Mayo Clinic Center for Tuberculosis

Diagnosis of LTBI and IGRA Testing

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Diagnosis of LTBI and IGRA Testing
(or Are You Using IGRA testing or is IGRA testing Using You?)

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September 2014
Disclosures

- Medical Consultant, TB Control Program, Indiana State Department of Health
- Clinical trials with Merck, Genzyme and Romark
- Have personally endured over 32 Tuberculin skin tests
Outline/Objectives

• Historical literary significance of TB
• Tuberculosis Incidence – U.S. and Indiana
• Latent TB Infection (LTBI) definition review
• Current Testing and Screening for LTBI
  • Tuberculin Skin Testing
  • Interferon Gamma Release Assay testing
• LTBI Treatment options
  • CDC Standard Recommendations
  • Data review of INH/Rifapentine regimen
  • Data review of alternative LTBI treatments
  • Future directions
Percival Pott’s Legacy (1714-1788)

• 1997, workers stumbled across several graves, one marked “In Memory. Timothy Cratchit. 1839–1884. Beloved Husband of Julia, Father of Robert, and Son of Robert and Martha.”

• Beneath the stone, skeletal remains of a man approx. 40 years of age wearing a frame of metal and leather on his legs and lower back.

• Skeletal analysis noted bony changes and PCR revealed *M.tuberculosis* DNA, consistent with Pott’s Disease.

Callaghan. The Journal of Infectious Diseases 1997;176:1653–4
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Callaghan. The Journal of Infectious Diseases 1997;176:1653–4
TB Progress over past decade used old tools:

- Increased use of Directly Observed Therapy
- Sputum smears and cultures to diagnose active TB (Nucleic Acid Testing)
- INH, Rifampin, Pyrazinamide and ethambutol for active TB
- Tuberculin skin test to diagnose Latent TB infection (LTBI)
- INH to treat LTBI
- So What’s New???
~ 30% of heavily exposed persons will become infected

Small, NEJM 2001
2013 stats:
9,582 cases
3.0 cases/100K
5% drop from ‘12!
Latent TB Infection (LTBI)

- LTBI is the presence of *M. tuberculosis* infection without symptoms or radiographic evidence of TB disease
- “Treatment of latent TB infection” replaces the terms “preventive therapy” & “chemoprophylaxis”.
- **Targeted** tuberculosis testing
  - Groups at the *highest* risk for TB
  - “Decision to test is a decision to treat”
Persons at Higher Risk for Exposure to or Infection with TB

- Close contacts of known or suspected TB
- Persons from high TB endemic areas
- Residents and employees of high-risk congregate settings
- Health care workers (HCWs)
  - high-risk clients
Persons at Higher Risk for Exposure to or Infection with TB (cont.)

- Medically underserved, low-income populations
- High-risk ethnic minority populations
- Children exposed to high-risk adults
- Persons who inject illicit drugs
TB Case Rates in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2011*

*Updated as of June 25, 2012.
Percentage of TB Cases Among Foreign-born Persons, United States*

Darker shading coming soon!

*Updated as of June 10, 2013.
State of Indiana tuberculosis - 2013

Cases = 94 (down 7.8% ! )
Crude Incidence Rate per 100,000 = 1.4
  (U.S. 2012 = 3.4)
Race and Ethnicity-specific Incidence Rates
White, not Hispanic or Latino = 0.8
Black or African-American = 5.1
Hispanic or Latino, all races = 2.6
Asian = 25.4
Hawaiian Native or other Pacific Islander = n/a
American Indian or Alaska Native = N/A
Males = 1.9
Female = 1.0
Medical Evaluation for TB
Tests for *M. tuberculosis* Infection

- Two methods for detecting TB infection: Tuberculin Skin Test (TST) and IGRAs
- TST and IGRAs help differentiate persons with TB infection from those *not* infected
- **No** differentiation between Active disease versus Latent infection – requires *further* assessment
- Negative reaction to either does *not exclude* diagnosis of TB or LTBI, especially in high-risk or high-suspicion patients
CDC LTBI Testing Recommendations

• The diagnosis of LTBI is based on medical history, TST or IGRA result, chest radiograph, physical examination, and in some cases, sputum examinations

• TB disease must be excluded before treatment for LTBI is initiated to avoid inadequate treatment and drug resistance

• CDC discourages testing for LTBI among individuals/populations at low risk for TB infection

