

TB Intensive
Tyler, Texas
June 1 - 3, 2009

***ATS/CDC Guidelines for
Treating Latent TB Infection***

Timothy Aksamit, MD



June 1, 2009

**ATS/CDC Guidelines for
Treating LTBI**

**Tuberculosis Intensive : UT Tyler
Heartland National TB Center
1 Jun 09**

Timothy R. Aksamit, MD

**Assistant Professor of Medicine:
Mayo Clinic
College of Medicine**

**Consultant
Pulmonary Disease and Critical Care Medicine
Department of Internal Medicine
Mayo Clinic
Rochester, Minnesota**

ATS/CDC Guidelines for Treating LTBI

DISCLOSURE

Relevant Financial Relationship(s)

None



ATS/CDC Guidelines for Treating LTBI

CC: Positive TST

HPI: 35 year old male non smoker

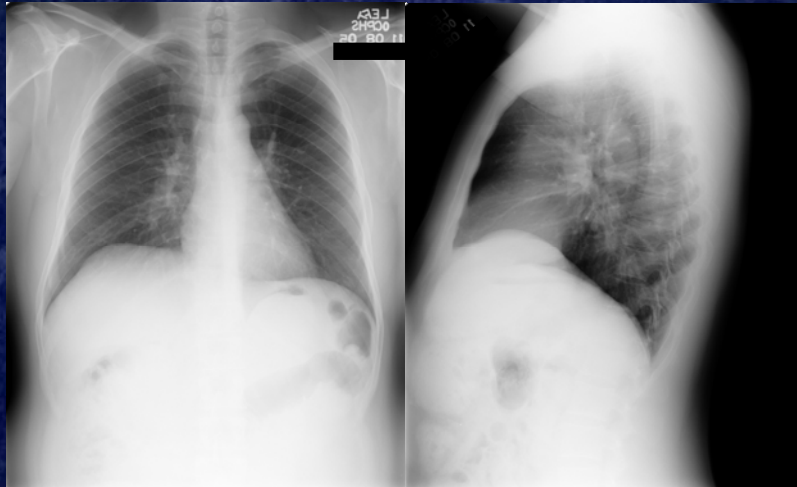
- Immigration evaluation, 20 mm positive TST
- No cough, sputum, hemoptysis, fever, chills, sweats, weight loss
- No known TB exposure or BCG
- No DM, polyneuropathy, h/o hepatitis, renal insufficiency, sz disorder
- HIV unknown, no risk factors;
- NO EtOH or IDU

SHx: School teacher, married without children.

EXAM: Mild obese Somali male NAD, VSS, WNL



ATS/CDC Guidelines for Treating LTBI



MAYO CLINIC

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

MAYO CLINIC

ATS/CDC Guidelines for Treating LTBI



CDC Clinician Communication

Information from Clinician Outreach and Communication Activity (COCA)

May 29, 2007

The following is an official CDC Health Advisory distributed via the Health Alert Network on May 29, 2007 at 12:40 p.m. EDT.

CDC Health Advisory

Investigation of U.S. Traveler with Extensively Drug Resistant Tuberculosis (XDR TB)



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 3 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 \leq 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 treatment¹

- 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 regimens²

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 death³

² *MMWR* August 31, 2001; 50(34): 733-735

³ *MMWR* August 8, 2003; 52(31): 735-739



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 antagonists⁴**
- **Skin-test conversion defined as increase of ≥ 10 mm of induration within a 2-year period, regardless of age**

⁴ *MMWR* August 61, 2004; 53(33): 683-686



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**



What's New: ATS/CDC Guidelines for Treating LTBI

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



LTBI vs. Pulmonary TB Disease

Latent TB Infection

- TST* or IGRA† positive
- Negative chest radiograph
- No symptoms or physical findings suggestive of TB disease (pulmonary or XP)

Pulmonary TB Disease

- TST or IGRA usually positive
- Chest radiograph may be abnormal
- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens *may* be smear or culture positive

*tuberculin skin test

†IGRA (interferon gamma release assay) is a blood test to detect *M. tuberculosis* infection.



