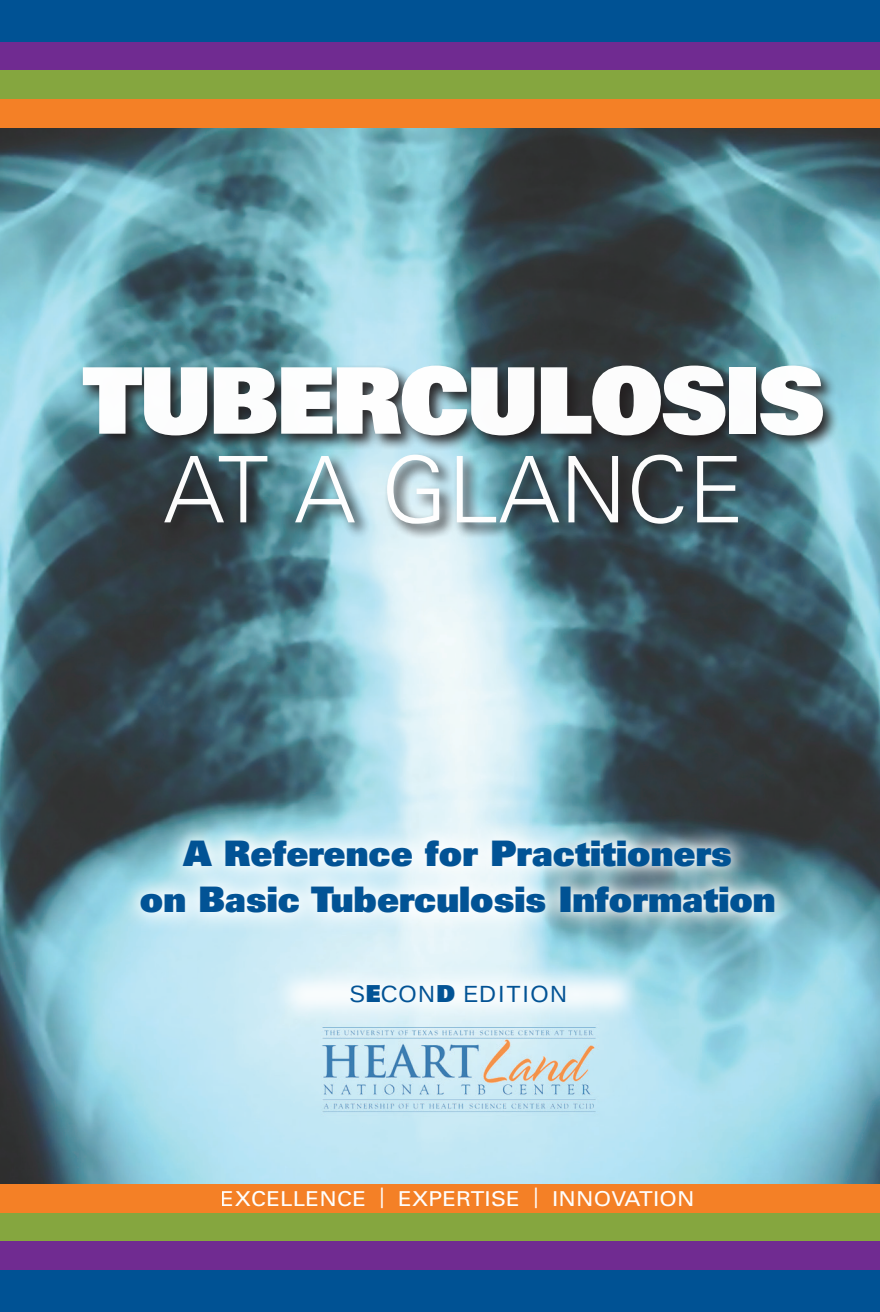

TUBERCULOSIS AT A GLANCE

A Reference for Practitioners on Basic Tuberculosis Information

SECOND EDITION

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT TYLER
HEARTLand NATIONAL TB CENTER
A PARTNERSHIP OF UT HEALTH SCIENCE CENTER AND TCID

EXCELLENCE | EXPERTISE | INNOVATION

December 2010
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,

David E. Griffith, MD
Assistant Medical Director
Heartland National TB Center
Professor of Medicine
University of Texas Health Science Center, Tyler
Email: david.griffith@uthct.edu

Barbara J. Seaworth, MD
Director, Heartland National TB Center
Professor of Medicine
University of Texas Health Science Center, Tyler
Email: Barbara.Seaworth@dshs.state.tx.us

Lisa Y. Armitige, MD, PhD
Medical Consultant, Heartland National TB Center
Associate Professor of Medicine & Pediatrics
University of Texas Health Science Center, Tyler
Email: lisa.armitige@uthct.edu

TB Education and Training:
Toll-Free # for Health Care Providers:
(800) 839-5864 or **(800) 428-7432**
FAX: 210-531-4590

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 9.4.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 three occasions.

HEARTLAND REGIONAL TB CONTROLLERS

ARIZONA
Cara Christ, MD, MS
Arizona Dept. of Health Services
Bureau of Epidemiology &
Disease Control
150 North 18th Avenue, Suite 140
Phoenix, AZ 85007-3237
Phone: 602-364-1923
Fax: 602-364-3267
Email: cara.christ@azdhs.gov

ILLINOIS - State
Michael Arbisi, BS (MT), MS
Illinois Department of Public Health
525 W. Jefferson Street, 1st Floor
Springfield, IL 62761-0001
Phone: 217-785-5371
Fax: 708-544-5830
Email: michael.arbisi@illinois.gov

ILLINOIS - Chicago
Joshua Jones, MD
Chicago Department of Public Health
TB Control Program
2160 West Ogden
Chicago, Illinois 60618
Phone: 312-746-6229
Fax: 312-746-5134
Email: jones_joshua@cityofchicago.org

IOWA
Allan Lynch
Iowa Department of Public Health
TB Control and Refugee Health Program
Lucas State Office Building
321 East 12th Street
Des Moines, Iowa 50319
Phone: 515-281-7504
Fax: 515-281-4570
Email: alynch@idph.iowa.gov

KANSAS
Phil Griffin, BBA, CPM
Kansas Department of Health and
Environment
Bureau of Disease Control and
Prevention, TB Program
1000 South West Jackson Street, Ste.
210
Topeka, Kansas 66612-1274
Phone: 785-296-8893
Fax: 785-291-3732
Email: pgriffin@kdheks.gov

MINNESOTA
Deborah Sodt, RN, PHN, MPH
Minnesota Department of Health
Immunization, TB and International
Health Section, TB Prevention and
Control Program
625 North Robert Street
P O Box 64975
St. Paul, Minnesota 55164-0975
Phone: 651-201-5550
Fax: 651-201-5500
Email: Deb.Sodt@state.mn.us

MISSOURI
Harvey Marx
Missouri Department of Health and
Senior Services
930 Wildwood Drive
P O Box 570
Jefferson City, Missouri 65102
Phone: 573-751-6113
Email: harvey.marx@health.mo.gov

