Approaches to LTBI Diagnosis and Treatment

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Curry International Tuberculosis Center,
Clinical Intensive, Sept 13, 2016

Treatment of LTBI

Objectives

• List four recommended treatment options for latent tuberculosis infection (LTBI)
• Compare the advantages and disadvantages of the recommended LTBI treatment regimens
• Identify adverse side effects of LTBI treatment regimens and discuss monitoring and treatment of these side effects
LTBI Treatment Options

- Isoniazid
- Isoniazid-Rifapentine
- Rifampin
- Fluoroquinolones +/- ethambutol (MDR)

Isoniazid

- INH remains the mainstay of LTBI treatment
- Duration of treatment?*

  Adults
  Children
  HIV-infected
  TB-4 (abnormal CXR)**

  ▶ 9 mo.

* Non-HIV adults 6 mo. acceptable, but 9 mo. preferred
** TB4 can also be treated with INH/RIF x 4 mo.

Why was 6 mo. recommended in past?

- Efficacy of INH based on duration of treatment and compliance

<table>
<thead>
<tr>
<th>Duration of INH</th>
<th>Risk Reduction</th>
<th>Compliance</th>
<th>Risk Reduction if Compliant</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mos</td>
<td>21%</td>
<td>87%</td>
<td>31%</td>
</tr>
<tr>
<td>6 mos</td>
<td>65%</td>
<td>78%</td>
<td>69%</td>
</tr>
<tr>
<td>12 mos</td>
<td>75%</td>
<td>68%</td>
<td>93%</td>
</tr>
</tbody>
</table>

N = 28,000, IUAT (fibrotic disease) Bull WHO 1982; 60:555
Isoniazid

**Why was 6 mo. recommended in past?**

- Cost-effectiveness of INH for LTBI treatment

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>3</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net costs, $</td>
<td>47,500</td>
<td>75,000</td>
<td>192,000</td>
</tr>
<tr>
<td>Cases prevented</td>
<td>3.28</td>
<td>10.54</td>
<td>11.99</td>
</tr>
<tr>
<td>Cost per case prevented</td>
<td>$14,488</td>
<td>$7,112</td>
<td>$16,024</td>
</tr>
</tbody>
</table>

Snider JAMA 1986; 255:1579

INH – Why 9 months?

- Maximize medical benefits

<table>
<thead>
<tr>
<th>Months of Treatment</th>
<th>Calculated curve</th>
<th>Calculated values</th>
<th>Observed values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


Completion of INH

**ATS/CDC LTBI guidelines, 2000**

- 9 months preferred for maximal benefit
- 6 months less effective, but may be more cost effective and result in greater adherence
  - Acceptable in non-HIV adults, program-based decision
- Completion based on total number of doses
- INH can be given either daily or twice weekly
  (Must be directly observed [DOT] if intermittent)
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menes, M.D., Amy Karrass, B.P., M.S.,
Stephen E. Weis, D.O., Marcie Wain, B.H., Marcus B. Canud, M.D.,


INH + Rifapentine (3HP)

INH + Rifapentine

• Recommended as an equal alternative to INH x 9mo in healthy patients ≥12 yo and HIV-infected patients not on ART.
• Must be provided by DOT
• Not recommended in the following:
  – Children <2yo
  – HIV-infected patients on any ART
  – Pregnant or planning to become pregnant
  – Contact to INH/RIF resistant cases

Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650-1653

<table>
<thead>
<tr>
<th>Administration</th>
<th>INH-RPT</th>
<th>INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3,986</td>
<td>3,745</td>
</tr>
<tr>
<td>Frequency</td>
<td>Weekly</td>
<td>Daily</td>
</tr>
<tr>
<td>Duration</td>
<td>12 weeks</td>
<td>9 months</td>
</tr>
</tbody>
</table>

• Slide courtesy, Dr. Neha Shah
Prevent TB Study Results

<table>
<thead>
<tr>
<th></th>
<th>INH-RPT</th>
<th>INH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>1.9 per 1,000</td>
<td>4.3 per 1,000</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Completion rate</td>
<td>82.1%</td>
<td>69.0%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>0.4%</td>
<td>2.7%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

- Slide courtesy, Dr. Neha Shah

Rifampin

- Rifampin daily for 4 months acceptable alternative when INH cannot be used
  - Contacts to INH-resistant cases
  - INH intolerance
- New Change: Rifampin daily for 4 months in children (previously 6 month AAP recommendation)
- Better completion rates, Lower rates of hepatotoxicity
- Cost effective
- Optimal duration is not known

