Approaches to LTBI diagnosis and management

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Diagnostic Testing

TB Skin Test (TST)  Interferon-gamma release assays (IGRAs)

Tuberculin Skin Test (TST)

- Also known as Mantoux or PPD (purified protein derivative), derived from tuberculin
- Measures delayed-type hypersensitivity reaction that is often detectable 2-8 weeks after infection
- Safe and reliable during pregnancy
- Contraindication: prior severe reaction, e.g. necrosis, blistering, anaphylaxis, ulceration
- Co-administer on same day as live-virus vaccine OR 4-6 weeks after vaccine (as may interfere with TST reaction)
TST- Locate and Clean

- Place forearm palm side up on a firm, well-lit surface
- Select an area free of barriers (e.g., scars, sores) to placing and reading
- Clean the area with an alcohol swab

TST- Prepare Syringe

- Check expiration date on vial and ensure vial contains tuberculin (5 TU per 0.1 ml)
- Use a single-dose tuberculin syringe with a 1/4 to 3/8 inch, 25 gauge needle with a short bevel
- Fill the syringe with 0.1 ml of tuberculin

TST- Inject tuberculin
TST- Check Wheal

• Wheal should be 6 to 10 mm in diameter. If not, repeat test at a site at least 2 inches away from original site.

TST- Read

• Visually inspect site under good light

- Erythema (reddening of the skin) – do not measure

- Induration (hard, dense, raised formation)

Positive Tuberculin Skin Test Criteria:
ATS/CDC guidelines 2000

<table>
<thead>
<tr>
<th>&gt;5 mm</th>
<th>&gt;10 mm</th>
<th>&gt;15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HBV</td>
<td>• Immune-suppression</td>
<td>• Recent immigrants</td>
</tr>
<tr>
<td>• Immune-suppression</td>
<td>• &lt;10 mg/day prednisone x1mo*</td>
<td>• Residents/employees jails/nursing homes, hospitals</td>
</tr>
<tr>
<td>• TNF inhibitor</td>
<td>• Recent contacts to TB</td>
<td>• Intravenous drug use</td>
</tr>
<tr>
<td>• Abnormal CXR/TB4</td>
<td>• Abnormal CXR/TB4</td>
<td>• Children</td>
</tr>
<tr>
<td>• Organ transplant</td>
<td>• Organ transplant</td>
<td>• High risk medical conditions</td>
</tr>
</tbody>
</table>

* Consideration for treatment regardless of age

No risk
Tuberculin skin test (TST)

Not a perfect test!
- Assume sensitivity = specificity = 95%
- When prevalence of infection is 90%, the positive predictive value is 99%
- When the prevalence of infection is 1%, the positive predictive value is 15% (i.e. 85% false positive)

TST conversion

- CDC definition: > 10 mm increase within a 2 year period
- Problems with interpretation: conversions may actually represent BOOSTED reactions in some individuals

Tuberculin skin test interpretation:

**False-negative results**

**Host factors**
- HIV
- Immunosuppressive drugs
- Recent TB infection (<3 months)
- Age (newborn, elderly)
- Infections (viral, fungal, bacterial)
- Live virus vaccination
- Overwhelming tuberculosis
- ESRD (anergy in 44% vs 16% general population)
- Other illness affecting lymphoid organs
- ESRD anergy (44% vs 16%)

**Technical factors**
- Tuberculin product (improper storage, contamination)
- Improper method of administration, reading and/or recording of results
Tuberculin skin test interpretation: False-positive results

- Cross-reactions from atypical mycobacterial infections
- Recent or multiple BCG vaccination
- Misinterpretation of immediate hypersensitivity to tuberculin
- Switching tuberculin products (aplisol > tubersol)

BCG vaccination and TST interpretation

- Remember: BCG doesn’t prevent TB infection
- Can cause false-positive result, especially within first 1-2 yr. after vaccination
- A large PPD reaction (≥15 – 20 mm) should be assumed to be from true TB infection
- CDC recommendations: Ignore history of BCG when interpreting tuberculin skin test.

