
THE UNIVERSITY OF TEXAS HEALTH CENTER AT TYLER
HEART Land
NATIONAL TB CENTER
A PARTNERSHIP OF UT HEALTH CENTER AND TCID
TUBERCULOSIS AT A GLANCE
A reference for Practitioners on Basic Tuberculosis Information
Revised December 2006

December 2006

Dear Medical Practitioner and Health Care Worker,

This booklet provides basic information on the diagnosis, treatment, and management of latent tuberculosis infection and tuberculosis disease, based on recommendations from the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society, and the American Thoracic Society. Because we cover the basic considerations only, all health care workers involved in tuberculosis care are encouraged to call consultants at the Regional Medical Consultation Center that serves your region. (See list of contact information in front of Book)
Sincerely,

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REPORTING: Physicians are required to report suspected or confirmed cases of tuberculosis according to pertinent State Law, such as the State of Texas Health & Safety Code Section 97.4.b. Information about TB reporting in states other than Texas can be obtained from the state TB controller.
According to the State of Texas Health & Safety Code, Section 97.4.b., it is the physician's responsibility to report all cases of tuberculosis disease, whether suspected or confirmed, to the local health authority within one working day of diagnosis.

Note: The information in this booklet was originally published by the New York City Bureau for Tuberculosis Control. It has been extensively modified and updated on two occasions.

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TABLE OF CONTENTS

TABLES:

ABBREVIATIONS

AFB: Acid-Fast Bacilli
BCG: Bacillus Calmette-Guerin
CBC: Complete Blood Count
DOT: Directly Observed Therapy
DTH: Delayed-type Hypersensitivity
EMB: Ethambutol
HIV: Human Immunodeficiency Virus
IM: Intramuscular
INH: Isoniazid
IV: Intravenous
LFT: Liver Function Tests
LTBI: Latent Tuberculosis Infection
MDR: Multidrug Resistant
PO: Oral
PPD: Purified Protein Derivative
PZA: Pyrazinamide
RIF: Rifampin
SM: Streptomycin
TU: Tuberculin Unit
TST: Tuberculin Skin Test

I. TESTING FOR TUBERCULOSIS INFECTION: Tuberculin skin testing and Interferon gamma based tests

A. Who to Test

Testing for tuberculosis infection with tuberculosis skin testing or the new interferon gamma based blood tests is performed for two purposes: (1) to provide evidence for or against the diagnosis of tuberculosis disease; and (2) to identify persons with latent tuberculosis infection (LTBI) who would benefit from therapy to prevent progression to disease. Persons with recent infection are at high risk for development of tuberculosis. Targeted tuberculin skin testing should be performed in those at high risk for recent infection or for progression of LTBI to disease. Screening low-risk groups is discouraged.

Persons at risk for recent infection include:

- Contacts of tuberculosis patients
- Health care workers with patient contact
- Residents and employees of high-risk congregate settings (e.g. homeless

  shelters, correctional facilities)
- Persons who emigrated from high-prevalence countries in the previous 5 years
- Children and adolescents exposed to high-risk adults

Conditions associated with increased risk for progression of LTBI to disease are:

- HIV infection
- Organ transplants
- Immunosuppressive therapy (prednisone 15 mg/day ≥ one month)

- Treatment with Tumor Necrosis Factor alpha antagonists
- Fibrotic chest x-ray lesions of prior tuberculosis
- Diabetes
- Intravenous drug use
- Chronic renal failure
- Leukemia, lymphoma
- Cancer of head, neck or lung
- Silicosis
- Weight loss ≥ 10% of ideal body weight
- Gastrectomy, jejunoileal bypass
- Silicosis
- Age < 5 years

B. Tuberculin Skin Testing with Purified Protein Derivative (PPD)

1. Performance of PPD

Tuberculin skin testing by the intradermal Mantoux method identifies persons infected with *M. tuberculosis*. **Repeated use of the tuberculin skin test (TST) will not cause an uninfected person to develop a positive skin test. Multiple puncture tests, such as the Tine test, should *not* be used** because they are not well-standardized and can yield false positive and false negative results.

Inject 0.1 ml of 5 TU PPD just under the skin, with the needle bevel facing up, to produce a wheal 6-10 mm in diameter. The test should be read after 48-72 hours by **a health care professional, not by the patient**. If the test is not read then, a positive reaction may be documented up to one week after testing. If the results appear negative and more than 72 hours have passed, the test must be repeated. The diameter of **induration**, not erythema, should be measured transversely across the forearm and recorded in millimeters. Do not record results as "positive" or "negative."

2. Test Interpretation

In persons with suspected active tuberculosis, 5 mm is considered positive. In persons being tested to detect LTBI, the threshold for a positive test varies from 5-15 mm, depending on clinical circumstances. These are detailed in Section III, on treatment of LTBI.

3. Anergy (Control) Skin Testing

Anergy testing is not recommended to detect TB infection or disease. Results of anergy tests are not reproducible and do not aid in the interpretation of an individual skin test.

4. Two-Step Tuberculin Testing

Adults who were infected with *Mycobacterium tuberculosis* in the distant past may have diminished tuberculin skin test reactivity. In some of these cases, an initial tuberculin skin test gives a negative or weakly positive reaction, but "boosts" the immune system so that subsequent PPD tests may be larger and positive, the "booster effect."

Because of the booster effect, persons such as health care workers who undergo periodic tuberculin skin testing should receive an initial two-step skin test. If the first test is positive, no further testing is needed. If the first test is negative, a second test is placed 1-3 weeks later. If the second test is positive, the person has LTBI. This "boosted" response is the valid baseline for the individual. If the second test is negative, the person is uninfected.

