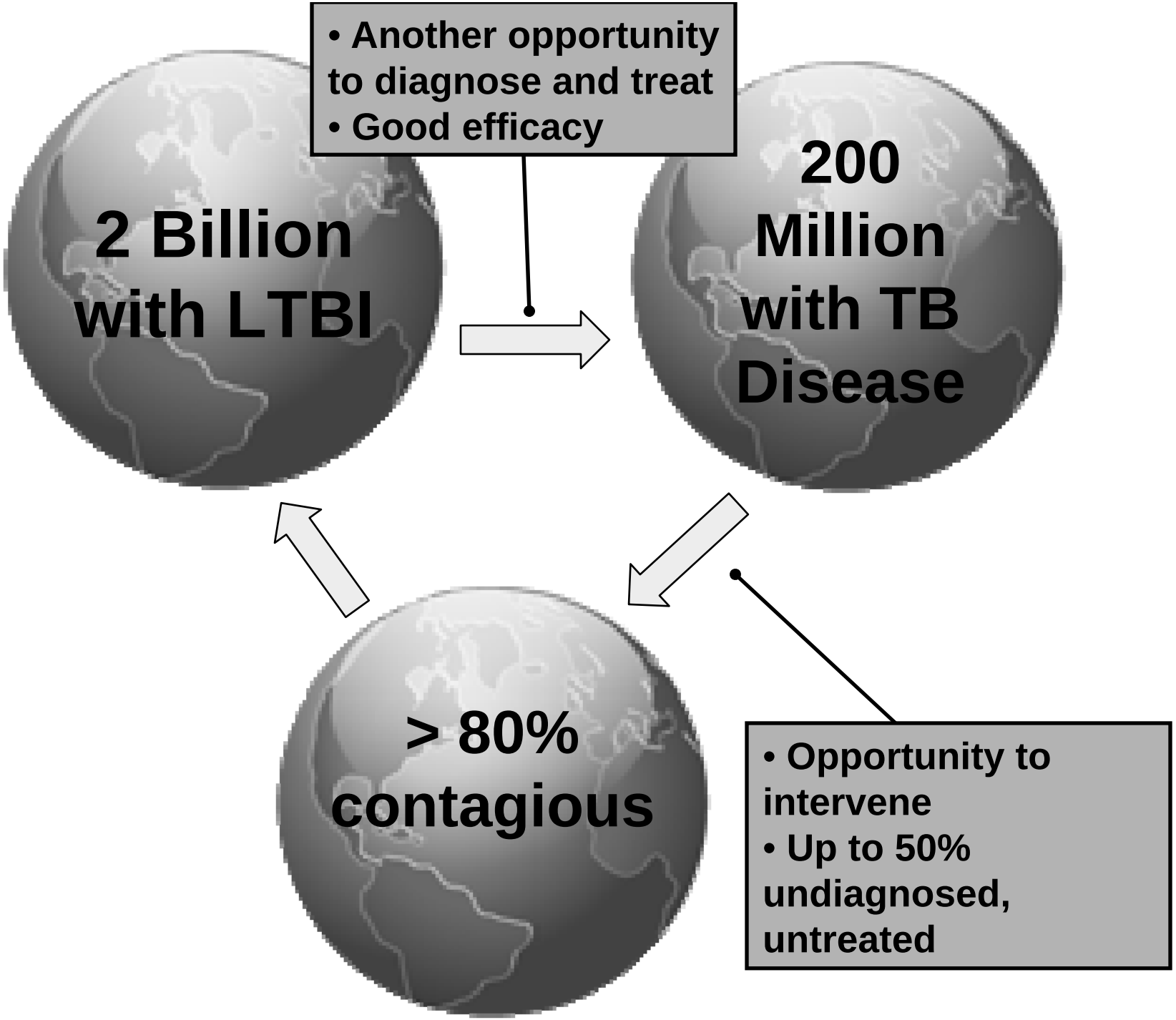
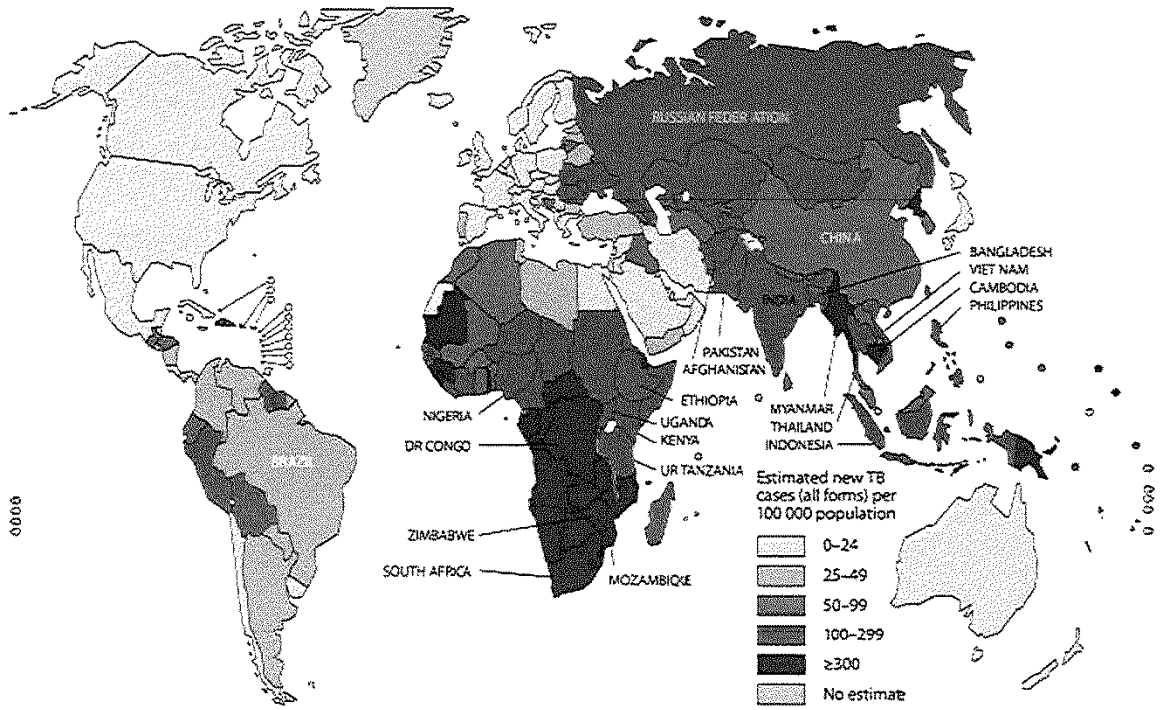
Latent TB Infection (LTBI)

