ATS/CDC Guidelines for Treating LTBI

Timothy R. Aksamit
Tuberculosis Clinical Intensive
November 19, 2013
Disclosure

• None
Objectives

• Discuss the ATS/CDC Guidelines for treating LTBI
Latent Tuberculosis Infection (LTBI) Update

• Background
• Diagnosis
• Treatment
• Summary
Latent Tuberculosis Infection (LTBI) Update

• Background
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ATS/CDC Guidelines for Treating LTBI

CC: Positive TST

HPI: 35 year-old male non-smoker

- Immigration evaluation, 20 mm positive TST
- No cough, sputum, hemoptysis, fever, chills, sweats, weight loss
- No known TB exposure or BCG
- No DM, polyneuropathy, h/o hepatitis, renal insufficiency, sz disorder
- HIV unknown, no risk factors;
- NO EtOH or IDU

SHx: School teacher, married without children.

EXAM: Mild obese Somali male NAD  VSS WNL
ATS/CDC Guidelines for Treating LTBI
ATS/CDC Guidelines for Treating LTBI

The chance of this patient developing active TB disease over his life time is greater than the chance of an American personal injury attorney flying on commercial airlines with active pulmonary XDR tuberculosis?

A. True
B. False
ATS/CDC Guidelines for Treating LTBI

The chance of this patient developing active TB disease over his life time is greater than the chance of an American personal injury attorney flying on commercial airlines with active pulmonary XDR tuberculosis?

A. True
B. False
ATS/CDC Guidelines for Treating LTBI
Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, 2005

Applying CDC/ATS Guidelines in Your Clinical Practice

Division of Tuberculosis Elimination
Centers for Disease Control and Prevention
Treatment of LTBI – Milestones

• For more than 4 decades, an essential component of TB prevention and control in the U.S. has been the treatment of persons with LTBI to prevent TB disease.
Treatment of LTBI – Milestones

1965: American Thoracic Society (ATS) recommends treatment of LTBI for those with previously untreated TB, tuberculin skin test (TST) converters, and young children.

1967: Recommendations expanded to include all TST positive reactors (>10 mm).
Treatment of LTBI – Milestones

1974: CDC and ATS guidelines established for pretreatment screening to decrease risk of hepatitis associated with treatment

- Treatment recommended for persons ≤ 35 years of age
Treatment of LTBI – Milestones

1983: CDC recommends clinical and laboratory monitoring of persons $\geq 35$ who require treatment for LTBI

1998: CDC recommends 2 months of rifampin (RIF) plus pyrazinamide (PZA) as an option for HIV-infected patients (later changed)
Treatment of LTBI – Milestones

2000: CDC and ATS issue updated guidelines for targeted testing and LTBI treatment

- 9-month regimen of isoniazid (INH) is preferred
- 2-month regimen of RIF and PZA and a 4-month regimen of RIF recommended as options (later changed)

1 MMWR June 9, 2000; 49(No. RR-6)
Treatment of LTBI – Milestones

2001: Owing to liver injury and death associated with 2-month regimen of RIF and PZA, use of this option de-emphasized in favor of other regimens

2003: 2-month regimen of RIZ and PZA generally not recommended — to be used only if the potential benefits outweigh the risk of severe liver injury and death

2011: 3-month Rx: weekly RPT & INH, DOT, select LTBI

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2 MMWR August 31, 2001; 50(34): 733-735
3 MMWR August 8, 2003; 52(31): 735-739
4 MMWR December 9, 2011; 60(48): 1650-1653
What’s ‘New’: ATS/CDC Guidelines for Treating LTBI

Tuberculin skin testing

• Emphasis on targeting persons at high risk

• 5-mm induration cutoff level for organ transplant recipients and other immunosuppressed patients being treated with prednisone or TNF-α antagonists

• Skin-test conversion defined as increase of ≥ 10 mm of induration within a 2-year period, regardless of age
What’s ‘New’: ATS/CDC Guidelines for Treating LTBI

Treatment of LTBI

- HIV-negative persons – INH for 9 months preferred regimen
- HIV-positive persons and those with fibrotic lesions on chest x-ray (consistent with previous TB) – INH should be given for 9 months
- For all persons – RIF for 4 months is an option
Clinical and laboratory monitoring

- Routine baseline and follow-up monitoring not required except for
  - HIV-infected persons
  - Pregnant women or those in early postpartum period
  - Persons with chronic liver disease or who use alcohol regularly
- Monthly monitoring for signs or symptoms of possible adverse effects
Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without symptoms or radiographic evidence of TB disease.