BCG vaccination and TST interpretation

- BCG during infancy has minimal effect on TST specificity, in particular if performed >10 years after BCG
- BCG given later in life (after 1yo) or given more than once leads to larger TST reactions

BCG Case Study

- 30 yo M, born in Uzbekistan
- Arrived to U.S. as new immigrant, TST 10mm, CXR neg
- No documentation of BCG, but thinks got as a child, possibly multiple
- Q: How to proceed? Check QFT or treat for LTBI?


BCG Case Study

THE BCG WORLD ATLAS
A DATABASE OF GLOBAL BCG VACCINATION POLICIES AND PRACTICES

• A: Likely received multiple BCG vaccinations post-infancy, which may seriously compromise specificity of the TST; clinician decides to order an IGRA, and based on a negative IGRA and other clinical factors, clinician decides against recommending isoniazid preventative therapy


Booster phenomenon

- Cause: Delayed hypersensitivity to tuberculin may gradually wane with time (especially older adults, >55 years)
- Initial PPD may be falsely negative. However, subsequent skin testing result will be “boosted” due to immunologic recall from the initial test
- A boosted response may incorrectly be interpreted as a “conversion”

Booster phenomenon

- The booster effect may persist for a year or more
- Individuals not infected will not boost (i.e. repeated PPDs will not sensitize uninfected persons)
- Occasionally, increased PPD response may represent “boosting” of cross-reactions to other non-TB mycobacteria and BCG
- Consider two-step for initial test of individuals who will be tested on a regular basis (i.e. yearly), or if >55 years age in high risk groups

TST: Two-step testing

- Used for initial skin testing of adults that need periodic retesting (e.g. occupational health)
- Less likelihood that a boosted response will be misinterpreted as a recent infection
- **Step 1** - Place 1st TST
  - If neg, proceed to Step 2
  - If pos, consider infected, no need to proceed.
- **Step 2** - Place 2nd TST 1-3 wks later
  - If neg, consider uninfected.
  - If pos, consider infected.

Problems with TST...

- Poor inter-reader reliability, subjective
- False-positives
  - Non-tuberculous mycobacteria (NTM) infection
  - Prior BCG vaccination
- Poor positive-predictive value in low prevalence populations
- Cost/time of patient visits
  - Unread tests
- Booster effect
  - Reaction wanes over time, confusing
Interferon-gamma release assays (IGRAs)

- Measures interferon-gamma (IFN-γ) produced by sensitized T cells stimulated by TB antigens
- Use of specific MTB complex antigens (ESAT-6, CFP-10) detect:
  - MTB complex (MTB, M. bovis, M. africanum)
  - Not found in any BCG substrains
  - Less cross-reactivity with NTM, but still to M. kansasii, M. marinum, M. szulgai

QuantiFERON®-TB In-Tube

Stage 1: Blood draw and Incubation
- Blood drawn into three 1cc tubes
- Incubate 16-24 hrs at 37°C at clinic or lab

Stage 2: Laboratory processing and testing
- Harvest Plasma and add to antibody-coated QFT plate
- Wash, add Substrate, incubate 30 min then stop reaction
- Measure OD and determine IFN-γ levels
- Report results Pos/Neg/Indeterminate

IGRA: QFT interpretation

Nil: Negative control (heparin)
TB Antigen: contains lyophilized TB antigens (ESAT-6, CFP-10, TB7.7)
Mitogen: Positive control (PHA)
### IGRA: QFT interpretation

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8.0</td>
<td>&lt; 0.35 and &lt; 25% of Nil value</td>
<td>&gt; 0.5</td>
<td>Negative</td>
<td>M. Avulvulosis infection NOT likely</td>
</tr>
<tr>
<td>&gt; 8.0</td>
<td>Any</td>
<td>Any</td>
<td>Positive</td>
<td>M. Avulvulosis infection likely</td>
</tr>
<tr>
<td>&lt; 0.35</td>
<td>&lt; 0.5</td>
<td>&lt; 0.5</td>
<td>Intermediate</td>
<td>Results are indeterminate for TB Antigen responsiveness</td>
</tr>
</tbody>
</table>