- Infection with *Mycobacterium tuberculosis* without manifestations of active disease
  - Asymptomatic
  - Normal or stable chest radiography
- >80% TB disease in the US is due to reactivation of latent infection
- Reactivation is preventable
- TB elimination focuses on targeting people with a high risk of LTBI for screening and treatment

Horsburgh & Rubin, NEJM 2011; 364 (154): 1441-8


• Another opportunity to diagnose and treat
• Good efficacy
2 Billion with LTBI
200 Million with TB Disease
> 80% contagious
• Opportunity to intervene
• Up to 50% undiagnosed, untreated

Estimated TB incidence rates, 2010



Source: *Global Tuberculosis Control 2011*. WHO, 2011.

World Health Organization

Prevalence of TB Infection: U.S. Residents

Population	Expected Prevalence
Foreign Born	18.7%
Close contacts of persons with infectious TB	37.1%
Homeless persons	12.8% - 32.4%
Injection-drug users	14.0% - 27.7%
Prisoners	17.0%
U.S.-born, no other risk	1.8%

Horsburgh CR, Rubin EJ. Latent Tuberculosis infection in the United States. NEJM 2011.Apr 14;364(15):1441-8

LTBI Treatment Challenges

- Lengthy treatment leading to limited adherence
- Adverse effects influencing patient and provider agreement
- Cost
- Relatively few accepted regimens
- Treatment of asymptomatic individuals

LTBI Treatment

- New INH-RPT regimen
- Pre-treatment evaluation
- Choosing a treatment regimen
- Monitoring
- Special circumstances

Rifapentine

Rifapentine

- An agent active against TB
- Contraindications are:
  - Hypersensitivity
  - Caution for hepatic impairment
  - Caution if concurrent nephrotoxic agents

Serious Adverse Reactions

- Neutropenia
- Leukopenia
- Thrombocytopenia
- Hepatotoxicity
- Interstitial nephritis
- Pseudomembranous colitis
- Anaphylaxis
- Pancreatitis

Rifapentine Side Effects

- Reddens secretions including urine and tears & thus can stain contact lenses
- Increased LFTs, hyperbilirubinemia (uncommon)
- Neutropenia, anemia, leukopenia (uncommon)
- Pyuria, proteinuria, hematuria, lymphopenia, urinary casts

