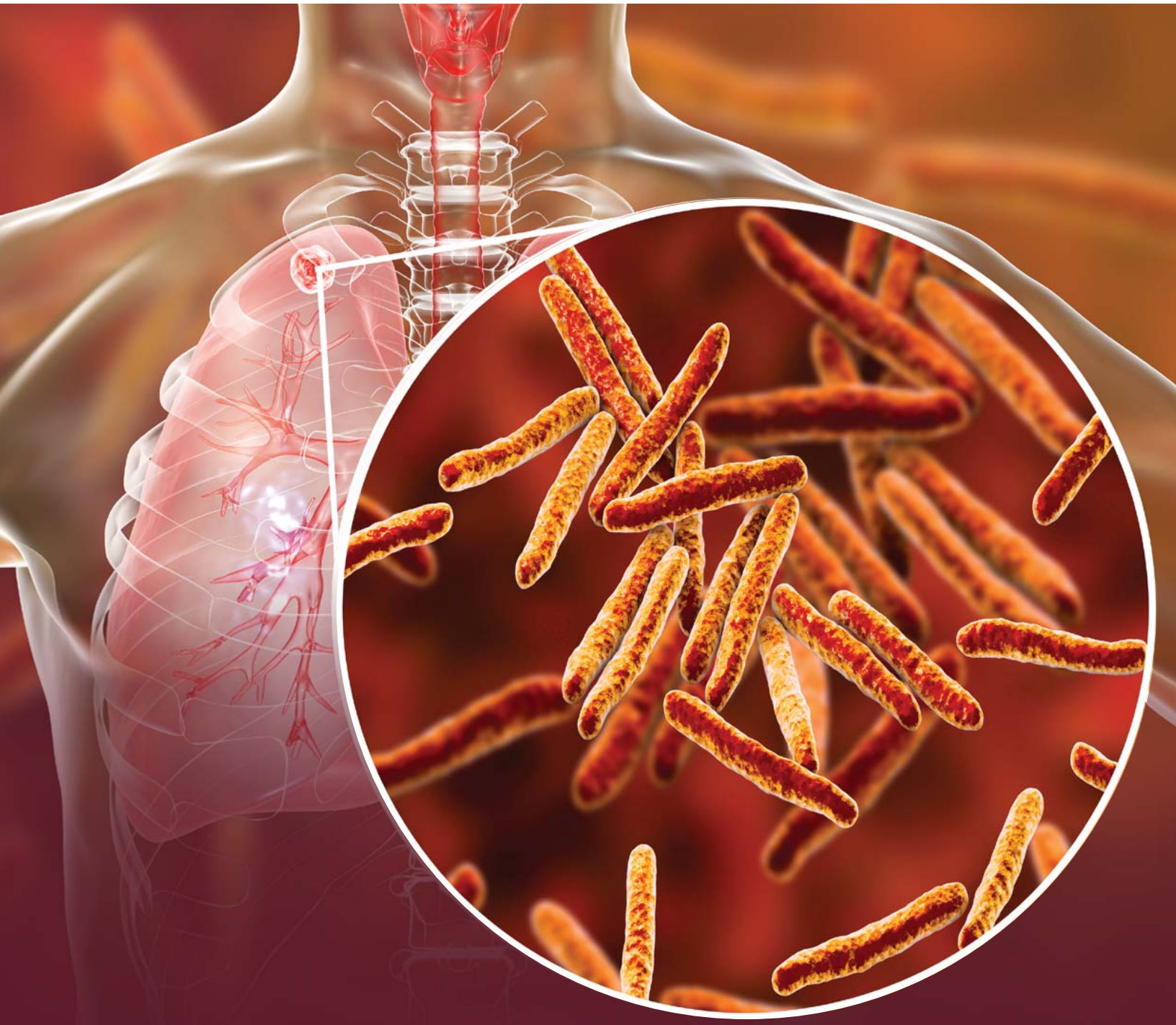


2020 Georgia TB Reference Guide

APRIL 2020

Dear Clinician:

This booklet responds to clinicians' questions about tuberculosis infection, disease, and control. The standards and guidelines are based on the work and experience of the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA), Emory University, the World Health Organization (WHO), and the Atlanta TB Prevention Coalition. This edition contains updated recommendations on the treatment of latent tuberculosis infection (LTBI) and treatment of active tuberculosis disease.

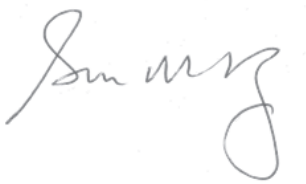
The treatment of a patient with TB always requires a clinician to exercise clinical and professional judgment. These guidelines provide a framework for the treatment of patients with TB infection or disease. Standardized treatment offers the greatest opportunity for controlling tuberculosis.