• Testing is sometimes done to meet administrative or legal requirements for groups who are not considered high risk (school or workplace)

Medical Evaluation for TB
Tests for *M. tuberculosis* Infection
Immune background of TB tests

Testing for TB-specific cell-mediated immunity

Presentation of mycobacterial antigens

Antigen presenting cell

Memory T cell

Measurement of induration and erythema

Skin test

IFN\(_{\gamma}\)

TNF\(_{\alpha}\)

IL8

In vitro blood test

IFN\(_{\gamma}\)

TNF\(_{\alpha}\)

IL8, etc

Measurement of induration and erythema

Delayed-type Hypersensitivity (Type IV)

Administration and reading of the Tuberculin Skin Test

- Inject intradermally
  - 0.1 ml of 5 TU PPD
- Read reaction 48-72 hrs
- Measure only induration
- Record diameter of reaction in millimeters
CDC TST Interpretation Recommendations

• Training is essential to gain proficiency in the administration and interpretation of the TST

• The TST should not be performed on a person with written documentation of previous positive TST or treatment for TB disease

• Patients or family members should never measure TST results; only by trained HCWs

• Interpretation of the TST result is the same for persons who have had BCG vaccination
  • most BCG cross-reactivity wanes with time

• A TST that was not measured and recorded in millimeters (mm) of induration in a timely manner must be repeated
Diagnosis of TB by TST

15 mm of induration

Considered positive in virtually all settings:

Including –

- Persons with no known risk factors
Diagnosis of TB by TST

10 mm of induration is positive with:

Exposure risks
- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents/employees of high-risk settings
- TB laboratory personnel

Host susceptibility
- High Risk clinical conditions:
  - DM, CRI, silicosis, cancer, gastrectomy, malnutrition
- Children <4 yrs or exposed to high-risk adults
Diagnosis of LTBI by TST

5 mm is positive with highest exposure or susceptibility risk groups:

- Recent contacts of TB cases
- Persons with fibrotic changes on CXR consistent with old healed TB
- HIV-positive persons
- Patients with organ transplants and other immunosuppressed patients
  - >15 mg/d of prednisone for 1 month
  - TNF-α antagonists (e.g. etanercept)
Limitations of TST

- False positive:
  - BCG, wanes over time
  - Non-tuberculous mycobacteria, usually < 10 mm

- False negative:
  - Recent TB infection, peak response at 6 weeks
  - Overwhelming active tuberculosis
  - Very young age (<6 months old)
  - Immuno-compromised: HIV, immunosuppressed
  - Severe illness
  - Poor technique*
Beyond the TST: Whole Blood IFN-γ assays

- Uses antigens *specific* to M. tuberculosis (RD1 antigens; ESAT-6, CFP-10), *not cross-reactive* with BCG or most NTMB species. **Specificity better than TST**
  - ELISA: QuantiFERON® assay of PBMCs
  - ELISpot: T SPOT-TB ® assay for reactive T-cells
  - Sensitivity only ~70-75%, no better than TST
  - The Negative Predictive Value is high for both
    - 99% for TST, and approaching 100% for the IGRAs
Interferon–Gamma Release Assays (IGRAs)

• Advantages of IGRAs:
  • Requires a single patient visit
  • Do not cause booster phenomenon
  • Reading of test not affected by reader’s perception or bias*
  • Results may be ready in 24 hrs
  • Not impacted by BCG / most NTB mycobacteria#

• Limitations of IGRAs include:
  • Blood processing within 8-30 hrs*
  • Limited data on use in children under 5, recent TB exposures, immunocompromised persons, and in serial testing*

# - Species *kansasii*, *marinum*, and *szulgei* still cross-react
Interpretation of IGRA Results

- The interpretation of IGRA results is based:
  - The amount of IFN-γ released for QFT, or
  - Number of cells that release IFN-γ, in T-SPOT®
  - Laboratories provide both the qualitative and quantitative results

- Qualitative results are reported as positive, negative, indeterminate or borderline.

