Diagnosis and Treatment of Latent Tuberculosis Infection

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Objectives

1. Identify factors associated with increased risk of exposure to TB or that increase the risk of progression from latent to active TB to prevent further spread of the disease.

2. Define targeted testing as an essential TB prevention and control strategy to identify high risk patients who would benefit from testing and treatment of latent TB infection.

3. Understand the differences between the tuberculin skin test and interferon gamma release assays and their appropriate clinical use for diagnosing latent TB infection.

4. Describe the recommended treatment options for latent TB infection that are effective in preventing progression to TB disease.
THAT'S ODD... MY NECK SUDDENLY FEELS BETTER...

EARLY ACUPUNCTURE
Section 1

Targeted Testing and Treatment of Latent TB Infection (LTBI)
Tuberculosis (TB) Disease: Only the Tip of the Iceberg

There are two types of TB conditions: TB disease and latent TB infection.

People with TB disease are sick from active TB germs. They usually have symptoms and may spread TB germs to others.

People with latent TB infection do not feel sick, do not have symptoms, and cannot spread TB germs to others.

But, if their TB germs become active, they can develop TB disease.

Millions of people in the U.S. have latent TB infection. Without treatment, they are at risk for developing TB disease.

To learn more about TB, visit www.cdc.gov/tb
**Figure: Population-level control strategies for tuberculosis elimination.**

Arrows show the dynamics of *M. tuberculosis* in the world’s population, with flow from latent infection to active disease, transmission to new hosts, followed by either rapid progression to disease and ongoing transmission or entry into the pool of latent infections. Bars show how different control measures affect these dynamics, interrupting the chain of events. Even if diagnosis and treatment of active tuberculosis is maximised and a new effective vaccine is developed, reactivation from the billions of latently infected will result in new cases for decades to come.
TB Control Priorities in the U.S.

1. Detection and treatment of persons with active tuberculosis (TB)
2. Investigation of infectious cases to detect contacts who may have active TB or may be infected with risk of future TB
3. Prevent TB disease through targeted testing and treatment of LTBI
Stages of Tuberculosis

- TB EXPOSED: 70%
- NOT TB INFECTED: 30%
- TB INFECTED: 5%
- PRIMARY TB DISEASE: 5%
- LATENT TB INFECTION: 95%
- REACTIVATION TB DISEASE: 5%
- PERSISTENT TB LATENCY: 95%

Infection with *M. tuberculosis*

- No single test confirms LTBI

- Diagnosis relies on combination of:
  - Assessment of individual risk factors and exposures
  - Clinical evaluation for signs/symptoms of active TB
  - Laboratory testing (TST, IGRA, HIV)
  - Radiographic studies
  - Determining that active TB is not present
# TB Infection vs. TB Disease

<table>
<thead>
<tr>
<th>Latent TB Infection (LTBI)</th>
<th>TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive, contained tubercle bacilli in the body</td>
<td>Active, multiplying tubercle bacilli in the body</td>
</tr>
<tr>
<td>TST or IGRA blood test results usually positive</td>
<td>TST or IGRA blood test results usually positive</td>
</tr>
<tr>
<td>Chest x-ray usually normal</td>
<td>Chest x-ray usually abnormal</td>
</tr>
<tr>
<td>Sputum smears and cultures negative</td>
<td>Sputum smears and cultures may be positive</td>
</tr>
<tr>
<td>No symptoms</td>
<td>Symptoms such as cough, fever, weight loss</td>
</tr>
<tr>
<td>Not infectious</td>
<td>Often infectious before treatment</td>
</tr>
<tr>
<td>Not a “case of TB”</td>
<td>A “case of TB”</td>
</tr>
</tbody>
</table>

*HIV+ persons may have false-negative TST and IGRA, atypical symptoms or CXR pattern, etc.*
Spectrum from LTBI to active TB: Proposed framework

- Clinical disease
- Bacterial replication maintained at a subclinical level by the immune system
- Infection controlled with some bacteria persisting in non-replicating form
- Infection eliminated in association with T cell priming
- Infection eliminated without priming antigen-specific T cells
- Disease
- Active infection
- Quiescent infection
- Acquired immune response
- Innate immune response

Targeted Testing and Treatment of TB Infection

• As U.S. TB cases decline, TB elimination will require identification and treatment of large pool of persons infected with *M. tuberculosis*

• LTBI therapy ↓↓ risk of TB disease
  - Reduce individual’s morbidity & mortality
  - Decrease community transmission
Targeted Testing and Treatment of TB Infection

- Identify high-risk persons who would benefit from screening and treatment of LTBI

- Screening of low-risk persons not recommended
  - Diverts limited resources
  - Risk of unnecessary treatment

Scope and Impact of Treatment of LTBI in the U.S. and Canada

• 2002 survey of clinics in U.S. (n=19) and Canada (n=2) that initiated LTBI treatment for ≥10 patients

• Extrapolated study data to entire U.S. population
  - Used estimated 20-60% treatment effectiveness (9 mos of INH) and assumed a 5% lifetime risk of active TB without treatment

❖ Results: Targeted screening and treatment of LTBI likely prevented 4,000 - 11,000 active TB cases in the U.S.
The Way Forward

• Mobilizing support for TB elimination has been challenging as TB cases continue to decline.
• TB seems less urgent for policy makers and the public compared to diseases that are increasing in prevalence.
• Modeling and surveillance studies indicate that the greatest reduction in future TB cases in the US will result from expanded testing and treatment of LTBI.
• Other health providers and stakeholders must be engaged to sufficiently expand LTBI testing and treatment.
US Preventive Services Task Force (USPSTF) Recommendation in 2016

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults who are at increased risk for tuberculosis</td>
<td>The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations that are at increased risk.</td>
<td>B</td>
</tr>
</tbody>
</table>
**Figure 3: Latent tuberculosis infection prevention cascade using the example of contact investigation**

The cascade consists of multiple steps: identifying the population at risk, testing the population at risk for latent tuberculosis infection, and evaluating those with positive tests to exclude tuberculosis; initiating treatment in those with latent tuberculosis infection, and completing treatment for those who start. People can fail to complete any of the steps, and the effect is multiplicative. In this example, it is assumed that 93% of contacts have been identified and 82% of those have a complete evaluation. Of the contacts with latent tuberculosis infection (21%), 71% start treatment, and 46% of those who start treatment complete it. Thus, only 33% of contacts with latent tuberculosis infection complete treatment.
Section 2

Risk Factors for LTBI
Which of these individuals should be evaluated for LTBI?