This is not an exhaustive treatment of the subjects covered. It is an accessible reference guide. Since guidelines for treating and controlling TB continue to evolve, it is appropriate for clinicians to check further for new treatment regimens.

Detailed information is available from:

- Your county public health department and the Georgia Department of Public Health, Tuberculosis Control Program: (404) 657-2634

Sincerely,



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Acknowledgements

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Abbreviations

AFB: Acid-Fast Bacilli
AG: Aminogylcoside
AIDS: Acquired Immunodeficiency Syndrome
ALT: Alanine Aminotransferase
ART: Antiretroviral Therapy
AST: Aspartate Aminotransferase
ATS: American Thoracic Society
BCG: Bacillus Calmette-Guerin
BID: *Bis in die* (Twice Daily)
CBC: Complete Blood Count
CDC: Centers for Disease Control and Prevention
CNS: Central Nervous System
CXR: Chest X-Ray
DST: Drug Susceptibility Tests
DTH: Delayed-type Hypersensitivity
DOPT: Directly Observed Preventive Therapy
DOT: Directly Observed Therapy
EMB: Ethambutol
FNA: Fine Needle Aspiration
FQN: Fluoroquinolone
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
IDSA: Infectious Diseases Society of America
IGRA: Interferon-γ Release Assay
INH: Isoniazid
IRIS: Immune reconstitution inflammatory syndrome
IV: Intravenous

LFT: Liver Function Test
LTBI: Latent Tuberculosis Infection
MDR: Multidrug Resistant
NAAT: Nucleic Acid Amplification Test
NRTI: Nucleoside Reverse Transcriptase Inhibitor
NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor
PI: Protease Inhibitor
PO: *Per os* (Oral)
PPD: Purified Protein Derivative
PZA: Pyrazinamide
RIF: Rifampin
RPT: Rifapentine
TB: Tuberculosis
TNF: Tumor Necrosis Factor
TST: Tuberculin Skin Test
TU: Tuberculin Unit
XDR: Extensively Drug-resistant

Contents

I. Epidemiology

- Worldwide, TB is an enormous global public health problem. The World Health Organization (WHO) estimates that there were 10 million new cases of TB disease and more than 1.5 million deaths due to TB in 2018.
- TB is the leading cause of death due to an infectious disease. TB is also the leading cause of death in persons with human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (HIV/AIDS) worldwide (although not in the United States).
- Approximately one-fourth of the world's population is estimated to be infected with and harbors *Mycobacterium tuberculosis* (i.e., have latent TB infection) and therefore is at risk for developing active disease.
- The interaction between the TB epidemic and the HIV/AIDS epidemic is lethal. TB adds to the burden of illness of HIV-infected people and shortens their life expectancy, while the HIV epidemic spurs the spread of TB.
- In the U.S. there was a resurgence of TB from 1985 to 1992. The number of cases increased 20% during this time period, peaking in 1992 with 26,673 cases reported. The increased case numbers were attributed to the HIV epidemic, decreased funding for public health, immigration from countries where TB is endemic, and transmission of TB in congregate settings such as hospitals, correctional institutions, and homeless shelters.

- Due to a number of public health interventions, TB cases began declining in 1992 in the U.S. From 1992 through 2018, there has been a 66% decrease in the number of cases, as TB control was strengthened nationally. In 2018, the U.S. reported 9,029 new TB cases (2.8 per 100,000 population). The decrease is attributed to strengthened public health infrastructure for TB prevention and control nationwide. Concern is rising about a new wave of complacency in TB control. In recent years, federal TB control funding has decreased when adjusted for inflation.