### T-SPOT.TB

T-Cell Xtend – 32 hours

1. Collect peripheral venous blood
2. Centrifuge
3. Remove PBMCs, wash and count
4. Incubate overnight
5. Wash, develop and dry plate
6. Count the coloured spots in each well


### T-Spot.TB

1. Collect the usual sample and centrifuge to separate Peripheral Blood Mononuclear Cells (PBMCs)
2. Wash and count the PBMCs
3. Add PBMCs to wells and incubate with appropriate control (IFN-γ, CD8+)
4. Add secondary antibody
5. Add substrate and cover the wells, incubate 15 min at 37°C

IGRAs: T-SPOT Interpretation

<table>
<thead>
<tr>
<th>T Spot TB</th>
<th>Positive</th>
<th>Negative</th>
<th>Borderline</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 spots*</td>
<td>Controls fail</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 spots*</td>
<td>High Nil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-7 spots*</td>
<td>Poor Mitogen response</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

QFT-Gold vs. TST

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mori T et al, AJRCCM, 2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QFT-gold</td>
<td>89%</td>
<td>98%</td>
</tr>
<tr>
<td>TST</td>
<td>66%</td>
<td>35%</td>
</tr>
<tr>
<td>Kang YA et al, JAMA, 2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QFT-gold</td>
<td>81%</td>
<td>96%</td>
</tr>
<tr>
<td>TST</td>
<td>78%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Sensitivity: data from culture-positive cases of active TB
Specificity: data from low risk, BCG-vaccinated subjects

IGRA: advantages over TST

• Single visit
• Less subject to reader bias, automated lab reporting
• Better at distinguishing between true TB infection and prior BCG or atypical mycobacterial infection
  – Reduced false-positives, although note possible positives in other situations (MTB complex: bovis, africanum; other NTM: kansasii, marinum, szulgai)
• Good in low prevalence populations
• No booster effect
• Cost-effective? – $15/test kit, $50 w/ lab fees (SF), > May be program / population dependent
IGRA: **disadvantages** over TST

- Blood draw
- Performance data for finding LTBI in certain target populations is still under study; young children, immunocompromised / HIV
- Limited long-term studies to determine IGRA ability to predict disease progression in humans
- "Indeterminate" results
- Unclear effect of TB treatment on IGRA results

IGRA: Specimen Collection / Handling

- **QFT**
  - Special training required
  - Vigorous shaking of tubes
  - Order of collection (nil, TB, mitogen)
  - Incubation ASAP, within 16 hours of collection
  - Availability in different settings (public, private, clinical labs)
- **T-Spot**
  - No special training
  - Standard lithium or sodium heparin tubes used (1-2)
  - Specimens must be shipped same day to Oxford Diagnostic Lab (TN)

IGRA: Test Variability

- Fluctuations in IFNg response in serially tested patients remains unexplained and nonspecific.
- May even result in conversion / reversions
- Reasons may include:
  - Fluctuations in general IFNg responses in patient
  - Precision of IGRA
  - TB treatment
  - Boosting following TST (only in previously infected individuals)
  - New infection

Updated Guidelines for Using interferon Gamma Release Assays to Detect Mycobacterium Tuberculosis Infection — United States, 2010 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5925a2.htm)
2010 CDC Recommendations

**IGRA preferred**

- Poor return rate for TST reading
- Persons who have received BCG vaccine

2010 CDC Recommendations

**IGRA or TST recommended**

(Without preference)

- Recent contacts to person infected with TB
- Periodic screening of persons with occupational exposure
### 2010 CDC Recommendations

**TST preferred**  
(but IGRA acceptable)

- Children <5 years of age

### While routine testing with both TST and an IGRA is not recommended, consider testing with both TST and IGRA...

- If the initial test is negative and
  - There is high risk of infection, progression, or poor outcomes (HIV positive, <5 years of age, immunocompromised)
  - There is high clinical suspicion of active TB

- If the initial test is positive and
  - There is need for additional evidence to encourage compliance
  - It is a healthy person with low risk of both infection and progression