NEBRASKA
Pat Infield, RN, BSN
Nebraska Health & Human Services Dept.
Public Health Infectious Disease Section, TB Control Program
301 Centennial Mall South, PO Box 95026
Lincoln, Nebraska 68508
Phone: 402-471-6441
Fax: 402-471-1377
Email: pat.infield@nebraska.gov

NEW MEXICO
Marcos Burgos, MD
New Mexico Department of Health
TB Program
1 University of New Mexico
MSC105550
Albuquerque, New Mexico 87131-0001
Phone: 505-205-2434
Fax: 505-841-4172
Email: mburgos@salud.unm.edu

NORTH DAKOTA
Craig W. Steffens, MPH
North Dakota Department of Health
Division of Disease Control
2635 E. Main Avenue
Bismarck, North Dakota 58506-5520
Phone: 701-328-2377
Fax: 701-328-2499
Email: csteffens@nd.gov

OKLAHOMA
Lauri Smithee, PhD, MES, MS
Oklahoma State Department of Health
Acute Disease Service
1000 North East 10th Street, Room 605
Oklahoma City, Oklahoma 73117-1299
Phone: 405-271-4060
Fax: 405-271-6680
Email: LauriS@health.ok.gov

SOUTH DAKOTA
Kristin Rounds
South Dakota Department of Health
TB Control Program
615 East 4th Street
Pierre, South Dakota 57501
Phone: 605-773-4784
Fax: 605-773-5509
Email: kristin.rounds@state.sd.us

TEXAS - State
Charles Wallace, PhD, MPH
Texas Dept. of State Health Services
TB Services Branch
1100 West 49th Street, Suite T801
Mail Code 1939, PO Box 149347
Austin, Texas 78714-9347
Phone: 512-458-7111 x2291
Fax: 512-458-7787
Email: charles.wallace@dshs.state.tx.us

TEXAS - Houston
Richard Stancil
Houston Department of Health and Human Services
Bureau of TB Control
8000 North Stadium Drive
Houston, Texas 77054
Phone: 832-393-4826
Fax: 832-393-5246
Email: Richard.Stancil@houstontx.gov

WISCONSIN
Lorna Will, RN, MA
Wisconsin Department of Health Services
Bureau of Communicable Diseases and Emergency Response,
Respiratory and International Health
1 West Wilson Street, Room 318
Madison, Wisconsin 53701-2659
Phone: 608-261-6319
Fax: 608-266-0049
Email: lorna.will@wisconsin.gov

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REFERENCES AND TABLES

ABBREVIATIONS

AFB:	Acid-Fast Bacilli
ATS:	American Thoracic Society
BCG:	Bacillus Calmette-Guerin
CDC:	Centers for Disease Control and Prevention
CXR:	Chest X-Ray
CBC:	Complete Blood Count
DOT:	Directly Observed Therapy
DTH:	Delayed-type Hypersensitivity
EMB:	Ethambutol
FDA:	Food and Drug Administration
HEPA:	High Efficiency Particulate Air (filter)
HIV:	Human Immunodeficiency Virus
IGRA:	Interferon Gamma Release Assay
IM:	Intramuscular
INH:	Isoniazid
IRIS:	Immune Reconstitution Inflammatory Syndrome
IV:	Intravenous
LFT:	Liver Function Tests
LTBI:	Latent Tuberculosis Infection
MDR:	Multi-drug Resistant
PO:	Oral - taken by mouth
PPD:	Purified Protein Derivative
PZA:	Pyrazinamide
QFT-G:	QuantiFERON® - TB Gold In-Tube test
RIF:	Rifampin
SM:	Streptomycin
T-SPOT:	T-SPOT.TB test
TU:	Tuberculin Unit
TST:	Tuberculin Skin Test

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

A. Who to Test

Testing for tuberculosis infection with the tuberculosis skin test (TST) or interferon gamma release assays (IGRA) 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 TB infection and individuals with certain co-existing medical conditions (if infected) are at high risk for progression to active tuberculosis. Targeted tuberculin skin testing should be performed in these at risk individuals. Screening should not be done in those without risk factors for TB exposure unless this is done as part of continuing workplace screening (heath care workers, correctional workers). Also see chapter III, Treatment of LTBI, for further identification and discussion of those at higher risk for progression to TB disease and infection.

Persons at risk for recent infection include:

- Contacts of patients with active pulmonary (includes pleural disease) or laryngeal TB disease
- 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 active tuberculosis disease are:

- HIV infection
- Organ transplant
- Immunosuppressive therapy (prednisone ≥ 15 mg/day for more than one month)

- Treatment with Tumor Necrosis Factor alpha antagonists
- Fibrotic chest x-ray lesions of old untreated tuberculosis
- Diabetes, especially those with poor glucose control
- Intravenous drug use
- Chronic kidney disease
- Leukemia, lymphoma, cancer of head, neck or lung
- Silicosis

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

1. Administration and Reading of the TST

Inject 0.1 ml of 5 TU PPD just under the skin. The needle bevel should be facing up and the injection should 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. If there is no reaction, record as 00mm. Do not record results as only "positive" or "negative."

Tuberculin skin testing by the intradermal Mantoux method with PPD 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.

2. TST Interpretation

In persons with suspected active tuberculosis, ≥ 5 mm of induration is considered to be positive. In persons being tested to detect LTBI, the threshold for a positive test varies from 5-15 mm. Cut points depend on the clinical status of the individual tested, see details described in section titled ***Treatment of LTBI.***

3. Anergy (Control) Skin Testing

Anergy testing is not recommended to detect TB infection or disease. Anergy tests are not reproducible and they should not be used to help with the interpretation of an individual TST.

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 TSTs may have a greater degree of induration which would be classified as positive, thus the term "booster effect."

Because of the booster effect, persons such as health care workers and others who undergo periodic tuberculin skin testing should receive an initial two-step TST. 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 Release Assay (IGRA)

1. Background information

The latest generation of IGRAs includes the QuantiFERON-TB Gold test (QFT-G), QuantiFERON-TB Gold In-Tube test (QFT-GIT), and the T-SPOT.*TB test* (T-Spot). These tests were developed to enhance the accuracy and simplicity of diagnosis of both LTBI and TB disease. IGRAs are blood-based tests which require only one patient visit and do not depend on a patient returning for reading as does a TST. They use proteins specific for *M. tuberculosis* that are not present in BCG and most non tuberculous mycobacteria. This eliminates the concern that a positive result may be due to old BCG vaccination. The IGRA tests will detect infection due to wild-type *M. bovis* infection. The proteins utilized in IGRA testing are also found in *M. kansasii, M. marinum* and *M. szulgai* infections. Infection with these organisms could potentially cause a false positive IGRA result.

The first of these tests, QFT-G, was approved by the FDA in 2005. The QFT-GIT was approved by the FDA in October 2007. This test eliminated the need for the specimen to be processed in the laboratory within 12 hours and allowed the initial steps of the assay to begin "in the tube". The T-Spot was approved by the FDA in 2008.