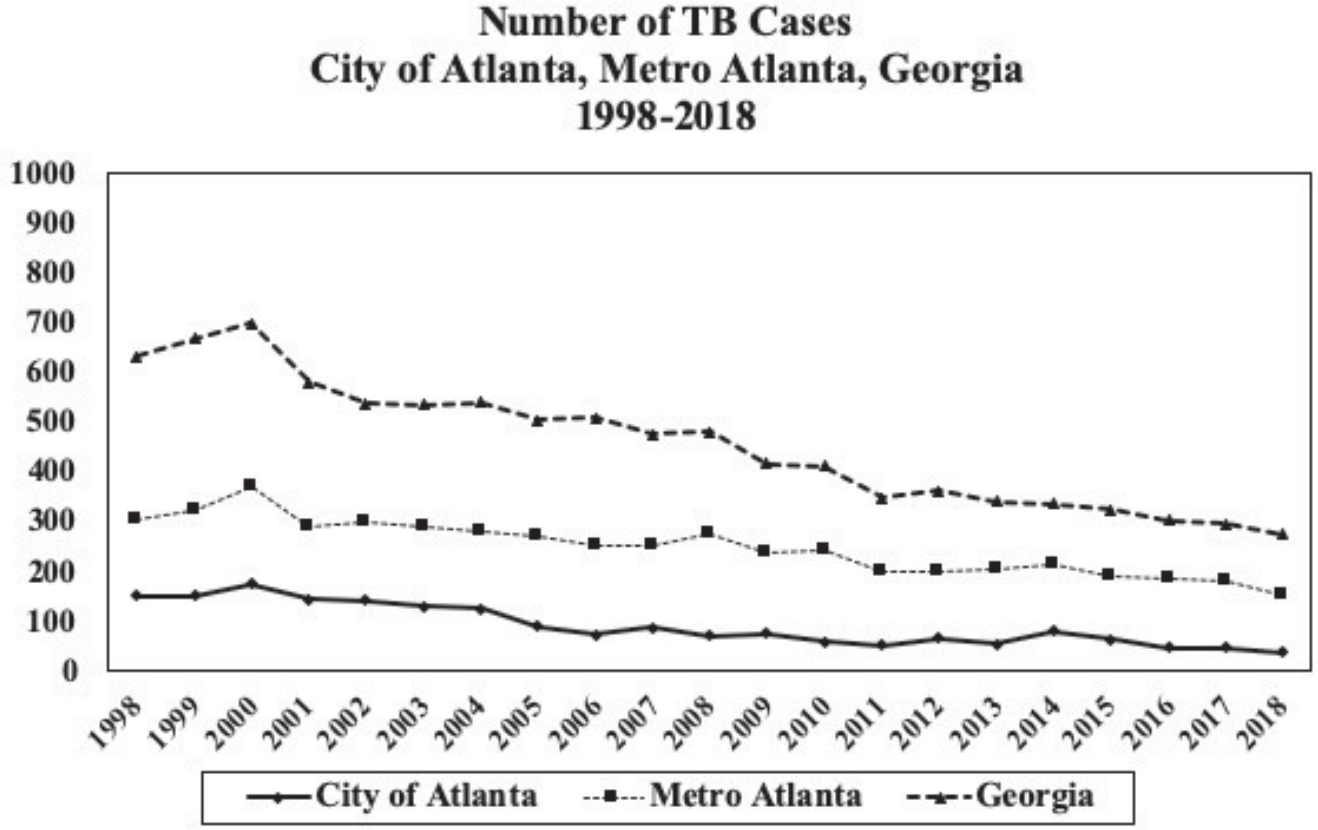
- TB is not evenly distributed among the U.S. population. Cases occur disproportionately in urban areas, in conditions of poverty and over-crowding, and among racial and ethnic minorities and foreign-born persons. In 2018, 69.5% of the U.S. TB cases occurred among foreign-born persons (52% in Georgia).