- Quantitative results are reported as numerical values that include a response to the TB antigen and 2 controls, nil and mitogen. Quantitative results may be useful for clinical decision making in individual cases, in combination with risk factors.
Sensitivity for detecting TB infection
Tuberculin Skin Test – pooled 70%

Sensitivity for detecting TB infection
T-spot testing – pooled 88%

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Pooled Sensitivity, %</th>
<th>Patients, n/n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Elispot</td>
<td>88</td>
<td>491/557</td>
</tr>
<tr>
<td>Elispot ESAT-6 and CFP-10</td>
<td>87</td>
<td>367/424</td>
</tr>
<tr>
<td>Goletti et al., 2006 (24)</td>
<td>21/23</td>
<td></td>
</tr>
<tr>
<td>Ferrara et al., 2006 (23)</td>
<td>20/24</td>
<td></td>
</tr>
<tr>
<td>Aiken et al., 2006 (38)</td>
<td>70/85</td>
<td></td>
</tr>
<tr>
<td>Nicol et al., 2005 (42)</td>
<td>10/12</td>
<td></td>
</tr>
<tr>
<td>Meier et al., 2005 (77)</td>
<td>70/73</td>
<td></td>
</tr>
<tr>
<td>Liebeschuetz et al., 2004 (45)</td>
<td>33/57</td>
<td></td>
</tr>
<tr>
<td>Schölvink et al., 2004 (81)</td>
<td>13/13</td>
<td></td>
</tr>
<tr>
<td>Chapman et al., 2002 (46)</td>
<td>47/50</td>
<td></td>
</tr>
<tr>
<td>Elispot ESAT-6</td>
<td>93</td>
<td>124/133</td>
</tr>
<tr>
<td>Pathan et al., 2001 (40)</td>
<td>33/36</td>
<td></td>
</tr>
<tr>
<td>Lalvani et al., 2001 (27)</td>
<td>45/47</td>
<td></td>
</tr>
<tr>
<td>Lalvani et al., 2001 (28)</td>
<td>46/50</td>
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</table>
Sensitivity for detecting TB infection
Quantiferon testing – pooled 76%

<table>
<thead>
<tr>
<th>All QFT</th>
<th>76</th>
<th>415/544</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESAT-6 and CFP-10/TB7.7</td>
<td>67</td>
<td>89/133</td>
</tr>
<tr>
<td>Dogra et al., 2006 (26)</td>
<td></td>
<td>5/8</td>
</tr>
<tr>
<td>Pai et al., 2005 (87)</td>
<td></td>
<td>59/80</td>
</tr>
<tr>
<td>Dewan et al., 2006 (82)</td>
<td></td>
<td>24/45</td>
</tr>
<tr>
<td>ESAT-6 and CFP-10</td>
<td>80</td>
<td>315/393</td>
</tr>
<tr>
<td>Goletti et al., 2006 (24)</td>
<td></td>
<td>19/23</td>
</tr>
<tr>
<td>Lee et al., 2006 (22)</td>
<td></td>
<td>61/87</td>
</tr>
<tr>
<td>Ferrara et al., 2006 (23)</td>
<td></td>
<td>17/24</td>
</tr>
<tr>
<td>Connell et al., 2006 (50)</td>
<td></td>
<td>9/9</td>
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<tr>
<td>Ravn et al., 2004 (83)</td>
<td></td>
<td>40/48</td>
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<tr>
<td>Kang et al., 2005 (30)</td>
<td></td>
<td>44/54</td>
</tr>
<tr>
<td>Ferrara et al., 2005 (84)</td>
<td></td>
<td>6/11</td>
</tr>
<tr>
<td>Mori et al., 2004 (85)</td>
<td></td>
<td>105/118</td>
</tr>
<tr>
<td>Brock et al., 2001 (68)</td>
<td></td>
<td>14/18</td>
</tr>
</tbody>
</table>
Interferon gamma release assays

- Sensitivity may not be greater than TST, 70–75% range
- IGRA tests – greater specificity than TST
  - IGRA are not affected by BCG or most NTMB
- Not useful in severe lymphopenia
- Access and expense may be issue
- Pediatric role unknown at present
- No test distinguishes active from latent disease 😞

Concerns with IGRA as a screening tool in HCWs

- **QFT reversions** — initial positive, followed by negative
  - Baseline TST+/QFT+: only 7% [N=28]
  - Baseline TST-/QFT+: 70% [N=10]

<table>
<thead>
<tr>
<th>Baseline QFT result</th>
<th>Retested (n)</th>
<th>Treated (n)</th>
<th>Reversions (n)</th>
<th>Reversions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35-0.69</td>
<td>11</td>
<td>1</td>
<td>6</td>
<td>55%</td>
</tr>
<tr>
<td>0.7-1.0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>1.1-5.0</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>11%</td>
</tr>
<tr>
<td>&gt; 5.0</td>
<td>16</td>
<td>9</td>
<td>1</td>
<td>6%</td>
</tr>
</tbody>
</table>