No GOLD STANDARD
Latent TB Infection (LTBI)
Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without symptoms or radiographic evidence of TB disease.

No GOLD STANDARD – Natural history is uncertain

? “LTBI” = Persistent adaptive *M. Tb* immune response
Testing for Latent TB Infection

PPD (TST):

“...A purified protein derivative (PPD) - TST ... at initial evaluation, ... a negative PPD-TST does not exclude the diagnosis of active tuberculosis...

...However, a positive PPD-TST supports ... diagnosis of culture-negative pulmonary tuberculosis, as well as LTBI in persons with stable abnormal chest radiograph consistent with inactive tuberculosis.”

AJRCCM 167: 603, 2003
Terminology

• “Treatment of latent TB infection” replaces the terms “preventive therapy” and “chemoprophylaxis” to promote greater understanding of the concept for both patients and providers.

• Targeted tuberculin testing is used to focus program activities and provider practices on groups at the highest risk for TB.
Testing for TB Disease and Infection

TB Infection (LTBI)

TB Disease
Pulm & XP
Targeted Tuberculin Testing

- Detects persons with LTBI who would benefit from treatment
- De-emphasizes testing of groups that are not at high risk for TB
- Can help reduce the waste of resources and prevent inappropriate treatment
Testing for Latent TB Infection

Targeted Tuberculin Testing:

“… strategic component of TB control … identify (patients with high) risk for developing TB …

… residents immigrating from high prevalence countries (and other individuals at risk for infection)

… recent M Tb infection (new conversion)…

… clinical conditions associated with progression to active tuberculosis.”

AJRCCM 161: S221, 2000
Testing for Latent TB Infection

What areas of the world are considered high TB incidence or prevalence?

- Asia
- Africa
- Latin America
- Eastern Europe
- Russia

Core Curriculum on Tuberculosis CDC 2000
Testing for Latent TB Infection

Targeted Tuberculin Testing:

“... individuals at risk for exposure to or infection with TB...

- residents immigrating from high prevalence countries (select foreign-born individuals)
- close contacts new/suspected disease
- residents and employees high-risk settings
- HCWs serving high-risk individuals
- medically underserved
- those using IV drugs.”

Core Curriculum on Tuberculosis CDC 2000
Testing for Latent TB Infection

Targeted Tuberculin Testing:

“… individuals at higher risk for TB disease once infected …

... recent M T. b infection (new conversion)

... clinical conditions associated with progression to active tuberculosis

• HIV infection
• certain medical conditions
• those using IV drugs
• h/o inadequately treated TB”

Core Curriculum on Tuberculosis CDC 2000
Conditions That Increase the Risk of Progression to TB Disease

- Diabetes mellitus
- Silicosis
- Prolonged corticosteroid therapy
- Other immunosuppressive therapy
- Cancer of the head and neck
- Hematologic and reticuloendothelial diseases
- End-stage renal disease
- Intestinal bypass or gastrectomy
- Chronic malabsorption syndromes
- Low body weight (10% or more below the ideal)
Latent Tuberculosis Infection (LTBI) Update

• Background
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Testing for Latent TB Infection

Tuberculin Skin Test (TST)

or

Interferon-γ Release Assay (IGRA):

- QuantiFERON®-TB Gold
- QuantiFERON®-TB Gold-IT (In-Tube)
- T-SPOT®. TB
New Insights in the Diagnosis of Tuberculosis Infection

**IFN-γ Release Assays (IGRAs)**

- ESAT-6 and CFP-10 (and TB 7.7(p4))
  - no cross reactivity with
    - BCG (TST no impact)
    - most NTM, except M. kansasii, M. szulgai, and M. marinum
  - + reactivity with M. bovis, africanum, microti

- Control antigens
  - nil (negative) control antigen
  - mitogen phytohemagglutinin (positive) control antigen
New Insights in the Diagnosis of Tuberculosis Infection

New Insights in the Diagnosis of Tuberculosis Infection

Interferon-γ release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis


**Abstract**

We conducted a systematic review and meta-analysis to compare the accuracy of the QuantiFERON-TB Gold In-Tube (QFT-GIT) and the T-SPOT.TB assays with the tuberculin skin test (TST) for the diagnosis of latent *Mycobacterium tuberculosis* infection (LTBI).