- Parents of a 3 y.o. being adopted from Vietnam
- 18 y.o. college student born in Nashville
- 50 y.o. woman who immigrated from Mexico at age 15 and has developed diabetes
- 46 y.o. male who has worked as a prison guard
- 25 y.o. male from Kazakhstan with a student visa to study engineering
- Female au pair from Japan caring for healthy child
- Student from Virginia about to start nursing school
- 60 y.o. school teacher waiting for liver transplant
Candidates for testing and treatment of LTBI

1. Persons with risk for recent infection with *M. tuberculosis* (exposure risk)

2. Persons with risk of progression to active TB if infected with *M. tuberculosis* (Medical risk)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Estimated risk for TB relative to persons with no known risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (testing and treatment for LTBI recommended for all ages)</td>
<td></td>
</tr>
<tr>
<td>AIDS (not on anti-HIV therapy)</td>
<td>110–170</td>
</tr>
<tr>
<td>HIV (not on anti-HIV therapy)</td>
<td>50–110</td>
</tr>
<tr>
<td>Transplantation (related to immunosuppressive therapy)</td>
<td>20–74</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30</td>
</tr>
<tr>
<td>Chronic renal failure requiring hemodialysis</td>
<td>10–25</td>
</tr>
<tr>
<td>Carcinoma of head and neck</td>
<td>16</td>
</tr>
<tr>
<td>Recent TB infection (&lt;2 yrs)</td>
<td>15</td>
</tr>
<tr>
<td>Abnormal chest X ray—with upper lobe fibronodular disease typical of healed TB infection</td>
<td>6–19</td>
</tr>
<tr>
<td>TNF-α inhibitors</td>
<td>2–9</td>
</tr>
<tr>
<td>Moderate risk (testing and treatment for LTBI recommended if age &lt; 65 yrs)</td>
<td></td>
</tr>
<tr>
<td>Treatment with glucocorticoids</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes mellitus (all types)</td>
<td>2–4</td>
</tr>
<tr>
<td>Young age when infected (0–4 yrs)</td>
<td>2–5</td>
</tr>
<tr>
<td>Slightly increased risk (testing and treatment for LTBI recommended if age &lt; 50 yrs)</td>
<td>2–3</td>
</tr>
<tr>
<td>Underweight (&lt;90% ideal body weight; for most persons, this is a BMI of 20)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoker (1 pack/day)</td>
<td>2–3</td>
</tr>
<tr>
<td>Abnormal chest X ray—granuloma</td>
<td>2</td>
</tr>
<tr>
<td>Low risk (testing and treatment for LTBI recommended if age &lt; 35 yrs)</td>
<td></td>
</tr>
<tr>
<td>Infected person, no known risk factor, normal chest X ray (&quot;low-risk reactor&quot;)</td>
<td>1</td>
</tr>
<tr>
<td>Very low risk (treatment of LTBI not usually recommended)</td>
<td></td>
</tr>
<tr>
<td>Person with positive two-step (&quot;boosting&quot;), no other known risk factor, and normal chest X ray</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Modified from the work of Lobue and Menzies (140) and the CDC.*
Criteria for classifying positive LTBI diagnostic test

<table>
<thead>
<tr>
<th>Positive IGRA or TST 5mm induration or more is considered positive in:</th>
<th>Positive IGRA or TST 10mm induration or more is considered positive in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV-infected persons</td>
<td>• Recent immigrants from high TB prevalence countries</td>
</tr>
<tr>
<td>• Recent contacts to a person with infectious TB</td>
<td>• Injection drug users</td>
</tr>
<tr>
<td>• People with fibrotic changes on a CXR consistent with old TB</td>
<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>• Organ transplant recipients</td>
<td></td>
</tr>
<tr>
<td>• People who are immunosuppressed for other reasons (e.g., taking the equivalent of &gt;15mg/day of for more than one month, or taking TNF-α antagonists)</td>
<td></td>
</tr>
</tbody>
</table>

Positive IGRA response or a TST 15mm of induration or more is considered positive in:

• A person who has no risk factors for TB

*Although skin testing programs should be conducted only among high-risk groups, certain individuals may require skin testing for employment or school attendance. An approach independent of risk assessment is not recommended by CDC or the American Thoracic Society.*
High Risk Contacts and “Window Prophylaxis”

• Some contacts should be evaluated and treated for LTBI even with (-) TST or IGRA results:
  - Young children <5 years of age
  - Immunosuppressed persons (e.g., HIV, TNF-α inhibitors)

• Always rule out TB disease with CXR and medical evaluation before treating for LTBI

• Give LTBI treatment as “window prophylaxis” regardless of initial IGRA/TST result

• Retest 8–10 weeks after last exposure to allow for delayed immune response
“All of the tests came back negative, except for one where you got a B+. We’re gonna try that one again.”
Section 3

Testing for Latent TB Infection
Testing for *M. tuberculosis* Infection

- Two methods:
  1. Mantoux tuberculin skin test (TST)
  2. Interferon-gamma release assays (IGRA)

- These tests *do not* exclude either LTBI or TB disease
- Diagnosis and treatment decisions must consider epidemiologic (risk) and clinical information *in addition* to TST or IGRA results
- Pre-test probability is critical!!
Mantoux Tuberculin Skin Test (TST)

- Interpretation of TST reaction depends on:
  1. Size of induration and
  2. Person’s risk factors for TB
True of False?

A. Persons with a positive TST (or IGRA) can be treated for LTBI without further evaluation.

B. If a healthcare worker has a positive TST (or IGRA) but does not receive LTBI treatment, annual CXR are recommended for future monitoring of TB risk.

C. Anergy testing recommended for HIV+ persons with CD4 count <200 cells/mm³ who have a negative TST.

D. No treatment is needed for a young child (<5y) who is exposed to adult with active TB if the initial TST is negative.
Case Study: Elderly Woman from Vietnam

• 75 yo woman from Vietnam
• 8 months ago her TST was negative (0mm) at admission to nursing home for “frailty”
• Repeat TST now is 12 mm

Which of the following might be true?

A. Current TST could be due to new exposure
B. Admission TST could have been a false-negative
C. Current TST could be due to boosting
Case Study: Elderly Woman from Vietnam

What should you do now?

A. Diagnose her with LTBI and offer treatment  
B. Get a CXR to rule out TB and assess for symptoms  
C. Confirm her results by repeating the TST  
D. Confirm her results by IGRA  
E. More than one of the above
“Is nut job hyphenated?”
Interferon Gamma Release Assays

1. Antigen-presentation (ESAT-6, CFP-10, TB7.7)

2. Ag-specific cytokine production (IFNγ)

3. Cytokine quantification

Using PBMC and EliSpot

Using plasma and ELISA
# QFT vs T-SPOT Results

<table>
<thead>
<tr>
<th>QFT-GIT</th>
<th>T.SPOT.TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (&gt; 0.35 IU/mL)</td>
<td>Positive (&gt; 8 spots)</td>
</tr>
<tr>
<td>Negative (&lt; 0.35 IU/mL)</td>
<td>Negative (&lt; 4 spots)</td>
</tr>
<tr>
<td>Borderline (5-7 spots)</td>
<td></td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Invalid</td>
</tr>
<tr>
<td>-Low mitogen</td>
<td>-Low mitogen</td>
</tr>
<tr>
<td>-High nil</td>
<td>-High nil</td>
</tr>
<tr>
<td>Failed</td>
<td>Failed</td>
</tr>
<tr>
<td>-Inadequate blood volume</td>
<td>-Inadequate blood volume</td>
</tr>
<tr>
<td>-Broken tube</td>
<td>-Broken tube</td>
</tr>
<tr>
<td>-Delayed incubation</td>
<td>-Delayed incubation</td>
</tr>
</tbody>
</table>
IGRA: Advantages