2. Test Characteristics

The QFT-G, QFT-GIT, and the T-Spot use synthetic peptides that represent *M. tuberculosis* specific proteins, ESAT-6 and CFP-10, placebo, and a nonspecific T cell stimulant (mitogen). The QFT-GIT also includes the peptide TB7.7. The QFT-G and QFT-GIT tests use whole blood which is drawn from a patient and then placed into a specimen tube. Blood is mixed with the *M. tuberculosis* specific proteins and then incubated. After incubation of the blood with the peptides, the amount of interferon gamma released in response is measured. If the patient is infected with *M. tuberculosis,* their white blood cells will release interferon gamma following exposure to the TB specific peptide antigens. The interpretation of the results is based on the amount of interferon gamma released. The T-Spot quantifies the number of interferon gamma producing cells in response to the TB specific peptides. The result is reported as a number of spots (cells) identified.

3. Interpretation and use of the IGRA

The CDC has recommended that IGRA tests can be used in place of (but not in addition to) the TST in all circumstances in which the TST is currently used with the preferences and special considerations listed below. IGRAs can be used in contact investigations, evaluation of recent immigrants who have had BCG vaccination, testing during pregnancy, and TB screening of health care workers and others undergoing serial evaluation for *M. tuberculosis* infection. Caution should be used when interpreting the results of IGRA tests in certain populations due to limited data for these groups (see Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection – United States, 2010 http://www.cdc.gov/mmwr/PDF/rr/rr5905.pdf). Despite the preferences noted below, the use of the alternative test is acceptable medical and public health practice.

Populations in which IGRAs are preferred for testing:

1. Persons who have received BCG (either as a vaccine or for cancer therapy); and
2. Persons from groups that historically have poor rates of return for TST reading

TST is preferred over IGRAs for testing children less than 5 years of age.

As with TST, IGRAs generally should not be used to test persons who have a low risk of TB infection or disease.

Routine testing with both TST and IGRA is **NOT** recommended. However results from both tests might be useful in the following situations:

When the initial test is negative; and

1. The risk for infection, the risk for progression to disease, and the risk for a poor outcome are high (e.g., HIV infected persons, those on anti-TNF alpha drugs, or children under 5 years of age who are exposed to infectious TB).

2. There is clinical suspicion for TB disease (symptoms, abnormal CXR) and an additional test is desired to enhance the sensitivity of testing in an effort to add supportive evidence for a diagnosis of tuberculosis. In such patients taking a positive result from a second test as evidence of infection increases sensitivity, but may decrease specificity.

It must be noted that multiple negative tests from any combination of IGRA tests and TST cannot exclude *M. tuberculosis* infection.

When the initial test is positive; and

1. Additional evidence of infection is required to encourage acceptance and adherence (e.g., foreign-born healthcare workers who believe their positive TST is due to BCG). A positive IGRA might prompt greater acceptance of the diagnosis and hence treatment for LTBI.

2. In healthy persons with low risk for either LTBI or progression to TB disease, a positive result from a second test increases the likelihood that the test result reflects infection. An alternative approach is to simply assume that the initial test was a false positive or that risk for disease does not warrant additional evaluation or treatment regardless of test results.

When the initial IGRA is indeterminate or borderline

When assay measurements from the initial test are unusual

4. Interpretation of QFT-GIT Results

The diagnosis of LTBI and the diagnosis or exclusion of active TB disease requires that a combination of epidemiologic, historic, medical, and diagnostic findings be assessed during the interpretation of the assays. IGRA tests as well as the TST should be used as aids in diagnosing infection with *M. tuberculosis*. They should be performed and interpreted according to established protocols using FDA-approved test formats. Both the standard qualitative test interpretation and the quantitative assay measurements should be reported together with the criteria used for test interpretation.

TABLE 1. Interpretation criteria for the QuantiFERON-TB Gold Test (QFT-G)

Interpretation	Nil*	TB Response†	Mitogen Response§
Positive¶	Any	≥0.35 IU/ml and ≥50% of Nil	Any
Negative**	≤0.7	<0.35 IU/ml	≥0.5
Indeterminate††	≤0.7	<0.35 IU/ml	<0.5
	>0.7	<50% of Nil	Any

Source: Based on Cellestis Limited. QuantiFERON-TB Gold [Package insert]. Available at http://www.cellestis.com/IRM/Company/ShowPage.aspx?CPID=1247 .

* The interferon gamma (IFN-γ) concentration in plasma from blood incubated with saline.

† The higher IFN-γ concentration in plasma from blood stimulated with a cocktail of peptides representing early secretory antigenic target-6 (ESAT-6) or a cocktail of peptides representing culture filtrate protein 10 (CFP-10) minus Nil.

§ The IFN-γ concentration in plasma from blood stimulated with mitogen minus Nil.

¶ Interpretation indicating that *Mycobacterium* tuberculosis infection is likely.

** Interpretation indicating that *M. tuberculosis* infection is not likely.

†† Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.

The table below describes the correlation between the quantitative and qualitative results of the QFT-GIT assay.

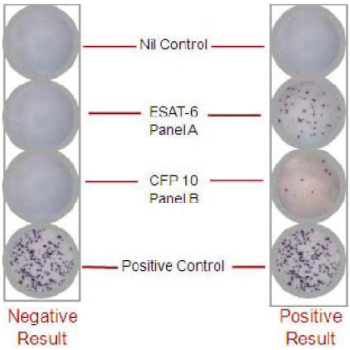
TABLE 2. Interpretation criteria for the QuantiFERON Gold In-Tube Test (QFT-GIT)

Nil (IU/mL)	TB Antigen minus Nil (IU/mL)	QFT-GIT (IU/mL)	Mitogen	Interpretation
≤ 8.0	≤ 0.35 or < 25% of Nil value	Negative	≥ 0.5	M TB infection unlikely
≤ 8.0	≥ 0.35 and ≥ 25% of Nil value	Positive	ANY	M TB infection likely
≥ 8.0	ANY	Indeterminate	ANY	indeterminate
≤ 8.0	≤ 0.35 and or < 25% of Nil value	Indeterminate	< 0.5	Indeterminate

Approach to Indeterminate QFT-GIT Result:
As noted in table 2, if the nil (negative) well is higher than 8 IU/mL, the results are considered indeterminate. An additional cause of an indeterminate response is a low mitogen response.

Potential causes of indeterminate results include host factors such as intrinsic gamma interferon secretion, recent vaccination, indiscriminate lymphocyte response leading to high nil result; immunosuppression leading to a low mitogen response. Alternatively, there can be technical factors such as incorrect handling of blood sample with poor shaking, delayed incubation or inappropriate filling of tubes leading to low mitogen. In the case of an indeterminate result, retesting by collecting another patient specimen is recommended. If retesting results in an additional Indeterminate assay then another diagnostic assay, such as the TST, and epidemiologic information should be used to help determine TB infection status of the patient.