### IGRA CDC guidelines

- A **positive IGRA** requires the same response as a **positive PPD result** (public health / medical interventions)
- A **negative IGRA (or PPD)** does not rule out active TB ➔ Clinical judgment prevails
Treatment of LTBI

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.
**Isoniazid**

**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

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**Isoniazid**

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

- Cost-effectiveness of INH for LTBI treatment

<table>
<thead>
<tr>
<th>Treatment Duration Months</th>
<th>3</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<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

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**INH – Why 9 months?**

- Maximize medical benefits

- 9 months appears optimal
- 6 months less efficacious
- No significant gains if rx extended to 12 months

Cases per 100

0 1 2 3 4 5

0 6 12 18 24 Months of Treatment


---
Completion of INH

ATS/CDC LTBI guidelines, 2000
- 9 months preferred for maximal benefit
- [6 months less effective, but 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)

Rifampin

- Rifampin daily for 4 months acceptable alternative when INH cannot be used
  - Contacts to INH-resistant cases
  - INH intolerance
- Rifampin daily for 6 months in children / immunocompromised
- Rifabutin may be substituted in setting of drug-drug interactions (ex. Methadone, ART)
- Better completion rates, Lower rates of hepatotoxicity
- Cost effective

Rifampin

- Cost-effective: less side effects, better compliance
- But less data on efficacy for rifampin alone*
- Recommendation for 4 mo RIF inferred from 3 mo treatment trial
- (3 mo INH/RIF used in UK)

* Phase 3 Randomized Clinical Trial of RIF versus INH ongoing (2009-present)
Rifampin

Adherence: favors RIF > INH

Hepatotoxicity: favors RIF > INH

INH + Rifapentine

Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterial Tuberculosis Infection

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

INH + Rifapentine

- Recommended as an equal alternative to INH x 9mo in healthy patients ≥12 yo and HIV-infected patients not on ART.
- 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

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>
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/yr</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haiti, 1994</td>
<td>6 mo INH</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2 mo RIF/PZA</td>
<td>1.8</td>
<td>1.1</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>1.3</td>
</tr>
<tr>
<td>Jasmer, SF/Bou/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>Total</td>
<td>151</td>
<td>7.7</td>
<td>7</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>6 months</td>
<td>Twice weekly</td>
<td>76</td>
</tr>
<tr>
<td>Isoniazid &amp; Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<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>Treatment</th>
<th>INH</th>
<th>INH + RIF</th>
<th>RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started Treatment</td>
<td>291</td>
<td>295</td>
<td>50</td>
</tr>
<tr>
<td>Completed</td>
<td>260 (85%)</td>
<td>213 (72%)</td>
<td>44 (88%)</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>3 (4%)</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Chose to Stop/Lost/Refused</td>
<td>16 (11%)</td>
<td>64 (22%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Moved</td>
<td>6 (2%)</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Provider Decision</td>
<td>0</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>8 (3%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

*Includes both TB Clinic and Study 33 patients.

### 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
  — Dark urine
  — Rash
  — Persistent numbness in hands or feet

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.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Cases/1000 N=13,838 Hepatitis</th>
<th>Age (yr)</th>
<th>Cases/1000 N=11,141 Hepatitis</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>0.8</td>
<td></td>
</tr>
<tr>
<td>35-49</td>
<td>12.0</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>23.0</td>
<td>&gt;65</td>
<td></td>
</tr>
<tr>
<td>&gt; 64</td>
<td>6.0</td>
<td></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 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)
Rifampin Adverse Reactions

- Gastrointestinal symptoms (most common)
- Hepatotoxicity (less than INH)
- Rash
- Fever, flu-like sx, thrombocytopenia
- Orange discoloration of body fluids
- Drug-drug interactions (always check): methadone, coumadin, psychiatric, HIV ART
- Rifabutin can be considered alternative; may have less hepatotoxicity

National Post-Marketing Implementation Project*
Side Effects

<table>
<thead>
<tr>
<th>Symptom</th>
<th># reported SE who had ≥1 dose</th>
<th>N= 2143</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptom</td>
<td>730</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>306</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>193</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Sore muscles/joints</td>
<td>148</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Fever/Chills</td>
<td>126</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Rash/hives</td>
<td>108</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>107</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Dizziness/fainting</td>
<td>102</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>90</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Numbness/Singling</td>
<td>90</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>82</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>350</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