• Both QFT and T-SPOT TB more specific than TST (~95% in low TB incidence areas)
• T-SPOT.TB assay has higher sensitivity than QFT or TST (90%, 80%, and 80%, respectively)
• Requires a single patient visit
• Results available in 24 hours
• Does not cause the booster phenomenon
• Results not affected by HCW perception or bias
• BCG vaccine does not affect IGRA results

Pai et al. Clinical Microbiology Reviews, 2014
IGRA Limitations

• Within-subject variability
• Serial testing of healthcare workers (HCW) using IGRA in low risk settings (U.S. and Canada):
  - Unusually high IGRA conversion rates (4-7%) compared to historical or concurrent TST conversions rates (0.0-0.9%)
  - 60-75% with IGRA conversion reverted to (-) on repeat testing
  - TST before IGRA may cause boosting (9% QFT, 11% TSPOT)
• Test agreement fair; discordance between tests more common than concordance among those with + tests
• Delay in IGRA conversion compared to TST may account for some discordant TST/IGRA results in recently exposed contacts
• Sensitivity by HIV infection, immunosuppression, in children

Dorman, Am J Respir Crit Care Med. 2014;189(1):77-87
Suggested approaches to reduce test variability with IGRAs

<table>
<thead>
<tr>
<th>Step during the assay</th>
<th>Suggestions for best practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disinfection</td>
<td>Standardize skin and tube septum disinfection, akin to that done for blood cultures.</td>
</tr>
<tr>
<td>Tube order</td>
<td>Standardize the order of the QFT-GIT tubes curing phlebotomy per the package insert (in the order purge tube, nil tube, antigen tube, and mitogen tube).</td>
</tr>
<tr>
<td>Blood volume</td>
<td>Standardize blood volume drawn into the QFT-GIT tubes, particularly for the antigen tube. Filling the tubes up to the 1-ml mark is practical. Collecting blood using a syringe and transferring 1 ml to each of the tubes is more accurate.</td>
</tr>
<tr>
<td>Tube shaking</td>
<td>Standardize gentle shaking of the QFT-GIT tubes per the package insert. Avoid separate shaking of the nil and antigen tubes, because differential shaking can result in a false-positive or false-negative result.</td>
</tr>
<tr>
<td>Processing delay</td>
<td>Minimize delays in incubation of cells. For the QFT-GIT assay, this can be achieved by placing an incubator at the collection site or by using a portable incubator to transport the tubes from the clinic to the laboratory. Further studies are needed to determine whether the T-Cell Xzend reagent can prolong processing time for the T-SPOT assay.</td>
</tr>
<tr>
<td>Analytical error</td>
<td>Use automated ELISA and ELISPOT instruments to reduce analytical variability.</td>
</tr>
<tr>
<td>Manufacturing defect</td>
<td>Institute a quality assurance program to monitor positivity and indeterminate rates. When rates cross a preset threshold and persist, halt utilization of potentially faulty lots and alert the manufacturer.</td>
</tr>
<tr>
<td>Immune boosting</td>
<td>When a two-step testing procedure (TST followed by IGRA) is used, TST boosting of the IGRA result can be avoided by drawing the blood sample for IGRA within 72 h of TST placement.</td>
</tr>
</tbody>
</table>

*Data from reference [40]. ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunospot assay; IGRA, interferon-gamma release assay; QFT-GIT, QuantiFERON-TB Gold In-Tube; TST, tuberculin skin test.*
Case: 70 year old Male with Psoriasis

• White male born in Chicago in the 1940s
• COPD and Psoriasis, HIV-
• He is not taking any immunosuppressive therapy
• He traveled internationally working on machinery
• Dermatologist obtained IGRA prior to TNF-α inhibitor therapy
• IGRA was read as “positive”
• He was referred you for further evaluation
• What would you do next?
Case: 70 year old Male with Psoriasis

- Quantiferon Gold in tube test (QFT-GIT) 8/8/17:
  - Antigen (TB) was 0.58
  - Antigen (TB) minus nil value was 0.52 (Positive is ≥0.35)
  - Mitogen was 0.14

- How do you interpret this?
  - Nil tube=Negative control to adjust for background IFN-γ
  - Antigen tube=To detect the CD4+ T cell responses to TB antigens
  - Mitogen tube=Low response may indicate inability to generate IFN-γ

- Now what would you do?
Case: 70 year old Male with Psoriasis

• Patient has no symptoms or signs of TB
• CXR consistent with COPD, no infiltrates or lesions
• Repeat test 8/15/17
  - Ag was 1.03
  - AG-nil was 0.99
  - Mitogen was 0.57

• What should you recommend to the patient?
Case: 70 year old Male with Psoriasis

• Test result is "positive" response
• His 2 positive control values (mitogen) are rather low suggesting that he may have a suppressed ability to respond to the test.
• Given that he could potentially been exposed to TB either overseas or even in the US early in his life when TB was more prevalent, and considering that he will begin immunosuppressive therapy it is reasonable to treat him for TB infection
• Be sure to assess him carefully for TB disease, including extrapulmonary sites
IGRA in Immunocompromised Patients

• Both IGRAAs rely on host immune response (as does TST)
  - HIV, steroids, TNF-a inhibitors, etc.
• Conflicting data on performance of IGRAAs in IC patients
• Possible increased sensitivity of T-SPOT over QFT, though more studies are required to make a fair comparison between tests
• Meta-analysis: IGRA alone may not be sufficient to diagnose LTBI in patients on immunosuppressive tx
• Higher rate of indeterminate results

LTBI screening with immunosuppression

Pre-treatment screening

• If patient likely to be immunosuppressed for prolonged period, screen while persons is relatively immunocompetent to define their TB status.
  - E.g., newly-diagnosed with RA, psoriasis, Crohn’s, etc.

• It is much harder to screen these people once they are immunosuppressed given the poor test performance
Figure 3. 2012 American College of Rheumatology recommendations update for tuberculosis (TB) screening with biologic agent use. Depending on a patient’s current therapy, the management may begin at an appropriate rectangle in the figure, rather than only at the top of the figure. The level of the figure is then adjusted to the specific point of the patient’s therapy, and the management recommendations are followed down to completion.
LTBI screening with immunosuppression

**Dual testing** can increase sensitivity of testing for TB infection, but both may still be false negative

- If high suspicion of infection and first test is negative, repeat testing with second test (2 IGRAs or IGRA/TST)

- Many experts would treat for infection if advanced immunosuppression and high risk of infection

- Must be CERTAIN TB disease is not present before giving LTBI treatment

- If moderate to high suspicion for active TB despite negative LTBI test, treat as TB disease while awaiting further diagnostic test results
LTBI screening with immunosuppression

• Consider pre-test probability:
  - *If you think they should be positive, they probably are*
  - *If you think they shouldn’t be positive, they probably aren’t*

• Consider dual testing in immunosuppressed patients, children <5 years

• Serial screening in immunosuppressed patients??
  - Consider if there is true risk of re-exposure (high risk travel, congregate settings, homeless shelter)
  - CDC doesn’t recommend repeat screening unless there is a risk factor for re-exposure
  - FDA labels for these drugs may suggest screening at baseline and periodically (*CDC was not consulted*)
Presence of TB Risk Factors

+ Immunosupression

- Immunosupression

+ IGRA & TST

- IGRA & TST

*TB risk factors include: a history of contact to a case of active TB; birth or extended living in regions where TB is prevalent (crude incidence ≥20/100,000 per year); history of working or living in jails, prisons, healthcare facilities providing care to TB patients, or homeless shelters; or history of intravenous drug use.

