Targeted Tuberculosis (TB) Testing and Treatment of Latent TB Infection

Targeted TB Testing and Treatment of Latent TB Infection

- Targeted TB testing is used to focus program activities and provider practices on groups at the highest risk for TB.

- Treatment of LTBI substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease.

Latent TB Infection (LTBI) diagnosis and treatment

Latent TB Infection (LTBI)

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

LTBI vs. Pulmonary TB Disease

Latent TB Infection	Pulmonary TB Disease
Positive TST* or IGRA† result	TST or IGRA is usually positive
Chest radiograph normal	Chest radiograph is usually abnormal

*tuberculin skin test
†Interferon-Gamma Release Assay

LTBI vs. Pulmonary TB Disease

Latent TB Infection	Pulmonary TB Disease
No symptoms or physical findings suggestive of TB	Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
If done, respiratory specimens are smear negative	Respiratory specimens are usually culture positive (smear positive in about 50% of patients) and culture

Targeted TB Testing

- Essential TB prevention and control strategy
- 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

Treatment of LTBI – Milestones

Treatment of persons with LTBI to prevent TB disease is for more than 3 decades an essential component of TB prevention and control in the United States.

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 ≥ 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[1]

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)

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[2]

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

Treatment of LTBI – Milestones

2011: CDC recommends 12-doses (3 months) of isoniazid (INH) and rifapentine (RPT) as an option equal to the standard 9-month INH regimen for certain groups*

Risk Factors That Lead to Development of TB Disease

Persons at Risk for Developing

TB Disease

Persons at high risk for developing TB disease fall into 2 categories:

- Those who have an increased likelihood of exposure to persons with TB disease

- Those with clinical conditions that increase their risk of progressing from LTBI to TB disease

Increased Likelihood of Exposure to

Persons with TB Disease

Persons at risk for exposure to persons with TB disease include:

- Close contacts to person with infectious TB
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)
- Recent immigrants from TB-endemic regions of the world (within 5 years of arrival to the country)

Increased Risk for Progression to TB Disease

Persons more likely to progress from LTBI to TB disease include:

- HIV-infected persons
- Those with a history of prior, untreated TB or fibrotic lesions on chest radiograph
- Children ≤ 5 years with a positive TST

Increased Risk for Progression to TB Disease

Persons more likely to progress from LTBI to TB disease include:

- Underweight or malnourished persons
- Injection drug users
- Those receiving TNF-α antagonists for treatment of rheumatoid arthritis or Crohn's disease

Increased Risk for Progression to TB Disease

Persons more likely to progress from LTBI to TB disease include:

- Those with certain medical conditions such as:
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation (e.g., heart, kidney)
  - Carcinoma of head or neck
  - Gastrectomy or jejunoilial bypass

Testing for *M. tuberculosis* Infection

Testing for *M. tuberculosis* Infection

- There are two testing methods available for the detection of *M. tuberculosis* infection
  - Mantoux tuberculin skin test (TST)
  - Interferon-gamma release assays (IGRA)

Mantoux Tuberculin Skin Test

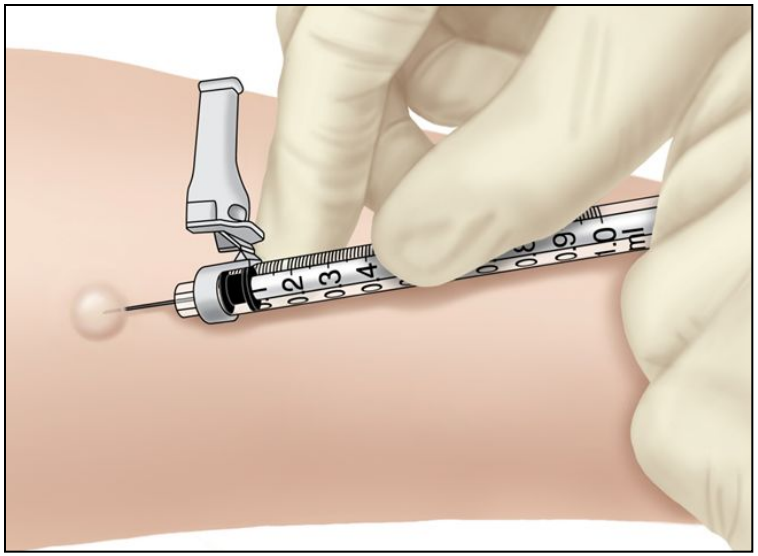
Skin test that produces delayed-type hypersensitivity reaction in persons with *M. tuberculosis* infection

