Diagnosis and Treatment of TB Infection
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TB Nurse Case Management
San Antonio, Texas
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Barbara Seaworth MD has the following disclosures to make:

- No conflict of interests

- No relevant financial relationships with any commercial companies pertaining to this educational activity
What We Will Cover

• Diagnosis of LTBI
  – Identifying those at risk of TB exposure

• Determining Who to Treat
  – Identifying those at risk of progression to TB disease

• LTBI Therapy – What Regimen is Best?
What We Will Not Cover: Active TB Disease

• Active infectious process involving the lungs ± other organs
  – CXR Abnormal in pulmonary TB in most persons
• Symptoms (may be absent in those persons found during a CI)
  – Fever
  – Chills
  – Night Sweats
  – Weight Loss
  – Fatigue
  – Cough (dry or productive)
  – Hemoptysis
• When TB disease involves the lungs, the person is infectious
Latent TB Infection

• Persons are infected with *Mycobacterium tuberculosis* but:
  – No Active TB Symptoms
  – Chest X-ray may be normal, or show granuloma, **stable** pleural or parenchymal scarring
  – Positive TST or IGRA
LATENT TB INFECTION

• Persons with LTBI are NOT infectious
• 90 +% chance of never getting Active TB Disease

• But the TB organism is in your body!

• “…a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB”

WHO Guidelines on the management of Latent Tuberculosis Infection 2015
LATENT TB INFECTION

• We used to think the bacteria were in a resting state or dormant but

  • TB Bacteria are metabolically active and dividing, but infection is controlled by the immune system.

– Current methods of LTBI diagnosis are less than perfect

– Active TB Disease may develop if immunity wanes.
The Spectrum of Activity of MTB – One Could Think of Popcorn
Progression of LTBI to Active TB Disease
Increased By

- HIV infection
- Chronic kidney disease
- Silicosis
- Recent exposure
- Diabetes
- Chest x-ray abnormality c/w previous inadequately treated TB
- Intravenous drug use
- Smoking – active and passive
- Underweight by >10%

ATS-CDC. Am J Respir Crit Care Med 2000;161:S221
Progression of LTBI to Active TB Disease
Increased By

• Pregnancy and first three months post partum
• Immunosuppression
  – Hematologic cancers and head and neck cancers
  – Medications
    • TNFα inhibitors
    • Prednisone >15 mg, > 4 weeks
    • Chemotherapy
    • Other immunosuppressive drugs
• **Recommend IGRA rather than TST** for persons ≥ 5
  
  – 1) likely to be infected with MTB
  – 2) **low or intermediate risk** of progression to disease
  – 3) decided testing is warranted and
  – 4) *have either a history of BCG or are unlikely to return for reading*

  • *(Strong recommendation, moderate quality evidence)*
  • TST acceptable if IGRA not available, too costly, too burdensome.
Strength of Recommendation

• **Strong**: confident that benefits > harms
  – Patients: should expect recommended course of action
  – Providers: should follow recommended course of action
  – Policy makers: recommendation can be adopted as policy
    “We **recommend** using/against using....”

• **Conditional**: benefits likely outweigh harms, but less confident
  – Patients: most but not all would want recommended course of action
  – Providers: different choices may be appropriate for some patients
  – Policy makers: policy making will require substantial debate
    “We **suggest** using/against using....”
Recommend IGRA rather than TST for persons ≥ 5

- 1) likely to be infected with MTB
- 2) low or intermediate risk of progression to disease
- 3) decided testing is warranted and
- 4) have either a history of BCG or are unlikely to return for reading

- (Strong recommendation, moderate quality evidence)
- TST acceptable if IGRA not available, too costly, too burdensome.
Suggest IGRA rather than TST for all other persons ≥ 5:

- 1) likely to be infected with MTB
- 2) low or intermediate risk of progression to disease
- 3) decided testing is warranted and
  - (Conditional recommendation, moderate quality evidence)
  - TST acceptable if IGRA not available, too costly, too burdensome.
ATS/IDSA/CDC
Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

• Insufficient data to recommend a preference either a TST or IGRA for all other persons ≥ 5:
  – 1) likely to be infected with MTB
  – 2) have a high risk of progression to disease
  – 3) decided testing is warranted
Guidelines **recommend** persons at low risk for MTB infection and disease progression **NOT** be tested.