The Medline, Embase, and Cochrane databases were explored for relevant articles in November 2009. Specificities, and negative (NPV) and positive (PPV) predictive values of interferon-γ release assays (IGRAs) and the TST, and the exposure gradient influences on test results among bacille Calmette-Guérin (BCG) vaccinees were evaluated.

Specificity of IGRAs varied 98–100%. In immunocompetent adults, NPV for progression to tuberculosis within 2 yrs were 97.8% for T-SPOT.TB and 99.8% for QFT-GIT. When test performance of an immunodiagnostic test was not restricted to prior positivity of another test, progression rates to tuberculosis among IGRA-positive individuals followed for 13–24 months varied 8–15%, exceeding those reported for the TST (2–3%). In multivariate analyses, the odd ratios for TST positivity following BCG vaccination varied 3–25, whereas IGRA results remained un influenced and IGRA positivity was clearly associated with exposure to contagious tuberculosis cases.

IGRAs may have a relative advantage over the TST in detecting LTBI and allow the exclusion of *M. tuberculosis* infection with higher reliability.

**Keywords:** ECGD, interferon-γ release assay, latent *Mycobacterium tuberculosis* infection, meta-analysis, systematic review, TSTNET
New Insights in the Diagnosis of Tuberculosis Infection

Negative and Positive Predictive Value of a Whole-Blood Interferon-γ Release Assay for Developing Active Tuberculosis

An Update

Roland Dietl, Robert Loddenkemper, Stefan Niemann, Karen Meywald-Walter, and Albert Nienhaus

1Department of Pneumology, Hannover Medical School, Hannover; 2German Central Committees against Tuberculosis, Berlin; 3National Reference Center for Mycobacteria, Research Center Borstel, Borstel; 4Public Health Department Hamburg Central, Hamburg, and 5Institution for Statutory Accident Insurance and Prevention in the Health and Welfare Services, Hamburg, Germany.

Rationale: Only limited data are available on the predictive value of interferon-γ release assays for progression from latent tuberculosis infection to active tuberculosis (TB).

Objectives: To build on our initial study comparing the QuantIFERON-TB Gold in-tube assay (QFT) with the tuberculin skin test (TST) in close contacts of patients with TB and evaluating progression to active TB for up to 4 years.

Methods: A cohort of close contacts of smear-positive index cases established between May 2005 and April 2008 was tested with QFT and TST. Through April 2010, progressors to active TB were consecutively recorded.

Measurements and Main Results: Of the 1,414 contacts (141 children), 1,033 were still resident in Hamburg at the end of the study period, and results of both tests were available for 954. QFT, but not TST, results were associated with exposure time (P < 0.0001). For QFT, 195 of 954 (20.3%) were positive; 63.3% (604) were TST positive at greater than 5 mm and 25.4% at greater than 10 mm. Nine hundred and three contacts refused chemotherapy and 19 developed active TB. All 19 (100%) had been QFT positive, with a progression rate of 12.9% (19 of 147) over the observation period. Corresponding values for the TST were significantly lower: 89.5% (17 of 19) and 3.1% (17 of 555) at greater than 5 mm, and 52.6% (10 of 19) and 4.8% (10 of 207) at greater than 10 mm, respectively. The progression rate of 28.6% (6 of 21) for QFT-positive children was significantly higher than 10.2% (13 of 126) for adults (P = 0.03).

Conclusions: Results suggest that QFT is more reliable than the TST for identifying those who will soon progress to active TB, especially in children.

Am J Respir Crit Care Med Vol 183, pp 88-95, 2011
Originally Published in Press as DOI: 10.1164/rccm.201006-0974OC on August 27, 2010

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Only limited data are available for progression of contact persons tested positive by an interferon-γ release assay (IGRA) to active tuberculosis (TB) disease.

What This Study Adds to the Field

This study provides evidence on the ability of an IGRA to identify contacts who will soon progress to active TB given Mycobacterium tuberculosis infection. In addition, it provides information about the respective negative predictive value for progression among close contacts with negative test results.