Pai M et al, Serial testing of health care workers for tuberculosis using interferon-g assay. AJRCCM 2006
## IGRAs use in HCW screening v. TST

<table>
<thead>
<tr>
<th>Definition of conversion from negative baseline</th>
<th>Cumulative conversions by 18 months N (%)</th>
<th>P value v. TST conversion rate (21/2293 [0.9%])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QFT-GIT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.35 IU/ml (mftr definition of positive)</td>
<td>138/2263 (6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;0.7 IU/ml</td>
<td>53/2263 (2.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;0.35 IU/ml and 2.6 times baseline value</td>
<td>79/2263 (3.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;0.35 IU/ml and positive repeat test</td>
<td>25/2263 (1.1%)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>T-spot</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;8 spots (mftr definition of positive)</td>
<td>177/2137 (8.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;8 spots and increase of 7 or more spots from baseline</td>
<td>142/2137 (6.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt; 8 spots and positive repeat test</td>
<td>27/2137 (1.3%)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Reference – Dr. Neil Schluger. CDC-sponsored trial comparing TST with QFT and T.SPOT in 2500 HCWs (NYC, Baltimore, Houston, Denver) All 3 tests performed every 6 months for 18 months.

• Validated model on a sample of 862 HCWs from three US hospitals to define a QuantiFERON Gold In-Tube retesting zone between 0.35 and 1.11 IU/mL

• The upper value was selected by a receiver operating characteristic (ROC) analysis

• Looked to maximize separation between HCWs
  • who have two consecutive positive tests, and
  • those who have reversions

• HCWs had a 75% risk for reversion if initial positive test fell within the 0.35 to 1.11 range

Delineating a Retesting Zone Using Receiver Operating Characteristic Analysis on Serial QuantiFERON Tuberculosis Test Results in US Healthcare Workers

• Determined 0.35–1.11 IU/mL as optimal retesting zone
• 0.35–0.72 IU/mL (80% reversion; P < 0.01) is another possible separation point
• Similar to the clinical situation much like the 5, 10, and 15 mm tuberculin skin test cut-off points
• Using higher cut-off values for QFT retesting could:
  • lessen patient anxiety
  • decrease unnecessary radiographs
  • prevent unnecessary exposure investigations
  • Possibly spare patients from inappropriate medical treatment due to a transiently “positive” QFT test

More problems with IGRA testing

Investigation of false-positive results given by the QuantiFERON-TB Gold In-Tube assay

Abstract - We investigated a sudden increase in the rate of positive QuantiFERON-TB Gold In-Tube results from 10% to 31% at a U.S. academic institution. Direct comparison of the TB antigen tubes with tubes from a different lot number identified that a potential problem with the TB antigen vials in a certain tube lot was the likely cause of the elevated positive rate. The underlying defect remains unknown. This finding warrants refinement of quality control programs by the manufacturer and users.

Interferon gamma release assays

Summary

• More work needed to define and interpret
  • Negative result range
  • Indeterminate result range
  • Positive result range

• Use in low-incidence populations, including HCW may be complicated by current “false-positive” rates

• Use in high-risk groups warranted, but care needed with immunocompromised pts with low white counts
Selecting a Test to Detect TB Infection

• IGRAs are the preferred for:
  • People who have poor rates of return for TST reading and interpretation (e.g., homeless)
  • Persons who have received BCG vaccination or are known to have NTBM infection
• TST is the preferred method for testing for:
  • Children under the age of 5 yrs
• Either TST or IGRA may be used for other groups tested for LTBI
• *Routine* testing with **both** TST and IGRAs is **NOT** recommended (with certain exceptions)
TB Advisory: Nationwide Shortage of Tuberculin

Sanofi-Pasteur reported a supply interruption for Tubersol®, until late-spring 2013. Allocations will go into effect.

• Indiana State Dept of Health’s TB Program recommends:
  • If appropriate, screen with an Interferon Gamma Release Assay (IGRA) (T-SPOT®.TB and QuantiFERON® Gold in-tube) instead of TST.

• Prioritize TSTs if necessary. High priority groups include:
  • Contacts to a person active TB, immunocompromised, symptoms suggestive of TB

• Defer annual screening until tuberculin available.