- American Academy of Pediatrics, Red Book 2015

Efficacy of 3R in silicosis

- RCT, n=679
- Silicosis, PPD+
  - P1- placebo
  - HR3- INH/RIF x 3 mo
  - H6- INH x 6 mo
  - R3- RIF x 3 mo
- Active pulmonary TB more frequent in placebo vs chemoprophylaxis groups (p<0.01)
- No significant difference between 3 chemoprophylaxis regimens

Efficacy of 3R in silicosis

- Limitations - regimens self-administered
- Serum ALT significantly higher in H6 and HR3 compared to R3 (p<0.001)
- Similar freq adverse effects in all 4 groups
- No evidence of development of drug resistance


Efficacy: Phase 3 RCT

- Multi-center Phase 3 RCT: 4R vs 9H
- Results expected in 2017
- Study sites: Canada, Australia, Benin, Brazil, Ghana, Guinea, Indonesia, Korea, Saudi Arabia
- Objectives:
  - Effectiveness - incidence of confirmed active TB within 28 months post-randomization
  - Efficacy - incidence of confirmed active TB in those who took at least 80% of doses within allowed time
  - Serious adverse events

Menzies, D. 4 Months of Rifampin for the Treatment of LTBI. As presented at National TB Controller’s Association Conference, Atlanta, GA, June 11, 2014

Hepatotoxicity: Favors RIF > INH

### Adherence: Favors RIF > INH

<table>
<thead>
<tr>
<th>Study or Reference</th>
<th>Treatment Completion</th>
<th>Adverse events: RIF vs INH</th>
<th></th>
</tr>
</thead>
</table>

### Treatment Completion / Adverse Events

<table>
<thead>
<tr>
<th>Study design</th>
<th>Treatment Completion: RIF vs INH</th>
<th>Adverse events: RIF vs INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lardizabal, et al, 2006 Retrospective New Jersey N=474</td>
<td>80.5 vs 53.1 % (p&lt;0.0001)</td>
<td>3.1% vs 5.8 % (p&lt;0.05)</td>
</tr>
<tr>
<td>Page, et al, 2006 Retrospective Maryland N=2255</td>
<td>71.6 vs 52.6 % (p=0.001)</td>
<td>Adverse events: 1.9 vs 4.6 % (p=0.001) Hepatotoxicity: 0.08 vs 1.8% (p=0.001)</td>
</tr>
<tr>
<td>Menzies, et al, 2008 Randomized, open label, multicenter (Canada, Saudi Arabia, Brazil) N=847</td>
<td>78 vs 60% (p=0.001)</td>
<td>Grade 3/4 hepatitis: 0.7 vs 3.8% (p=0.03) Decreased platelet/WBC: RIF&gt;INH</td>
</tr>
<tr>
<td>Fresard, et al, 2011 Retrospective Switzerland N=624</td>
<td>83 vs 74% (p=0.02)</td>
<td>Hepatotoxicity: 2.0 vs 6.1% (p=0.03)</td>
</tr>
</tbody>
</table>

### Pros / Cons Rifampin

<table>
<thead>
<tr>
<th>Potential Benefit</th>
<th>Potential Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorter duration</td>
<td>Development of resistance</td>
</tr>
<tr>
<td>Decreased hepatotoxicity</td>
<td>Increased immune phenomenon (anemia, rash)</td>
</tr>
<tr>
<td>Cost</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Efficacy data limited</td>
</tr>
</tbody>
</table>
Lessons Learned: RIF + PZA

HIV/LTBI studies: Good news: 2 mo. RIF/PZA works

<table>
<thead>
<tr>
<th>Location, Year</th>
<th>Treatment</th>
<th>Rate of TB per 100 person/ys</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haiti, 1994</td>
<td>6 mo INH</td>
<td>1.7</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>2 mo RIF/PZA</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Zambia, 1999</td>
<td>6 mo placebo</td>
<td>8.1</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>6 mo INH</td>
<td>4.9</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>3 mo RIF/PZA</td>
<td>4.6</td>
<td>0.58</td>
</tr>
<tr>
<td>US, Haiti, Brazil, Mexico, 1999</td>
<td>12 mo INH</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>2 mo RIF/PZA</td>
<td>0.8</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Lessons Learned: RIF + PZA