– If testing is performed in those unlikely to be infected despite guidelines to contrary:
  • We **suggest** performing an IGRA instead of a TST.
    – *(conditional recommendation, very low-quality evidence)*
  • We **suggest** a 2\(^{nd}\) diagnostic test if initial test positive
    – Confirmatory test may be either IGRA or TST
    – Person **considered infected only if both tests positive**.
    – *(conditional recommendation, very low-quality evidence)*
ATS/IDSA/CDC
Clinical Practice Guidelines: Diagnosis of TB in Adults and Children

• We suggest performing a TST rather than an IGRA in healthy children under 5:
  – 1) for whom it has been decided testing is warranted
    • (conditional recommendation, very low-quality evidence)

New 2018 version of Pediatric Red Book recommends IGRA down to age 2
Treating TB Infection

Wait — Are We There Yet?

“NO!”
Active TB Disease or TB Infection?
The Clinical Evaluation

The single most important thing prior to starting treatment for TB Infection is to exclude active TB disease.

If in doubt – wait!
Evaluate for TB disease
Consider consultation with TB expert
Evaluate to Exclude Active TB Disease

• If the TST or IGRA is Positive –
  » OR

• Patient has been exposed and is symptomatic
  – At least 10% of persons with active TB disease are IGRA/TST negative

• Child < 5 or immunocompromised person with recent exposure even if TST/IGRA negative –

• Evaluation includes:
  ✓ History
  ✓ Physical examination
  ✓ Chest X-Ray
Remember that the TST or IGRA may be negative in those with active TB!
Is There Evidence of Disease?

- Medical History:
  - HIV
  - Silicosis
  - Chronic Kidney Disease
  - Diabetes
  - Immunosuppression
  - Drug/alcohol/tobacco
  - TB exposure

Is Patient at Risk of Progression to Disease?

- Symptoms*
  - Fever
  - Chills
  - Night Sweats
  - Weight Loss
  - Cough (dry/productive)
  - Hemoptysis
  - Fatigue
  * only one may be present
Physical Exam

• General assessment – does person look well?
• Lung exam
• Check for lymph nodes
• Palpate liver
• *In children* look at growth curve/weight/activity
• Look for anything that will complicate therapy!
Radiologic Exam

• CXR must be done **before treatment of TB Infection**
  – Must be read as normal
  
  Or
  
  – IF abnormal:
    • Not consistent with Active TB
    • Stable abnormality confirmed over a 3 month period
Mycobacteriological Laboratory Exam

• If you suspect TB disease due to an abnormal CXR and/or symptoms – collect sputum specimens:
  – Gene Xpert (1) AFB smear (3), and culture(3)

• If Gene Xpert and AFB smears are negative, don’t start TB Infection treatment until cultures are negative – 6 weeks
  – Remember you suspected possible TB disease and you cannot exclude this without a negative culture
  – May be appropriate to start RIPE for disease
Management of Positive TST or IGRA
When the CXR is Not Normal

• Assess likelihood that the CXR abnormality is really TB
• If Patient has NO signs or symptoms of Active TB, CXR possibly c/w TB but no classic findings:
  – Collect 3 sputum specimens for smears and culture
  – Evaluate for symptoms
• If no symptoms and AFB smear/Xpert negative - Wait
  – Repeat CXR after 2 – 3 months
• If CXR stable at 2 – 3 months and cultures negative, treat for TB Infection
Management of Positive TST or IGRA
When CXR is Abnormal c/w TB disease or If Patient Has Signs or Symptoms of Active TB Disease

– The patient should be suspected of having TB disease
– Collect 3 sputa for smear and culture
– Strongly consider starting standard 4 drug (RIPE) treatment – if started report!