A further question raised since the advent of the more specific IGRA is that of the reliability of their negative results. Where, in low burden countries, so many fewer positive results are generally produced with IGRA than with the TST, is it not probable that the new tests are “missing positives”? That is, do the IGRA fail to detect people who will progress to active TB and who would have been identified by the TST? Only a few studies have evaluated the outcome of high-risk subjects with negative commercial IGRA results over a significant observation period (3-6). Results from these studies are promising and...
Latent Tuberculosis Infection (LTBI) Update

• Background
• Diagnosis
• Treatment
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Initiating Treatment

Before initiating treatment for LTBI:

• Rule out TB disease (i.e., wait for culture result if specimen obtained)

• Determine prior history of treatment for LTBI or TB disease

• Assess risks and benefits of treatment

• Determine current and previous drug therapy
LTBI Treatment Regimens
LTBI Treatment Regimens

- **ISONIAZID (INH)** *
  - 9 months

- Combination: **RIFAPENTINE (RPT) plus ISONIAZID** *
  - 3 months, weekly dosing

- **RIFAMPIN (RIF)**
  - 4 months

- Others: 6INH, intermittent INH, 3IR

*preferred
Isoniazid Regimens

- **9-month regimen of DAILY isoniazid (INH) self-administered** is the historical preferred regimen

- **3-month, WEEKLY RPT and INH, DOT**
  - Age >12, LTBI and risk for developing TB disease:
    - Recent exposure, new conversion, or x-ray healed TB
Isoniazid Regimens

• 6-month regimen is less effective but may be used if unable to complete 9 months

• May be given daily or intermittently (twice weekly)
  • Use directly observed therapy (DOT) for intermittent regimen
ATS/CDC Guidelines for Treating LTBI

Figure 7. Tuberculosis case rates (%) in the Bethlehem Isanized Studies population according to the number of months isanized was taken in the combined program. Dots represent observed values; thin line, the calculated curve (y = a + bx); and dotted lines the calculated values based on the first four and the last five observations (y = a + bx). Source: Croninck, C. W. 1969. How much isanized is needed for prevention of tuberculosis among immunocompetent adults? Brit. J. Tuberc. Lung Dis. 3:847-850. Reprinted by permission of the International Union Against Tuberculosis and Lung Disease.
Isoniazid Regimens

• INH daily for 9 months
  (270 doses within 12 months)

• INH twice/week for 9 months
  (76 doses within 12 months)

• INH daily for 6 months
  (180 doses within 9 months)

• INH twice/week for 6 months
  (52 doses within 9 months)
Isoniazid Regimens
Pyridoxine: Vitamin B6 Supplementation

- **Pyridoxine** is recommended:
  - known or suspected neuropathy or at risk for neuropathy:
    - diabetes, thyroid disease, paraproteinemias, alcohol use, uremia, malnutrition, and HIV infection
  - Pregnant women and breastfeeding women
  - Persons with seizure disorder
  - Infants being breast fed by mothers taking isoniazid should also receive Poly-Vi-Sol 1 mL per day.
Latent TB Infection (LTBI) Treatment – 3RPT/INH

The NEW ENGLAND JOURNAL of MEDICINE

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

NEJM 365: 2155, 2011
Latent TB Infection (LTBI) Treatment – 3RPT/INH

- PREVENT TB Study – TBTC Study 26
- N= 8,053, 10 years; US, Brazil, and Spain 33wk f/u
- Randomized 9INH versus 3Rifapentine plus INH(weekly)

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- PREVENT TB Study – TBTC Study 26
- N= 8,053, 10 years; US, Brazil, and Spain 33wk f/u
- Randomized 9INH versus 3Rifapentine plus INH (weekly)
  - 3Rifapentine plus INH safe and effective
- TB dis: 7 cases 3RPT/INH (0.19%) vs 15 cases 9INH (0.43%)
- Completion: 82% 3RPT/INH versus 69% 9INH (p<0.001)
- AE: 4.9% vs 3.7% (p=0.009), hepatotoxicity: 0.4% vs 2.7% (p<0.001)

Applicable to:
- Countries with low-to-medium TB incidence
- Treatment given via DOT (directly observed therapy)

NEJM 365: 2155, 2011
Latent TB Infection (LTBI) Treatment

3RPT-INH - CDC 2011

MMWR 60: 1650, 2011

Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection
Latent TB Infection (LTBI) Treatment
3RPT-INH - CDC 2011

- 23 expert consultants, reviewed TBTC 26 as well as other INH-RPT trials

**RECOMMENDED** via DOT!
  - Age >12, LTBI and risk for developing TB disease
    - Recent exposure, new conversion, or x-ray healed TB
    - DOT resources available

**NOT RECOMMENDED:**
  - Age < 2 years
  - HIV / AIDS taking antiretroviral treatment
  - Presumed infected with INH or RIF-resistant *M. tuberculosis* and
  - Pregnant women or women expecting to become pregnant within the 12 week regimen

MMWR 60: 1650, 2011
Latent TB Infection (LTBI) Treatment
3RPT-INH - CDC 2011

- FAVORED ALTERNATIVE (to 9INH):
  - Practical advantage – correctional settings, recent immigrants, homeless shelters
  - Social circumstances that makes adherence questionable

N.B. ? Decreased tolerability of RPT-INH in DM pts.