• Aplisol®, is an acceptable alternative to Tubersol®. Recommend to use the same preparation of tuberculin to avoid reported false-positive tests with switching.
# Treatment of LTBI

<table>
<thead>
<tr>
<th>TREATMENT REGIMEN</th>
<th>DOSE</th>
<th>TOXIC EFFECTS</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| **Isoniazid**  
for 9 mo  
(6 mo if unable to do 9mo) | 5 mg/kg of body weight (maximum 300 mg) daily  
270 doses  
or  
900 mg twice weekly (DOT) | Hepatitis; rash; peripheral neuropathy  
Risk of hepatitis increases with age and alcohol use  
*MUST give pyridoxine supplement* | Clinical monitoring monthly;  
base-line & F/u LFT only in persons with risk factors for hepatitis |
| **Rifampin**  
for 4 mo | 10 mg/kg (maximum 600 mg) | Hepatitis; rash; thrombocytopenia; fever; orange-colored body fluids | Drug interactions can result in decreased levels of many drugs (e.g., warfarin, OCP, and Methadone). |
| **Isoniazid & Rifapentine** | Three month combination therapy appears equivalent and nearly superior to INH for 9 months (3 RCT of 400, 1200, and 8,000 pts, mainly outside the U.S. and all with DOT.). 12 doses | Rash and hypersensitivity  
~5% discontinuation rate for INH/RPT | MMWR 12/2011  
Stay tuned for data on efficacy in HIV co infection and children |

LTBI Treatment Regimens

An optimal LTBI treatment should be minimally toxic and as short as possible to ensure high completion rates.

Globally, 6 to 9 mo, and U.S. 9 mo of INH monotherapy is recommended.

Alternatives include that may be equal:

- 3 mo INH plus rifampicin
- 3 - 4 mo rifampin alone
- 12 wks INH plus rifapentine

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. 2011. NEJM

• Open-label, randomized noninferiority trial

• Compared 3 mo of DOT once-weekly rifapentine plus isoniazid with 9 months of self-administered daily isoniazid in subjects at high risk for TB in Brazil, Spain, Canada and U.S. and followed for 33 mo

• Primary end point was confirmed active TB, and the noninferiority margin was 0.75%

TR Sterling, et al. PREVENT TB Study Team NEJM 2011; 365:2155-66
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. 2011. NEJM

- Modified intention-to-treat analysis, TB developed in 7 of 3986 subjects in the combo group (0.19%) and in 15 of 3745 of the INH-only group (0.43%)

- Treatment completion rate
  - 82.1% in the combo group
  - 69.0% in the INH-only group (P<0.001)
  - Rates of investigator-assessed drug-related hepatotoxicity were 0.4% and 2.7% (P<0.001)

TR Sterling, et al. PREVENT TB Study Team NEJM 2011; 365:2155-66
Dosage for a combination regimen of isoniazid and rifapentine in 12 once-weekly doses under direct observation for treating latent Mycobacterium tuberculosis infection. MMWR December 9, 2011

- **MUST BE DONE WITHIN A DOT PROGRAM***

- **Isoniazid**
  - 15 mg/kg rounded up to the nearest 50 or 100 ;
  - 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

- INH is formulated as 100 mg and 300 mg tablets. Rifapentine (RPT) is formulated as 150 mg tablets, new formulations and fixed-dose INH-RPT combos are in development.
LTBI Treatment

• Randomized trial of placebo, 6INH, 3 mo INH plus Rifampin, or 3 mo Rifampin alone with five yr follow up
  • 27% of placebo developed active TB
  • 16, 13, and 10% of the INH, INH/RIF, or RIF alone developed active TB

• 3 mo rifampin was approximately 65 per cent; better than the other regimens although the differences between regimens was not significant, and all were better than placebo

LTBI Treatment

• There are no other published trial evaluating mono-RIF therapy

• Several studies report completion rates with 4RIF are better than 9INH

• Rates of serious adverse events with 4RIF are very low, particularly hepatotoxicity

LTBI Treatment Regimen Alternatives

- Past reviews of LTBI treatment used conventional meta-analyses
- Bayesian hierarchical models allow indirect comparison of regimens and produce inferences of relative efficacy
- Systematic review of RCTs of LTBI treatment were done to determine relative efficacies and adverse event profiles of different regimens
- 53 studies were reviewed and compare