Immunosupression includes poorly controlled rheumatoid arthritis or other inflammatory immune mediate disease, current use of biologic or non-biologic disease modifying therapies, or current use of corticosteroids, and other conditions.

In regions of BCG use (or individuals with BCG history), consider a dual strategy of using both commercially available IGRA (Quantiferon-Tube® and T.Spot.TB*) in lieu of the TST.

For patients with risk factors and immunosuppressed in whom false negative results are more likely, consider repeat screening with one or both tools.

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test
Q: IGRAs are reliable tests to tell practitioners who among those with LTBI will progress to active TB disease.

A. True
B. False
No diagnostic gold standard for LTBI!

• IGRAs and TSTs are indirect markers of infection - indicate immune response to *M. tuberculosis*

• Neither TGRA or TST accurately:
  - Differentiates LTBI vs TB
  - Distinguish reactivation from reinfection
  - Identifies stages within spectrum of *M. tuberculosis* infection

• Both TST/IGRA have reduced sensitivity in immuno-compromised, low predictive value for progression to TB

• To maximize positive predictive value, screen only persons at high risk of progressing to disease

• Consider pre-test probability, and interpret test results with epidemiologic and clinical context
IGRA: Unanswered Questions

Key questions still unanswered:

- Whether a person has cleared their infection or has true LTBI?
- How well do IGRA s predict which patients will progress from LTBI to TB disease?
- What is the significance of discordant test results?
- How do we deal with test-retest variability?
- Should “borderline zone” for QFT-GIT similar to T-SPOT help prevent misclassification of these individuals?
- Reliability/accuracy of T-spot vs. QFT-GIT in specific situations?
Recommendation

We suggest performing an IGRA instead of a TST test in individuals 5 years or older.

*conditional recommendation, low quality evidence*

Remarks: A TST is an acceptable alternative in settings where an IGRA is unavailable, too costly, or too burdensome.
Recommendation

We suggest a second diagnostic test if the initial test is positive in individuals 5 years or older.

conditional recommendation, very low quality evidence

Remarks: The confirmatory test may be either an IGRA or a TST. When such testing is performed, the person is considered infected only if both tests are positive.
Longitudinal Testing
(Testing of Health Care Workers)

• Do not recommend routine testing those at low risk.
• Committee felt that there was not sufficient evidence to make a specific recommendation.
  - Criteria for TST boosting and conversions have been established.
  - While FDA has established criteria for positive and negative tests, criteria for conversions and reversions are not established for IGRAs.
  - However, IGRAs have not proven to be the solution to the problem of falsely positive results associated with serial testing in low risk individuals.
    • In 2563 HCW IGRA conversions occurred at a rate of 6-8% with many not confirmed on repeat testing.
• Therefore, TST and IGRA are both acceptable in this setting.
• May consider confirmatory testing in this setting.
“I think we should cut back on my antidepressant. I watched ‘Old Yeller’ and it was hysterical.”
Section 4

LTBI Treatment Regimens
Evaluation of Persons with Positive TB Test Results

Person has a positive test for TB infection

TB disease ruled out

Consider for LTBI treatment

Person accepts and is able to receive treatment of LTBI

Develop a plan of treatment with patient to ensure adherence

If person refuses or is unable to receive treatment for LTBI, follow-up TST or IGRA and serial chest radiographs are unnecessary

Educate patient about the signs and symptoms of TB disease

Foreign-born Health Care Worker

• 50 year old HCW, born in Haiti, travels home often
• Asymptomatic
• QFT-GIT is positive (=1.35), was negative 3 y ago
• CXR normal
• Denies any known TB contact

Which of the following statements are true?
A. She is latently infected with TB
B. She would benefit from treatment of LTBI
C. 9 months of INH is the best treatment for her
Approach to Diagnosis and Treatment of TB Infection

1. Is patient likely infected?

2. Is there any evidence of active TB?
   - Pulmonary or extra-pulmonary symptoms
   - Radiology

3. Do benefits of treatment outweigh the risk?
   - Review medical history, other medications, plans for future immunosuppression.

4. Which regimen is most effective and has least risk?

5. Is patient going to take treatment if recommended?
Foreign-born Health Care Worker

1. Is patient likely infected?
   Haiti, HCW, converter

2. Is there any evidence of active TB?
   - Pulmonary or extra-pulmonary symptoms
     No
   - Radiology
     Normal

3. Do benefits of treatment outweigh the risk?
   Review medical history, other medications, plans for future immunosuppression.
   Yes

4. Which regimen most effective and least risk?
   - ???

5. Is patient going to take treatment if recommended?
# LTBI Treatment – Susceptible Disease

## Recommended regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Daily</td>
<td>9 months (6 months)</td>
<td>Long duration, poor adherence</td>
<td>9H</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Twice weekly</td>
<td>9 months (6 months)</td>
<td>Directly-observed, long duration</td>
<td>9H-DOT</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily</td>
<td>4 months**</td>
<td>Drug interactions</td>
<td>4R</td>
</tr>
<tr>
<td>Isoniazid + rifapentine</td>
<td>Once weekly</td>
<td>3 months</td>
<td>DOT</td>
<td>3HP</td>
</tr>
</tbody>
</table>

## Other regimens *(not recommended in the US)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid + rifampin</td>
<td>Daily</td>
<td>3 months</td>
<td>Not in U.S. recommendations</td>
<td>3HR</td>
</tr>
<tr>
<td>Rifampin + pyrazinamide</td>
<td>Daily or 2x/week</td>
<td>2 months</td>
<td>Potentially fatal: <strong>NOT RECOMMENDED</strong></td>
<td>2RZ</td>
</tr>
</tbody>
</table>

** 4 months of Rifampin now recommended for children
LTBI Treatment: 9 months Isoniazid (9INH)

• >20 randomized, placebo-controlled trials of INH for LTBI treatment involving >100,000 subjects
• Combined average 60% reduction in TB during the period of observation after treatment
  - Results based on total study populations treated, regardless of how regularly medication was taken
  - Reduction highest during year of treatment
• Efficacy ~90% when analyses limited to participants who took INH for most of treatment year
• Protection lasted 20 years after treatment

International Union Against Tuberculosis Committee on Prophylaxis. 1982.
Bull World Health Organ 60:555-64.
9 months Isoniazid (9INH)

• INH action:
  - Bactericidal, especially for rapidly dividing cells; inhibits Mycobacterial cell wall synthesis; active against intracellular and extracellular M. Tb