C. Interferon gamma (IFN-gamma) based blood tests: QuantiFERON®-TB Gold Test

1. Performance of QuantiFERON®-TB Gold test (QFT-G)

The QFT-G is a whole blood test for use in identifying persons infected with *M. tuberculosis*, including LTBI and tuberculosis disease. This test was approved by the U.S. Food and Drug Administration (FDA) in 2005. **The CDC has recommended that the QFT-G can be used in all circumstances in which the (TST) is currently used, including contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of health care workers and others undergoing serial**

evaluation for *M. tuberculosis* infection.

2. Before the QFT-G is attempted, arrangements should be made with a qualified laboratory and courier service, if needed, to insure prompt and proper processing of blood. Whole blood is drawn from the patient into a specimen tube containing heparin. **Blood samples must be processed within 12 hours after collection.** Venous blood samples are mixed with two synthetic peptides representing two *M. tuberculosis* proteins, ESAT-6 and CFP-10, placebo, and a nonspecific mitogen. After incubation of the blood with the antigens, the amount of IFN-gamma is measured. If the patient is infected with *M. tuberculosis*, their white blood cells will release IFN-gamma in response to contact with the TB antigens. The interpretation of QFT-G results is based on the amount of IFN-gamma that is released in response to the antigens.

3. Clinical experience is still limited with the QFT-G test. There are limited data on the use of QFT-G in children younger than 17 years of age, among persons recently exposed to *M. tuberculosis*, and in immunocompromised persons (including HIV seropositive patients).

4. A QFT-G based test that does not require processing of blood within 12 hours (QFT-G in tube) is in development. An additional IFN-gamma based test, called T-Spot or Ellispot, is also in development but not currently FDA approved. This test quantifies the number of IFN-gamma producing cells in response to the ESAT-6 and CFP-10 antigens.

D. Follow-up Evaluation

In persons with a positive tuberculin skin test or positive QFT-G, a clinical evaluation and a chest x-ray should be done to evaluate the possibility of tuberculosis. If tuberculosis is excluded, treatment of LTBI should be considered. No subsequent skin tests, QFT-G tests, or chest x-rays should be done on a routine basis.

A. Pulmonary Tuberculosis

A presumptive diagnosis of pulmonary tuberculosis is usually based on clinical symptoms, an abnormal chest x-ray, and a sputum smear that contains acid-fast bacilli (AFB). Approximately 50% of patients with culture-proven tuberculosis have AFB-negative smears. Patients with nontuberculous mycobacterial disease can also have AFB+ smears, so definitive confirmation of the diagnosis usually depends on a positive culture for *M. tuberculosis*. In a minority of cases, cultures are negative and the diagnosis is based on clinical and radiographic findings, combined with a response to antituberculosis therapy.

The MTD (GenProbe) and Amplicor (Roche) nucleic acid amplification tests detect ribosomal RNA or DNA of *M. tuberculosis*, respectively. These tests are more sensitive and specific than the AFB smear. However, they are expensive and do not replace the AFB smear or mycobacterial culture. A positive AFB smear is an important indicator of infectivity, and a culture is essential to determine drug susceptibility. Therefore, even if nucleic acid amplification tests are performed, AFB smears and cultures should be done.

Both nucleic acid amplification tests are approved for AFB+ sputum samples because the sensitivity and specificity are >95%. The MTD test is approved for AFB-negative sputum samples, but sensitivity is lower than in AFB+ samples. Nucleic acid amplification tests are most useful in the following situations:

- Patients with AFB+ sputum in whom the clinical suspicion of tuberculosis is low, such as patients with prior M. avium complex disease.
  If the nucleic acid amplification test is negative for Mycobacterium tuberculosis, antituberculosis therapy can be discontinued and therapy administered for nontuberculous mycobacteria.

- Patients with AFB-negative sputum in whom the clinical suspicion

of tuberculosis is moderate or high, and in whom the results of the nucleic acid amplification will affect the decision to give antituberculosis therapy or to perform invasive diagnostic procedures. For example, in an HIV-infected person with chest radiographic infiltrates, a positive nucleic acid amplification test for Mycobacterium tuberculosis will prompt initiation of antituberculosis therapy, and avoid bronchoscopy.

B. Extrapulmonary Tuberculosis

The diagnosis of extrapulmonary tuberculosis is difficult because AFB are rarely present in body fluids (blood, urine, cerebrospinal, pleural or peritoneal fluid) and tissue biopsies are generally needed to make a rapid diagnosis, based on the presence of AFB or granulomata. Because the sensitivities of these tests are not high, negative tests do not exclude tuberculosis. Nucleic acid amplification tests are not approved for use on extrapulmonary samples.

A. Who to Treat

Before prescribing treatment for LTBI, EXCLUDE ACTIVE TUBERCULOSIS since treatment of tuberculosis with INH alone invites development of drug resistance. Patients with a positive tuberculin skin test or QFT-G should be questioned regarding symptoms of tuberculosis and a chest radiograph should be performed.

In asymptomatic TST or QFT-G positive persons with normal chest radiographs, treatment can be given for LTBI. If symptoms are present or the CXR is abnormal and consistent with possible active TB, sputum cultures should be obtained. The patient should either be observed without therapy (if the likelihood of tuberculosis is low) or started on four drugs (if the likelihood of tuberculosis is moderate or high). NEVER start such a patient on INH alone. **If there is enough clinical suspicion of tuberculosis to send samples for mycobacterial culture, do not treat for LTBI until culture results are available. If cultures are negative, the CXR should be repeated to document stability of the radiograph (over at least two months) before treatment of LTBI is started.**

Treatment reduces the likelihood of progression of LTBI to disease. In persons at high risk for LTBI or at high risk for progression of LTBI to disease, a lower threshold of tuberculin sensitivity is used. Decisions regarding treatment of LTBI should be made regardless of BCG vaccination status (see Section VII, B). **In most cases, the patient's age does not influence the decision to treat LTBI.** All persons with LTBI who do not receive treatment should be told to seek prompt medical attention if they develop symptoms of tuberculosis.