- TST is useful for:
  - Determining how many people in a group are infected (e.g., contact investigation)
  - Examining persons who have symptoms of TB disease
- Multiple puncture tests (e.g., Tine Test) are inaccurate and not recommended

Administering the TST

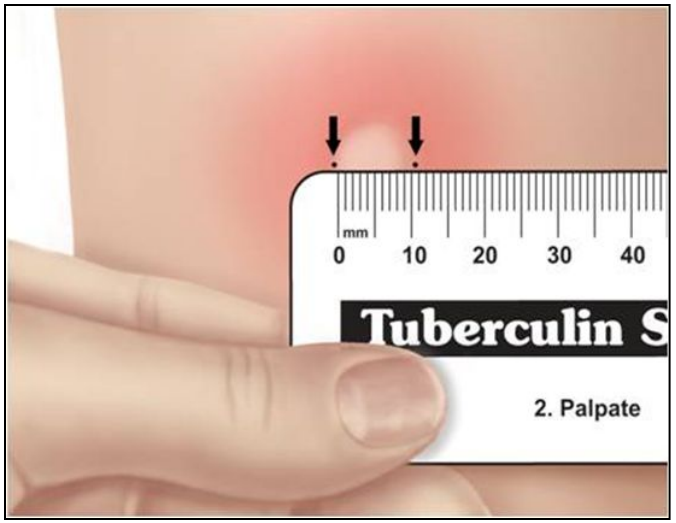
- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-guage needle

- Produce a wheal 6 to 10 mm in diameter



Reading the TST

- Measure reaction in 48 to 72 hours
- Measure induration, not erythema
- Record reaction in millimeters, not "negative" or "positive"
- Ensure trained health care professional measures and interprets the TST



Reading the TST

- Educate patient and family regarding significance of a positive TST result
- Positive TST reactions can be measured accurately for up to 7 days
- Negative reactions can be read accurately for only 72 hours

TST Interpretation

≥ 5 mm induration is interpreted as positive in

- HIV-infected persons
- Close contacts to an infectious TB case
- Persons with chest radiographs consistent with prior untreated TB

TST Interpretation

≥ 5 mm induration is interpreted as positive in

- Organ transplant recipients
- Other immunosuppressed patients (e.g. , those taking the equivalent of > 15 mg/d of prednisone for 1 month or those taking TNF-α antagonists)

TST Interpretation

≥ 10 mm induration is interpreted as positive in

- Recent immigrants
- Injection drug users
- Residents or employees of congregate settings
- Mycobacteriology laboratory personnel

TST Interpretation

≥ 10 mm induration is interpreted as positive in

- Persons with clinical conditions that place them at high risk
- Children < 4 years; infants, children, and adolescents exposed to adults at high-risk

TST Interpretation

≥ 15 mm induration is interpreted as positive in

- Persons with no known risk factors for TB.
  - Although skin testing programs should be conducted only among high-risk groups, certain individuals may require TST for employment or school attendance. Diagnosis and treatment of LTBI should always be tied to risk assessment.