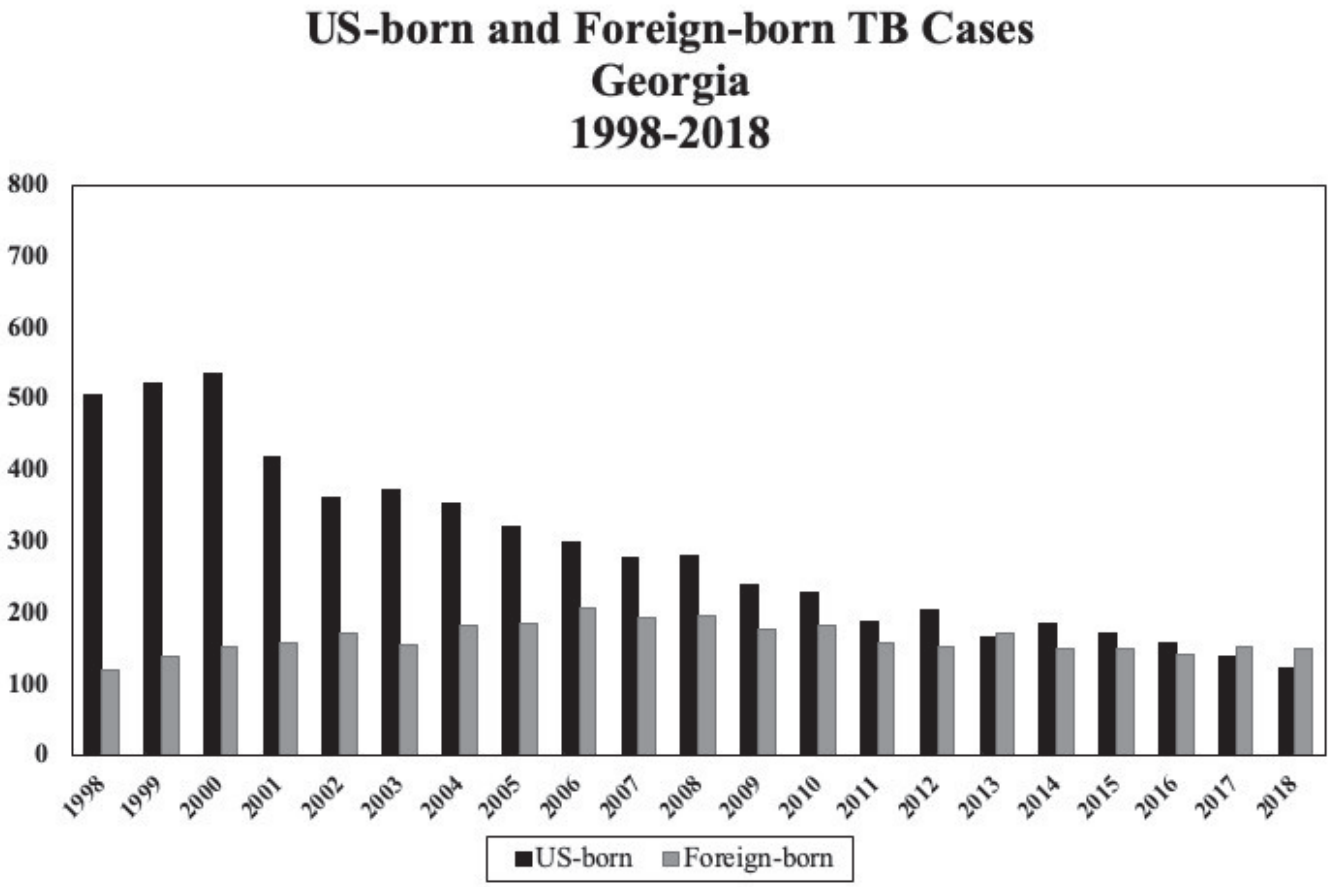
- The average lifetime risk of developing active TB following TB infection, if no treatment of latent TB infection is received, is approximately 5-10% (with the greatest risk occurring in the first two years after infection). UNAIDS estimates that persons infected with both TB and HIV are 30 to 50 times more likely to develop TB disease than those infected with TB but who do not have HIV infection (10% per year risk of progression to active TB disease among people living with HIV who have LTBI).

- Drug-resistant TB is a major challenge to global TB control and associated with higher morbidity and mortality compared to drug-susceptible disease. The treatment of highly drug-resistant *M. tuberculosis* requires longer, more complex and expensive treatment regimens. Multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid (INH) and ri-

fampin (RIF); extensively drug resistant (XDR)-TB is defined as MDR-TB plus resistance to a fluoroquinolone (FQN) drug plus an injectable drug (kanamycin, amikacin, and/or capreomycin). MDR-TB treatment regimens are complicated with many potential adverse effects and may require up to 24 months of treatment.

- The State of Georgia has had TB rates higher than the U.S. average for the last several decades. However, in recent years, cases in Georgia have declined more rapidly than in the rest of the U.S. In 2018, Georgia had 273 new TB cases and the incidence in Georgia was less than that for the U.S. (2.6 TB cases per 100,000 population in Georgia vs. 2.8 cases per 100,000 populatoin in the U.S.). Of the culture-confirmed TB cases





tested for drug susceptibility in Georgia in 2017, 7% had primary resistance to INH, 2% had primary resistance to RIF, and 1.5% were MDR.

- More than half of TB cases in Georgia occur in the metropolitan Atlanta area.

II. Diagnostic Tests for Latent TB Infection (LTBI)

There is no "gold standard" test for latent TB infection (LTBI). Two types of diagnostic tests to detect LTBI are now available. These include the tuberculin skin test (TST) which has been available for > 100 years and a newer generation of diagnostic tests, the interferon-γ release assays (IGRAs), which are T-cell-based in - vitro blood tests. Two IGRAs are approved for use by the U.S. FDA. Neither the TST nor IGRA tests can distinguish LTBI from active TB disease.