5. Interpretation of T-SPOT.TB results:
There are 4 panels in the T-Spot assay: the positive and negative (NIL) controls and Panels A and B (TB specific antigens) http://www.oxfordimmunotec.com



1. Results are **negative when** (Panel A – Nil) and/or (Panel B –Nil) ≤ 4 spots, including values less than 0.
2. Results are **positive when** (Panel A – Nil) or (Panel B –Nil) ≥ 8 spots.
3. Results are invalid when:
   a. The Nil control has > 10 spots and/or
   b. The positive control has < 20 spots and when both (Panel A – Nil) and (Panel B –Nil) ≤ 4 spots.
4. **Borderline results** occur when the highest of either (Panel A – Nil) or (Panel B –Nil) = 5, 6, or 7 spots, but less than 8 spots and the other antigen Panel has ≤ 4 spots.

Approach to a Borderline T-SPOT.TB Result

Retesting by collecting another patient specimen is recommended. If retesting of a Borderline assay results in an additional Borderline assay then another diagnostic assay, such as the TST, and epidemiologic information should be used to help determine TB infection.

Boosting

Repeated testing using the IGRA does not cause boosting of the IGRA result. However limited observational studies suggest a prior TST may increase the quantity of interferon released.

Although relatively uncommon, boosting has been shown to occur as early as 3 days after a TST and as late as 2 months. Boosting of an initially negative IGRA by a TST is less likely than *boosting which causes an increase in the quantity of interferon gamma released* (this is not clear), however it may occur. If a positive TST is to be

confirmed with an IGRA, in general, the testing should be done within 3 days of the TST or the test should be delayed 2 months.

Reversions and Conversions
Individuals who have had serial testing using IGRA have been noted to have a significant incidence of both reversions and conversions. Data to assess the significance of these findings is not yet available. Careful clinical assessment is important in determining the approach to a healthcare worker with a newly positive IGRA when the previous tests have been negative.

D. Follow-up Evaluation
In persons with a positive TST or positive IGRA, 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, IGRA tests, or chest x-rays should be done on a routine basis. In a number of states LTBI is a Reportable condition (refer to Section I and II for the TB Controller in your state).

E. Advantages of Using IGRA Tests
1. IGRAs require only one patient visit and are not dependent upon a patient returning for reading as does a TST.

2. The proteins used in IGRAs are not found in BCG. This eliminates the concern that a positive result may represent old BCG vaccination rather than infection with *M. tuberculosis.*

3. IGRAs have overall higher sensitivity and specificity than the TST because the proteins used in the assay are not generally found in most non-tuberculosis mycobacteria. The exceptions are *M. kansasii, M. szulgai* and *M. marinum.*

4. IGRAs are less affected by tester error (such as incorrect placement or reading of the TST).

F. Disadvantages of IGRA Tests

1. Both IGRA assays require a blood draw. This is not possible in some field situations or with populations where phlebotomy is difficult.

2. As with all laboratory tests, there is a possibility of laboratory error (e.g. mislabeling, broken tubes, delays in processing, improperly handled specimens).

3. Indeterminate or borderline results are frequent in some populations and cannot be interpreted.

II. DIAGNOSIS OF TUBERCULOSIS DISEASE

A. Pulmonary Tuberculosis

A presumptive diagnosis of pulmonary tuberculosis is most easily made when a patient at risk for tuberculosis presents with classic clinical symptoms of cough, fever, night sweats and weight loss and is found to have a positive TST or IGRA along with an abnormal CXR. Sputum smears for acid fast bacilli (AFB) are positive approximately 50% of the time but this varies with the extent of radiographic disease and the immune status of the individual patient. A series of at least 3 sputum specimens should be collected 8-24 hours apart (at least one should be obtained in the early morning). Sputum induction may be performed for patients who are unable to produce natural sputum. Sputum is preferred over bronchoalveolar lavage with respect to safety and cost. Bronchoscopy with bronchoalveeolar lavage should be reserved for patients unable to give a natural or induced sputum and for patients with negative sputum studies in the setting of a high clinical suspicion for TB. The diagnosis is confirmed by growth of *Mycobacterium tuberculosis* (MTB) from the sputum or other body sites. Approximately 20% of cases are culture negative. In these individuals the diagnosis is confirmed by a patient at risk with a positive TST or IGRA and an abnormal CXR who responds clinically and/or radiographically to the standard treatment regimen (INH, rifampin, ethambutol, and PZA) at the two month mark.

The diagnostic accuracy can be improved by the use of a nucleic acid amplification test (NAA). The CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations.

NAA testing can reliably detect tuberculosis bacteria in specimens at least one week earlier than a culture for at least 80% of those patients who have disease confirmed with a positive culture. As few as 1 to 10 organisms/ml may give a positive result. Results are available within 24-48 hours. The NAA can confirm the presence of MTB in 50-80% of AFB smear negative, culture positive specimens

and can provide confirmation of the presence of MTB in smear positive specimen in clinical situations in which a nontuberculous mycobacterium are also common. Use of NAA tests can impact patient care and TB control efforts, reducing unnecessary contact investigations or respiratory isolation for patients whose AFB smear positive specimens do not contain MTB.

Currently two tests are approved for use by the Food and Drug Administration (FDA). The enhanced Amplified Mycobacterium tuberculosis Direct Test (MTD, Gen-Probe, San Diego, California) was approved in 1999 for both AFB smear positive and negative respiratory specimens in patients suspected to have TB disease (with fewer than seven days of antimycobacterial therapy). Amplicor Mycobacterium tuberculosis Test (Amplicor, Roche Diagnostics, Basel, Switzerland) was approved in 1996 for smear positive respiratory specimens in patients suspected to have TB.

Other NAA tests have been developed by various laboratories but have not been FDA-approved; these are often referred to as "home-brew" or "in-house" tests. They are quality controlled for use in a specific laboratory setting in which they have been validated.

NAA tests are useful in the following situations:

1. Patients with AFB smear positive sputum in whom the clinical suspicion of tuberculosis is low can have a diagnosis of TB disease excluded by a negative NAA test. Many of these individuals will have a non-tuberculous mycobacterium. Treatment for MTB disease is not indicated in this situation.

2. 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. A positive test in this setting should prompt the initiation of treatment for MTB disease and eliminate the need for further invasive testing. Cultures however should always be done in addition to an NAA in order to assist in confirmation of the diagnosis and to identify drug susceptibility of the isolate.

3. A negative NAA test in patients with pulmonary infiltrates and clinical symptoms who have no risk factors for TB disease and who have negative TST or IGRA results should indicate a need for continued evaluation to determine the etiology of the disease. These individuals usually do not need to have anti-tuberculous therapy initiated. A second NAA can be done to increase the sensitivity. Clinical judgment is needed. Currently available NAA tests are not sufficiently sensitive (detecting 50%–80% of AFB smear negative, culture positive pulmonary TB cases) to exclude the diagnosis of TB in AFB smear negative patients suspected to have TB.