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 and
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 Tb 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)



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



Testing for Latent TB Infection

Tuberculin Skin Test (TST)

or

Interferon- γ Release Assay (IGRA):

QuantiFERON®-TB Gold

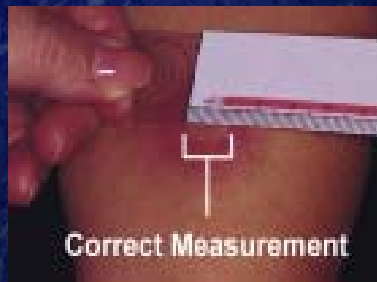
QuantiFERON®-TB Gold-IT (In-Tube)

T-SPOT®.TB



New Insights in the Diagnosis of Tuberculosis Infection Tuberculin Skin Test (TST)

- Century old
- False +ve: BCG and Non-tuberculous mycobacteria
- Limited sensitivity: LTBI and active disease
- Variable interpretation and need for return visit



Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

Classifying the Tuberculin Reaction (cont.)

10 mm is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Classifying the Tuberculin Reaction (cont.)

15 mm is classified as positive in

- Persons with no known risk factors for TB
- Targeted skin testing programs should only be conducted among high-risk groups

Boosting

- Some people with LTBI may have negative skin test reaction when tested years after infection
- Initial skin test may stimulate (boost) ability to react to tuberculin
- Positive reactions to subsequent tests may be misinterpreted as a new infection

Two-Step Testing

Use two-step testing for initial skin testing of adults who will be retested periodically

- If first test positive, consider the person infected
- If first test negative, give second test 1-3 weeks later
- If second test positive, consider person infected
- If second test negative, consider person uninfected

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)

- **QuantiFERON[®]-TB Gold (QFT-G) FDA approved 3 December 2004 (Cellestis)**
- **QuantiFERON[®]-TB Gold In-Tube (QFT-IT) FDA approved 10 October 2007 (Cellestis)**
- **T-SPOT[®].TB approved 30 July 2008 (Oxford Immunotec)**



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs)

- Quantifies IFN- γ release by peripheral blood cells (T-cells CMI response) after stimulation with *M. tuberculosis* specific:
 - ESAT-6: early-secreted antigen target 6
 - CFP-10: culture filtrate protein 10
 - TB 7.7(p4): (QuantiFERON®-TB Gold IT only)

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 IFN- γ Release Assays (IGRAs)

- POSITIVE IFN- γ signal:
 - ESAT-6 - nil or
 - CFP-10 - nil or
 - (or TB 7.7(p4) - nil)
- NEGATIVE IFN- γ signal:
- INDETERMINATE:
 - Low mitogen response (positive control)
 - Large nil response (negative control)

New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs)

Advantages over TST:

- Single visit
- Blood draw versus ID injection -acceptance
- Less variation in application and interpretation
- No cross reactivity with BCG
- No boosting with serial IGRA testing
- Cost-effectiveness in select populations
 - Contacts
 - HCW
 - FB(?)

New Insights in the Diagnosis of Tuberculosis Infection

Diagnosis of LTBI:

1. TST versus IGRAs ? : DEPENDS

2. QFT-Gold IT versus T-SPOT.TB ? : DEPENDS



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs)

Serial IGRAs testing for response to treatment to LTBI or TB disease?

NO (at this time...)

- Natural history of conversion and reversions is unknown and unpredictable.
- IGRA may increase, decrease, or demonstrate no change.

AJRCCM 174:349, 2006 CID 40: 1301, 2005
JID 193: 354, 2006 JImmun 167: 5217, 2001
IJTLD 9: 1034, 2005



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs)

Does boosting occur with IGRAs testing following TST testing?

Boosting of QFT-GIT is possible, but unusual, from serial TST testing.

ERJ 29: 1212, 2007
IUTLD 9:985, 2005
IUTLD 11: 788, 2007



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs)

Does a positive IGRAs mean that an individual with latent TB infection is at greater risk of developing TB disease in the future?

- Uncertain
- Longitudinal studies pending
- Contacts at increased risk, relative to TST (BCG exposure 46%)

ARJCCM 177: 1164, 2008



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs)

Is IGRAs testing cost effective for testing for latent TB infection?

- Yes, but depends...on local culture
- Single visit
- Higher specificity than TST (BCG, NTM)
- Reduce personnel cost, time away
- Less chest x-rays, investigation, LTBI treatment
- Direct and indirect costs



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs)

- Markov models
 - Close contacts: Diel et al. (Western Europe)
 - HCW: dePerio et al. (Cincinnati VA)
- Both suggest that IGRAs are cost-effective

ERJ 30: 321, 2007
IUATLD Abstract N Amer 2008
InfConHospEpi 24: 814, 2003



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs)

Can IGRAs testing be used in place of TST?