A. Tuberculin Skin Test (TST)

The tuberculin skin test (TST) measures a delayed-type hypersensitivity (DTH) reaction (recruitment of memory T cells to the site of an intradermal injection of purified protein derivative [PPD]). The TST should be carried out using the Mantoux method. Multiple puncture tests (Tine and Heaf) should **not** be used. Tuberculin skin tests should be administered and read by trained healthcare personnel. The TST is administered by injecting 0.1 ml of 5 tuberculin units (TU) PPD into the dorsal or volar surface of the forearm. The injection is made with a disposable tuberculin syringe, with the needle bevel facing upward and placed just under the surface of the skin, so that a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter is produced.

Needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by

hand. Dispose of needles and syringes in puncture-resistant containers. Follow standard precautions for infection control.

TSTs should be read 48 to 72 hours after administration. If test reading is delayed, a positive reaction may still be measurable up to one week after testing. A test cannot be read as negative if more than 72 hours have passed since it was placed. The transverse diameter of palpable **induration** should be measured and **recorded in millimeters**. If no induration is present, record "0 mm." Do not measure erythema (redness).

Limitations of the TST include cross reactions between TST and Bacillus Calmette-Guerin (BCG) and non-tuberculous mycobacteria. Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG, but an advantage of the IGRAs is that they do not cross react with BCG (see below). A positive TST in a BCG-vaccinated person is assumed to indicate infection with *M. tuberculosis* when the person tested is at increased risk for recent infection, is from an area with high rates of TB, or has a medical condition that increases the risk for disease (Section II, B).

B. Criteria for a Positive Tuberculin Test, by Risk Group

Reaction ≥ 5 mm of induration

- Persons living with Human Immunodeficiency Virus (HIV)
- Recent contact with an infectious TB case
- Fibrous changes on chest radiograph consistent with prior TB

- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/d of prednisone for 1 month or more including patients who will receive TNF-α inhibitors)

Reaction ≥ 10 mm of induration

- Recent immigrants to the U.S. (within the last 5 years) who came from high TB incidence countries
- Injection drug users
- Residents and employees of the following high-risk congregate settings: prisons and jails, nursing homes, hospitals (if applicable, most hospitals in the U.S. are not high-risk settings given the changing epidemiology of TB in the U.S.), residential facilities for persons with HIV/AIDS and homeless shelters
- Mycobacteriology laboratory personnel
- Persons with the following clinical conditions that place them at risk of progression from latent TB infection to active TB disease: silicosis, diabetes mellitus, chronic renal failure, leukemia and lymphoma, carcinoma of the head, neck or lung, weight loss of ≥ 10% of ideal body weight, gastrectomy, and jejunoileal bypass
- Children < 5 years of age or infants, children, and adolescents exposed to adults at high risk
- Recent TST conversion (increase of ≥ 10 mm of induration within the past 2 years)

Reaction ≥ 15 mm of induration

- Persons with no risk factors for TB (ideally such persons should not be tested)
- Persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥ 15 mm is considered positive

C. Two-Step Testing and the Booster Reaction

In some persons (especially individuals > 50 years of age) with LTBI, delayed-type hypersensitivity reactions to tuberculin may wane over time. When a TST is performed years after infection has occurred, these persons may have an initial negative tuberculin skin test result. However, this initial test may stimulate (boost) their ability to react to subsequent tuberculin testing, causing a positive reaction to subsequent tuberculin skin tests. The boosted reaction represents a true positive result but not a true conversion due to recent infection. Two-step tuberculin skin testing is used to distinguish between boosted reactions and reactions due to new infection.

Two-step testing (at baseline) is recommended for employees or residents in institutional settings (such as health care workers or correctional facility employees) who may undergo periodic tuberculin screening (and have not had a TST in the past year), and for whom it is important to distinguish between new infection and a boosted reaction from past infection.

Two-Step Testing

1. Place the first test with 0.1 ml (5 TU) of tuberculin.
2. If the reaction to the first test is negative, give a second test with the same dose and strength of tuberculin, 1-3 weeks later. (If the reaction to the first test is positive, consider the person infected, and there is no need for a second test.)
3. If the second test is positive, consider the person infected.
4. If the second test is negative, consider the person uninfected.
5. Individuals who have a positive reaction to either test require a follow-up evaluation with chest x-ray.
6. For individuals who will undergo serial testing (e.g., annual tuberculin testing), two-step testing is required for only the first test to establish a baseline negative test. Subsequent tuberculin testing should include only one test.

D. Anergy Testing

Anergy testing is not recommended for routine use in persons living with HIV or otherwise immunocompromised. Factors limiting the usefulness of anergy skin testing include problems with the standardization and reproducibility, the low risk for TB disease associated with a diagnosis of anergy, and the lack of apparent benefit of treatment of LTBI for groups of anergic HIV-infected persons in the U.S.