Rifapentine Side Effects continued

- Rash, petchiae, purpura, pruritis, acne
- Nausea, vomiting, anorexia, musculoskeletal pain, arthralgia
- Fever, headache, dizziness
- Increases the metabolism of many medications medications (esp. cytochrome P450 isoenzyme 3A). Avoid with warfarin & methadone except with careful monitoring.
- Birth control- add or switch to a barrier method

Contraindicated Drugs

- Emtricitabine/rilpivirine/tenofovir- decreases rilpivirine
- Etravirine- decreases levels
- Lurasidone- decreases levels
- Praziquantel- decreases levels
- Ranolazine- decreases levels

Isoniazid-Rifapentine for LTBI

- MMWR December 9, 2011/ 60(48); 1650-1653.
- Recommendations from a 23 member panel of experts
- Reviewed 3 completed trials recognizing these were open-label trials

Clinical Trial Data - Brazil

- Compared 12 weekly DOT INH-RPT doses with 2 months of RIF-pyrazinamide among aged>17
- Trial stopped at 399 participants due to hepatotoxicity in the RIF-PZA group and then followed for two years
- TB in 3 IHN-RPT patients vs. 1 INH-PZA, for an incidence rate ratio of 2.8, but Confidence Interval (CI) was wide 0.2-26.8

Clinical Trial - South Africa

- 1148 HIV-infected, TST+ participants>17 y.o
- Randomized to one of four arms with four years of follow up:
  - INH-RPT weekly for 12 doses (DOT)
  - INH-RIF twice weekly for 12 weeks (DOT)
  - Daily INH for 6 months (self-supervised)
  - Daily INH indefinitely (self-supervised)
- Incidence rates were similar in all four arms (1.2-2.0 per 100 person-years), but grade 3 or 4 adverse events were higher in the group on INH indefinitely)

Clinical Trial - Multinational

- Performed in Brazil, Canada, Spain & US
- Compared 12 doses of INH-RPT given weekly with DOT to 9 months of INH (self-supervised) in patients 2 or more years old
- 7731 participants in the Modified Intention-to-Treat (MITT) analysis with 33 months of follow up post-treatment:
  - 5466 close contacts
  - 1925 TST conversions
  - 179 with evidence of healed TB
  - 161 HIV positive patients not on ART

Clinical Trial - Multinational part 2

- Completion rate was 82% for INH-RPT but only 69% of INH
- Seven cases of TB in INH-RPT group and 15 in the INH group for a hazard ratio of 0.38 (CI= 0.15-0.99)
- Efficacy of 0.19% vs. 0.43% in terms of TB disease
- Drug resistant M. bovis in one INH-RPT patient who was HIV-infected and two INH-resistant TB cases in the INH group

Clinical Trial - Adverse Events

- Permanent drug discontinuations were more common in the INH group (31% vs 18%)
- Grade 3 or 4 AEs were more common with INH (3% vs 1.6%)
- Permanent drug discontinuations due to AEs were more common with INH-RPT (4.9% vs 0.4%) as were stoppages for possible hypersensitivity (2.9% vs. 0.4%) including 6 of 152 in the INH-RPT group for hypotension
- Hepatotoxicity was more common in the INH group (2% vs. 0.3%)

CDC Recommendations

- INH-RPT is now considered an equal alternative to INH (12 weekly DOT doses vs 9 month regimen) in otherwise healthy patients 12 years or older
- Choice depends on feasibility of DOT, resources for drug, program operations including patient monitoring, expectance of treatment completion as foreseen from the medical and social circumstances of the patient and patient and doctor preference

Children age 2-11

- 9 months of daily INH is recommended
- INH-RPT can be considered on a case-by-case basis when both the circumstances make the completion of 9 months of Rx unlikely AND the likelihood or hazard of TB is great
- INH-RPT is not recommended under age 2, in HIV-infected patients on ART, in patients who are or are expecting to become pregnant and in those with drug resistance expected

Cautions with INH-RPT

- Ensure TB disease is not present
- Patients with fibrotic or ‘old healed’ lesions on CXR
- HIV infected patients
  - CXR may appear normal despite presence of TB disease
  - More extra-pulmonary disease

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

Monitoring

- DOT workers should use a symptom checklist at each visit
- Seek medical attention for fever, yellow eyes, dizziness, rash, aches, >1 day of nausea, vomiting, weakness, abdominal pain or loss of appetite.
- Monthly clinical assessment & physical exam recommended
- Lab testing for some

Lab Tests

- LFTs for:
  - HIV infected
  - Liver disorders
  - Regular alcohol usage
  - Up to three months following delivery
- Discontinue drug for LFTs>5X ULN without symptoms or >3X ULN with symptoms
- Adverse events: use MedWatch Form 3500 or call 1-800-FDA-1088

Dosing

BOX 1. Dosage for a combination regimen of isoniazid and rifapentine in 12 once-weekly doses under direct observation for treating latent *Mycobacterium tuberculosis* infection.