• If positive smear and/or Gene Xpert
  – Report to public health and start 4 drug (RIPE) treatment

• Never (ever!) start a treatment for TB infection in a patient with possible active TB
**Deciding When to Treat LTBI**

**Groups Who Should be Given High Priority for LTBI Treatment**

<table>
<thead>
<tr>
<th>People with a positive IGRA result or a TST reaction of ≥ 5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV-infected persons</td>
</tr>
<tr>
<td>• Recent contacts of a TB case</td>
</tr>
<tr>
<td>• Persons with fibrotic changes on CXR c/w old TB</td>
</tr>
<tr>
<td>• Organ transplant recipients</td>
</tr>
<tr>
<td>• Persons immunosuppressed for other reasons</td>
</tr>
<tr>
<td>– taking the equivalent of &gt;15 mg/day of prednisone for ≥ 1 month,</td>
</tr>
<tr>
<td>– taking TNF-α antagonists</td>
</tr>
<tr>
<td>– receiving chemo/radiation therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>People with a positive IGRA result or a TST reaction of ≥ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Persons from high-prevalence countries</td>
</tr>
<tr>
<td>• Injection drug users</td>
</tr>
<tr>
<td>• Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)</td>
</tr>
<tr>
<td>• Mycobacteriology lab personnel</td>
</tr>
<tr>
<td>• Children &lt; 4 years of age,</td>
</tr>
<tr>
<td>• Children and adolescents exposed to adults in high-risk categories</td>
</tr>
</tbody>
</table>
Children Who Should Be Treated Due to Risk of Recent Exposure Once TB Disease Excluded

- Contacts < 5 identified during an investigation surrounding an identified case
  - Treat even if initial TST or IGRA is negative

- Those > 5 who are TST or IGRA positive

- Recent immigrants and refugee children with positive IGRA or in those < 2 positive TST
Why Should Small Children Who Are Exposed to Active TB Disease Be Treated Even When TST or IGRA is Negative?

- Very high rate of infection
- Takes up to 3 months for the skin test to turn positive
  - Small children can very quickly become very sick
- U.S. studies – 10% to 20% of childhood TB cases can be prevented if children exposed in a household are treated
- WHO standards – children <5 years old exposed in a TB household should be treated
Percent Risk of Disease by Age

<table>
<thead>
<tr>
<th>Age at Infection</th>
<th>Risk of Active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – 1 year*</td>
<td>43%</td>
</tr>
<tr>
<td>1 – 5 years*</td>
<td>24%</td>
</tr>
<tr>
<td>6 – 10 years*</td>
<td>2%</td>
</tr>
<tr>
<td>11 – 15 years*</td>
<td>16%</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>5-10% lifetime risk</td>
</tr>
<tr>
<td>HIV Infected Adults+</td>
<td>30-50% lifetime</td>
</tr>
</tbody>
</table>

*Miller, Tuberculosis in Children Little Brown, Boston, 1963
+WHO, 2004
### Risk of Progression to TB Disease by Age

<table>
<thead>
<tr>
<th>Age @ primary infection</th>
<th>Risk of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB Disease</strong></td>
<td>up to 50%</td>
</tr>
<tr>
<td><strong>Pulmonary Disease</strong></td>
<td>30-40%</td>
</tr>
<tr>
<td><strong>Miliary or TB Meningitis</strong></td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>1-2 years</strong></td>
<td>20-25%</td>
</tr>
<tr>
<td><strong>Pulmonary Disease</strong></td>
<td>75%</td>
</tr>
<tr>
<td><strong>Miliary or TB Meningitis</strong></td>
<td>2-5%</td>
</tr>
</tbody>
</table>