The following persons should receive treatment for LTBI:

1. **Highest risk groups:** These patients should be treated for presumed LTBI, regardless of tuberculin skin or QFT-G test results, i.e., even with a negative tuberculin skin test or indeterminate QFT-G result. This is usually referred to as "window

period prophylaxis" Treatment should be started and a repeat TST performed after 8 to 10 weeks. If the repeat TST is positive, a full course of treatment for LTBI should be given to all converters. In persons with significant immunosuppression, treatment should often be continued even if the repeat TST remains negative. In children <5 years but older than 6 months when a repeat TST is negative, treatment can be stopped. The following groups should be treated despite a repeat negative TST:

- All persons with known or strongly suspected HIV infection with either: (1) recent close contact with a tuberculosis patient; or (2) a history of a positive tuberculin skin test.
- Persons who are receiving treatment with a tumor necrosis factor antagonist or plan to initiate such therapy and have either: (1) a recent close contact with an infectious tuberculosis patient; or (2) a history of a positive tuberculin skin test should be considered for treatment of LTBI even if a TST or QFT-G is negative. If treatment for LTBI is not given, these individuals should be educated regarding the signs and symptoms of TB and followed closely.
- Those taking immunosuppressive therapy for organ transplants.
- Infants less than six months of age.

2. **High-risk groups:** These patients should be treated for LTBI if the tuberculin skin test is ≥ 5 mm or if the QFT-G test is positive:

- Persons with known or suspected HIV infection who are not in the highest risk groups noted above.
- Organ transplant recipients.
- Persons receiving immunosuppressive therapy equivalent to ≥15 mg/day of prednisone for ≥ 1 month.
- Close contacts of infectious tuberculosis patients.
- Persons with fibrotic chest radiographic changes consistent with prior tuberculosis. (This does not include minimal apical scarring or small calcified granulomas as the only abnormality.)

- Persons with rheumatoid arthritis.

3. **Moderate-risk groups:** The following groups should be treated for LTBI if the skin test is ≥ 10 mm or if the QFT-G is positive:

- Intravenous drug use
- Diabetes
- Chronic renal failure
- Silicosis
- Substantial weight loss (> 10% of ideal body weight) or malnutrition, including gastrectomy and jejunoileal bypass
- Leukemia, lymphoma, head and neck cancer, lung cancer
- Persons who emigrated from high-prevalence countries in the previous 5 years
- Residents and employees of high-risk congregate settings (prisons, jails, chronic care facilities for the elderly, hospitals, residential facilities for AIDS patients, homeless shelters)
- Mycobacteriology laboratory personnel
- Children younger than 4 years

- Children and adolescents exposed to high-risk adults
- Persons with documented skin test conversion (≥ 10 mm increase in size) in previous two years

4. **Low-risk groups:** Because resources should be focused on targeted testing of persons at increased risk for progression of LTBI to disease, persons in low-risk groups should not be tested (either TST or QFT-G). However, some testing is inevitably performed, for example, in persons who begin employment as health care workers. In persons who have none of the risk factors listed above, a skin test ≥ 15 mm is considered positive.

In these low-risk persons with positive tuberculin skin tests, no national recommendations are provided to guide the decision to treat LTBI. We believe that the following guidelines are reasonable:

- The patient should be informed of the benefits and risks of treatment of LTBI.
- For persons $\leq$ 35 years old, treatment is recommended.
- For persons > 50 years old, treatment is not recommended.
- For persons 36-50 years old, the decision should be individualized, based in part on the patient's wishes., risks and possible benefits of treatment.
- Treatment is favored for persons in whom development of tuberculosis would lead to extensive spread of disease (for example, an employee in a newborn nursery).

B. Treatment of LTBI

1. Regimens

Table 1 shows the recommended regimens for treatment of LTBI, in order of preference. INH for 9 months is the preferred regimen because it is more effective than INH for 6 months. If INH is not used, RIF daily for 4-6 months should be given. There is much more experience with INH than with RIF. In patients receiving INH, Directly Observed Therapy (DOT) twice weekly is preferred in high-risk groups. If public health resources do not permit administration of INH for 9 months, 6 months of INH either daily or biweekly is acceptable, **except for HIV-infected persons, children < 18 years old, and persons with fibrotic lesions on chest x-ray.**

Rifampin daily for 4 months (adults) or 6 months (children or HIV infected) is recommended for:

- Persons with INH intolerance
- Persons exposed to an INH-resistant source case

RIF and PZA daily for 2 months is no longer recommended. RIF and PZA cause significant hepatotoxicity in 5-8% of cases. Fatalities have occurred even in persons who have been closely monitored.

This regimen is, therefore, no longer recommended for treatment of LTBI. In HIV-infected persons, rifabutin (dose depends on specific antiretroviral therapy used), may be substituted for RIF because of interactions with antiretroviral drugs. Consult a physician experienced in these interactions prior to using RIF or rifabutin.

2. Use of Pyridoxine (Vitamin B_6)

Pyridoxine (25-50 mg/day) is recommended with INH in patients who are pregnant and in those with a poor diet, seizures or illnesses that predispose to neuropathy, such as diabetes, alcoholism, malnutrition and HIV infection.