Factors That May Cause False-

Positive TST Reactions

- **Nontuberculous myobacteria**
  - Reactions caused by nontuberculous mycobacteria are usually ≤10 mm of induration

- **BCG vaccination**
  - Reactivity in BCG vaccine recipients generally wanes over time;
  - positive TST result is likely due to TB infection if risk factors are present

Factors That May Cause False-Negative TST Reactions

- **Anergy**
  - Inability to react to a TST because of a weakened immune system
  - Usefulness of anergy testing in TST-negative persons who are HIV infected has not been demonstrated

Factors That May Cause False-Negative TST Reactions

- **Recent TB Infection**
  - Defined as less than 10 weeks after exposure
- **Very young age**
  - Newborns (< 6 months)

Factors That May Cause False-Negative TST Reactions

- **Live virus vaccination**
  - For example, measles or smallpox
  - Can temporarily suppress TST reactivity
- **Overwhelming TB Disease**
- **Poor TST administration technique**
  - For example, TST injection too shallow or too deep, or wheal is too small

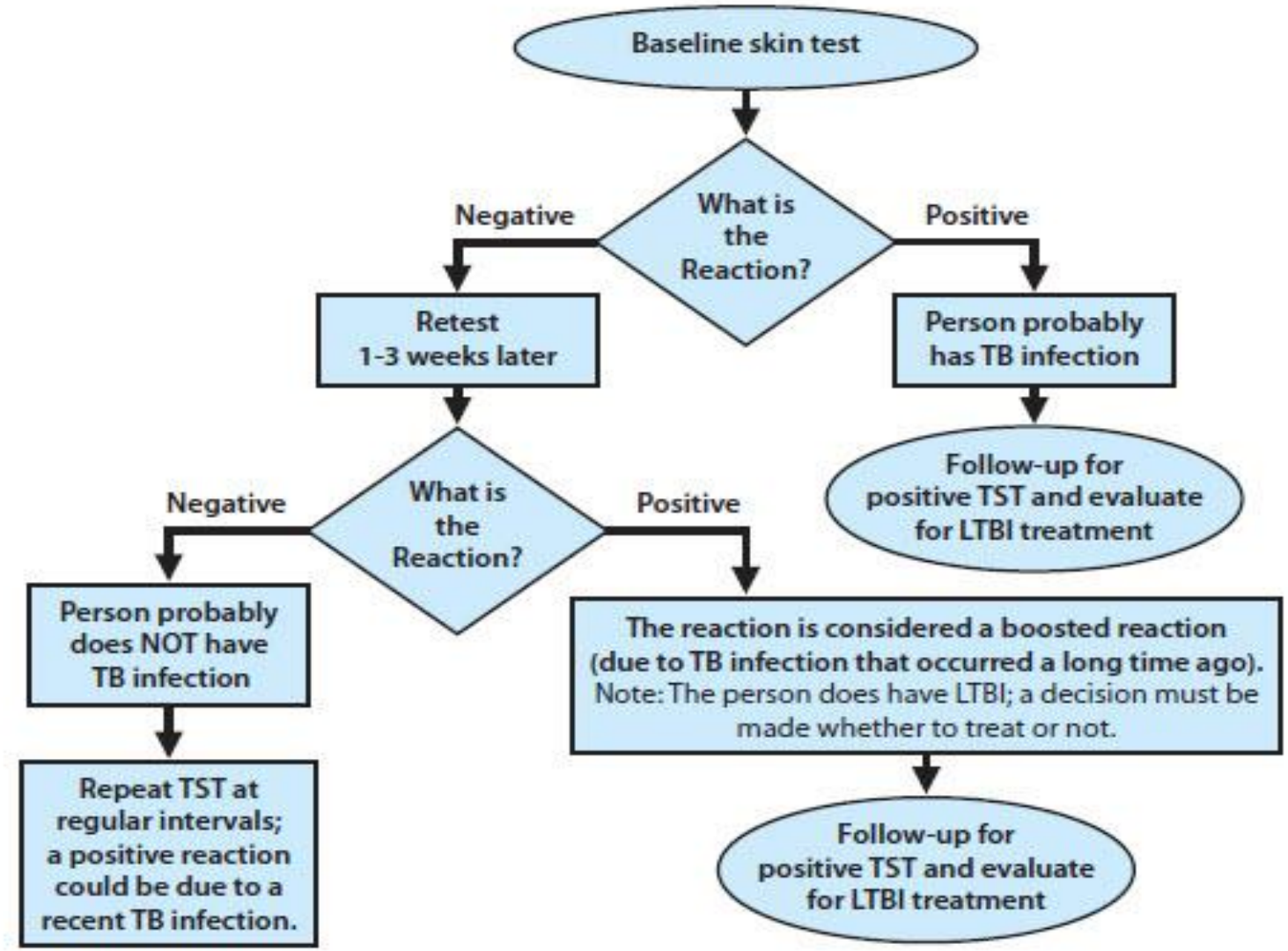
Boosting

- Some people with LTBI may have a negative skin test reaction when tested years after infection because of a waning response.
- An initial skin test may stimulate (boost) the ability to react to tuberculin.
- Positive reactions to subsequent tests may be misinterpreted as new infections rather than “boosted” reactions.

Two-Step Testing

- **A strategy to determine the difference between boosted reactions and reactions due to recent infection.**
  - If 1st test positive, consider infected; if negative, give 2nd test 1–3 weeks later
  - If 2nd test positive, consider infected; if negative, consider uninfected
- Use **two-step tests** for initial baseline skin testing of adults who will be retested periodically (e.g., health care workers).

Two-step TST Testing



Interferon-Gamma Release Assays (IGRAs)