NAA results often remain positive after culture results become negative during therapy. A positive NAA results does not give any information on the viability of mycobacteria in a particular patient.

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.) Tissue biopsies are generally needed to make a rapid diagnosis. Granulomatous inflammation, especially caseating granuloma, is characteristic of MTB disease. AFB smears are frequently negative even when significant granulomatous inflammation is present. The absence of AFB in a tissue biopsy should not be considered as evidence to exclude a diagnosis of TB disease. Insufficient information is available regarding the performance of NAA tests for nonrespiratory specimens. More research is needed before specific recommendations can be made, however there is evidence that supports the usefulness of NAA testing for diagnosis of extrapulmonary TB in individual cases. Fluids should be sent to the laboratory for cell counts, protein, and glucose in addition to smear and culture. It is especially important to ensure that tissue specimens have a portion allotted for culture and are not completely placed in formalin.

Extrapulmonary tuberculosis is reported more often in specific groups of individuals such as individuals who are foreign born, children, those with HIV or other immunosuppression (anti-tumor necrosis factor agents, patients with chronic renal disease,

especially dialysis), and those with disease due to *Mycobacterium bovis* (M.bovis).

Culture remains the gold standard for laboratory confirmation of TB and is required for isolating bacteria for drug-susceptibility testing and genotyping. It is important that sufficient numbers and portions of specimens always are reserved for culture.

C. Interpretation of NAA Test Results

NAA test results should be interpreted in correlation with the AFB smear results.

	Smear+	Smear-
NAA+	It should be presumed the patient has active tuberculosis and anti-TB treatment should be started while awaiting culture results. In this case, the positive predictive value of FDA-approved NAA tests for TB is >95% in AFB smear-positive cases.	Clinical judgment should be used as to whether to begin anti-TB treatment while awaiting culture results and to determine if additional diagnostic testing is needed. One might consider testing an additional specimen using NAA to confirm the NAA result. Pending culture results, if two or more specimens are NAA positive, the patient can be presumed to have TB.
NAA-	In this case, a test for inhibitors should be performed and an additional specimen tested with NAA. Sputum specimens (3%–7%) can contain inhibitors that reduce or prevent amplification and cause false-negative NAA results. ***Consult with your laboratory!*** If an inhibitor is detected, the NAA tst is of no diagnostic help for this specimen. Either another specimen should be tested or clinical judgment should be used to determine whether to begin anti-TB treatment while awaiting results of culture and additional diagnostic testing. If inhibitors are not detected, clinical judgment should be used to determine whether to begin anti-TB treatment while awaiting culture results and determine if additional diagnostic testing is needed. A patient can be presumed to be infected with a nontuberculous mycobacteria if a second specimen is also smear positive and the NAA is again negative and no inhibitors are detected.	Use clinical judgment to determine whether to begin anti-TB treatment while awaiting results of culture and additional diagnostic tests.

A. Latent TB Infection (LTBI):
Individuals with LTBI have viable M TB organisms, which are believed to be in a state of dormancy. They have no evidence of active disease. Direct detection of the organism is not possible so persons with LTBI are defined by a positive Tuberculin Skin Test (TST) and/or Interferon Gamma Release Assay (IGRA) which measures the immune reaction to tuberculous proteins. Neither of these tests have adequate sensitivity or specificity to absolutely confirm or exclude either LTBI or active TB disease. However, they provide important supportive evidence, along with a history of exposure to a case of active TB disease or inclusion in groups at increased risk of exposure.

Before LTBI can be diagnosed, active disease must be excluded. This is done with a medical evaluation and a chest radiograph for each individual with a newly positive TST or IGRA. Whenever any suspicion of active disease is present, cultures should be obtained (see diagnosis of TB disease). Radiographic abnormalities possibly consistent with active tuberculosis or symptoms suggesting active tuberculosis should be further evaluated with three sputum specimens for mycobacterial smear and culture and a repeat chest x-ray after 2 to 3 months to check for stability. Abnormalities such as nodules, opacifications, adenopathy, or pleural effusion are suggestive of active disease while volume loss, scarring, and calcifications suggest old disease. Individuals at risk for extrapulmonary disease, such as young children, HIV seropositive persons or foreign-born individuals, may be difficult to accurately assess and confidently exclude active disease.

Individuals with LTBI are believed to have the greatest risk of progressing to active disease during the initial one to two years following exposure. Individuals with recent infection or conditions that weaken the immune system are those at most risk of disease and should be those targeted for evaluation of LTBI and if infected, treatment.

B. Who should be tested?
Public health 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 IGRA). A decision to test should usually be regarded as a decision to treat if the test is positive. Some individuals who are exposed to persons at increased risk of TB disease are offered serial testing (health care workers, employees in correctional settings or homeless shelters). A positive test at the time of employment in an individual without identified risk factors for TB may not be an indication for treatment. Individual assessment and clinical judgment will factor into the final decision regarding such an individual's management.

C. Who should be treated?

Active tuberculosis should always be excluded prior to prescribing treatment for LTBI. Treatment of TB disease with INH alone risks development of INH resistance **(See Above)**.

Asymptomatic TST or IGRA positive persons with normal chest radiographs should be offered treatment for LTBI unless significant contraindications such as risk of liver toxicity are present.

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, the patient is not coughing or if coughing, the smears are negative) 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. Treatment is especially important for the reduction of the progression of LTBI to disease among groups such as HIV positive, other immunosuppressed persons, recently infected contacts, and children. Decisions regarding treatment of LTBI should be made

without consideration of BCG vaccination status. If available, an IGRA is preferred in those with a history of BCG vaccination as these tests eliminate the possibility of a false positive test due to old BCG vaccination.

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 educated regarding the signs and symptoms of active TB disease and told to seek prompt medical attention if these develop.

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 IGRA test results, i.e., even with a negative tuberculin skin test or indeterminate IGRA 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 children <5 years but older than 6 months without other co morbid illnesses, when a repeat TST is negative, window period prophylaxis can be stopped if contact was been broken at least 8 weeks earlier. Evidence suggests that IGRA results can be influenced by therapy with reversion to negative after treatment. Therefore, their role in the evaluation of patients undergoing "window prophylaxis" is yet to be determined with certainty.

In persons with significant immunosuppression, treatment should often be continued even if the repeat TST remains negative.

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 and no prior treatment. All HIV positive persons identified as contacts should be treated for LTBI once disease is excluded, even if they have previously been treated for LTBI or TB disease. Recurrent TB in those who are HIV positive is usually due to a new infection.

- Those taking immunosuppressive therapy for organ transplants or tumor necrosis factor- alpha antagonists (TNF-α).
- Infants less than six months of age.

Persons who are receiving treatment with a TNF-α 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 IGRA is negative. If treatment for LTBI is not given, these individuals should be educated regarding the signs and symptoms of TB and followed closely. After initial 2 step TST or single IGRA, testing should be repeated yearly.