Marais BJ. Int J Tuberc Lung Dis 2004;8:392-402
“Window Period” TB Prophylaxis After Exposure

• Household contact with infectious person
  – Initial TST negative
     Window period for TST/IGRA conversion (8-12 weeks)
  – CXR and physical exam normal
  ❖ ‘Window’ prophylaxis recommended:
    ➢ For children <5 yrs of age
    ➢ Immunosuppressed patients, especially HIV positive
    ➢ Patients on tumor necrosis factor-alpha blockers
      ➢ May prevent progression to disease during window period
• Repeat TST or IGRA 8-12 wks after exposure
• May stop treatment if 2nd TST (<5mm) or IGRA is negative in immunocompetent patients
• Consider completion of full course of treatment in HIV + and other immunosuppressed or children < 6 months
• Treating LTBI (to prevent TB disease) - *Indications:*
  
  • (+) screening test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB (*AI*)

  • Close contact with a person with infectious TB, regardless of screening test result (*AII*)


Last updated: Sept 22, 2017; last reviewed: September 22, 2017)
HIV Positive Persons

• All HIV positive persons with TB infection should be treated

• Careful evaluation is needed to exclude TB disease – CXR, symptom screen, sputum if any symptoms present
  – Remember in HIV + persons a positive TST is 5mm or >
  – Both IGRA and TST may be negative – if recently exposed should be treated despite negative screening tests. These may be negative > 10% of the time.
  – A CXR may be negative > 20% of the time (symptoms are important)
Treatment Options for LTBI

- INH +RPT once weekly
- Rifampin daily
- INH 9 daily
- INH 6 daily
- 12 weeks (12 doses)
- 4 months (120 doses)
- 9 months (270 doses)
- 6 months (180 doses)

The longer the duration/more doses, the less likely your patient is to complete treatment

Fewer than 60% complete 9 months of INH
INH and Rifapentine Treatment “3HP”

For those who qualify 3 HP is recommended first option in Texas

Recommendation TB Expert TB Workgroup; 2014
Standing Delegation Orders Texas DSHS 2017
Active TB disease: 7/3986 in 3 HP arm; 15/3745 in 9H arm
Completion of treatment: 82.1% 3HP arm; 69% 9 H arm
Hepatotoxicity: 0.4% 3HP arm; 2.7% 9 H arm.

Conclusion: Use of 3 HP x 3 months was as effective as 9 months of INH and had a higher treatment completion rate.
INH and Rifapentine (3HP) for TB Infection

CDC recommendations 2011:

• 3 HP is another effective regimen option for otherwise healthy patients aged ≥ 2 years who have a predictive factor for greater likelihood of TB developing including:
  – Recent TB contacts
  – TST/IGRA Converters
  – Radiographic findings of healed pulmonary TB
  – HIV positive persons not taking ARV agents

CDC. November 2011.

• Rapidly becoming the regimen of choice for many programs
3HP

• Initially recommended only if given by directly observed treatment (DOT). Recent study showed 3HP was as safe and effective as self administered treatment

• Approved for individuals 2 years and older
  – Pediatric arm published in 2015 shows safety and efficacy down to age 2
    • Completion rates higher,
    • No child had hepatotoxicity,
    • Effective
  – Further studies in progress for newborn to age 2
Tolerability and Effectiveness in Children
TBTC S26 + IMPAACT

- Study 26 amended to enroll 352 additional children; 1,058 total
- There were 908 for efficacy evaluation
- Follow-up complete September 30, 2013
- No hepatotoxicity, grade 4 events, or deaths

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>3HP N=472</th>
<th>9H N=436</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion</td>
<td>88%</td>
<td>81%</td>
<td>0.003</td>
</tr>
<tr>
<td>D/C—adverse drug reaction</td>
<td>2%</td>
<td>0.5%</td>
<td>0.11</td>
</tr>
<tr>
<td>Grade 3 toxicity</td>
<td>0.6%</td>
<td>0.2%</td>
<td>0.49</td>
</tr>
<tr>
<td>TB</td>
<td>0 (0%)</td>
<td>3 (0.78%)</td>
<td>Upper bound of difference: 0.44%</td>
</tr>
</tbody>
</table>