E. Interferon-γ Release Assays (IGRAs)

Two FDA-approved IGRA tests are commercially available in the U.S. These include the QuantiFERON-TB Gold Plus (QFT) test and the TSPOT.TB (TSPOT) test. Guidelines on the use of these IGRAs as diagnostic tests for LTBI have been published by the American Thoracic Society (ATS), CDC, and the Infectious Diseases Society of America (IDSA) [Clin Infect Dis 2017; 64(2):111–5]. IGRAs are in-vitro blood tests that are based on interferon-γ (IFN-γ) release after stimulation by relatively TB-specific antigens (i.e., ESAT-6 and CFP-10 in both assays). The QFT is a whole blood assay that uses an ELISA technique to measure IFN-γ production. TSPOT uses peripheral blood mononuclear cells (PBMCs) and detects (by use of ELISPOT) the number of T cells producing IFN-γ. Because the antigens used in the IGRAs are not found in *M. bovis* BCG (or most non-tuberculous mycobacteria), the IGRAs are more specific than the TST when used to test persons who have received BCG vaccination and do not cross react with most non-tuberculous mycobacteria. Criteria on what constitutes a positive IGRA test have been published and are shown in Tables 1 and 2.

The cut-off points are static, and there are no criteria for what constitutes an IGRA conversion when serial testing is performed. IGRAs can provide a positive, negative, or indeterminate result. Indeterminate results more commonly occur among HIV-seropositive and other immunocompromised persons but can occasionally occur among healthy individuals. If the result of the IGRA test is indeterminate, it is recommended that the test be repeated. The risk of developing active TB after a positive TST result has been defined in large prospective longitudinal studies, but data are more limited for the IGRAs. The IGRAs cost significantly more per test than the TST but are logistically easier to perform as they only require a single visit. In certain situations or selected populations (e.g., BCG-vaccinated persons), IGRAs may be cost-effective when considering cost of chest radiographs avoided compared to the TST when cross reactions may be seen.

Table 1. Interpretation Criteria for the QuantiFERON-TB Gold Plus Test (QFT-Plus)

<table>
<tr><th>Nil (IU/ml)</th><th>TB1 minus Nil (IU/ml)</th><th>TB2 minus Nil (IU/ml)</th><th>Mitogen minus Nil</th><th>QFT-Plus Result</th><th>Report/ Interpretation</th></tr>
<tr><td rowspan="4">≤ 8.0</td><td>≥ 0.35 and ≥ 25% of Nil</td><td>Any</td><td rowspan="2">Any</td><td rowspan="2">Positive</td><td rowspan="2">*M. tuberculosis* infection likely</td></tr>
<tr><td>Any</td><td>≥ 0.35 and ≥ 25% of Nil</td></tr>
<tr><td>< 0.35 or ≥ 0.35 and < 25% of Nil</td><td>< 0.35 or ≥ 0.35 and < 25% of Nil</td><td>≥ 0.50</td><td>Negative</td><td>*M. tuberculosis* infection NOT likely</td></tr>
<tr><td>< 0.35 or ≥ 0.35 and < 25 % of Nil</td><td>< 0.35 or ≥ 0.35 and < 25% of Nil</td><td>< 0.50</td><td rowspan="2">Indeterminate</td><td rowspan="2">Likelihood of *M. tuberculosis* infection cannot be determined</td></tr>
<tr><td>> 8.0</td><td colspan="3">Any</td></tr>
</table>

Source: Based on manufacturer recommendations for QuantiFERON-TB Gold Plus [Package insert]. Available at: https://www.quantiferon.com/us/wp-content/uploads/sites/13/2020/01/L1095849-R06-QFT-Plus-ELISA-IFU.pdf

Table 2. Interpretation Criteria for the T-SPOT.TB Test (T-Spot)

Interpretation	Nil*	TB Response†	Mitogen§
Positive¶	≤10 spots	≥8 spots	Any
Borderline**	≤10 spots	5, 6, or 7 spots	Any
Negative††	≤10 spots	≤4 spots	≥20 spots
Invalid**	>10 spots	Any	Any
	≤10 spots	<5 spots	<20 spots

Source: Based on Oxford Immunotec T-Spot.TB package insert. Available at: http://www.oxfordimmunotec.com/international/wp-content/uploads/sites/3/Final-File-PI-TB-US-V6.pdf

* The number of spots resulting from incubation of PBMCs in culture media without antigens.

† The greater number of spots resulting from stimulation of peripheral blood mononuclear cells (PBMCs) with two separate cocktails of peptides representing early secretory antigenic target-6 (ESAT-6) or culture filtrate protein-10 (CFP-10) minus Nil.