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

- Intravenous drug use
- Diabetes
- Chronic kidney disease
- Silicosis - persons with silicosis and a positive TST or IGRA often

require empirical and prolonged (8 – 9 month regimen) multi-drug treatment for TB disease.

- Substantial weight loss (> 10% of ideal body weight) or malnutrition, including gastrectomy and jejunoileal-bypass or other bariatric surgery.
- 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 IGRA). 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 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).

D. 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 there is more accumulated data substantiating efficacy of this approach than for any other treatment regimen including INH for 6 months.

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
- Persons who are more likely to complete a 4 month treatment course but likely will not complete 9 months.
- Rifampin therapy for LTBI is associated with less hepatotoxicity and improved treatment compliance compared with INH regimens.

The combination of RIF and PZA daily for 2 months is no longer recommended as a treatment for LTBI. RIF and PZA used together for LTBI prophylaxis cause significant hepatotoxicity in 5-8% of cases. Fatalities have occurred even in persons who have been closely monitored.

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. Rifabutin monotherapy has been associated with the emergence of rifamycin resistant *M. tuberculosis* when used this drug is used for prophylaxis against disseminated *M. avium* complex.

Rifabutin may also be used to avoid other drug drug interactions in persons who would best be treated for LTBI with a rifamycin.

A new short course regimen of once weekly INH and rifapentine (3HP) given for a total of 12 weeks by DOT has been shown to be as effective as 9 months of self administered INH. Guidelines on using this regimen are currently being developed. For more information on using this regimen, please visit www.cdc.gov/tb.

Clinical expertise is available from the regional training and medical consultation centers at http://www.cdc.gov/tb/education/rtmc/default.htm, and state and local health departments.

2. Use of Pyridoxine (Vitamin B6)

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

3. Contraindications to Treatment of LTBI

- Past history of serious reactions to drugs used to treat LTBI.
- Patients with severe acute or chronic liver disease. In patients with high risk for progression to TB disease, patients can be treated with caution if closely monitored.
- 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 (see above) 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 if they are at risk for hepatotoxicity, such as persons with prior or current liver disease or alcohol abuse, those who are pregnant or **recently** postpartum, HIV infected, or those receiving concurrent medications for chronic illness. If it is difficult to obtain an adequate history of possible underlying liver disease or other medical conditions, baseline liver tests should be ordered. Liver tests should include a total bilirubin, AST, and ALT at a minimum. Persons receiving RIF or rifabutin should have a baseline CBC with platelets. This does not need to be repeated. Patients receiving treatment for LTBI should be seen in person at least monthly and clinically monitored for signs and symptoms of adverse drug reactions, adherence to treatment, and for evidence of signs or symptoms consistent with active TB disease. Persons with baseline liver test abnormalities, or a history of liver disease, should have liver tests evaluated at least monthly during treatment.

Patients should be educated regarding the signs and symptoms of drug induced liver toxicity, the need to stop their medication and to call their provider. Such patients should have liver enzymes drawn the same day if at all possible.

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, if the total bilirubin is ≥ 2, or if jaundice or other clinical signs of hepatotoxicity develop. Patients with symptoms of hepatitis while on INH and/or rifampin should be carefully reevaluated from a risk/benefit standpoint, regardless of the level of liver enzymes or bilirubin to determine the safety of continued therapy for LTBI.

IV. TREATMENT OF TUBERCULOSIS DISEASE

A. General Considerations

1. Tuberculosis should be treated in consultation with a physician who is experienced in its management. Active TB is a **Reportable Condition**. Physicians should report any patient suspected or confirmed to have active TB to the local health department within 24 hours.

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 length of treatment.

5. All tuberculosis patients should be tested for HIV infection. For patients with confirmed 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. Adult patients with extensive disease may need at least 9 months of therapy, especially if there is extensive disease and/or response to therapy is delayed.

8. Addition of corticosteroids in addition to anti-tuberculosis drugs is recommended for patients with meningitis or

pericarditis. 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 as well as their recommended doses are shown in Table 2.

C. Recommended Drug Regimens (Tables 3 and 4)

1. Initial Therapy (Months 1 and 2): Unless drug susceptibilities are known, patients diagnosed with TB 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 extended from 4 to 7 months. Immunocompetent patients with cavitary disease OR a positive 2-month culture should receive at least 4 months of INH and RIF in the continuation phase of treatment but prolongation of the continuation phase can be considered. 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. (Refer to BMI chart at www.HeartlandNTBC.org).

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. For patients with drug susceptible tuberculosis initial daily therapy followed by thrice weekly therapy during the initiation phase is associated with lower relapse rates than a twice weekly dosing regimen.

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 patients who are HIV-infected, who have drug-resistant tuberculosis, are retreatment cases or who have disseminated on extensive disease benefit from follow-up.

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 always 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. In these cases, 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 evaluated. A patient with relapse may have drug susceptible TB if the initial regimen was given by DOT and the patient was adherent with treatment. Despite this, every effort should be made to obtain a culture and susceptibility on a

patient with suspected relapse. Patients who relapse after receiving a rifampin-based regimen by DOT can be started on a standard regimen consisting of INH, rifampin, ethambutol, and pyrazinamide unless there was evidence of poor adherence with their initial treatment, 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 to three sputum AFB smears should be obtained every 1-2 weeks until AFB smears are negative. Cultures need not be performed on these specimens. Airborne isolation can be usually be discontinued in persons once smears have converted to negative and the patient has had two to three weeks of therapy and is clinically improving. (See section VIII D for more detailed information on discontinuation of isolation).

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 should 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 radiographic response to therapy.

6. In patients whose original sputum cultures are positive, chest x-rays after 2 months and at the completion of therapy may be useful.

7. If sputum cultures remain positive after 2 months of therapy and the patient is not improving clinically, 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 to therapy should be documented at least monthly. This includes their weight, general health, and improvement or resolution 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. In this case, that would consist of extension of the continuation phase of therapy from 4 to 7 months (for a total of 9 months of therapy).

F. Monitoring for Drug Toxicity

Baseline liver function tests, total bilirubin, a complete blood count and serum creatinine are recommended in all patients prior to initiating treatment for tuberculosis. 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 hepatotoxicity or jaundice (see discussion in section on LTBI).

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. Patient Education

Patients should be educated regarding the toxicities of their medications and cautioned to immediately report these to their providers.

H. 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.

V. TUBERCULOSIS AND HIV

A. General Considerations

In patients infected with *M. tuberculosis*, co-infection with HIV markedly increases the likelihood of progression to active disease. Approximately 10% of all tuberculosis cases in the U.S. 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, contact with prostitutes, incarceration). Because HIV therapy markedly improves prognosis, HIV testing is recommended by the CDC 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 or even a completely normal CXR. Mid-zone and lower lobe infiltrates are also more common, whereas apical disease and cavities are less commonly seen in these patients. Extrapulmonary tuberculosis is much more frequent in HIV-infected patients. The traditional apical cavitary disease typical of reactivation tuberculosis is more commonly seen in patients with a CD4 count >200.