CDC Sponsored Post Marketing Study

3,307 Eligible
• 2,884 (87%) completed
• 423 (13%) stopped
  – 247 (7.5%) symptoms
  – 176 (5.3%) other reason

Observational Cohort in 16 sites
7/1/2011 – 12/31/2013
Clinical Toxicity with 3 HP

- **NEW** - Important to educate about the possibility of dizziness +/- hypotension
- Side effects reported more commonly in patients on other medications
- Hepatotoxicity is less common but still important; monitor ALT as you would with INH
- Drug-drug interactions are important to consider
- Monthly **in-person** monitoring for toxicity and adherence is strongly recommended
3 HP weekly for treatment of M. tuberculosis infection in HIV co-infected persons: TBTC Study 26 ACTG 5259; AIDS Sterling et al. June 2016

Objective: Compare effectiveness, tolerability, and safety of 3 months of weekly 3 HP by DOT vs. 9 months of daily INH in HIV-infected persons.
Median baseline CD4+ counts were 495 and 538 in the 3HP and 9 INH arms (P = 0.09)

In the modified intention to treat analysis:
- 2 TB cases among 206 persons in the 3HP arm
- 6 TB cases among 193 persons in the 9H arm.

Cumulative tuberculosis rates were: 1.01% vs. 3.50% in the 3HP and 9H arms

Treatment completion was higher with 3HP (89%) than 9H (64%) (P < 0.001)
Drug discontinuation due to an adverse reaction was similar (3% vs. 4%); (P = 0.79)

Conclusions: Among HIV-infected persons with median CD4+ count of approximately 500 cells/mm3, 3HP was as effective and safe for treatment of latent M. tuberculosis infection as 9H, and better tolerated.
Panel's Recommendations

Only efavirenz (EFV)- or raltegravir (RAL)-based regimens (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used with once-weekly isoniazid plus rifapentine (AIII).


*Mycobacterium Tuberculosis Disease with HIV Coinfection*  
(Last updated: Sept 22, 2017; last reviewed: September 22, 2017)
# Dosing for 3 HP

<table>
<thead>
<tr>
<th>Adults and children &gt; 45 kg</th>
<th>Children 2 – 12 years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 900 mg INH once weekly</td>
<td>• INH 15 mg/kg (round to nearest 50 or 100 mg tablet)</td>
</tr>
<tr>
<td>• 900 mg Rifapentine once weekly</td>
<td>• Rifapentine</td>
</tr>
<tr>
<td>• Vitamin B 6 50 mg once weekly</td>
<td>– 10-14 kg: 300 mg</td>
</tr>
<tr>
<td>• Completion - 11 to 12 doses in 16 weeks</td>
<td>– 14.1-25 kg: 450 mg</td>
</tr>
</tbody>
</table>

* Especially when short course is desirable; pill burden may be a problem
Pill Burden With 3HP is Currently a Problem for Some

- Current: 10 pills (6 rifapentine, 3 INH, 1 Vit B6)
- Future: 4 pills (3 RPT/INH + 1 B6)

2xPriftin® 150mg + Isoniazid® = PH 300/300
I-Adhere - Protocol Synopsis

- Phase IV open label, randomized design
- Target Population: adults with LTBI
- All patients received 3HP
  1. DOT (control)
  2. Standard SAT
  3. SAT with weekly SMS reminders
- Sample size to detect a difference in study arms of 15% or greater based on cost modelling
- Enrollment targeted \( \geq 75\% \) from U.S.