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

Isoniazid (INH) is formulated as 100 mg and 300 mg tablets. Rifapentine (RPT)is formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

Source: Three months of weekly rifapentine and isoniazid for *Mycobacterium tuberculosis* infection (PREVENT TB). Information available at http://clinicaltrials.gov/ct2/show/nct00023452?term=rifapentine&rank=9.

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

Pyridoxine

- In the multi-national clinical trial, treating physicians had the option of prescribing 50 mg of oral pyridoxine with each dose of either the weekly INH-RPT regimen or with each dose of the daily INH regimen
- Weekly pyridoxine should be considered with the INH-RPT regimen especially for persons who are malnourished or predisposed by other illnesses to peripheral neuropathy

Elkhart County Experience

- 11/14 (79%) have completed treatment with INH-RPT since 9/2011
- One discontinued for nausea, fatigue and muscle aches after 3 weeks, but completed INH monotherapy
- One had nausea, rash, itching, swelling of legs and muscle aches after 5 weeks
- One had nausea, rash, itching, swelling of legs, muscle aches & was also unable to tolerate INH monotherapy

Pre-Treatment Evaluation

Medical history

- History of TB or HIV treatment
- TB exposure
- Risks for drug toxicity
  - e.g., alcoholism, liver disease, pregnancy
- Complete medication list
- 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

- Chest x-ray
  - Rule out TB disease
- Laboratory tests
  - CBC and chemistry panel, if indicated e.g. history of liver disease
  - 3 sputum samples for AFB smear, culture, & NAA testing if TB symptoms or findings on chest x-ray

Baseline Laboratory Evaluation

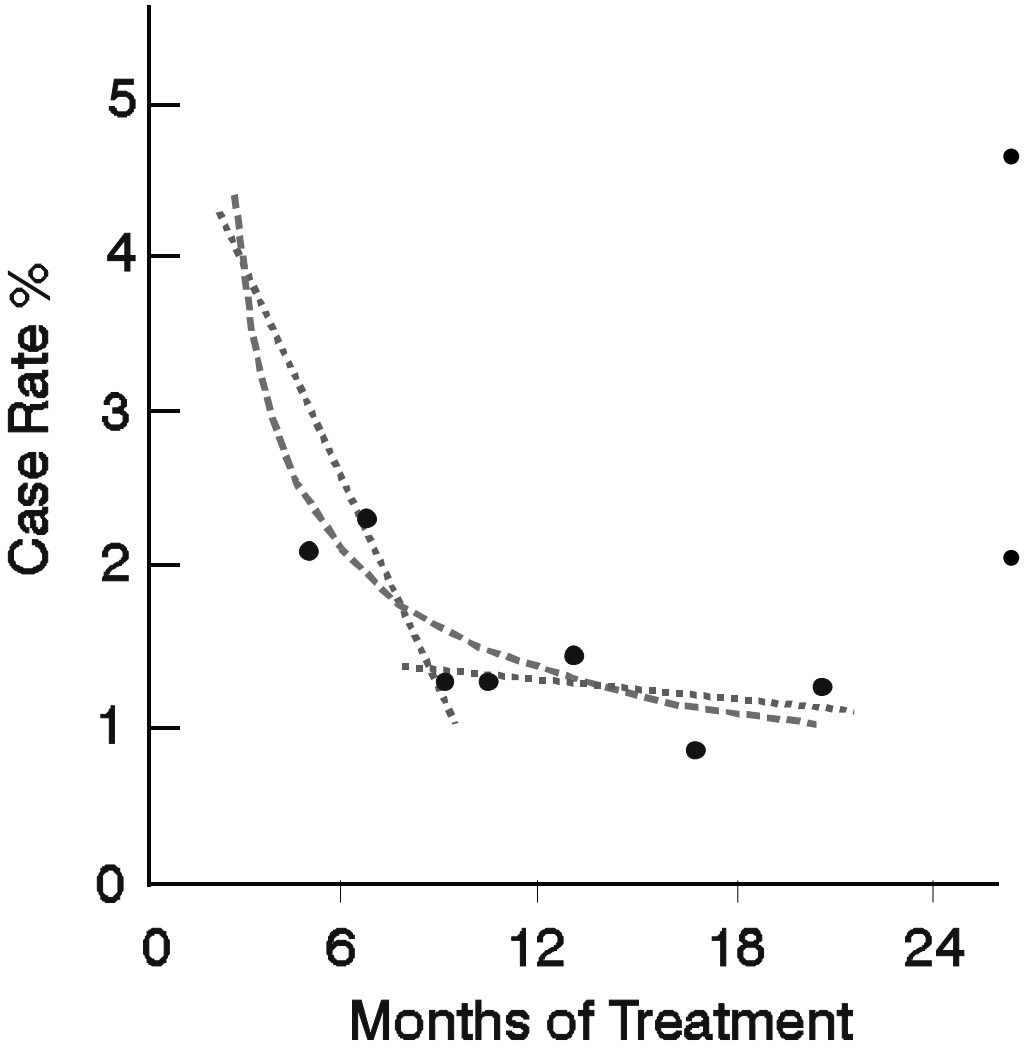
- Not indicated routinely
- Indicated for:
  - Persons with HIV infection
  - Pregnant & postpartum women (up to 2-3 mos. after delivery)
  - Individuals with history/risk of liver disease
    - Heavy alcohol use
    - Chronic hepatitis
    - History of injection drug use
    - On two or more meds or potentially hepatotoxic medications
    - At risk for NASH (nonalcoholic steatohepatitis)
  - Consider in older individuals with other chronic medical conditions/medications prior to INH-RPT