§ The number of spots resulting from stimulation of PBMCs with mitogen without adjustment for the number of spots resulting from incubation of PBMCs without antigens.

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

** Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection. In the case of Invalid results, these should be reported as "Invalid" and it is recommended to collect another sample and retest the individual.

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

F. Targeted Testing and Diagnostic Tests for LTBI

Diagnostic testing for LTBI should be targeted at those who are at **increased risk** for having LTBI and those who if infected with *M. tuberculosis* are at increased risk of progression to active TB disease (see page 17 and Table 3). HIV-infected persons with LTBI have the greatest risk of progressing to active TB (at rates up to 8 -10% per year). All persons living with HIV should undergo testing for LTBI, and if LTBI is found, should strongly be encouraged to initiate and complete treatment for LTBI. Patients who take **immunomodulating drugs** are also at very high risk for progression to active TB if infected with *M. tuberculosis*. This includes patients with LTBI who are treated with TNF-α inhibitors such as infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), certolizumab pegol (Cimzia), or golimumab (Simponi). Following the initial introduction of TNF-α inhibitor drugs, there were reports of the subsequent development of extrapulmonary and disseminated disease and in some cases, death. All patients who will be treated with TNF-α inhibitor drugs should be screened for LTBI before starting the medication; if found to have LTBI, they should be started on therapy for LTBI (after active TB is excluded) before starting the TNF-α inhibitor. Whether treatment for LTBI should be completed before a TNF-α inhibitor is started is controversial. Patients preparing to receive a **solid organ transplant** should also be screened for LTBI**.** Children less than 5 years of age are at increased risk for progression to active TB disease if infected but should not be tested for LTBI unless they are at increased risk for TB exposure (see page 17). Persons who recently converted to a positive skin test (or positive IGRA) should be

medically evaluated, and active TB disease ruled out (see section II. G. page 21) and LTBI treatment considered. Also, persons with a chest radiograph suggestive of old TB are at increased risk for progression to active TB disease.

Who should be targeted for LTBI testing?

Diagnostic tests for LTBI are not recommended for people with low risk of infection with *M. tuberculosis*. Testing of low-risk persons can result in false-positive tests. Certain persons with increased risk of developing TB if they have LTBI should be targeted for testing. These include:

- People who have spent time with someone who has TB disease (contacts of active TB cases)
- People living with HIV or those who have other immune-compromising illnesses
- Immigrants from high TB incidence countries (e.g., Asia, Africa, most countries in Latin America, the Caribbean, Eastern Europe, and Russia)
- People who live or work somewhere in the United States where TB disease is more common (homeless shelters, correctional facilities including prisons and jails, or some nursing homes)
- People who use illegal drugs, especially injection drug users
- People who are preparing to initiate treatment with a TNF-α inhibitor.

- People preparing to receive a solid organ transplant or hematopoetic stem cell transplant.

U.S. Preventive Services Task Force (USPSTF) Recommendations for Screening for Latent TB Infection (LTBI):

The U.S. Preventive Services Task Force (USPSTF) recommends testing populations that are at increased risk for TB infection (https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/latent-tuberculosis-infection-screening). This is a "B" recommendation ("offer or provide this service") indicating that given the current evidence, the USPSTF has concluded with moderate certainty that benefits of screening for LTBI in people who are at increased risk of infection outweigh the potential harms. However, the highest-risk populations and thus those with the greatest benefit for targeted screening and treatment (persons living with HIV, close contacts of persons with active TB, and those being treated with immunosuppressive agents such as TNF-α inhibitors) were excluded from the USPSTF review of evidence because "screening in these populations may be considered standard care as part of disease management or indicated prior to the use of certain medications." Once these highest-risk groups which should be screened for LTBI are removed, patients considered high risk in the primary care setting that should be screened for LTBI include non-U.S. born persons who have immigrated to the U.S. from high burden TB countries.

High-risk groups for TB infection that should be targeted for testing and treatment are outlined above and also listed in Table 3.

Table 3. High Prevalence and High-Risk Groups[1]

Groups with a High Prevalence of Latent TB Infection	Groups with a High Risk of Progression to Active TB Disease if Infected with *M. tuberculosis*
Persons born in countries with high rates of TB	Persons living with HIV
	Persons who are close contacts of persons with infectious active TB
Groups with poor access to healthcare	Children less than 5 years of age
Persons who live or spend time in certain facilities (e.g., nursing homes, correctional institutions, homeless shelters, drug treatment centers)	Persons with recent infection with *M. tuberculosis* (e.g., have had a diagnostic test result for LTBI convert to positive in the past 1-2 years)
	Persons who have chest radiographs suggestive of old TB
Persons who inject drugs	Persons with certain medical conditions*