- Dosing 3RPT/INH - DOT
  - Completion 11 or 12 doses within 16 weeks
  - Doses separated by > 72 hours to be counted

MMWR 60: 1650, 2011
Latent TB Infection (LTBI) Treatment  
3RPT-INH - CDC 2011

• 3RPT/INH for age 2 – 11 years old:
  • If completion of 9INH unlikely
  • (and) likelihood of TB high

• 9INH monotherapy PREFERRED age 2-11
Latent TB Infection (LTBI) Treatment
3RPT-INH - CDC 2011

Eligibility Criteria for the Use of the 12-week INH-RPT Regimen

Treatment for latent tuberculosis infection (LTBI) can prevent progression to active tuberculosis (TB) disease. Currently, isoniazid (INH) once daily for 9 months is the preferred treatment regimen for treating LTBI. In December 2011, the Centers for Disease Control and Prevention (CDC) issued recommendations in which 12-week once-weekly INH and rifapentine (INH-RPT) administered by Directly Observed Therapy (DOT) is considered an equal alternative to the 9-month regimen for some individuals.

This regimen is NOT recommended for all patients. For patients that meet the eligibility criteria, MDH will provide medication on a case-by-case basis. DOT by a local public health agency is mandatory for the INH-RPT regimen but may not be available at every local health department. Requests for INH-RPT must be accompanied by a completed "Individual Plan for Using the INH-RPT Regimen" form.

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<td>• Patients aged ≥ 12 years with recent exposure to infectious TB</td>
<td>• Children under age 2 years</td>
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<td>• Patients aged ≥ 12 years with TST or IGRA conversion from negative to positive within the previous 2 years</td>
<td>• Patients with HIV/AIDS currently receiving antiretroviral treatment</td>
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<td>• Patients aged ≥ 12 years with radiographic findings of inactive, &quot;healed&quot; pulmonary TB</td>
<td>• Pregnant women or women expecting to become pregnant during treatment</td>
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<td>• Patients aged ≥ 12 years with HIV/AIDS who are not taking antiretroviral medications</td>
<td>• Persons with presumed INH or rifampin-resistant LTBI</td>
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<td>• Patients aged ≥ 12 years with medical predictive risk factor(s) for developing active TB disease</td>
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<td>• Patients aged ≥ 12 years with social circumstances that make adherence and completion of longer regimen unlikely</td>
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The preferred regimen for children aged 2-11 years is 9 months of daily INH. However, INH-RPT can be considered on a case-by-case basis when both (1) the circumstances make the completion of 9 months of daily INH unlikely and (2) the likelihood of the risk of TB is great (e.g., recent Mycobacterium tuberculosis infection in a preschool-aged child).

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MDH Tuberculosis (TB) Prevention and Control Program
P.O. Box 54975, St Paul, MN 55164-0975
Phone: (651) 201-5414  Fax: (651) 201-5500  May 2012

### Eligibility Criteria for the Use of the 12-week INH-RPT Regimen

**Treatment for latent tuberculosis infection (LTBI) can prevent progression to active tuberculosis (TB).**

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Latent TB Infection (LTBI) Treatment
3RPT-INH - CDC 2011

- Dosing 3 RPT/INH arm:

  - **Rifapentine:**
    - Persons weighing > 50.0 kg received rifapentine 900 mg once-weekly.
    -Persons weighing < 50.0 kg were dosed once-weekly according to the following scale:
    - 10.0-14.0 kg 300 mg
    - 14.1-25.0 kg 450 mg
    - 25.1-32.0 kg 600 mg
    - 32.1-50.0 kg 750 mg

  - **Isoniazid:**
    - Persons 2-11 years old received isoniazid 25 mg/kg (rounded up to the nearest 50 or 100 mg; 900mg max) once-weekly.
    - Persons > 12 years old received isoniazid 15 mg/kg (rounded up to nearest 50 or 100 mg; 900mg max) once-weekly.