Interferon-Gamma Release Assays (IGRAs)

- **Whole-blood test used to detect *M. tuberculosis* infection**

- **Two U.S. Food and Drug Administration (FDA) approved IGRAs are commercially available in the U.S.**
  - QuantiFERON® -TB Gold-in-tube test (QFT-GIT)
  - T.SPOT® .*TB* test (T-Spot)

How IGRAs Works

- Blood test that measures and compares amount of interferon-gamma (IFN-γ) released by blood cells in response to antigens

- Entails mixing blood samples with antigens from *M. tuberculosis* and controls

How IGRAs Work

- Cells that recognize the antigen release interferon-γ
- Amount of interferon released in response to *M. tuberculosis* antigens is compared to amount released in response to other antigens

Administering IGRAs

- Confirm and arrange for delivery of blood sample within specific time-frame to ensure viability of blood samples
- Draw blood sample according to test manufacturer's instructions
- Schedule a follow up appointment to receive test results, medical evaluation and possible treatment if needed

Interpretation of IGRA Test Results

IGRA Test	Results Reported as
QFT-GIT	Positive, negative, indeterminate
T-Spot	Positive, negative, indeterminate, borderline

Advantages of IGRAs

- Requires a single patient visit to conduct test
- Results can be available within 24 hours
- Does not boost responses measured by subsequent tests
- Prior BCG vaccination does not cause false-positive IGRA test result

Disadvantages/Limitations of IGRAs

- Errors in collecting and transporting blood, or in interpreting assays can decrease accuracy of IGRAs
- Limited data on use of IGRAs to predict who will progress to TB disease in the future

Disadvantages/Limitations of IGRAs

- **Tests may be expensive**
- **Limited data on the use of IGRAS for**
  - Children < 5 years of age;
  - Persons recently exposed to *M. tuberculosis*;
  - Immunocompromised persons; and
  - Serial testing