3. Contraindications to Treatment of LTBI

- Past history of serious reactions to drugs used to treat LTBI.
- Severe acute or chronic liver disease.
- Prior adequate treatment for tuberculosis or for LTBI. However, repeat treatment is recommended for HIV-infected persons or others who are immunocompromised or are otherwise susceptible (such as very young children) who have significant recent exposure to tuberculosis disease. (Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis, MMWR Dec 16, 2005)

4. Monitoring for Drug Toxicity

Persons receiving INH or RIF alone should have baseline measurements of liver tests only if they are at risk for hepatotoxicity, such as persons with prior or current liver disease or alcoholism, pregnancy or postpartum, HIV infection, or those receiving concurrent medications for chronic illness. Patients receiving INH or RIF alone should be seen monthly to evaluate for adverse drug reactions. Persons with baseline liver test abnormalities or symptoms of hepatotoxicity should also have liver function tests evaluated at least monthly during treatment.

INH or RIF should be discontinued if transaminases are more than 5 times normal in asymptomatic patients or more than three times normal in symptomatic patients or if jaundice or other clinical signs of hepatotoxicity develop.

IV. TREATMENT OF TUBERCULOSIS DISEASE

A. General Considerations

1. Tuberculosis should be treated in consultation with a physician who is experienced in its management.

2. All tuberculosis patients should have drug susceptibility testing done and results reported to the appropriate State Tuberculosis Elimination Division and the local health authority by the laboratory performing the tests.

3. All patients should be treated with DIRECTLY OBSERVED THERAPY (DOT).

4. Completion of therapy should be judged by the number of doses taken, not by the duration of treatment.

5. All tuberculosis patients should be tested for HIV infection. For patients with HIV infection, a CD4 cell count should be obtained.

6. Daily therapy refers to therapy given by DOT 5 or 7 days per week. Medications may be self administered on the weekend.

7. Most extrapulmonary tuberculosis in adults is treated in the same manner as pulmonary tuberculosis with 6-9 months of therapy, except for meningitis, which should be treated for 9-12 months. Children with meningitis or miliary disease should receive 9-12 months of therapy. Corticosteroids are recommended for patients with meningitis or pericarditis, respectively, in addition to antituberculosis therapy. Taper of steroids should be done cautiously in patients with extensive CNS disease. If the taper is associated with recurrence of neurological symptoms, the steroid dose should be increased and the taper done more slowly.

B. First-Line Agents

The first-line antituberculosis drugs are shown in Table 2. Medications that include drug combinations should reduce the likelihood of development of drug resistance. These include

Rifamate (150 mg of INH and 300 mg of RIF) and Rifater (50 mg of INH, 120 mg of RIF, and 300 mg of PZA). The usual dose of Rifamate in adults is 2 capsules/day. The daily dosage of Rifater is 4 tablets in patients weighing <45 kg, 5 tablets in patients weighing 45-54 kg, and 6 tablets in patients weighing >54 kg. Rifater and Rifamate should be used in all patients who are not receiving DOT.

C. Recommended Drug Regimens (Tables 3 and 4)

1. Initial Therapy (Months 1 and 2): Most patients in the United States should receive INH, RIF, PZA, and EMB initially (Table 3). Ethambutol can be discontinued when the isolate is known to be susceptible to INH and RIF. INH, RIF, and PZA should be given for the first 2 months. If PZA is not given for the first 2 months, INH and RIF must be given for 9 months instead of 6 (Table 3).

2. Continuation Therapy (Month 3 and later): The duration and nature of therapy depends primarily on two factors: the presence of cavitary disease at the time of diagnosis and the result of the sputum culture after 2 months of therapy (Table 4). Patients with cavitary disease and positive 2-month cultures are at increased risk for relapse with only 6 months of therapy; therefore, the continuation phase of INH and RIF should be prolonged from 4 to 7 months. Immunocompetent patients with cavitary disease and negative 2-month cultures, along with those with non-cavitary disease and either positive or negative 2 month cultures, should receive 4 months of INH and RIF in the continuation phase of treatment. The treating physician has the prerogative to prolong the continuation phase of therapy for patients if there is a question about the adequacy of treatment response (a slow clinical response), or if the patient was severely malnourished with extensive disease at diagnosis.

3. Intermittent Therapy (Table 3): Intermittent therapy twice or thrice weekly is as effective as daily treatment for patients with drug-susceptible organisms. Intermittent therapy should only be given for drug-susceptible tuberculosis, and only by DOT. Twice weekly regimens can be started after two weeks of daily treatment. Thrice weekly regimens can be used from the outset of treatment, but therapy should continue at least a three times per week, for the

duration of therapy. If drug resistance is suspected, drug susceptibility results should be obtained before beginning intermittent therapy. Twice weekly therapy should not be given to HIV-infected patients with a CD4 cell count <100.

4. Follow-up: For patients who have a satisfactory bacteriologic response (negative cultures after 2 months of therapy) and who have completed a 6- or 9-month INH and RIF-containing regimen, routine follow-up is not recommended by the CDC. Some authorities continue to follow patients who are HIV-infected or who have drug-resistant tuberculosis.

D. Therapy for Patients with Drug Resistance, Drug Intolerance, Treatment Failure, or Relapse

All patients with any of these conditions should be treated in close consultation with an expert in tuberculosis. Patients with drug-resistant tuberculosis should receive daily therapy. For drug intolerance, individualized regimens are needed. A patient who fails to convert sputum cultures to negative after 4 months of standard therapy should be considered a treatment failure. Treatment should be augmented with at least two, and preferably three new drugs to which the isolate is known to be susceptible. New cultures and susceptibility studies should be requested, and a review of compliance or factors interfering with absorption of medication should be done. A patient with relapse may have drug susceptible TB if the initial regimen was given by DOT and the patient was compliant. Despite this, every effort should be made to obtain a culture and susceptibility on a patient with suspected relapse. A standard regimen with INH, rifampin, ethambutol, and pyrazinamide should be started unless there was evidence of non-compliance, in which case an expanded regimen should be considered. This should be planned in conjunction with an expert in TB.