• Dose: 300mg daily

• Completion rate of 6-9 mo. INH: 20-60%

• Drug Interactions
9 months Isoniazid: Safety

- 10-20% develop transient, asymptomatic liver enzyme abnormalities (most not clinically significant)
- Hepatotoxicity ~ 0.1%-0.5%
  - Increased risk with age, liver disease, HCV, alcohol use, prior INH hepatotoxicity, other hepatotoxic meds
  - Mortality 0.3/1000 (increases w/ age, alcohol use)
- Peripheral neuropathy uncommon at 5 mg/kg
  - Give pyridoxine (vit B\(^6\)) 10-50 mg/day for persons with:
    - DM, uremia, alcoholism, malnutrition, HIV, pregnancy, seizures, Signs and symptoms of peripheral neuropathy
Rifampin Based Regimens
Rifamycins

• Inhibit DNA-dependent RNA polymerase
  - Active against dormant and semi-dormant bacteria that characterize LTBI
    - (INH only active against replicating bacteria)

• Active against a broad array of bacteria (including *M. tuberculosis*)

• Examples:
  - Rifampin
  - Rifabutin (RBN)
  - Rifapentine (RPT)
Rifampin

- **Efficacy:** One randomized clinical trial\(^1\)
  - From 1981 to 1987, a cohort of older Chinese men with silicosis (n=679) randomized to placebo or:
    - Rifampin for *three* months (3R)
    - Rifampin plus INH for three months (3HR)
    - Isoniazid for six months (6H)
  - Effectiveness of 3R vs. placebo was \(\sim 50\%\) among persons who completed the 5-year study

- 2 small observational studies suggesting efficacy\(^2,3\)
- New RCT being conducted (D. Menzies)\(^4\)

---

\(^4\)https://clinicaltrials.gov/ct2/show/NCT00931736?term=Rifampin%2C+LTBI&rank=2
Why 4 months of RIF???

• 6H < 12H ~ 9H, so 9H is the recommendation
• 3R ~ 6H < 9H, so....
• 4R daily is the recommendation (not intermittent)

No direct efficacy data for 4R---Yet

• In situations where RIF cannot be used daily rifabutin (RFB) may be substituted
  - HIV-infected persons receiving protease inhibitors
  - Not studied for LTBI treatment
Rifampin (4R)

- Dose: 600 mg daily x 4 months (adults and children)
- Completion rates superior: 60-91%
- Well-tolerated: Mild rashes, GI sx(s), orange body fluids
- Low rates of hepatotoxicity (0.3% for RIF vs. 1.4% for INH in one study)
- Hypersensitivity syndrome
  - “Flu-like” symptoms (fever, malaise, myalgias)
  - Anemia, thrombocytopenia
  - More common with intermittent doses
- Carefully rule out TB if used in HIV, avoid with ART
Rifamycins – Drug Interactions


- Oral anticoagulants
- Oral contraceptives
- Cyclosporine
- Glucocorticoids
- Itraconazole
- Ketoconazole
- Methadone
- Midazolam or triazolam
- Phenytoin
- Quinidine
- Theophylline
- Verapamil
- β-Adrenergic blocking agents
- Chloramphenicol
- Clarithromycin
- Dapsone
- Diazepam
- Digoxin (oral)
- Diltiazem
- Disopyramide
- Doxycycline
- Fluconazole
- Haloperidol
- Losartan potassium
- Nifedipine
- Nortriptyline
- Sulfonylureas
- Tacrolimus
- Tocainide
Rifapentine

• Longer half-life enables intermittent therapy
• Initially approved for once-weekly therapy of active TB in continuation phase
• 3 studies of efficacy using INH plus RPT for treatment of LTBI once per week x12 weeks (3HP)
  - 399 household contacts in Brazil\textsuperscript{1}
  - 1,150 HIV+ patients in South Africa\textsuperscript{2}
- TB Trials Consortium PREVENT-TB Trial (TBTC study 26)\textsuperscript{3}

\textsuperscript{1}Schechter M. Am J Respir CCM. 2006 Apr 15;173(8):922-6
\textsuperscript{2}Martinson N et al. 39th IUATLD World Conference on Lung Health, late breaker abstract, Paris, 2008
TBTC Study 26 (PREVENT-TB)

- 8,053 “high-risk” patients in U.S., Brazil, Spain
  - Contacts, converters; HIV+; Children ≥2y
- Compared self-admin 9H vs. 12 wk 3HP weekly by DOT
  - Rifapentine 900mg + INH 15-25mg/kg; 900mg max
- Both arms similar efficacy: (3HP=0.19%; 9H=0.43%)
- Completion much higher with 3HP (80%)
- Toxicity slightly higher with 3HP (5% vs. 3% in 9H)
  - Hepatotoxicity the same
  - “Excess” toxicity was hypersensitivity (over-reported?)

3HP CDC Recommendations, 2011

• Dose: Rifapentine 900 mg plus INH 900 mg once per week for 12 doses

• 3HP is an equal alternative to 9H for the following:
  - Contacts
  - Recent converters
  - Old, healed (Class IV) TB* (rule out active TB)

• Adults and children ≥12 years
  - Can be used in children 2-11y on a “case by case” basis
  - **Some experts now use 3HP routinely in young children

• HIV+ if healthy and on no ARVs
  - HIV gls now differ from TB-ok with EFV or RAL based ART +NRTI

CDC, 3HP Recommendations; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
3HP CDC Recommendations, 2011

• Precautions:
  - RPT rarely can cause neutropenia, increased liver enzymes, hypersensitivity reactions (fever, dizziness, musculoskeletal pain, rash, pruritus)
  - RPT induces increased metabolism of many medications, particularly those metabolized by cytochrome P450 enzymes – avoid with methadone, coumadin and hormonal birth control
  - Women who use any form of hormonal birth control should be advised to add, or switch to a barrier method

CDC, 3HP Recommendations; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
3HP CDC Recommendations, 2011

• Choice between 9INH and 3HP depends on:
  - Feasibility of DOT
  - Ability to obtain drugs
  - Ability to monitor side effects
  - Ability to complete treatment
  - Preference of patient and physician

• Practical advantages: corrections, shelters, clinics for recent immigrants
3HP CDC Recommendations (2011)

• INH-RPT NOT recommended for:
  - Children under 2y
  - HIV patients on ART (*HIV gls allow with EFV or RAL +NRTI*)
  - Pregnant women or women wanting to become pregnant
  - Contacts to INH or Rif-resistant TB

*CDC, 3HP Recommendations; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w*
"I've been taking this medication for 50 years and I'm going to sue! The side effects made me wrinkled, fat and bald!"
Section 5: Treatment of LTBI in Special Situations
Case: Child from El Salvador

• 4 year old child from El Salvador
• Contact to a household visitor with active TB
• No symptoms and has been developing normally
• Initial skin test is negative a week after her exposure to the index case.