Bob Belknap
SMS = short messengering service
## I-Adhere: Active TB

<table>
<thead>
<tr>
<th></th>
<th>DOT (n=337)</th>
<th>SAT (n=337)</th>
<th>SAT + SMS (n=328)</th>
<th>Total 3HP (N=1002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>337</td>
<td>337</td>
<td>328</td>
<td>1002</td>
</tr>
<tr>
<td>Follow up (days)</td>
<td>105,885</td>
<td>97,033</td>
<td>98,702</td>
<td>301,620</td>
</tr>
<tr>
<td>Follow up (years)</td>
<td>294.1</td>
<td>269.5</td>
<td>274.2</td>
<td>837.8</td>
</tr>
<tr>
<td>TB cases (N)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TB rate (per year)</td>
<td>0</td>
<td>0</td>
<td>0.36 – ITT 0 – PC*</td>
<td>0.12 (95% CI 0.10-0.14)</td>
</tr>
</tbody>
</table>

*TB case: White 19 year old female, HIV negative, U.S. born, white, hispanic ethnic origin, was enrolled into eSAT. Indication for treatment of LTBI was contact with a patient diagnosed with smear positive TB. Pregnancy was diagnosed in study participant shortly after enrollment (pregnancy test prior to enrollment was negative). The patient did NOT receive any doses of 3HP*
3HP - Self Administered versus Directly Observed Treatment

- Data continues to support that 3HP is safe and effective compared to INH
- DOT should be used in settings where the cost and logistics make sense (schools, jails, etc.)
- Completion with 3HP SAT in adults was comparable to historical results with rifampin and better than INH
- Shorter-course, patient-centered therapy is critical for expanding the scope and effectiveness of TB prevention efforts
**Preferred Therapy (Duration of Therapy = 9 Months):**
- INH 300 mg PO daily + pyridoxine 25-50 mg PO daily (AII) or
- INH 900 mg PO twice weekly (by DOT) + pyridoxine 25-50 mg PO daily (BII)

**Alternative Therapies:**
- RIF 600 mg PO daily x 4 months (BIII) or
- RFB (dose adjusted based on concomitant ART) x 4 months (BIII) or
- **3HP RPT (wt-based, 900 mg max) PO weekly + INH 15 mg/kg weekly (900 mg max) +** pyridoxine 50 mg weekly x 12 weeks – in patients receiving an EFV- or RAL-based ART regimen (BIII)
  - 32.1–49.9 kg 750 mg
  - ≥50.0 kg 900 mg


Last updated: Sept 22, 2017; last reviewed: September 22, 2017)
Dolutegravir with 3HP

Patients with stable viral suppression on efavirenz changed to Dolutegravir x 8 weeks

Given 3HP and Dolutegravir 500 mg q day + tenofovir/emtricitabine (Truvada)

Viral load at baseline, week 11 and week 24 (one month after 3 HP completion)

- Viral load < 40 copies/ml
- AUC (overall amount of drug in bloodstream after dose) reduced by approximately 30% with 3HP
- Median values were above target value of 300 ng/ml at all time points

Reassuring -
INH + RPT (3HP) is NOT Recommended For:

• Children under 2 y/o
• HIV infected persons on Antiretroviral Therapy with drug drug interactions
• Presumed INH or Rifampin Resistance in the source case
• Pregnant women
Treatment of Latent Tuberculosis Infection
A Network Meta-analysis

Helen R. Stagg, PhD*; Dominik Zenner, MD*; Ross J. Harris, MSc; Laura Muñoz, MD; Marc C. Lipman, MD;
and Ibrahim ABrubaker, MBBS, PhD

Background: Effective treatment of latent tuberculosis infection (LTBI) is an important component of tuberculosis (TB) elimination programs. Promising new regimens that may be more effective are being introduced. As few regimens can be directly compared, network meta-analyses, which allow indirect comparisons to be made, strengthen conclusions.

Purpose: To determine the most efficacious regimen for preventing active TB with the lowest likelihood of adverse events in order to inform LTBI treatment policies.