E. Monitoring for Efficacy of Treatment

1. Three sputum specimens should be obtained initially for AFB smear and mycobacterial culture.
2. Two-three sputum AFB smears should be obtained every 1-2 weeks until AFB smears are negative. Cultures need not be

performed on these specimens. Respiratory isolation can be discontinued in persons with negative AFB smears unless the patient has multidrug-resistant tuberculosis.

3. Two to three sputum samples should be obtained monthly for AFB smear and mycobacterial culture until cultures are negative for two consecutive months.
4. It is especially important to obtain a culture at the end of two months of therapy as duration of therapy may be determined by the result of this culture.
5. In patients whose original sputum cultures are negative, a chest x-ray after 2 months of therapy is necessary to assess the response to therapy. In these patients, a chest x-ray after completion of therapy is also desirable.
6. In patients whose original sputum cultures are positive, chest x-rays after 2 months and at the completion of therapy may be useful, but are not essential.
7. If sputum cultures remain positive after 2 months of therapy, patient non-adherence, drug-resistant tuberculosis, or malabsorption should be considered. Drug susceptibility studies should be repeated, and patients not already on DOT should be placed on DOT. An expert in treating tuberculosis should be consulted.
8. An assessment of the patient's clinical response should be documented at least monthly. This includes their weight, general health, and resolution or improvement of symptoms. This is especially important to assess at two months in patients who have negative cultures, as a clinical response to treatment helps to establish a diagnosis of culture negative TB.
9. Patients who respond slowly to therapy should receive more prolonged treatment.

F. Monitoring for Drug Toxicity

Baseline liver tests, a complete blood count, serum creatinine, and uric acid are recommended in all patients. During therapy, patients should be seen in clinic monthly and questioned for symptoms of hepatotoxicity, neuropathy, and other common adverse reactions associated with antituberculosis agents. If symptoms of hepatotoxicity develop, the patient should be evaluated carefully, liver tests (hepatic transaminase and bilirubin levels) should be

obtained, and therapy adjusted if the transaminases are more than five times the upper limit of normal, or if the patient has clinical symptoms of hepatotoxicty or jaundice. Monthly liver tests should be performed in patients with risk factors for INH hepatotoxicity (e.g. baseline liver test abnormalities, age 35 or older, chronic medical problems daily alcohol use, chronic liver disease). Other blood tests should be performed only if baseline abnormalities are present or if there are clinical reasons to obtain the measurements. Patients receiving EMB should be questioned monthly regarding visual disturbances. Monthly testing of visual acuity and color vision is recommended for patients receiving EMB at >20 mg/kg/day or for more than 2 months. Note that up to 10% of males of European ancestry may have baseline abnormalities in red-green color discrimination, and this is not a contraindication to administration of EMB.

G. Monitoring for Adherence to Therapy

Non-adherence to therapy is the most common cause of treatment failure and relapse. Compliance must therefore be monitored carefully in all patients who are not receiving DOT. This can be done by:

- Pill counts.
- Obtaining a urine sample at each visit, which should be orange-red if RIF has been taken that morning.
- Measuring serum uric acid levels in patients taking PZA. Uric acid levels should be higher than baseline values in adherent patients.

A. General Considerations

If a patient is infected with *M. tuberculosis*, HIV infection markedly increases the likelihood of development of active disease. Approximately 10% of all tuberculosis cases are in HIV-infected individuals. Tuberculosis in HIV-infected persons is transmissible, curable, and preventable.

Many HIV-infected tuberculosis patients are unaware of their HIV status and do not acknowledge HIV risk factors, particularly those related to heterosexual contact (e.g. multiple sexual partners, prostitute contact). Because HIV therapy markedly improves prognosis, HIV counseling and testing should be done for all patients with suspected or confirmed tuberculosis.

The clinical presentation of tuberculosis in HIV-infected persons may differ from that in immunocompetent persons, especially when the CD4 count is less than 200. For patients with CD4 counts < 200, the most common chest radiographic abnormalities are those associated with progressive primary tuberculosis such as mediastinal adenopathy, pleural effusions, a miliary pattern, and the CXR may also be comletely normal. Mid-zone and lower lobe infiltrates are also common, whereas apical disease and cavities are uncommon in these patients. Extrapulmonary tuberculosis is much more frequent in HIV-infected patients than in immunocompetent ones. Apical cavitary disease typical of reactivation tuberculosis is the usual presentation for patients with a CD4 count >200.

B. Treatment of Tuberculosis

Antituberculosis therapy should be started in all patients in whom a specimen is AFB+. **In AFB+ cases where clinical factors strongly suggest nontuberculous mycobacterial disease**, a nucleic acid amplification test should be performed. If the nucleic acid amplification test is negative, antituberculosis therapy can be discontinued and the patient treated for nontuberculous mycobacterial disease.

HIV-infected persons with drug-susceptible tuberculosis respond

well to standard antituberculosis drugs. However, because of the increased risk for treatment failure and relapse with suboptimal therapy, DOT is essential in all HIV-infected patients. Because of the potential for drug-drug interactions, there should be close communication between the health care providers treating tuberculosis and those treating HIV infection and its complications. An expert should be consulted to guide management of all cases of tuberculosis in HIV-infected persons. A repeat consultation is recommended if:

- The clinical response to therapy is slow.
- Sputum cultures remain positive after 2 months of therapy.
- Drug resistance is suspected or documented.
- The patient will be started on HAART therapy.
- Treatment is associated with adverse drug reactions or drug intolerance.