• What should you do next?
Case: Child from El Salvador

1. Is patient likely infected?
   exposed; window period before tests may detect infection

2. Is there any evidence of active TB?
   No
   - Pulmonary or extra-pulmonary symptoms
     No
   - Radiology
     normal

3. Do the benefits of treatment outweigh the risk?
   Yes-young child, recently exposed, risk of progression to TB
   - Review history, other meds, plans for future immunosuppr tx

4. Which regimen most effective and least risk?
   4R or 3HP

5. Is patient going to take treatment if recommended?
   Consider DOPT
New data on 3 months of weekly isoniazid + rifapentine (3HP)

• Several studies recently published in special populations or settings:
  - Children
  - HIV-infected persons
  - Possible flu syndrome
  - Hepatotoxicity and hepatitis C virus infection
  - Self-administered vs. DOT
  - Health department clinics, jails
T tolerability and Effectiveness of 3HP in Children: TBTC S26 + IMPAACT

• Study 26 amended to enroll 352 additional children;
  - 1,058 total, 908 for efficacy evaluation
• 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>

3HP in Children: Summary

• Benefits of LTBI treatment greater for children:
  - <5 y recently acquired, higher risk progression to TB;
  - Increased risk severe TB (meningitis, disseminated ds)
  - More years at risk for development of TB
  - Tolerate treatment for LTBI better than adults

• In children 2 - 17y, 3HP:
  - Was well tolerated and safe
  - Had higher treatment completion rate than 9INH
  - Had few treatment discontinuations attributed to an AE
  - Hepatotoxicity not observed
  - Deaths, serious AE rare

Tolerability and Safety of 3HP in HIV + Persons
TBTC S26 + ACTG 5259

- Study 26 amended to enroll 191 additional HIV+ persons;
- Total 403 (399 for efficacy evaluation); Median CD4 ~500

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3HP (N=207)</th>
<th>9H (N=186)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion (MITT)</td>
<td>183/206 (89%)</td>
<td>123/193 (64%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinue—adverse drug reaction</td>
<td>7 (3%)</td>
<td>8 (4%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Grade 3 toxicity</td>
<td>14 (7%)</td>
<td>18 (10%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Grade 4 toxicity</td>
<td>4 (2%)</td>
<td>10 (5%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Grade 5 (death)</td>
<td>6 (3%)</td>
<td>5 (3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hepatotoxicity → drug discontinuation</td>
<td>2 (1%)</td>
<td>8 (4%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Possible flu syndrome</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Sterling TR, Scott N et al. AIDS 2016, 30:1607–1615
## Effectiveness in HIV+ Persons

Modified Intention to Treat Population

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>#TB Cases</th>
<th>TB per 100 p-y</th>
<th>Cumulative TB Rate (%)</th>
<th>Difference in Cumulative TB Rate</th>
<th>Upper bound 95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9H</td>
<td>193</td>
<td>6</td>
<td>1.25</td>
<td>3.50</td>
<td>-2.49</td>
<td>0.60</td>
</tr>
<tr>
<td>3HP</td>
<td>206</td>
<td>2</td>
<td>0.39</td>
<td>1.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3HP in HIV-infected Persons
Conclusions

• Among HIV (+) persons with median CD4 ~500 and not on ART:
   3HP as effective and safe for treatment of LTBI as 9H, and better tolerated

   3HP should be considered for treatment of LTBI in HIV-infected persons (with high CD4 and no ART)
Case: HIV-infected man with LTBI

• 25 y.o. male newly diagnosed with HIV (CD4 = 450)
• Positive T-spot
• He is asymptomatic and has a negative CXR
Case: HIV-infected man with LTBI

1. Is he likely infected?
   Yes-HIV+, positive T-spot
2. Was there evidence of TB?
   No - asymptomatic and has a negative CXR
3. Do benefits of treatment outweigh the risk?
   Yes - high risk progression to active TB
4. The best treatment option to prevent TB:
   A. Isoniazid alone
   B. ART alone
   C. Isoniazid + ART
   D. No treatment necessary at this time
TB Prevention in HIV
ART and INH

• Observational study, Rio de Janeiro, BR, 9/2003-9/2005
• 11,026 HIV + persons receiving care at 29 public clinics

<table>
<thead>
<tr>
<th>Intervention</th>
<th>TB per 100 p-y</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART/No INH</td>
<td>4.01</td>
</tr>
<tr>
<td>ART</td>
<td>1.90</td>
</tr>
<tr>
<td>INH</td>
<td>1.27</td>
</tr>
<tr>
<td>ART and INH</td>
<td>0.80</td>
</tr>
</tbody>
</table>

• 76% ↓ in TB risk for persons who received ART and INH compared to no ART/no INH
  - After adjusting for age, previous TB, and baseline CD4

Case: Mexican Female with RA

• 43 y/o Mexican female with Rheumatoid arthritis
• On methotrexate and low dose prednisone, being considered for TNF-alpha inhibitor therapy
  - 23 mm TST (by report)
  - QFT negative (TB antigen minus nil was 0.09, low Mitogen)
  - Normal CXR
  - Repeat TST 27mm
  - QFT negative
Case: Mexican Female with RA

1. Is patient likely infected?
   Foreign-born, MTX, low dose steroids—starting biologic

2. Is there any evidence of active TB?
   No Pulmonary or extra-pulmonary symptoms
   Normal radiology

3. Do benefits of treatment outweigh the risk?
   About to start TNF-alpha inhibitor

4. Which regimen most effective and least risk?
   • Methotrexate may cause liver AE,
   • Rifamycins decrease steroids.
   • Discuss with rheumatologist-hold MTX?

5. Is patient going to take treatment if recommended?
   • Discuss with patient her preference, consider increasing steroids for 3HP or 4R
Where's the nearest bar?

Oh, they's been hibernatin' fer weeks!
Case: Man with Hep C, Alcohol Use

• A 35 y.o. male with hepatitis C and EtOH abuse
• Close contact of a smear-positive TB case.
• His IGRA is positive, HIV negative
• He is asymptomatic; CXR negative.
• SGOT = 100; SGPT = 115.

• What is the best treatment option:
  A. 9 months of INH
  B. 4 months of rifampin
  C. 3 months of INH + rifampin (IR)
  D. 3 months of once-weekly INH + rifapentine (3HP)
Hepatotoxicity and Hepatitis C Virus Infection

• Two study components:
  - Rates and risk factors for hepatotoxicity among all adults in Study 26, stratified by regimen
    - Of 6,862 adults who took ≥ 1 dose, 79 developed hepatotoxicity
      • 15/3545 (0.4%) on 3HP vs. 61/3317 (1.8%) on 9H (P < 0.001)
  - Case-control analysis for the role of viral hepatitis in hepatotoxicity associated with 9H vs. 3HP
    • 51 cases + 255 age-matched controls
Hepatotoxicity and Hepatitis C Virus Infection
Multivariate analyses

<table>
<thead>
<tr>
<th></th>
<th>PREVENT TB</th>
<th>Nested case-control study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Risk Ratio (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age, per year change</td>
<td>1.03 (1.02-1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.70 (1.65-4.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White non-Hispanic race/ethnicity</td>
<td>2.22 (1.28-3.85)</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI, per kg/m² increase</td>
<td>0.94 (0.90-0.99)</td>
<td>0.008</td>
</tr>
<tr>
<td>Elevated baseline AST</td>
<td>5.57 (3.31-9.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9INH</td>
<td>4.55 (2.53-8.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic hepatitis C virus</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
## Hepatotoxicity and Hepatitis C Virus Infection
### Multivariate analyses