B. Diagnosis

Due to the increased likelihood of progression to active disease in HIV infected patients with LTBI, screening and treatment in this group is critical. Patients with HIV, especially those with low CD4 counts, may not react to either the TST or IGRA. Clinical judgment should be given the most consideration when assessing these patients.

Individuals infected with HIV who are a contact to an active pulmonary case of tuberculosis should receive a full course of treatment for LTBI regardless of CD4 count. This recommendation

is regardless of previous history of diagnosis or treatment for LTBI or previous treatment for active TB.

C. Treatment of LTBI
LTBI treatment in this population is the same as that for immunocompetent individuals (see section III). HIV infected patients should receive 9 months of therapy with INH. Pyridoxine should be given to any patient with HIV receiving INH.

In the event a patient is unable to tolerate INH or is exposed to an INH-resistant case, treatment with rifampin for 4 months is an acceptable alternative. If the patient is taking a HAART medication that interacts with rifampin, rifabutin can be substituted. The most up-to-date information on drug-drug interactions between currently used HIV medications and the rifamycins can be found at http://www.aidsinfo.nih.gov. These recommendations are evolving and substitution of rifabutin should be done in conjunction with consultation of an expert.

HIV infected patients receiving treatment for LTBI should be monitored monthly with a clinical assessment and LFTs.

D. Treatment of Tuberculosis
Antituberculosis therapy should be started in all patients in whom a specimen is positive for 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 and no inhibitors are present, 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 while on TB therapy.
- Treatment is associated with adverse drug reactions or drug intolerance.

Antiretroviral therapy is recommended in all HIV-infected tuberculosis patients. 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 receiving antiretroviral therapy and in whom therapy cannot be started, standard antituberculosis therapy is administered for 6-9 months, as for immunocompetent patients (see tables 3 and 4). 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. Every effort should be made to start co-infected patients on HIV treatment, especially those with low CD4 counts.

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 4 and 5 in the Reference section; also see http://www.aidsinfo.nih.gov) and evolving. In some patients, rifabutin can be substituted for rifampin.

In patients who are not receiving antiretroviral therapy but in whom future therapy is planned, standard antituberculosis therapy should be initiated. 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 from rifampin to rifabutin therapy, this should be done at least two weeks prior to the introduction of the antiretroviral regimen to allow the rifampin induction of 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 may be 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 and can often be managed with symptomatic relief.

Before a diagnosis of an IRIS reaction is made, treatment failure (due to poor compliance or resistance) or diagnosis of other opportunistic infections must be excluded. In some cases, a brief course of non-steroidal anti-inflammation agents or corticosteroids is helpful.

VI. PREGNANCY

A. Evaluation

A pregnant woman suspected of tuberculosis infection or disease should be tested with a TST or an IGRA. As with the general population, testing of pregnant women should be targeted with only individuals at high risk of TB infection or disease being tested. Testing in this population should be done with the intent to treat if the TST or IGRA is positive.

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. While treatment with INH is generally safe, all pregnant and peripartum women should have monthly clinical monitoring with LFTs. An increase in hepatotoxicity has been noted during the peripartum period and women should be closely monitored during that time.

For women whose risk of progression to disease is low, some experts recommend waiting until after delivery to start treatment. In this case, the woman should be monitored regularly and educated about the signs and symptoms of active disease. Cases of congenital tuberculosis requiring treatment of both mother and child with concomitant risks of disease and multi-drug regimens can be avoided by careful screening and treatment of at-risk pregnant women.

Standard recommendations for LTBI treatment should be followed when treating pregnant women (Table 1). INH given daily or twice weekly for 9 months is recommended and considered safe. **Pyridoxine should always be given to a pregnant woman being treated with INH.** For patients with LTBI who cannot take INH because of intolerance or because of exposure to an INH-resistant source case, rifampin may be safely substituted for 4 months.

C. 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. Though recommended by the World Health Organization (WHO), PZA is generally avoided in the U.S. because inadequate data are available on the risk of its teratogenicity. EMB may be discontinued if the isolate is shown to be susceptible to INH and RIF. If PZA is not used, INH and RIF should be continued for a total duration of 9 months.

2. Pyridoxine supplementation is recommended for all pregnant women taking INH.

3. Rifapentine should not be used.

4. All pregnant and peripartum women should have monthly clinical monitoring with LFTs. An increase in hepatotoxicity has been noted during the peripartum period and women should be closely monitored during that time.

D. Breastfeeding

The low concentrations of antituberculosis drugs in breast milk are not adequate to cause toxicity in the nursing newborn. Therefore, breastfeeding should not be discouraged in women being treated for tuberculosis.

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 breastfed infants.

VII. TUBERCULOSIS IN CHILDREN

A. Diagnosis

Most Tuberculosis in children frequently causes no respiratory or pulmonary exam findings. Characteristic chest x-ray changes such as hilar and/or paratracheal adenopathy are suggestive of primary disease. Parenchymal changes secondary to bronchial obstruction by enlarged lymph nodes are sometimes noted.

The TST is the preferred diagnostic test in children under 5 years of age. Either a TST or IGRA can be used in children over 5 years of age. Many experts recommend testing with both the TST and the IGRA to increase sensitivity in diagnosing TB infection.

Positive sputum cultures in children are difficult to obtain, as children are unlikely to produce sputum. Every effort should be made to identify the presumed source case to provide an organism for drug susceptibility testing. Gastric washings for AFB and mycobacterial culture should be done if pulmonary specimens from the presumed source case are unavailable or are 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 TST or IGRA, 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 of any age who are contacts to an active case should be evaluated with a PA and lateral CXR and medical evaluation if they have any signs or symptoms of active tuberculosis. Even if the TST or IGRA is negative, if another diagnosis is not identified, presumptive treatment for active tuberculosis should be considered. Consultation with an expert in the treatment of pediatric TB is recommended.

B. Treatment for LTBI
Children identified in a contact investigation should be evaluated immediately for tuberculosis infection or disease. In children under 5 years of age, this consists of a medical evaluation, a TST and a PA and lateral CXR. If the medical evaluation rules out active disease, **children less than 5 years of age should be started on window prophylaxis for LTBI (doses in Table 1) until the TST can be repeated 8-12 weeks after the break in contact with the source case.** If the repeat TST is negative, LTBI treatment can be stopped unless the infant is younger than 4 – 6 months. Very young children may not be able to manifest a positive TST or IGRA even if infected. If the repeat TST is positive, LTBI treatment with INH should continue for a total of 9 months.

Children over 5 years of age identified as contacts to an active case, as with adults, should have a medical evaluation and either a TST or IGRA. If the medical evaluation rules out active disease and the TST or IGRA are negative, the child should have a repeat 8-12 weeks after the break in contact with the source case. If the TST or IGRA is positive at any point, the child should receive a CXR, repeat medical evaluation and, if no sign of active disease, LTBI treatment for 9 months with INH.