Data Sources: PubMed, EMBASE, and Web of Science to the end of January 2014; clinical trial registries, and conference abstracts.

Study Selection: Randomized, controlled trials that evaluated human LTBI treatment and recorded at least one of two prespecified end points (preventing active TB or hepatotoxicity), without language or date restrictions.

Data Extraction: Data from eligible studies were independently extracted by 2 investigators according to a standard protocol.

Data Synthesis: Of the 1516 articles identified, 53 studies met the inclusion criteria. Data on 15 regimens were available; of 105 possible comparisons, 42 (40%) were compared directly. Compared with placebo, isoniazid for 6 months (odds ratio [OR], 0.64 [95% credible interval (CrI), 0.48 to 0.83]) or 12 months or longer (OR, 0.52 [CrI, 0.41 to 0.65]), rifampicin for 3 to 4 months (OR, 0.41 [CrI, 0.18 to 0.86]), rifapentine-isoniazid (OR, 0.61 [CrI, 0.29 to 1.22]), and rifampicin-isoniazid (OR, 0.52 [CrI, 0.34 to 0.79]) were efficacious within the network.

Limitations: The risk of bias was unclear for many studies across various domains. Evidence was sparse for some comparisons, particularly hepatotoxicity.

Conclusion: Comparison of different LTBI treatment regimens showed that therapies containing rifampicin for 3 months or more were efficacious at preventing active TB, potentially more so than isoniazid alone. Regimens containing rifampicin may be effective alternatives to isoniazid monotherapy.

Primary Funding Source: None.
Rifampin Treatment of TB Infection

**Pros:**
- Higher Completion Rates
- Equally effective
- Fewer Side Effects
- Less Hepatotoxicity
- Cost effective
- Rifampin resistance uncommon
  - Globally 3%

**Cons:**
- Drug Interactions
  - Hormone Contraceptives
  - Warfarin
  - Prednisone
  - **HIV Antiretroviral agents**
  - And many more...must look up all drugs for interactions
  - Orange Body Fluids

- Other Potential Side Effects (rare):
  - Rash
  - Thrombocytopenia
  - Anemia
  - Leukopenia
  - Allergic Interstitial Nephritis
4 Months Rifampin vs 9 Months INH for Treatment of TB Infection

• Menzies et al AJRCCM 2004, 170; 445
  – **Completion** of therapy **significantly better** with rifampin with fewer side effects than INH

• Lardizabal et al Chest 2006, 130; 1712
  – Patients receiving rifampin were **significantly more likely to complete** therapy than those receiving INH

• Menzies et al Ann Int Med 2008, 149; 689
  – **Significantly higher rate of treatment completion** with fewer serious adverse events
Rifampin Dosing for TB Infection

• Adults
  – 600 mg daily x 4 months

• Children:
  – 10 – 20 mg/kg daily x 4 months
  – Capsules 150mg/300 mg round up - use higher range
  – Higher rifampin doses well tolerated
**INCREASING ADHERENCE FOR LATENT TUBERCULOSIS INFECTION THERAPY WITH HEALTH DEPARTMENT-ADMINISTERED THERAPY**

*Andrea T. Cruz, MD, MPH,*† and *Jeffrey R. Starke, MD,*

**Abstract:** Therapy is almost universally recommended for children with latent tuberculosis infection, but long courses of therapy can decrease adherence to drug therapy. The only variable positively associated with adherence to latent tuberculosis infection therapy in our population was health department–assisted administration of drugs (odds ratio, 7.2; 95% confidence interval, 3.8–13.8).