<table>
<thead>
<tr>
<th></th>
<th>PREVENT TB</th>
<th>Nested case-control study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjustment</strong></td>
<td>Adjusted Risk Ratio (95%CI)</td>
<td>Adjusted Odds Ratio (95%CI)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Age, per year change</strong></td>
<td>1.03 (1.02-1.05)</td>
<td>---</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>2.70 (1.65-4.42)</td>
<td>2.75 (1.28-5.91)</td>
</tr>
<tr>
<td><strong>White non-Hispanic race/ethnicity</strong></td>
<td>2.22 (1.28-3.85)</td>
<td>2.97 (1.13-7.86)</td>
</tr>
<tr>
<td><strong>BMI, per kg/m² increase</strong></td>
<td>0.94 (0.90-0.99)</td>
<td>0.92 (0.86-0.99)</td>
</tr>
<tr>
<td><strong>Elevated baseline AST</strong></td>
<td>5.57 (3.31-9.37)</td>
<td>---</td>
</tr>
<tr>
<td><strong>9INH</strong></td>
<td>4.55 (2.53-8.18)</td>
<td>9.20 (3.79-22.4)</td>
</tr>
<tr>
<td><strong>Chronic hepatitis C virus</strong></td>
<td>---</td>
<td>3.24 (1.12-9.3)</td>
</tr>
</tbody>
</table>

Hepatotoxicity and Hepatitis C Virus Infection: Conclusions

• The risk of hepatotoxicity was significantly lower in persons treated with 3HP than 9H.

• Underlying hepatitis C virus infection and elevated baseline AST were risk factors for hepatotoxicity.

• 3HP may be preferred in persons at increased risk of hepatotoxicity

Adherence to Once-Weekly Self-Administered 3HP for LTBI: iAdhere (TBTC study 33)

- International, open-label, randomized controlled trial of 3HP for treatment of *M. tb* infection
- Non-inferiority trial; margin 15%
- MEMS caps to measure adherence

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Completion rate</th>
<th>Discontinuation due to AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directly observed</td>
<td>337</td>
<td>87%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Self-administered</td>
<td>337</td>
<td>74%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Self-admin with text message reminder</td>
<td>328</td>
<td>76%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>
Adherence to Once-Weekly Self-Administered 3HP for LTBI: iAdhere (TBTC study 33)

- SAT was non-inferior to DOT in the US but not overall
- eSAT did not achieve non-inferiority
- Discontinuation rates due to adverse effects were similar by arm, 3.6% DOT, 5.4% SAT, 4.3% eSAT (P=0.52).

Section 6

LTBI Therapy: Monitoring and Treatment Completion
“Imagine yourself in a boxing ring. In one corner is the Easter Bunny, in another Santa Claus, and in the third corner your highly adherent patient....

What do they have in common?
......All are figments of your imagination.”

-Dr. John Sbarbaro
LTBI Pretreatment Clinical Evaluation and Counseling

Identify TB DILI risks:
- Chronic ethanol consumption?
- Viral hepatitis?
- Pre-existing liver disease?
- Within 3 months post-partum?
- Concomitant hepatotoxic medication?
- Previous ALT or bilirubin abnormal?

Defer LTBI treatment

Assess TB risk

Low

No

High

Pregnant?

Yes

No

Check ALT, bilirubin (INR, PTT)

Yes

ALT > 3 x ULN, Bili >2, or liver-related coagulopathy

Defer treatment & re-evaluate.

Regimen selection according to indication and TB DILI risks:
- Isoniazid x 9 months, 6 months acceptable
- Rifampin x 4 months
  - e.g. if ALT 2-3 x ULN, isoniazid-resistance or -hepatotoxicity)
- Isoniazid with rifampin x 4 months

Monitoring plan in medical record

Patient education:
- Use patient’s preferred language
- Hepatitis symptoms and signs
- Discontinue treatment at symptom onset & contact clinic

Saukkonen et al. Respir Crit Care Med, 2006
Monitoring for Hepatotoxicity During LTBI Treatment

Identify liver risk factors:
- Chronic ethanol consumption?
- Viral hepatitis?
- Pre-existing liver disease?
- Pregnant /3 months post-partum?
- Other hepatotoxic medications?
- ALT/AST or bilirubin abnormal?
- Chronic medical conditions?

Check:
ALT (AST, bili): Baseline & q 2-4 weeks,
If biochemical monitoring desired for age >35:
  - baseline, then options include q 4-8 weeks, or at 1, 3, & 6 m

Nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue?

Baseline: ALT > 3 X ULN
- ALT 5 x ULN,
  - ALT 3 x ULN with nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue.
  - Or - Change of 2-3 x baseline, If latter ≥ 3 x ULN.

Hold treatment

No, age >35 y

Yes

Continue treatment

No

Yes

Treatment option:
- Rifampin x 4 m
- Isoniazid rechallenge? (when ALT < 2 X ULN)

Halt treatment

Saukkonen et al. Respir Crit Care Med, 2006
## Treatment Completion for LTBI Regimens

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses for completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>9 months</td>
<td>Daily</td>
<td>270 within 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76 within 12 months</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>Daily</td>
<td>180 within 9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52 within 9 months</td>
</tr>
<tr>
<td><strong>Isoniazid &amp; Rifapentine</strong></td>
<td>3 months</td>
<td>Once weekly</td>
<td>12 within 16 weeks</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>4 months</td>
<td>Daily</td>
<td>120 within 6 months</td>
</tr>
</tbody>
</table>
“You caught a virus from your computer and we had to erase your brain. I hope you’ve got a back-up copy!”
Case: Male U.S. born Pediatrician

- Occupational Health Provider consults you
- 35 year old, healthy, U.S. born physician applying for a job at Pediatric Health Center
- Pre-hire health screening, “positive” QFN-GIT
- Prior annual TSTs all negative, last one 3 months ago
- No known TB risk factors or exposure
  - “What about effect of recent TST on IGRA result?”
  - “If positive, and refuses to take treatment, should I recommend not hiring him?”
Case: Male U.S. born Pediatrician

• What are the quantitative results?
  - Nil=0.08 (negative control)
  - Mitogen=5.37 (positive control)
  - Antigen=0.52
  - TB antigen-nil= 0.44
  - Mitogen-nil=5.29

• What should you recommend now?
  - Treatment?
  - Employment?
Case: Male U.S. born Pediatrician

1. Is patient likely infected?
   Low positive result, low risk of TB exposure

2. Is there any evidence of active TB?
   - Pulmonary or extra-pulmonary symptoms
     No
   - Radiology
     Normal

3. Do benefits of treatment outweigh the risk?
   HCW will undergo serial testing, repeat test, if positive again treat. If negative, counsel him as low risk of infection.
   - Review medical history, other medications, plans for future immunosuppression.