HIV-infected tuberculosis patients should be evaluated to determine if antiretroviral therapy will be beneficial, based on HIV viral load, CD4 cell count, patient commitment, and other clinical factors. A summary of updated guidelines can be found at ***http://www.aidsinfo.nih.gov***. **HIV-infected patients with a CD4 count of <100 should receive daily or at least thrice weekly treatment throughout therapy, and should not receive highly intermittent therapy (< 3 times weekly).**

In patients who are not candidates for antiretroviral therapy, standard antituberculosis therapy is administered for 6-9 months, as for immunocompetent patients (Tables 3 and 4, Section IV C). Treatment should be prolonged to 9 months if clinical improvement is slow or if cultures remain positive after 2 months of therapy. For drug-susceptible TB, intermittent therapy, twice or thrice weekly, when the CD4 is >100 may be given after the patient has had two weeks of daily therapy and there has been a definite clinical response.

In patients who are receiving antiretroviral therapy, treatment is complicated by the interactions between rifamycins, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors. Consultation should be sought from a person with expertise

in the management of these drug-drug interactions. Recommendations are complex (references 3 and 4 and http://www.aidsinfo.nih.gov) and evolving. In some patients, rifabutin is substituted for rifampin.

In patients who are not receiving antiretroviral therapy but in whom future therapy is planned, standard antituberculosis therapy should be initiated until there is a clinical response and the patient is tolerating all medications. The timing of antiretroviral therapy depends on the severity of the immune suppression, but most experts delay introduction for at least one or two months to minimize the likelihood of an immune reconstitution inflammatory syndrome (IRIS) reaction. When antiretroviral therapy is begun, antituberculosis therapy should be altered, in conjunction with a health care provider with expertise in this area. When a drug-drug interaction with a planned antiretroviral drug requires a change to rifabutin therapy, this should be done two weeks prior to the introduction of the antiretroviral regimen to allow the rifampin induction of the cytochrome P450 to be washed out.

Paradoxical or Immune reconstitution inflammatory syndrome (IRIS) reactions during therapy. Tuberculosis patients receiving antiretroviral therapy occasionally develop paradoxical reactions during antituberculosis therapy. These are characterized by fever, lymphadenopathy, and tissue inflammation, often associated with reduced HIV viral load and enhanced cell-mediated immunity. This phenomenon has been termed "immune reconstitution inflammatory syndrome" or IRIS. These reactions are not indicators of treatment failure and can often be managed with symptomatic relief. Before a diagnosis of an IRIS reaction is made, treatment failure and other opportunistic infections must be excluded. In some cases, a brief course of non-steroidal anti-inflammation agents or corticosteroids is helpful.

C. Treatment of LTBI

See sections III A1, III A2, III B and Table 1.

A. Treatment of Tuberculosis

A pregnant woman in whom tuberculosis is strongly suspected or confirmed should be treated without delay. Outcomes for both pregnant women and their infants are worse when treatment is delayed.

1. The initial treatment regimen should consist of INH, RIF, and EMB. PZA is avoided because inadequate data are available on the risk of teratogenicity of PZA. EMB may be discontinued if the isolate is shown to be susceptible to INH and RIF. Because PZA is not used, INH and RIF should be continued for a total duration of 9 months.

2. Pyridoxine is recommended for pregnant women taking INH.

3. Rifapentine should not be used.

B. Treatment of LTBI

For women at high risk for progression of LTBI to tuberculosis, especially those who are HIV-infected or are likely to have been infected recently, treatment should be given, even during the first trimester. For women whose risk of disease is lower, some experts recommend waiting until after delivery to start treatment. For pregnant women, INH given daily or twice weekly for 9 months is recommended. In HIV-negative women, 6 months of INH is an alternative, but less efficacious, regimen when 9 months of therapy is not possible. For patients who cannot take INH because of intolerance or exposure to an INH-resistant source case, rifampin should be substituted for 4 months .

C. Breastfeeding

The low concentrations of antituberculosis drugs in breast milk do not cause toxicity in the nursing newborn, and breastfeeding should not be discouraged. Conversely, drugs in breast milk are ineffective to treat or prevent tuberculosis in a nursing infant. Pyridoxine is recommended for both nursing mothers receiving INH and their infants.

VII. TUBERCULOSIS IN CHILDREN

Tuberculosis in children usually causes no respiratory symptoms or findings. Characteristic chest x-ray changes are hilar and/or paratracheal adenopathy, sometimes with parenchymal changes secondary to bronchial obstruction by enlarged lymph nodes.

Positive sputum cultures in children are difficult to obtain, as children are unlikely to cough and produce sputum. Gastric washings for AFB and mycobacterial culture should be done if pulmonary specimens are unavailable or negative. Some clinical settings have had good results with sputum induction even in children as young as five. Bronchoalveolar lavage may also be helpful in obtaining specimens for culture. Tuberculosis is usually diagnosed in a child with a suggestive chest x-ray, a positive tuberculin skin test, and a history of exposure to an adult case. If *M. tuberculosis* is not cultured from the child, therapy should be based on drug susceptibility of the presumed source case. When a source case is not identified or drug resistance is suspected, there should be an aggressive attempt to obtain a specimen for culture.

Children with tuberculosis are generally treated with the same medications and regimens used in adults (see Section IV, Tables 2 and 4). However, there are some differences:

1. Ethambutol is not used routinely in the initial phase of therapy because the bacillary burden is lower and the risk of drug resistance is reduced.

2. Ethambutol should be used in children with "adult-type" disease, characterized by upper lobe infiltrates and cavitation.