Non-HIV/LTBI studies: Bad news: Severe hepatotoxicity/deaths

<table>
<thead>
<tr>
<th>Study, Site</th>
<th>N</th>
<th>% Liver Injury, Grade 1-2</th>
<th>% Liver Injury, Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bock, ATL</td>
<td>168</td>
<td>4.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Jasmer, SF/Bos/ATL</td>
<td>207</td>
<td>18.3</td>
<td>7.8</td>
</tr>
<tr>
<td>Lobato, jails</td>
<td>715</td>
<td>4.9</td>
<td>6.0</td>
</tr>
<tr>
<td>McNeill, NC</td>
<td>110</td>
<td>5.5</td>
<td>7.3</td>
</tr>
<tr>
<td>Stout, NC</td>
<td>114</td>
<td>12.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Leung, Hong Kong</td>
<td>40</td>
<td>12.5</td>
<td>35</td>
</tr>
<tr>
<td>Lee, Chicago</td>
<td>157</td>
<td>ND</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1511</td>
<td><strong>7.7</strong></td>
<td><strong>7</strong></td>
</tr>
</tbody>
</table>

Treatment Regimens for Latent TB Infection

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid &amp; Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
</tbody>
</table>

Rifampin

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

Note: Rifampin (RIF) and Pyrazinamide (PZA) should not be offered to persons with LTBI. RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.
Outcome of LTBI Treatment
San Francisco, 2012-2013

Cohort: All TB clinic patients starting LTBI treatment from 9/1/12 to present with known treatment end reason.

<table>
<thead>
<tr>
<th></th>
<th>SHR*</th>
<th>INH</th>
<th>INH + RIF</th>
<th>RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started Treatment</td>
<td>71</td>
<td>295</td>
<td>50</td>
<td>180</td>
</tr>
<tr>
<td>Completed</td>
<td>60 (85%)</td>
<td>213 (72%)</td>
<td>44 (88%)</td>
<td>154 (86%)</td>
</tr>
<tr>
<td>Adverse Reaction Chose to Stop/Lost/Refused Moved Provider Decision Other</td>
<td>3 (4%)</td>
<td>2 (1%)</td>
<td>64 (22%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td></td>
<td>6 (11%)</td>
<td>22 (44%)</td>
<td>5 (10%)</td>
<td>6 (2%)</td>
</tr>
</tbody>
</table>

*Treatment of Latent Tuberculosis Infection

Monitoring and adverse reactions

Monitoring

ATS/CDC LTBI guidelines, 2000

- Routine baseline / follow-up laboratory testing → Not needed
- Except for:
  - HIV infection
  - Pregnancy / Early postpartum (<3mo)
  - History of liver disease / hepatitis
  - Regular EtOH use
  Also consider for: Statin/other hepatotoxic meds, age >50
Monitoring

Evaluate monthly for:

- Adherence
- Symptoms of hepatitis or other side effects
  - Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
  - Fatigue or weakness >3 days
  - Dark urine
  - Rash, icterus, jaundice, easy bruising/bleeding
  - Persistent numbness in hands or feet
  - Arthralgias
  - Fever

INH adverse reactions

- Clinical hepatitis
- Asymptomatic hepatic enzyme elevation
- Peripheral neuropathy
- Rash
- Mild neurologic symptoms
- Drug interaction – increases dilantin, carbamazepine and antabuse levels

INH-induced hepatitis

- 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
INH-induced hepatitis

- Past data suggested much higher rates of hepatotoxicity, but that included asymptomatic rise in transaminases. Newer data, used signs and sx to trigger lab diagnosis (AST/ALT >5x nl)
- Good clinical monitoring, rather than routine lab testing can produce reasonably low rates of adverse events.

### INH-induced hepatitis

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>N=13,838</th>
<th>Hepatitis</th>
<th>Cases/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>20-34</td>
<td>3.0</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>35-49</td>
<td>12.0</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>23.0</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 64</td>
<td>8.0</td>
<td>8.0</td>
<td></td>
</tr>
</tbody>
</table>

Kopanoff, Am Rev Resp Dis 1976
US public health survey

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>N=11,141</th>
<th>Hepatitis</th>
<th>Cases/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>15-34</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>35-64</td>
<td>2.1</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>2.8</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

Nolan Cl, JAMA 1999
Seattle Public health TB clinic

INH Adverse Reactions

- Asymptomatic elevation of hepatic enzymes are more common - seen in 10%-20% of people taking INH
- Levels usually return to normal even when treatment is continued (and after completion of treatment)

INH Adverse Reactions

**Peripheral neuropathy**

- Occurs in <0.2 % using conventional INH doses
- Consider pyridoxine supplement (B6) 25 – 50 mg daily:
  - Diabetes, HIV, renal failure, alcoholism, malnutrition
  - Pregnant or breastfeeding mothers (and infant)
Rifamycin Adverse Effects