MMWR 60: 1650, 2011
Rifampin Regimens

- Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.
- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.
Rifampin Regimens

- RIF daily for 4 months
  \textit{(120 doses within 6 months)}
- RIF and PZA for 2 months should generally not be offered due to risk of severe adverse events$^6$
Completion of Therapy

- Completion of therapy is based on the total number of doses administered, not on duration alone.
Management of Patient Who Missed Doses

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

• When treatment has been interrupted for more than 2 months, patient should be examined to rule out TB disease

• Recommend and arrange for DOT as needed
Short Course Therapy with RIF plus INH  
3 Months versus Standard INH

• Not CDC approved for LTBI (as of 2000 with updates)
• Meta-analysis LTBI treatment
• Pooled 1926 patients (5 studies) Hong Kong, Spain, and Uganda
• Equivalent to standard therapy with INH (IR3 vs I6-12):
  • Efficacy (4.2% vs. 4.1%)
  • Severe side effects (4.9% vs. 4.8%)
  • Mortality (9.5% vs. 10.4%)

• Also equally effective in pediatric population, better completion (Greece)

CID 40: 670-676, 2005
CID 45: 715-722, 2007
Latent TB Infection (LTBI) Treatment

- Prospective MC treatment trial 4RIF vs 9INH - LTBI
- N=847 Canada, Saudi Arabia, Brazil
- Treatment completion: 78% vs. 60% (p<0.001)
- AE: 1.7% vs. 4.0%
  - Grade 3-4 hepatitis: 0.7% vs. 3.8%

Ann Intern Med 149: 689,
Latent TB Infection (LTBI) Treatment

- Prospective MC treatment trial 4RIF vs 9INH - LTBI
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  - Grade 3-4 hepatitis: 0.7% vs. 3.8%

- Mouse model: 2RPTdaily+INH = 2RIF+PZA
- RIF cost-saving Markov: 4RIF, 3RPT+INHdot, 9INH, 9INHdot

World Cong TB Wash DC Jun 2002
AJRCCM 179: 1055, 2009
Class V versus LTBI

- Class V pulmonary TB evaluation and treatment
- Start treatment for culture negative disease
- Four drugs: RIF, INH, EMB, and PZA
- Reassess at 2 months
- If no change in radiograph noted and patient felt to have LTBI – receives credit for LTBI treatment and medication discontinued
Inhibition of tumor necrosis factor and tuberculosis infection

Increased incidence of tuberculosis infection (and other infections) with FDA approved exposure to TNF inhibitors

- **Infliximab** (Remicade®) chimeric, murine-human monoclonal antibody, soluble and transmembrane TNF
- **Etanercept** (Enbrel®) recombinant fusion protein, soluble TNF
- **Adalimumab** (Humira®) humanized monoclonal antibody against TNF
- **Certolizumab** (Cimzia®) recombinant monoclonal humanized Fab pegylated antibody against
Inhibition of tumor necrosis factor and tuberculosis infection

• Increased extrapulmonary TB disease (57%) and disseminated TB disease (25%) with TNF inhibitor Rx

• **TBI rate** inhibitor specific (?)
  • infliximab (33-54/100k) > etanercept (27-28/100k)
  • ? adalimumab (27.1/100k)

• **Onset** of TB disease inhibitor specific
  • Infliximab (median 3 mo) > etanercept (median 11.5 mo)

Nature Clinical Practice Rheum 2: 602, 2006
Inhibition of tumor necrosis factor and tuberculosis infection

- Guidelines for evaluation and treatment:
  - Screening required for all prior to TNF-Rx
  - Exclude active disease prior to LTBI
  - TBI pre-test assessment, CXR, TST ≥ 5 mm
  - Two-step testing “boosting” may increase sensitivity but decrease specificity
  - Consider LTBI even if TST negative if risk sufficiently high
  - INH 9 months (RIF 4 months alternative)

Nature Clinical Practice Rheum 2: 602, 2006
Inhibition of tumor necrosis factor and tuberculosis infection
TB disease despite LTBI

• Retrospective study of 613 patients Aristotle University, Greece receiving TNF inhibitors for rheumatic disease

• All screened with TST (10mm) and CXR

• 36 of 45 “LTBI” patients received proper LTBI therapy

• 11 patients TB disease (2-35 mos into TNF-Rx, 7/11 <6 mos)
  • 7/11 correct Rx, 2 incorrect, 1 declined, 1 neg TST and CXR