4. Which regimen most effective and least risk?
   If treating, 3HP or 4R

5. Is patient going to take treatment if recommended?
   Assess
U.S. born Female from Colorado

• 77 y.o. U.S. born Female from Colorado
• History of exposure to TB as a child
• TST 17mm at age 62 but not treated
• Has rheumatoid arthritis, and is taking methotrexate and plaquenil as well as oxycontin
• Quantiferon now done and is positive.
• CXR normal, no pulmonary or EP symptoms of TB
• Should you treat her for LTBI?
U.S. born Female from Colorado (cont)

1. Is she likely infected?
   Yes - remote contact to TB

2. Is there any evidence of active TB?
   No

3. Do benefits of treatment outweigh the risk?
   Contacted rheumatologist, RA stable, no plans for TNF-α inhibitor

4. Which regimen most effective and least risk?
   - RIF intrxn with oxycontin would affect pain mangmt
   - After discussion with patient and provider, decision not to treat LTBI, educated about S/S of TB disease

5. Is patient going to take therapy if recommended?
William Osler

“Medicine is a science of uncertainty and an art of probability.”

“It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.”
College Student from India

• 20 yo student from India; student visa
• TST required for University at entry
• TST 11mm, CXR normal
• Student health offered treatment but he refused.

• “IT IS DUE TO MY BCG VACCINATION AS A CHILD”

• What should you do now?
College Student from India (con’t)

• QFT-GIT: TB-nil =1.15
• He still refuses therapy for TB infection.
• What should you do now?

• “IT WAS ONLY POSITIVE BECAUSE OF THE INITIAL TST”
College Student from India

1. Is patient likely infected?
   Probably-FB high risk
2. Is there any evidence of active TB?
   - No Pulmonary or extra-pulmonary symptoms
   - Normal Radiology
3. Do benefits of treatment outweigh the risk?
   Review medical history, other medications, plans for future immunosuppression.
   Yes-young and healthy
4. Which regimen most effective and least risk?
   4R or 3HP
5. Is patient going to take treatment if recommended?
   ??????
College Student from India (con’t)

• Repeat QFN-GIT: TB-nil=0.34

• “I TOLD YOU IT WAS NEGATIVE”
Don’t order a test unless you have a plan for what to do with the results!!
31 year-old Healthy Female

- 31 yo woman, T-spot (+), normal CXR, otherwise healthy.
- Recent contact to highly infectious patient
- Advised precautions to prevent pregnancy during TB prophylaxis, reported using birth control
- Completed 11 doses of 3HP
- At 12th dose, reported late menses during weekly questions
- Pregnancy test (+)

1. Can we consider <12 3HP doses as completed therapy?
2. If we cannot count this regimen as complete, do we restart 12 weeks of 3 HP after delivery?
31 year-old Healthy Female

- **Answer**: I agree with stopping the 3HP at this time.
- **Definition of completion of therapy in Prevent TB study** was receiving ≥11 of 12 doses.
- **Given** that the patient received 11 doses, this patient should be considered to have completed therapy for LTBI.
LTBI Treatment Summary, 2016

• Rifamycins allow shorter LTBI tx, better completion
  - 4R is well-tolerated, effective; limited efficacy data
  - 3HP has good efficacy data; safe and well tolerated; DOT
• 9INH preferred
  - Children <12y (some experts use 4R and 3HP to age 5)
  - HIV patients on ART
  - Pregnant women or those wanting to become pregnant
• New gls may expand use of short course-rifamycin based LTBI therapy
• LTBI treatment is cost-effective
Opportunities to Better Address LTBI

• Relatively low burden of TB disease in the US
• Very high treatment completion rates; not much room for improvement
• Can we reduce diagnostic delays?
  - No easy answer because delays arise from patients not seeking care and providers not consider TB as diagnosis
• Newer tests that have advantages in key populations
• Newer and better treatment regimens
• Recommendation by US Preventive Services Task Force

Phile LoBue, NAR 2017
1-800-4TB-INFO
Additional Resources

• Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection  *MMWR* 2000; 49 (No. RR-6)  
  [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm)

• Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection  
  [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w)

• Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection --- United States, 2010  
  [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_e)
Additional Resources

  http://ajrccm.atsjournals.org/content/174/8/935.full.pdf+html

  http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5908a3.htm?s_cid=mm5908a3_e

• Latent Tuberculosis Infection: A Guide for Primary Health Care Providers  
Additional Resources

• Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis

• CDC TB Website  http://www.cdc.gov/tb

• Southeastern National TB Center
  http://sntc.medicine.ufl.edu/

• National TB Controllers Association www.ntca-tb.org/

• CDC’s Morbidity and Mortality Weekly Report
  http://www.cdc.gov/tb/publications/reportsarticles/mmwr/default.htm

• American Thoracic Society http://www.thoracic.org/statements/

• Risk Calculator: www.tstin3d.com
THANK YOU!!!
* TST/IGRA may be negative in active disease
Estimating LTBI: NHANES

• NHANES is a series of sequentially run cross-sectional studies, implemented in 2-year cycles that assess the health of the civilian, non-institutionalized U.S. population

• To obtain a nationally representative sample of the civilian, non-institutionalized U.S. population, NHANES employs a complex, stratified, multistage probability cluster sampling design

• Approximately 5,000 persons participate in the survey in approximately 15 counties per year

• In 2011-2012, NHANES included a TB component with TST and Quantiferon testing
How Much LTBI Is There in the United States?

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Prevalence</th>
<th>Number of People</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST positive</td>
<td>4.7%</td>
<td>13.1 million</td>
</tr>
<tr>
<td>Quantiferon positive</td>
<td>5.0%</td>
<td>13.9 million</td>
</tr>
<tr>
<td>Both positive</td>
<td>2.1%</td>
<td>5.9 million</td>
</tr>
</tbody>
</table>

Estimates from National Health and Nutrition Examination Survey, 2011-2012, manuscript submitted
How Much LTBI Is There in the United States in Foreign-born Persons?

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Number of People</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST positive</td>
<td>20.5%</td>
<td>8.2 million</td>
</tr>
<tr>
<td>Quantiferon positive</td>
<td>15.9%</td>
<td>6.4 million</td>
</tr>
<tr>
<td>Both positive</td>
<td>9.3%</td>
<td>3.7 million</td>
</tr>
</tbody>
</table>

Estimates from National Health and Nutrition Examination Survey, 2011-2012, manuscript submitted
Targeted Testing and Treatment of TB Infection

• Of 39,920 TB cases reported in U.S. 2006-2008, 80% likely due to reactivation of LTBI (NHANES and genotyping\(^1\) data)

• USPSTF recommends screening for LTBI in populations at increased risk. (Grade B\(^2\))
  - Highest-risk populations with greatest benefit for targeted screening/treatment were excluded from USPSTF review because “screening in these populations may be considered standard care as part of disease management or indicated prior to the use of certain medications....”
  - E.g. Persons living with HIV, close contacts, and persons treated with immunosuppressive agents such as TNF-\(\alpha\) inhibitors

Case: Mexican Female with RA

- 43y/o Mexican female with Rheumatoid arthritis
- On methotrexate and low dose prednisone, being considered for TNF-alpha inhibitor therapy
  - 23 mm TST (by report)
  - QFT negative (TB antigen minus nil was 0.09, low Mitogen)
  - Normal CXR

- What would you do?
  A. Repeat the TST
  B. Repeat the QFT
  C. Do a T-SPOT
  D. Treat for TB infection