- Hepatotoxicity
  - Rare severe hepatitis, more common when combined with other medications
- Asymptomatic hyperbilirubinemia (0.6%)
- Dermatologic: Pruritis, rash (up to 6%)
- Hypersensitivity reaction (0.07-0.3%)
- GI: nausea, anorexia, abdominal pain
- Immune-mediated: thrombocytopenia, TTP, hemolytic anemia (<0.1%)
- Orange discoloration of body fluids

National Post-Marketing Implementation Project*

<table>
<thead>
<tr>
<th>Symptom</th>
<th># reported SE who had ≥1 dose</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptom</td>
<td>730</td>
<td>34</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>306</td>
<td>14</td>
</tr>
<tr>
<td>Fatigue</td>
<td>193</td>
<td>9</td>
</tr>
<tr>
<td>Sore muscles/joints</td>
<td>148</td>
<td>7</td>
</tr>
<tr>
<td>Fever/Chills</td>
<td>126</td>
<td>6</td>
</tr>
<tr>
<td>Rash/hives</td>
<td>108</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>107</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness/fainting</td>
<td>102</td>
<td>5</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>Numbness/tingling</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>82</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>350</td>
<td>16</td>
</tr>
</tbody>
</table>

*Slide adapted from IoAUITD 2014

Rifamycin: Drug-drug Interaction

Requires re-dosing or alternate: Monitor and titrate:
- Coumadin
- Opioids (e.g., Methadone)
- Antiretrovirals
- OCP’s
- Proton-pump Inhibitor
- Chemotherapy
  - Cyclosporine
  - Tacrolimus
  - Tamoxifen
- Endo:
  - Levothyroxine
  - Corticosteroids
  - sulfonylureas
- CNS
  - Benzodiazepines
  - Phenyoitoin, lamotrigine
  - SSRI
- Cardiac
  - Statins
  - Anti-HTN: b-blocker, ACE-I, ARB, Ca-channel blockers
Rifamycin: Drug-drug Interaction

- Rifabutin is a less potent inducer of CYP3A4 than rifampin. Thus, can be considered in certain cases with close monitoring (methadone, anti-coagulation)

Resources:
- Lexicomp / Micromedex Drug Interaction Look-up

Management of side effects: DILI (Drug-induced liver injury)

- Review hepatotoxic meds (tylenol, statins, etc), ETOH use, prior hepatitis risk/screen
- HOLD Treatment if:
  - AST/ALT > 3 times the upper limit of normal + symptoms of hepatotoxicity
  - AST/ALT > 5 times the upper limit of normal + asymptomatic
- If less than parameters above, continue treatment with plan to repeat labs in 1-4 weeks.
- Depending on above, consider alternate therapy with close LFT monitoring.

Management of Side Effects: Derm

- Fixed drug eruption
- Rash, itching (1-5%, RIF)
- Pemphigoid reaction
- DRESS (drug reaction w/ eosinophilia and systemic symptoms)
- Anaphylaxis, urticaria
- Mild: anti-histamine, topical steroids, f/u visit
- Mild-moderate: hold meds and above, consider re-challenge once resolves
- Mod-severe: hold meds and above, emergency care / derrm consult as needed. Consider alternate therapy once resolves
How can we improve adherence?

• Directly observed therapy (DOT) if patient is high risk or on an intermittent regimen
• Alternatives: video DOT, pharmacy DOT, collaboration with programs (methadone clinic, jail/prison, residential/rehab programs)
• Incentives/Enablers
• Free/low-cost medication
• Patient education, cultural sensitivity

Resources

• Webinar: Drug-Induced Liver Injury. [http://www.currytbcenter.ucsf.edu/training/webarchive/tbdili/arch_tbdili.cfm](http://www.currytbcenter.ucsf.edu/training/webarchive/tbdili/arch_tbdili.cfm)

Special situations

• Missed doses
• Pregnancy and Lactation
• LTBI re-treatment
• Window prophylaxis
• Drug-resistant contacts
**LTBI Treatment: Completion of INH**

**Help!**
I have a 45 yr. old physician with LTBI on INH who consistently arrives one week late for monthly refills. She has missed seven weeks in the past eight months.

When can I call her treatment completed?

---

**Treatment completion / Missed Doses**

Based on total number of doses, not duration

<table>
<thead>
<tr>
<th>Regimen</th>
<th># doses</th>
<th>Timeframe to complete within</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH daily x 9 months</td>
<td>270</td>
<td>12 months</td>
</tr>
<tr>
<td>INH BIW x 9 months</td>
<td>76</td>
<td>12 months</td>
</tr>
<tr>
<td>INH daily x 6 months</td>
<td>180</td>
<td>9 months</td>
</tr>
<tr>
<td>INH BIW x 6 months</td>
<td>52</td>
<td>9 months</td>
</tr>
<tr>
<td>RIF/RFP daily x 4 months</td>
<td>120</td>
<td>6 months</td>
</tr>
<tr>
<td>INH+RFP</td>
<td>12</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000.