- Yes

CDC Guidelines QFT-Gold 2005:

QFT-Gold can be used in all circumstances in which the TST is used including:

- contact investigations
- evaluation of recent immigrants (BCG)
- TB screening HCW, including serial screening



MMWR 54: RR 15, 2005 MMWR 54: RR 17, 2005

New Insights in the D Tuberculosis Inf IFN- γ Release Assay

Should IGRAs testing always be testing in place of TST?

- No



- National Institute for Health and Clinical Excellence (NICE) UK
- Two step strategy: 1st TST, if positive TST then IGRA
- If +ve TST, -ve IGRAs: consider false positive TST, infection unlikely

HPE guideline March 2008, NICE NHS guideline March 2006



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays

Should IGRAs testing always be testing in place of TST?

- No

- IGRAs as sole testing:

- those with potential false negative TST, immunocompromised
- screening large numbers PHD
- HCW

HPE guideline March 2008, NICE NHS guideline March 2006



New Insights in the Diagnosis of Tuberculosis Infection IFN- γ Release Assays (IGRAs) Future directions

- Predictive of TB disease in LTBI (natural history)
- Indeterminate results
- Cut points – TST (5,10,15) vs. IGRAs (0.35 QFT, 8 spots T-SPOT)
- Specific IGRAs for specific patients – TNF inhibitor, immunocompromised
- Cost effectiveness for varying practices



LTBI Treatment Regimens

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**

Isoniazid Regimens

- 9-month regimen of isoniazid (INH) is the preferred regimen
- 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

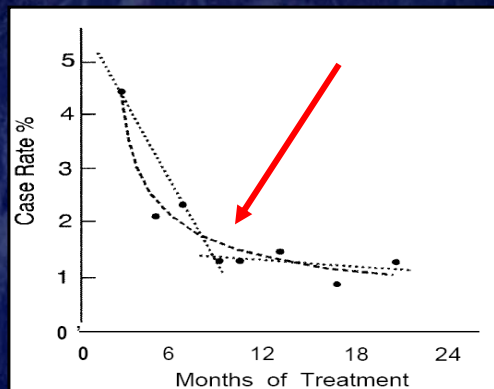


Figure 7. Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; thin line, the calculated curve ($y = a + b/x$); and dotted lines the calculated values based on the first four and the last five observations ($y = a + bx$). Source: Comstock, G. W. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int. 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*)

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
(120 doses within 6 months)
- RIF and PZA for 2 months should generally not be offered due to risk of severe adverse events⁶

⁶MMWR August 8, 2003; 52 (31): 735-739



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



ATS/CDC Guidelines for Treating LTBI

TABLE. Revised drug regimens for treatment of latent tuberculosis infection (LTBI) in adults*

| Drug | Interval and duration | Comments | Rating [†] (Evidence) [‡] | |
|---------------------------------|--------------------------------|--|---|--------------|
| | | | HIV-negative | HIV-infected |
| isoniazid | Daily for 9 months**†† | In HIV-infected persons, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs). | A (II) | A (II) |
| | Twice weekly for 9 months***†† | Directly observed therapy (DOT) must be used with twice-weekly dosing. | B (II) | B (II) |
| isoniazid | Daily for 6 months†† | Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children. | B (I) | C (I) |
| | Twice weekly for 6 months†† | DOT must be used with twice-weekly dosing. | B (II) | C (I) |
| Rifampin ^{§§} | Daily for 4 months | Used for persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB. In HIV-infected persons, most protease inhibitors or delavirdine should not be administered concurrently with rifampin. Rifabutin with appropriate dose adjustments can be used with protease inhibitors (saquinavir should be augmented with ritonavir) and NNRTIs (except delavirdine). Clinicians should consult web-based updates for the latest specific recommendations. | B (II) | B (III) |
| Rifampin plus pyrazinamide (RZ) | Daily for 2 months | RZ generally should not be offered for treatment of LTBI for HIV-infected or HIV-negative persons. | D (II) | D (II) |
| | Twice weekly for 2–3 months | | D (III) | D (III) |



MMWR 52: 735, 2003

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, 20007



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

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)

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



Monitoring During 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 asymptomatic⁷

 MMWR June 9, 2000; 49(No. RR-6): 39

Fibrotic Lesions

Acceptable regimens include

- 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

 MAYO CLINIC

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



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 recency of his 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 ≥ 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

- 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