Selecting a Test to Detect TB Infection

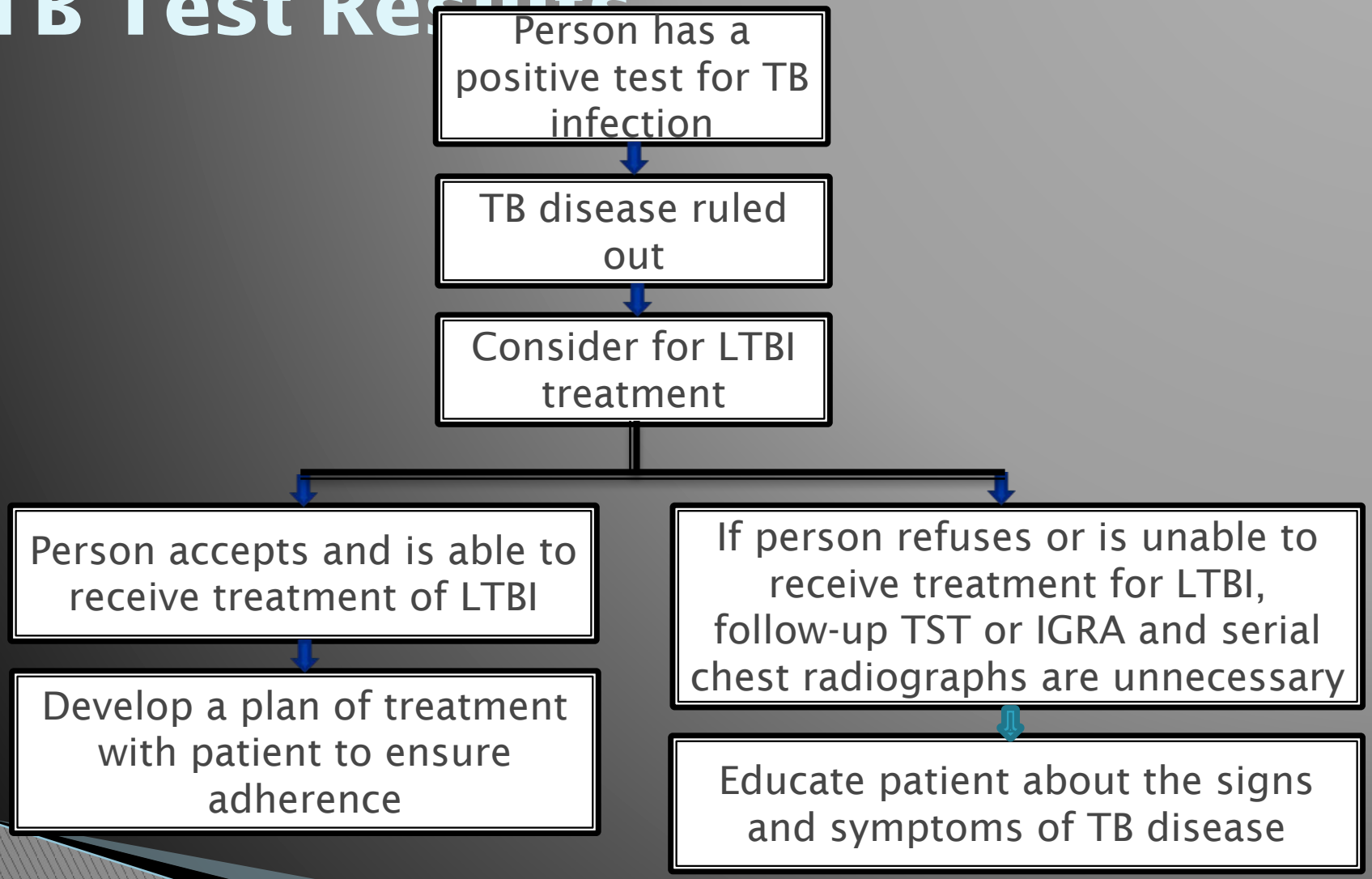
- **IGRAs are preferred method of testing for**
  - Groups of people who have poor rates of returning to have TST read
  - Persons who have received BCG vaccine
- **TST is the preferred method of testing for**
  - Children under the age of 5

Selecting a Test to Detect TB Infection

Before initiating treatment for LTBI

- Either TST or IGRA can be used without preference for other groups that are tested for LTBI
- Routine testing with TST and IGRA is *NOT* recommended

Evaluation of Persons with Positive TB Test Results



LTBI Treatment regimens

Initiating Treatment

Before initiating treatment for LTBI

- Rule out TB disease by history, physical examination, chest radiography and, when indicated, bacteriologic studies
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy

Treatment Regimens for LTB I

Drug(s)	Duration	Interval	Minimum Doses
Isoniazid	9 months	Daily	270
		Twice weekly	76
	6 months	Daily	180
		Twice weekly	52
Isoniazid & Rifapentine	3 months	Once weekly	12
Rifampin	4 months	Daily	120

Note: Rifampin (RIF) and Pyrazinamide (PZA) should not be offered to persons with LTBI. RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.