• Of correct Rx:
  • 3/7 while on LTBI, 4/7 after LTBI

• TNF inhibition stopped, +/- etanercept restarted after TB Rx

Int J Tuberc Lung Dis 10: 1127, 2006
LTBI Regimens

- **ISONIAZID (INH)** *
  - 9 months

- Combination: **RIFAPENTINE (RPT) plus ISONIAZID** *
  - 3 months, weekly dosing

- **RIFAMPIN (RIF)**
  - 4 months

- Others: 6INH, intermittent INH, 3IR

*preferred
Monitoring During LTBI Treatment
Clinical Monitoring

Instruct patient to report signs or symptoms of adverse drug reactions

- Rash
- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet
Clinical Monitoring

Monthly visits should include a brief physical exam and a review of:

- Rationale for treatment
- Adherence with therapy
- Symptoms of adverse drug reactions
- Plans to continue treatment
Clinical Monitoring

• Incidence of hepatitis in persons taking INH is lower than previously thought (0.1 to 0.15%)  

• Hepatitis risk increases with age  
  • Uncommon in persons < 20 years old  
  • Nearly 2% in persons 50 to 64 years old  

• Risk increased with underlying liver disease or heavy alcohol consumption
Laboratory Monitoring

Baseline liver function tests (e.g., AST, ALT, and bilirubin) are not necessary except for patients with the following risk factors:

- HIV infection
- History of liver disease
- Alcoholism
- Pregnancy or in early postpartum period
Laboratory Monitoring

Repeat laboratory monitoring if patient has

- Abnormal baseline results
- Current or recent pregnancy
- High risk for adverse reactions
- Symptoms of adverse reaction
- Liver enlargement or tenderness during examination
Laboratory Monitoring

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
- Levels usually return to normal after completion of treatment
- Some experts recommend withholding INH if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic

MMWR June 9, 2000; 49(No. RR-6): 39
Latent TB Infection (LTBI) Treatment
Rifamycin Monitoring

• Monitoring: Rifamycin
  • Normal red or orange discoloration of body fluids – urine, perspiration, and tears. Contact lenses may be permanently discolored

• Drug – drug interaction common, review medication list, hepatic metabolism (INH increases phenytoin and disulfiram)

• RIF and RPT decrease blood levels of oral contraceptives (requires alternative family planning), warfarin, sulfonylurea, and methadone
Latent TB Infection (LTBI) Treatment Monitoring RPT-INH - CDC 2011

• Monitoring 3RPT/INH arm
  • DOT:
    • Symptom checklist: fever, yellow eyes, dizziness, paresthesias, rash, aches or > 1 day of nausea, vomiting, weakness, abdominal pain, dark urine, easy bruising, bleeding, or loss of appetite
    • REFER if positive
  • Monthly:
    • Clinical assessment
      • Assess adverse effects
      • Physical exam (icterus, liver tenderness, or rash)
    • Blood work
      • (liver disease, post-partum, EtOH use, HIV)

MMWR 60: 1650, 2011
Dear Colleagues,

At the Conference of the National Tuberculosis Controllers Association in June 2013, concerns were raised about adverse effects from the 12-dose regimen of directly-observed therapy (DOT) of once-weekly isoniazid-rifapentine (INH-RPT) in treating latent *Mycobacterium tuberculosis* infection (LTBI).

I am writing to update you on what we are learning about this regimen. In brief, the experience to-date shows that serious adverse effects associated with DOT INH-RPT are uncommon and similar to those that were observed during the controlled treatment trials. At sentinel U.S. sites where DOT INH-RPT has been used under routine conditions, the completion of therapy has been 80% or more, notably...
Latent TB Infection (LTBI) Treatment Monitoring RPT-INH - CDC 2013

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"possible hypersensitivity": INH-RPT 3.8% vs. SAT 9H 0.5%

- Fever, chills, HA, fatigue, red eyes, urticaria, pruritus, petechiae

- Implementation and safety of the DOT INH-RPT regimen
- TBTC Study 33: “iAdhere study” – SAT INH-RPT
- Ongoing LTBI surveillance for severe AE (hosp or death)
- Post-marketing sentinel site evaluation DOT INH-RPT
- In-depth evaluation of “possible hypersensitivity” TBTC 26
- State health department evaluation of DOT INH-RPT
- Collaboration with Sanofi
Fibrotic lesions

- 9 months of INH
- 2 months RIF plus PZA
- 4 months of RIF (with or without INH)

Pregnancy and Breast-feeding

- INH daily or twice weekly
- Pyridoxine supplementation
- Breast-feeding not contraindicated
Latent TB Infection (LTBI) Treatment - miscellaneous