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**Treatment completion / Missed Doses**

- Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion
- 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

CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000.
Treatment changes / Partial Credit

• No guidelines or data. Recommend consultation with TB expert.
• Options: start over vs partial credit for time taken

• SFDPH example:
  – Pt completes 4.5 months of INH (50% of planned regimen). Needs 50% left of RIF regimen (i.e. 2 mo if using 4 mo RIF regimen)

Pregnancy

• Treatment for LTBI controversial
  • Pregnancy does not increase risk for reactivation
  • Risk for increased hepatotoxicity during pregnancy and early post-partum
  • Proceed to LTBI tx if HIV infected, close contact, or converter. Otherwise, consider waiting until 3 mo post-partum.
  • INH = preferred treatment
   • Crosses placental barrier, but no teratogenicity
   • Supplement with Vitamin B6
  • RIF likely safe
   • lacks efficacy data, possibly higher rate of fetal abnormalities

  CDC. Targeted tuberculosis testing and treatment of latent TB infection. MMWR 2000.

Lactation

• Breastfeeding not contraindication:
  • Infant will get small amount of INH (sub-therapeutic)
  • In one study, no more than 20% of usual therapeutic levels of INH; <11% of other anti-TB meds
  • No toxic effects reported
  • Give both mother and breastfeeding infant Vit B6
  • Levels of INH in breast milk not adequate for treatment of infant

  CDC. Targeted tuberculosis testing and treatment of latent TB infection. MMWR 2000.
Contacts

Once active disease is ruled out:
- Contacts with PPD >5 mm should be treated for LTBI regardless of age

Contacts: “Window-prophylaxis”

Definition: LTBI tx of high-risk contacts with initial negative TB testing and active disease ruled out
Purpose: Prevent progression to active TB in high-risk contacts that may have initial negative testing (early TB infection)
- Recommended in the following:
  - Children <5 y.o.
  - HIV/immunosuppressed contacts should be fully treated, even if repeat testing remains negative
Follow-up: Repeat TB testing 8-10 weeks after exposure ended or contact no longer contagious

Contacts: Re-treatment for LTBI

- Real issue is the probability of acquiring new infection can happen
- Recommended in:
  - Those at risk for rapid progression: HIV infected or other immune-compromise, prior to severe immune suppression (e.g. transplant, anti-TNF), < 5 years old
  - Contact to MDR or drug-resistant case
- Consider transmission and infectiousness:
  - E.g. in <21 years old who have been in contact with a smear-positive case
MDR contacts

- No consensus – 1994 Delphi review with 31 experts
- Select drugs based on source case drug susceptibility test results
  - ATS/CDC 2000 guidelines suggest:
    - Fluoroquinolone (levo, moxi) + ethambutol
    - Ethambutol + pyrazinamide
    - Pyrazinamide + fluoroquinolone*
- Micronesia study**: 104 patients started 12-month FQ based MDR LTBI treatment (+/- EMB)
  - None developed MDR TB over 36 month f/u
  - 3/15 that refused Rx + 15 unidentified contacts developed MDR disease


MDR contacts

- Immunocompetent:
  - Can be observed (closely) without treatment
  - Or treated for at least 6-12 months
- Immunocompromised:
  - Treat for 12 months
  - If suspect MDR infection:
    - follow for 2 years, irrespective of treatment

Resources: Special Situations

- CDC. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection – United States - 2010. MMWR 2010;59(RR05).
- Treating LTBI in Special Situations.
  [http://sntc.medicine.ufl.edu/TrainingOnline.aspx#VB9z7CtdVro](http://sntc.medicine.ufl.edu/TrainingOnline.aspx#VB9z7CtdVro)
Treatment: Summary

- The following choices are available:
  - 9 months INH
  - 3 months/12 dose INH+RFP (DOT)
  - 6 months INH (acceptable in non-immunocompromised adults)
  - 4 months RIF
  - 2 months RIPE (e.g. in setting of TB suspect with rule-out; this is essentially R/P x 2 mo)
  - 4 months INH/RIF (for TB4, evidence of old TB, culture neg/stable CXR)
  - 6-12 months FQ+/EMB, EMB+PZA, or PZA+FQ (MDR contact, DST driven)