Treatment

Regimens – Isoniazid (INH)

- **9-month regimen of isoniazid (INH) is one of the preferred 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**
- **Preferred regimen for children 2-11 years of age**

Latent TB Infection Treatment Regimens – Isoniazid (INH)

- **Doses**
  - 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

LTBI Treatment Regimens – Isoniazid (INH) and Rifapentine (RPT)

- 3-month regimen of INH and RPT is an option equal to 9-month INH regimen for treating LTBI in certain groups, such as otherwise healthy people, 12 years of age and older, who were recently in contact with infectious TB or who had tuberculin skin test conversions or positive blood test for TB

- Must use directly observed therapy (DOT)

LTBI Treatment Regimens – Isoniazid (INH) and Rifapentine (RPT)

- Not recommended for children younger than 12 years of age, HIV-infected people taking antiretroviral therapy, pregnant women, or women expecting to be pregnant within the 12-week regimen

- INH and RPT once a week for 3 months - 12 doses within 4 months

Latent TB Infection Treatment Regimens – Rifampin

- 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.
- RIF daily for 4 months - 120 doses within 6 months

Specific

Situations – HIV-Infected Persons

HIV-Infected Persons

- Consult an expert in managing HIV and TB
- INH daily for 9-mo, rather than 6-mo, is optimal: 270 doses within 12 months
- RIF is generally contraindicated for persons taking protease inhibitors or delavirdine
- Rifabutin with dose adjustments can sometimes be substituted for RIF
- INH/RPT regimen not recommended for HIV-infected people taking antiretroviral therapy

LTBI Regimens for Specific Situations – Fibrotic Lesions

Persons with Fibrotic Lesions Suggesting Previous TB

- **Should be treated for LTBI if they have**
  - A positive TST reaction (at least 5 mm) or IGRA result
  - No symptoms of infectious TB disease
  - No history of treatment for TB disease

- **Treat only after active disease excluded with sputum testing**

- **Acceptable regimens include**
  - 9 months of INH
  - 4 months of RIF (with or without INH)
  - 3 months of INH and RPT (12-dose regimen)

LTBI Treatment Regimens for Specific Situations – Multidrug-Resistant TB

Contacts of Persons with Multidrug-Resistant TB

- Consider risk for progressing to MDR disease before recommending LTBI treatment
- When prescribing treatment for these contacts, consult an MDR TB expert

LTBI Treatment Regimens for Specific Situations - Pregnancy

Pregnancy and Breast-Feeding

- 9 months of INH daily or twice weekly; give with vitamin B6
- If cannot take INH, consult with TB expert
- Women at high risk for progression to TB disease should not delay LTBI treatment; monitor carefully
- Breast-feeding not contraindicated

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

Monitoring Drug Treatment

Clinical Monitoring

Instruct patient to report signs and symptoms of adverse drug reactions:

- Fever
- Headache
- 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 (as low as 0.1%)**

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

- **Risk increases 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 risk factors:

- HIV infection
- History of liver disease
- Regular alcohol use
- 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 therapy

- **Discontinue treatment** if transminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatoxicity, and 5 times the upper limit of normal if patient is asymptomatic

Meeting the Challenge of TB Prevention

For every patient:

- Assess TB risk factors
- If risk is present, perform TST or IGRA
- If TST or IGRA is positive, rule out TB disease
- If TB disease is ruled out, initiate treatment for LTBI
- If treatment is initiated, ensure completion