Contacts of INH-Resistant TB

- Treatment with a rifamycin and PZA
- If unable to tolerate PZA, 4-month regimen of daily RIF
- HIV-positive persons: 2 month regimen with a rifamycin and PZA

Contacts of Multidrug-Resistant TB

- Use 2 drugs to which the infecting organism has demonstrated susceptibility
- Treat for 6 months or observe without treatment (HIV-negative)
- Treat HIV-positive persons for 12 months
- Follow for 2 years regardless of treatment
Latent Tuberculosis Infection (LTBI) Update

• Background
• Diagnosis
• Treatment
• Summary
Meeting the Challenge of TB Prevention

For every patient

- Assess TB risk factors
- If risk is present, perform TST or QFT
- If TST or QFT is positive, rule out active TB disease
- If active TB disease is ruled out, initiate treatment for LTBI
- If treatment is initiated, ensure completion
Case Studies
Case Study A

Patient history

• 29-year-old African-American female
• History of diabetes
• 35 weeks pregnant
• TST = 20 mm of induration
• No symptoms of TB disease
• CXR, CBC, LFTs normal
• No known contact with TB patient
Case Study A

Questions

1. What are this patient’s risk factors for TB infection or disease?

2. What is the appropriate management for this patient?
Case Study A

Discussion of risk factors

• Persons with diabetes mellitus are 2 to 4 times more likely to develop TB disease than those without diabetes

• Risk may be higher in insulin-dependent diabetics and those with poorly controlled diabetes
Case Study A

Discussion of management

- Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease
- Pregnant women should be targeted for TB testing only if they have specific risk factors for LTBI or progression to disease
Case Study A

Discussion of management

• Some experts prefer to delay treatment until after the early postpartum period, unless the person has recent TB infection or HIV infection
Case Study B

Patient history

- 47-year-old Hispanic male
- Moved to U.S. from Bolivia 4 years ago
- Known contact of infectious TB case
- TST = 5 mm of induration
- 3 months later TST = 23 mm of induration
- No symptoms of TB disease
- Normal CXR, CBC, AST, and bilirubin
Case Study B

Questions

1. What are the patient’s risk factors for TB infection or disease?

2. Has the management of this patient to date been appropriate?
Case Study B

Discussion of risk factors

• Patient is a contact of an infectious TB case

• Recent immigrant to the U.S. from a country with a high prevalence of TB
Case Study B

Discussion of risk factors

• If the patient had not been a contact, the recent immigration (less than 4 years) would have made him a candidate for TB testing, but the 5-mm reaction would not be considered positive

• Persons who immigrate from TB-endemic countries have increased rates of TB
Case Study B

Discussion of risk factors

• Rates of TB approach those of their countries of origin for 5 years after arrival in the U.S.

• These increased rates most likely result from recent *M. tuberculosis* infection in their native country
Case Study B

Discussion of management

• Should be treated for LTBI if TST reactions $\geq 10$ mm of induration

• As a contact of an active TB case, 5 mm of induration is considered positive

• This patient should have been treated for LTBI immediately after the first TST
Case Study C

Patient history

• 36-year-old Asian female
• Moved to U.S. from Philippines > 15 years ago
• Plans to work in a correctional facility
• TST result negative 1 year ago
• TST for pre-employment physical = 26 mm of induration
• CXR normal
• No symptoms of TB disease
• No known contact with a TB patient
Case Study C

Questions

1. What are the patient’s risk factors for TB infection or disease?

2. What is the appropriate management for this patient?
Case Study C

Discussion of risk factors

- Patient’s TST converted from negative to positive (within a 2-year period)
- TST conversion increases risk for progressing from LTBI to TB disease
- Foreign-born status is less of a risk factor, i.e., she immigrated more than 5 years ago
Case Study C

Discussion of management

• Patient’s TST conversion indicates failure to identify this person as high risk for recent exposure to TB
• Patient may have had extended travel to her country of origin or other high-prevalence parts of the world
Case Study C

Discussion of management

- Patient is a recent converter and, as such, is a candidate for treatment of LTBI with INH
Meeting the Challenge of TB Prevention

For every patient

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• If risk is present, perform TST or QFT
• If TST or QFT is positive, rule out active TB disease
• If active TB disease is ruled out, initiate treatment for LTBI
• If treatment is initiated, ensure completion
Questions & Discussion