Table 1. Odds Ratios for the Prevention of Active Tuberculosis, Derived From the Network Meta-analysis*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Odds Ratio (95% Credible Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>1.82 (1.05–3.05)</td>
</tr>
<tr>
<td>INH 3–4 mo</td>
<td>0.94 (0.53–1.56)</td>
</tr>
<tr>
<td>INH 6 mo</td>
<td>0.64 (0.48–0.83)</td>
</tr>
<tr>
<td>INH 9 mo</td>
<td>0.94 (0.40–2.10)</td>
</tr>
<tr>
<td>INH 12–72 mo</td>
<td>0.52 (0.41–0.66)</td>
</tr>
<tr>
<td>RFB-INH</td>
<td>0.28 (0.05–1.49)</td>
</tr>
<tr>
<td>RFB-INH (high)</td>
<td>0.31 (0.06–1.59)</td>
</tr>
<tr>
<td>RPT-INH</td>
<td>0.61 (0.29–1.22)</td>
</tr>
<tr>
<td>RMP</td>
<td>0.41 (0.18–0.86)</td>
</tr>
<tr>
<td>RMP-INH 1 mo</td>
<td>1.07 (0.36–2.79)</td>
</tr>
<tr>
<td>RMP-INH 3–4 mo</td>
<td>0.52 (0.34–0.79)</td>
</tr>
<tr>
<td>RMP-INH-PZA</td>
<td>0.34 (0.18–0.62)</td>
</tr>
<tr>
<td>RMP-PZA</td>
<td>0.55 (0.33–0.92)</td>
</tr>
<tr>
<td>INH-EMB</td>
<td>0.91 (0.32–2.42)</td>
</tr>
</tbody>
</table>

EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RFB = rifabutin; RMP = rifampicin; RPT = rifapentine.

* All comparisons vs. placebo.
### Table 3. Standard Random-Effects Meta-analysis for Hepatotoxicity*

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Treatment</th>
<th>Comparisons, n†</th>
<th>Odds Ratio (95% CI)</th>
<th>I², %</th>
<th>P Value</th>
<th>Publication Bias‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>INH 6 mo</td>
<td>1</td>
<td>0.99 (0.42–2.32)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>No treatment</td>
<td>INH 12–72 mo</td>
<td>2</td>
<td>4.96 (0.27–90.37)</td>
<td>73.3</td>
<td>0.053</td>
<td>–</td>
</tr>
<tr>
<td>Placebo</td>
<td>INH 12–72 mo</td>
<td>3</td>
<td>0.59 (0.23–1.55)</td>
<td>46.3</td>
<td>0.156</td>
<td>–</td>
</tr>
<tr>
<td>INH 6 mo</td>
<td>INH 12–72 mo</td>
<td>2</td>
<td>2.92 (0.90–9.44)</td>
<td>74.1</td>
<td>0.049</td>
<td>–</td>
</tr>
<tr>
<td>INH 6 mo</td>
<td>RPT-INH</td>
<td>1</td>
<td>1.00 (0.50–1.99)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>INH 9 mo</td>
<td>RPT-INH</td>
<td>1</td>
<td>0.16 (0.10–0.27)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>INH 12–72 mo</td>
<td>RPT-INH</td>
<td>1</td>
<td>0.20 (0.11–0.37)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>INH 6 mo</td>
<td>RMP</td>
<td>1</td>
<td>0.03 (0.00–0.48)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>INH 9 mo</td>
<td>RMP</td>
<td>3</td>
<td>0.17 (0.06–0.47)</td>
<td>0.0</td>
<td>0.982</td>
<td>–</td>
</tr>
<tr>
<td>INH 6 mo</td>
<td>RMP-INH 3–4 mo</td>
<td>4</td>
<td>0.89 (0.52–1.55)</td>
<td>0.0</td>
<td>0.921</td>
<td>–</td>
</tr>
<tr>
<td>INH 9 mo</td>
<td>RMP-INH 3–4 mo</td>
<td>1</td>
<td>0.73 (0.24–2.20)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>INH 12–72 mo</td>
<td>RMP-INH 3–4 mo</td>
<td>2</td>
<td>0.20 (0.11–0.35)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RPT-INH</td>
<td>RMP-INH 3–4 mo</td>
<td>1</td>
<td>0.87 (0.43–1.78)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Placebo</td>
<td>RMP-INH-PZA</td>
<td>1</td>
<td>3.02 (0.12–74.31)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>INH 6 mo</td>
<td>RMP-INH-PZA</td>
<td>1</td>
<td>3.49 (0.14–85.82)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RMP-INH 3–4 mo</td>
<td>RMP-INH-PZA</td>
<td>1</td>
<td>3.62 (0.15–89.01)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>INH 6 mo</td>
<td>RMP-PZA</td>
<td>4</td>
<td>3.47 (1.46–8.25)</td>
<td>36.3</td>
<td>0.195</td>
<td>–</td>
</tr>
<tr>
<td>INH 12–72 mo</td>
<td>RMP-PZA</td>
<td>1</td>
<td>1.26 (0.58–2.70)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RPT-INH</td>
<td>RMP-PZA</td>
<td>1</td>
<td>7.98 (1.79–35.58)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RMP-INH 3–4 mo</td>
<td>RMP-PZA</td>
<td>1</td>
<td>1.79 (0.67–4.76)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**EMB** = ethambutol; **INH** = isoniazid; **PZA** = pyrazinamide; **RFB** = rifabutin; **RMP** = rifampicin; **RPT** = rifapentine.