**TABLE 1.** Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subcategory</th>
<th>All Patients N (%)</th>
<th>Completed N (%)</th>
<th>Defaulted N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>248</td>
<td>186 (75%)</td>
<td>62 (25%)</td>
</tr>
<tr>
<td>How medications administered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-medicated</td>
<td></td>
<td>99 (40%)</td>
<td>49 (49%)</td>
<td>50 (51%)</td>
</tr>
<tr>
<td>ESAT</td>
<td></td>
<td>20 (8%)</td>
<td>17 (85%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>DOPT</td>
<td></td>
<td>129 (52%)</td>
<td>120 (93%)</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>ESAT or DOPT</td>
<td></td>
<td>149 (60%)</td>
<td>137 (92%)</td>
<td>12 (8%)</td>
</tr>
</tbody>
</table>
INH Treatment for TB Infection
INH TBI Therapy

• The standard treatment regimen for TBI has been nine months of daily INH.
  – The regimen is effective and is the preferred regimen for HIV infected people taking antiretroviral therapy with drug-drug interactions that do not allow a rifamycin
  – Is the option when drug-drug interactions are significant and must be avoided

• But less than 60% complete
  – Primarily due to long duration of treatment but also increased adverse effects
INH Hepatotoxicity

- Asymptomatic elevation of aminotransferases: 20% of patients
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure)
  - Approximately 4/100,000 persons completing therapy (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition).
"Medical providers should emphasize to patients that INH treatment should be stopped immediately upon the earliest onset of symptoms (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice."
INH Side Effects

• Hepatotoxicity
• Migraine Headaches
• Gastrointestinal
  – Nausea, Diarrhea, Constipation
• Rash
• Peripheral Neuropathy
  – Pyridoxine 50mg daily can help prevent this
Isoniazid (INH) Dosing

- Adults: 300 mg single daily dose or 900 mg twice weekly*

- Children: 10-15 mg/kg single daily dose (max dose 300 mg daily)
  - 20-30 mg/kg twice weekly*

- Duration of treatment for TB Infection: 6 - 9 months
  - 9 month regimen more effective
  - 9 month regimen is very difficult to complete
  - 6 months is considered adequate therapy by ATS/IDSA/CDC guidelines

* twice weekly treatment must be given by directly observed therapy through health department
TBI Treatment

Special considerations
Should Pregnant Women Be Treated for TB Infection during Pregnancy?

- Increased risk of serious, even fatal hepatotoxicity with INH during pregnancy and the immediate post-partum period (3 months following delivery)
- Treatment usually only given to those with recent contact to a person with active TB disease, HIV positive women or those with other immunosuppressive conditions
- Monitoring should be very close
  - Blood work for any symptoms and hold medication if taking
  - Monitor liver enzymes and patient at every monthly visit.

However for many women the only time they have access to care or willingly seek care is during pregnancy or immediate post-partum period. The next time you see them they may be pregnant again and still without treatment for TB infection.
• Findings:

• One study suggested increased risk of active TB in 180 days postpartum
• In USA prevalence of LTBI ranged from 14-18% of women tested
• Excellent adherence with CXR and TST/IGRA evaluation during pregnancy (> 95%)
• Poor adherence with post partum evaluations and treatment
• Only 14 – 69% attended F/U visits; only 5 – 42% of these women completed at least 6 months of INH
Among women exposed to IPT during pregnancy, the researchers observed a lower proportion of poor birth outcomes compared with unexposed women, 16% vs. 28%. “This was true even after we accounted for other reasons for poor birth outcomes such as advanced HIV disease, advanced maternal age and low weight gain.
Monitoring for Toxicity and Progression to Active Disease

• Baseline liver enzymes - all with risk of liver toxicity
  – Those with underlying liver disease due to Hepatitis B or C or alcohol
  – Those taking other potentially hepatotoxic medications
  – Those with a medical co-morbidity
  – Pregnant women and those in immediate post-partum (3 months) period
  – Elderly
  – Generally not needed for children; healthy young adults

• Monitor monthly “in person” for toxicity and for evidence of progression to TB disease
  – Monthly liver enzymes if baseline LFTs abnormal or above risks
Pearls of Wisdom for Treating TBI

• Consider the shortest regimen possible to increase the odds of completion
• Be vigilant
• Be supportive.....and forgiving