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
INH-RPT	3	Weekly**	12

*Preferred ** Intermittent treatment only with DOT

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

- RIF 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
- 120 doses should be completed within 6 months
- Children should receive 6 months
- Be aware of predicable drug interactions
- ~~RIF + PZA~~ for 2 months

Comparison of INH vs. RIF for Treatment of LTBI

Comparison of Regimen Features: 9H and 4R

Regimen Feature	9H	4R
High efficacy	X	*
Lower hepatotoxicity		X
Lower overall cost		X
Higher adherence		X
More effective against INH-resistant strains *(e.g., among foreign-born persons)*		X
Shorter duration		X
Fewer drug-drug interactions	X	

*** Good evidence that 3R is at least as efficacious as 6H. Inferential reasoning from other evidence suggests that efficacy of 4R may approach that of 9H.**

***AJRCCM* 170; 832-835, 2004**

Drug Costs

- 9 months of isoniazid= $17-$51
- 4 months of rifampin= $64-$130
- 12 weeks of RPT= $226- ? +DOT

Special Situations – 1

- CXR consistent with old TB disease:
  - i.e., old fibrotic lesions consistent with prior tuberculosis – e.g. dense nodules, scar, volume loss, sharp margins, ‘hard’, bronchiectasis
  - TST reaction 5mm or greater
  - In addition to standard LTBI regimens, some prefer INH + RIF for 4 months, if previously untreated

Special Situations – 2

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

Choosing INH-RPT

- DOT feasibility
- Drug availability and resources
- Program operations
- Expectance of treatment completion
- Patient/Provider preferences

Tumor Necrosis Factor-alpha Inhibitors

- Infliximab- chimeric (mouse/human) monoclonal Ab
- Adalimumab- fully human monoclonal Ab
- Etanercept- soluble receptor fusion protein
- Certolizumab pegol- pegolated Fab fragment
- Golimumab- a human monoclonal Ab

TNF-alpha inhibitor complications

- Mycobacterial infections
- Bacterial, fungal and viral infections
- Injection site and infusion reactions
- Induction of autoimmunity
- Demyelinating disease
- Heart failure
- Malignancy

Monthly Monitoring During LTBI Treatment – 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 LTBI Treatment – 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 the Patient Who Misses Doses

- Extend or re-start treatment for frequent or prolonged interruptions that preclude completion within recommended time frame
- Examine patients to rule out TB disease when treatment interruption > 2 months
- Recommend and arrange for DOT as needed

<u>Completion of therapy</u> is based on the total number of doses administered, not on duration alone

Completion of Therapy

Regimen	Duration	Doses	Complete Within
Daily INH	9 months	270	12 months
Twice weekly INH	9 months	76	12 months
Daily INH	6 months	180	9 months
Twice weekly INH	6 months	52	9 months
Rifampin	4 months	120	6 months
INH-RPT	3 months	11-12	16 weeks

Re-treatment of LTBI

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

Take Home Points

- Prior to initiating LTBI treatment, assess for presence of TB disease
- Choose treatment regimen based on individualized evaluation of each patient and available resources
- Monthly clinical assessments and ongoing patient education important
- Consider DOT for high-priority patients
- DOT for INH-RPT