3. Ethambutol should be used in children for whom the risk of INH resistance is increased, such as children near the Mexican border and those who are likely to have acquired infection from adults with treatment failure or relapse.

4. Ethambutol is safe in children who are too young for monitoring of visual acuity and color vision.

5. Three times weekly therapy is not used.

6. DOT should always be used.

7. Disseminated tuberculosis and tuberculous meningitis should be treated for 9-12 months.

8. HIV-infected children should be treated for at least 9 months.

VIII. HOSPITALIZATION AND ISOLATION

A. Hospitalization

Most tuberculosis patients who are clinically stable, likely to adhere to therapy, and who live in stable family settings can be treated as outpatients without further increasing the risk of transmission of tuberculosis to household contacts. Hospitalization is advised if: non-adherence is suspected, if any household contacts are highly susceptible, such as infants or immunocompromised persons, or if the patient's living situation will expose new contacts to infection, e.g. homeless persons.

B. Who to Isolate

Hospitalized patients with suspected or confirmed infectious tuberculosis should be placed in respiratory isolation. Staff should maintain a high index of suspicion for tuberculosis (i.e., "Think TB"). "Cohorting" of tuberculosis patients prior to determination of drug susceptibility is unacceptable because *M. tuberculosis* superinfection can occur. Cohorting is acceptable only for patients with fully drug-susceptible organisms.

When respiratory isolation rooms are not available for all patients requiring isolation, patients should be transferred to another facility that has an isolation room. If this is not possible, patients should be prioritized, based on the following criteria:

1. Patients with AFB+ laryngeal or pulmonary tuberculosis have highest priority.

2. For patients with the same AFB smear status, those with known or suspected drug-resistant disease have priority.

3. Patients who have received the shortest duration of antituberculosis therapy have priority.

C. How to Isolate

1. Units that care for tuberculosis patients should have a minimum of 6 room air exchanges/hour, with negative air flow which

does not recirculate into the system. Air should be vented to the outside at least 25 feet from intake vents. Ultraviolet lights and/or HEPA filters are useful adjuncts.

2. Isolation room doors should remain closed as much as possible.

3. Movement of tuberculosis patients outside the room is minimized. During transfer, they should wear a surgical mask.

4. Isolation rooms should be clearly identified and specific precautions posted on the door.
5. Staff who enter the room must wear a mask which provides a tight facial seal and filters particles 1 to 5 microns in size (such as N-95 or HEPA filter masks).

6. During procedures that induce aerosols (aerosolized pentamidine, sputum induction, gastric aspiration or bronchoscopy), negative air flow ventilation is mandatory, and health care workers should wear N-95 or HEPA filters masks. Infectious patients should be scheduled as the last case of the day.

D. How Long to Isolate

Respiratory isolation is maintained until the patient is non-infectious, the diagnosis of tuberculosis is excluded, or the patient can be discharged to a safe environment. The patient should be isolated until:

1. Three negative AFB smears are obtained within an eight hour period, at least one of which should be a first morning specimen if drug-susceptible tuberculosis is suspected.

2. The patient is symptomatically improved and has received at least 2 weeks of appropriate antituberculous therapy.

3. If the patient has multi-drug resistant tuberculosis, they should remain in an airborne isolation room until three negative cultures are obtained.

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TABLE 1: REGIMENS FOR TREATMENT OF LTBI*			
DRUG(S)	**DAILY DOSE (MAXIMUM)**	**TWICE WEEKLY DOSE (MAXIMUM)**	**DURATION**
Isoniazid	C:10-20 mg/kg A:5 mg/kg (300 mg)	C:20-30 mg/kg A:15 mg/kg (900 mg)	9 months
Isoniazid	Adults only 5 mg/kg (300 mg)	Adults only 15 mg/kg (900 mg)	6 months
Rifampin	C:10-20 mg/kg A:10 mg/kg (600 mg)	Not recommended	C:6 months A:4 months HIV+ : 6 months
*C = children, A = Adults			

TABLE 2: DOSAGES OF FIRST-LINE MEDICATIONS

DRUG	DAILY (MAX)	TWICE WEEKLY (MAX)	THRICE WEEKLY (MAX)	ADVERSE EFFECTS
Isoniazid PO or IM	C:10-15 mg/kg A:5 mg/kg (300 mg)	C:20-30 mg/kg A:15 mg/kg (900 mg)	Adults only 15 mg/kg (900 mg)	Hepatotoxicity, peripheral neuropathy, headache, anorexia, nausea, rash, drug induced lupus, hematologic toxicity
Rifampin PO or IV	C:10-20 mg/kg A:10 mg/kg (600 mg)	C:10-20 mg/kg A:10 mg/kg (600 mg)	Adults only 10 mg/kg (600 mg)	Fever, rash, hepatotoxicity, renal failure, thrombocytopenia, flu-like syndrome; increases metabolism of many drugs, e.g. methadone, many HIV medications, coumadin; oral contraceptives (unreliable with rifampin)
Pyrazinamide[2] PO	C:15-30 mg/kg (2 g) A:40-55 kg, 1 g 56-75 kg, 1.5 g >75 kg, 2 g	C:50 mg/kg (2 g) A:40-55 kg, 2 g 56-75 kg, 3 g >75 kg, 4 g	Adults only 40-55 kg, 1.5 g 56-75 kg, 2.5 g >75 kg, 3 g	Nausea, hepatotoxicity, arthralgias, gout, rash
Ethambutol[2] PO	C:15-20 mg/kg (1 g) A:40-55 kg, 800 mg 56-75 kg, 1.2 g >75 kg, 1.6 g	C:50 mg/kg (2.5 g) A:40-55 kg, 2 g 56-75 kg, 2.8 g >75 kg, 4 g	A:40-55 kg, 1.2 g 56-75 kg, 2 g >75 kg, 2.4 g	Decreased red-green color discrimination, decreased visual acuity, rash