* Slide adapted from Ho JAUHD 2014

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
- 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 / derm consult as needed. Consider alternate therapy once resolves

Adherence / DOPT

- Directly observed preventive therapy (DOPT)
- Used to increase completion rates in patients
- Alternatives- video DOT, pharmacy DOT, collaboration with programs (methadone clinic, jail / prison, residential / rehab programs)

- And now for a little break... (courtesy of Dr. Richard Garfein, UCSD)
Resources

- Webinar: Drug-Induced Liver Injury. 
  http://www.currytbcenter.ucsf.edu/training/webarchive/tbdili/archtbdili.cfm
- Flowchart: Assessing and Managing the Risk of Liver Disease in the Treatment of LTBI. 

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/RFB 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.

**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. 2-3 mo depending on if using 4 or 6 mo regimen)
### Pregnancy

- Treatment for LTBI controversial
  - Wait until after delivery?
  - Risk for increased hepatotoxicity during pregnancy and early post-partum
  - Proceed to LTBI tx if HIV infected, close contact, or converter
- INH preferred treatment
  - Crosses placental barrier, but no teratogenicity
  - RIF likely safe
  - Lacks efficacy data, possibly higher rate of fetal abnormalities

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### 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

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### Contacts

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

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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 for:
  - HIV infected
  - <21 years old who have been in contact with a smear-positive case
  - Immunocompromised
  - Prior to severe immune suppression (e.g. transplant, anti-TNF)

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

Treatment: Summary

- The following choices are available:
  - 9 months INH
  - 3 months/12 dose INH+RFP (DOPT)
  - 6 months INH (acceptable in non-immunocompromised adults)
  - 4 months RIF (6 months for children or immunocompromised)
  - 2 months RIF (e.g. in setting of TB5 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)
TST vs. IGRA –
What to do with Discordant Results

- Avoid using two tests for TB screening

- TST+ / IGRA−
  - Foreign born with BCG and no severe immunocompromising condition - attribute to BCG
  - Caveat - abnormal CXR confirmed old TB and with risk factor for progression to disease, consider treatment
  - U.S. born - with no risk factors for exposure or risk factors for progression - may be NTM colonization

- TST− / IGRA+
  - Foreign born with BCG and no severe immunocompromising condition - consider repeat IGRA if near cutoff point, e.g. TB Ag-nil < 0.7
  - U.S. born with no risk factors for exposure or progression - repeat IGRA

- If discordant TST/IGRA and severe immunocompromising condition, offer LTBI

- If severe immunocompromising condition and if TST-/IGRA− and abnormal CXR confirmed old TB, offer LTBI treatment

Example of local TST/IGRA evaluation, SF

<table>
<thead>
<tr>
<th></th>
<th>Homeless</th>
<th>TB Clinic</th>
<th>Methadone</th>
<th>Immigrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (2001-2003)</td>
<td>26%</td>
<td>~50%</td>
<td>10%</td>
<td>37%</td>
</tr>
<tr>
<td>QFT-1 (11/01-2/05)</td>
<td>17% (n=1848)</td>
<td>48% (n=292)</td>
<td>18% (n=346)</td>
<td>37% (n=344)</td>
</tr>
<tr>
<td>QFT-G (1/05-11/06)</td>
<td>7% (n=956)</td>
<td>23% (n=4042)</td>
<td>4% (n=1261)</td>
<td>14% (n=2505)</td>
</tr>
<tr>
<td>QFT-IT (4/08-2/09)</td>
<td>6% (n=1625)</td>
<td>22% (n=1555)</td>
<td>----</td>
<td>20% (n=323)</td>
</tr>
<tr>
<td>Decline in positive rate from TST</td>
<td>↓ 73%</td>
<td>↓ 54%</td>
<td>↓ 60%</td>
<td>↓ 62%</td>
</tr>
</tbody>
</table>