* Results of standard random-effects meta-analysis (or single-study estimates) for all comparisons of regimens for hepatotoxicity.
† Where n > 1, heterogeneity is assessed via the I² statistic (with P value). Where n > 4, publication bias is assessed via the Harbord test.
‡ P value from the Harbord test.
LTBI Regimen Comparisons

• In comparison with INH monotherapy, the evidence base for other drug treatments is small.

• 3 to 4 months of RMP monotherapy ranked highly for efficacy and a low hepatotoxicity.

• Short duration RMP monotherapy has been reported to be at least as effective as INH with possibly higher rates of completion.

• Regimens with PZA were efficacious but generally had unacceptable toxicity.

The Future of LTBI treatment?

- The HALT [Hepatitis and Latent Tuberculosis]: LTBI, ISRCTN04379941 and Centers for Disease Control and Prevention study 33 (NCT01582711) are investigating RPT-INH adherence without direct observation.

- The long half-life of RPT is a key factor in weekly RPT-INH being noninferior to SOC

- Even shorter regimens may be feasible with other anti-TB drugs that also have a long half-life, such as bedaquiline, assuming a good AE profile compared to existing TB drugs

The Future of LTBI treatment?

- Regimens containing rifamycins may be just as, if not more, effective than INH monotherapy for treating LTBI

- The post-2015 WHO strategy of global elimination of TB in our lifetime depends on shorter, effective, and well-tolerated LTBI regimens.

Recent Shortages of Antituberculosis Drugs - INH

- **National Shortage of Isoniazid 300 mg Tablets.**

  MMWR December 21, 2012 / 61(50);1029-1029

  The three U.S. suppliers of INH: Teva, Sandoz, and VersaPharm. Teva is reporting low inventory and possible backorder of INH 300 mg because of a delay in receiving its shipment of INH. Sandoz is reporting a shortage of the active ingredient from its supplier. VersaPharm estimates it will be able to fill orders in December 2012.

- CDC and FDA are collaborating to identify solutions to ensure a continuous supply of anti-TB medication. TB programs experiencing any difficulties obtaining medications are encouraged to report them to Sundari Mase, smase@cdc.gov, at CDC or to their state TB program. Programs should contact their pharmacy to coordinate obtaining alternative combination pills. Up-to-date information on drug availability is available at http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm

  As of 4/2/2013, two of the three suppliers were online again.
References/Resources

- Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005 MMWR Dec. 30, 2005 / 54(RR17);1-141
  http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm?s_cid=rr5417a1_e

- CDC – TB 101 for Health Care Workers

- CDC Core Curriculum on Tuberculosis – updated 2011

- Dr. Neil Schluger. CDC-sponsored trial comparing TST with QFT and T.SPOT in 2500 HCWs (NYC, Baltimore, Houston, Denver)


- Pai M et al, Serial testing of health care workers for tuberculosis using interferon-g assay. AJRCCM 2006
References/Resources

  Dick Menzies, MD, MSc; Madhukar Pai, MD, PhD; and George Comstock, MD, DrPH


• Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection.
  MMWR December 9, 2011 / 60(48);1650-1653
  http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_e%0d%0a