TABLE 3: DRUG REGIMENS FOR DRUG-SUSCEPTIBLE PULMONARY TUBERCULOSIS[1]

INITIAL PHASE		CONTINUATION PHASE	
DRUGS	**SCHEDULE OF DOSES**	**DRUGS**	**SCHEDULE OF DOSES**
INH, RIF, PZA, EMB	7 days/wk for 8 wks (56 doses) OR 5 days/wk for 8 wks (40 doses)	INH, RIF[2]	7 days/wk for 18 wks (126 doses) OR 5 days/wk for 18 wks (90 doses) OR 2 days/wk for 18 wks (36 doses)
INH, RIF, PZA, EMB	7 days/wk for 2 wks (14 doses) OR 5 days/wk for 2 wks (10 doses), FOLLOWED by 2 days/wk for 6 wks (12 doses)	INH, RIF[2]	2 days/wk for 18 wks (36 doses)
INH, RIF, PZA, EMB	3 days/wk for 8 wk (24 doses)	INH, RIF[2]	3 days/wk for 18 wks (54 doses)
INH, RIF, EMB	7 days/wk for 8 wks (56 doses) OR 5 days/wk for 8 wks (40 doses)	INH, RIF[2]	7 days/wk for 31 wks (217 doses) OR 5 days/wk for 31 wks (155 doses) OR 2 days/wk for 31 wks (62 doses)

TABLE 4: DURATION AND NATURE OF THE CONTINUATION PHASE OF TREATMENT		
PATIENT FEATURES	**HIV STATUS**	**DURATION AND TYPE OF THERAPY**
Cavitary disease AND Positive 2 month culture	Positive or Negative	INH and RIF for 7 months
Cavitary disease AND Negative 2 month culture	Positive or Negative	INH and RIF for 4 months
Non-cavitary disease AND Positive 2 month culture	Negative	INH and RIF for 4 months
Non-cavitary disease AND Positive 2 month culture	Positive	INH and RIF for 7 months
Non-cavitary disease AND Negative 2 month culture	Positive or Negative	INH and RIF for 4 months

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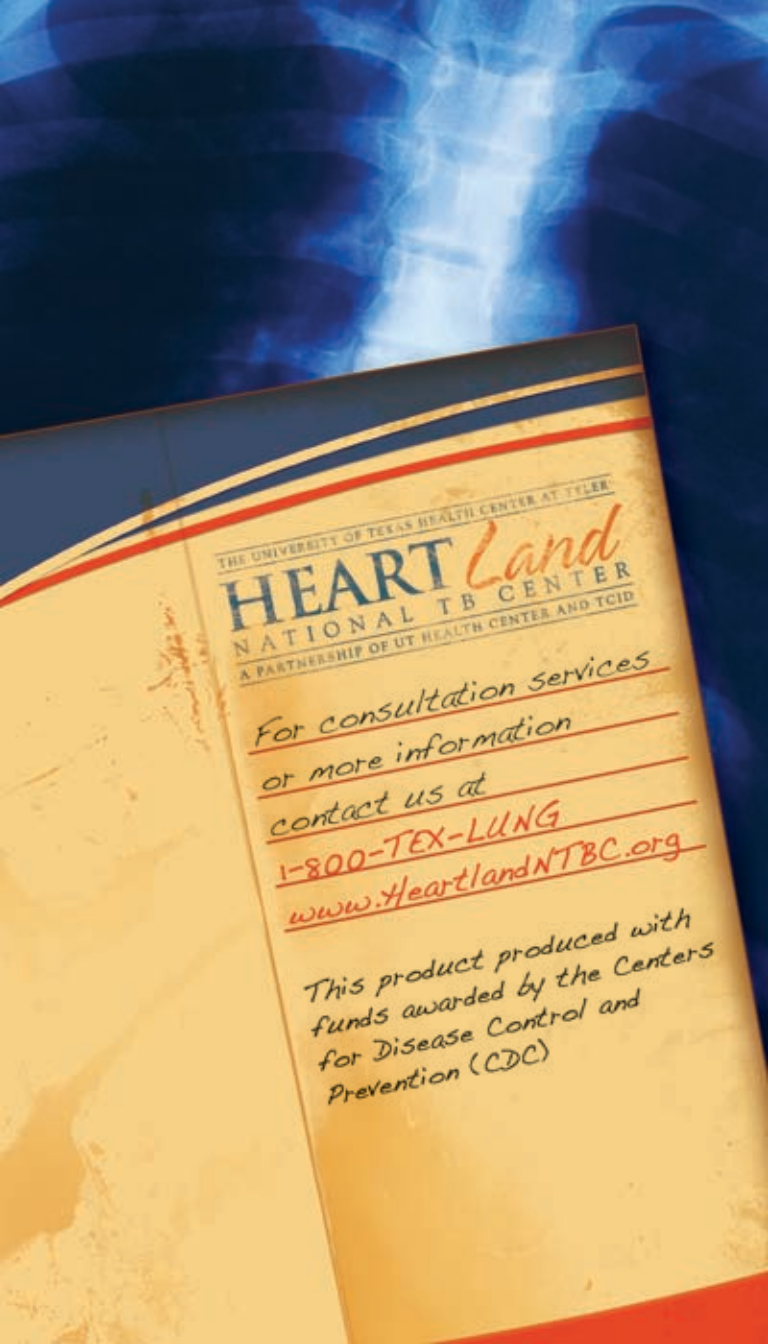
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