Children on window prophylaxis or being treated for LTBI who are exposed to an INH-resistant source case can take rifampin for 6 months as an alternative.

C. Treatment for Tuberculosis
Children with tuberculosis are generally treated with the same medications and regimens used in adults (see Tables 2 and 4). Medications for treatment of tuberculosis are generally well tolerated by infants and children.

Considerations unique to children include:

1. Ethambutol is safe in children who are too young for monitoring of visual acuity and color vision when dosing is kept near the recommended 15 mg/kg.

2. Three times weekly therapy is not commonly used though twice weekly dosing is used frequently in children.

3. DOT should always be used in treating children with tuberculosis infection (LTBI) or disease.

4. Children with tuberculosis disease should be treated for a minimum of 6 months regardless of culture status.

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

6. HIV-infected children should receive at least 9 months of therapy.

D. Breastfeeding

Infants may safely breastfeed from a mother on treatment for LTBI or active tuberculosis. The amount of medication found in breast milk is negligible and should not be considered adequate to treat the infant for LTBI. Infants that are breastfed by a mother taking INH should receive pyridoxine at 1-2 mg/kg/day.

VIII. HOSPITALIZATION AND ISOLATION

A. Hospitalization

Most tuberculosis patients can be treated as outpatients without further increasing the risk of transmission of tuberculosis to household contacts. This is especially relevant to those who are:

1. Clinically stable
2. Likely to adhere to therapy, and
3. Who live in stable family settings

Hospitalization is advised for:

1. Clinically unstable patients with debilitating disease
2. Patients with poorly controlled comorbidities
3. Patients with difficult to manage medical or surgical complications
4. If non-adherence is suspected
5. If any household contacts are highly susceptible, such as infants or immunocompromised persons, or
6. 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 airborne 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 super-infection can occur. Cohorting is acceptable only for patients with fully drug-susceptible organisms.* When airborne 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 for isolation.

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. Isolation rooms should be clearly identified and specific precautions posted on the door.
4. Movement of tuberculosis patients outside the room should be minimized. During transfer, the patient should wear a surgical mask.
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 (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 Should Patients be Isolated?

Airborne isolation should be maintained until the patient is non-infectious, the diagnosis of tuberculosis is excluded, or the patient can be discharged to a safe environment. Criteria for removal of isolation differs in the outpatient versus inpatient setting. The criteria below apply to patients who have a negligible likelihood of multidrug resistant TB (no known exposure to multidrug resistant tuberculosis, no history of prior episodes of TB with poor compliance during therapy and no history of treatment failure).

While in the hospital patients with low likelihood of MDR-TB should remain in airborne infection isolation until they:

1. Are receiving standard multidrug anti-TB therapy
2. Have demonstrated clinical improvement, and
3. Have had three consecutive AFB-negative smear results of sputum specimens collected 8 - 24 hours apart, with at least one being an early morning specimen.

Patients being discharged to a congregate setting should meet the criteria for hospitalized patients.

Generally, patients in outpatient settings can be considered non-infectious when they:

1. Have received standard multidrug antituberculous therapy for at least 2 weeks for those sputum smear positive or for those with AFB smears that are negative or rarely positive, treatment should be in place for 5 - 7 days.
2. Have demonstrated complete adherence to treatment (patient is on DOT).
3. Have demonstrated evidence of clinical improvement (reduction in the frequency and severity of cough and reduction of the grade of the sputum AFB smear result), and
4. Have identified all close contacts and these contacts have been evaluated, advised, and if indicated, started on treatment for LTBI.

These criterion are critical, especially when children aged <4 and persons of any age with immunocompromising health conditions are present in the household.

The criteria above are general guidelines. State programs may have specific criteria for programs to follow. Decisions on infectivity of a person should depend on the extent of illness and the specific nature and circumstances of potential contact between the patient with TB and others in the community.

Some patient groups may require more stringent microbiologic criteria such as AFB culture negativity before diminishing or modifying isolation precautions. Patients who are persistently AFB smear positive after several months of therapy may convert sputum AFB cultures to negative before AFB smears become negative. Patients with MDR TB isolates and healthcare workers in contact with vulnerable populations should also attain sputum AFB culture negativity prior to elimination of respiratory isolation precautions.

Patients with multidrug resistant tuberculosis should be regarded as infectious until they have three negative sputum cultures.

FOR MORE INFORMATION

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT TYLER

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A PARTNERSHIP OF UT HEALTH SCIENCE CENTER AND TCID

Heartland National TB Center

Toll-free number 1-800-839-5864
for Arizona, Illinois, Iowa, Kansas, Minnesota, Missouri, Nebraska, New Mexico, North Dakota, Oklahoma, South Dakota, Texas, and Wisconsin
FAX: 1-210-531-4590
2303 SE Military Drive
San Antonio, TX 78223

CPIDC

CENTER FOR PULMONARY AND INFECTIOUS DISEASE CONTROL

Center for Pulmonary and Infectious Disease Control

The University of Texas Health Center at Tyler
11937 U.S. Highway 271
Tyler, Texas 75708-3154
Education & Training Unit: 903-877-7327
Toll-free number for Texas Health Care Providers:
1-800-428-7432
FAX: 1-903-877-7989

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Current Editors and Contributors to TB at a Glance:
Barbara Seaworth, MD; Lisa Armitige, MD, PhD; David Griffith, MD; Robert Longfield, MD; Adriana Vasquez, MD; and Lynn Horvath, MD

Original Contributors to TB at a Glance:
Don Nash, PhD; Peter Cegielski, M.D., M.P.H.; Peter Barnes, M.D.; and David Lakey, M.D.

TABLE 1: PREFERRED REGIMENS FOR TREATMENT OF LTBI			
DRUG(S)	DAILY DOSE (MAXIMUM)	TWICE WEEKLY DOSE (MAXIMUM)	DURATION
Isoniazid	Children: 10-20 mg/kg Adult: 5 mg/kg (300 mg)	Children: 20-30 mg/kg Adult: 15 mg/kg (900 mg)	9 months*
Rifampin	Children: 10-20 mg/kg Adult: 10 mg/kg (600 mg)	Not recommended	Children: 6 months Adult: 4 months

*Six months of INH (daily or 2x/wk by DOT) is an acceptable alternative for HIV negative adults when nine months of treatment is not possible

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 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 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	Adults only 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[3]	
DRUGS[2]	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	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 days/wk for 18 wks (36 doses)
INH, RIF, PZA, EMB	3 days/wk for 8 wk (24 doses)	INH, RIF	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	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)

[1] HIV-infected persons with CD4 cell counts <100 should receive medications at least 3 times weekly. Twice weekly regimens should not be used in this population.

[2]EMB can be stopped once drug susceptibility to INH and RIF is confirmed.

[3] Patients with cavitation on the initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7 month continuation phase.

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 -7 months*
Non-cavitary disease AND Positive 2 month culture	Negative	INH and RIF for 4-7 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

*Depending on clinical assessment and clinical or radiographic response

NOTES

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