*Diabetes mellitus, silicosis, prolonged therapy with corticosteroids, immunosuppressive therapy particularly TNF-α blockers, leukemia, Hodgkin's disease, head and neck cancers, severe kidney disease, certain intestinal conditions, malnutrition

[1]***From: MMWR 2010;59(RR-5):1-25***

Testing of low risk individuals for LTBI is discouraged because false-positive results are more likely to occur in this setting. Because QFT, TSPOT, and TST each measure different aspects of

the immune response and use different antigens and interpretation criteria, test results might not be interchangeable. Different tests can yield different results. Studies which employed multiple diagnostic tests have demonstrated that discordant test results are not uncommon.

Which diagnostic test for LTBI should be used?

General Recommendations for Use of Diagnostic Tests for LTBI:

- ATS/CDC/IDSA guidelines [Clin Infect Dis 2017; 64(2):111–5] note that either an FDA-approved IGRA (i.e., QFT or TSPOT) or TST can be used for diagnostic testing, and use of either test is an acceptable medical and public health practice. **As noted below, there are preferences and special circumstances in which one of these tests may be preferred**.
- The ATS/CDC/IDSA guidelines note that "There are insufficient data to recommend a preference for either a TST or an IGRA as the first-line diagnostic test in individuals 5 years or older who are likely to be infected with *M. tuberculosis*, who have a high risk of progression to disease, and in whom it has been determined that diagnostic testing for LTBI is warranted."

Situations in which an IGRA is preferred but a TST is acceptable:

- Testing of BCG-vaccinated persons (because of improved specificity of the IGRA vs. TST in this population)

- Testing of persons who may be unlikely to return to have the TST read (e.g., homeless individuals and injection drug users or those with substance abuse)

Situations in which a TST is preferred but an IGRA is acceptable:

- Testing children aged < 5 years (TST is recommended by the American Academy of Pediatrics)
- Serial testing (e.g., for selected health care workers). While not a CDC recommendation, we recommend that the TST be used for serial testing programs. Several reports have indicated very high rates of diagnostic test "conversion" (e.g., up to 10-fold higher than the TST) when IGRAs were used for serial testing of health care workers in low-risk/low-prevalence situations in the U.S. and Canada (thus suggesting the IGRA results were false positive). Most health care workers in the U.S. are at low risk for occupational infection with *M. tuberculosis* and national guidelines on serial testing of health care workers have recently been updated by CDC based on the changing epidemiology of TB in the U.S. over the past few decades. These updated CDC guidelines no longer recommend routine serial screening of low-risk U.S. health care workers in the absence of exposure or ongoing transmission. Baseline testing at the time of employment is recommended.

Situations in which a TST or IGRA may be used without preference:

- Contact investigations (i.e., testing of recent contacts of persons known or suspected to have active TB)

Situations in which testing with *both* an IGRA and a TST may be considered:

- When additional evidence of infection is required to encourage a person that they have LTBI and should take and adhere to therapy for LTBI (e.g., foreign-born health care worker who believes that their positive TST result is attributable to BCG)
- When the initial diagnostic test performed in a healthy person at low risk for both infection and progression is positive (and thought to be a false positive). This situation could be prevented by using targeted testing and not testing low risk individuals.
- Repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid and a reason for testing persists.
- In selected very high-risk individuals when missing the presence of LTBI could have serious consequences (e.g., individuals to be started on a TNF-α blocker or other immunocompromising medications).

G. Medical Evaluation After Testing for LTBI

- **Neither an IGRA nor a TST can distinguish LTBI from active TB disease.** A negative IGRA or TST does not rule out active TB disease.
- Persons with a positive IGRA or TST should be evaluated for the likelihood of *M. tuberculosis* infection, for risks for progression to active TB if infected, and for symptoms and signs of active TB.
- **A diagnosis of LTBI requires that active TB be excluded by medical evaluation** which should include taking a medical history and a physical exam to check for suggestive symptoms and signs, a chest x-ray (CXR), and when indicated, testing of sputum or other clinical samples for the presence of *M. tuberculosis*.
- Persons with a newly documented diagnostic test for LTBI (positive IGRA or TST) should have a chest x-ray performed to ensure that they do not have active TB disease. After an initial negative chest x-ray, **no routine follow-up chest x-rays are necessary**. Persons with a positive diagnostic test for LTBI should be educated about the signs and symptoms of active TB disease and instructed to consult with a physician if these symptoms occur.
- In healthy persons who have a low likelihood both of *M. tuberculosis* infection and of progression to active TB disease if infected, a single positive IGRA or TST result should not be taken as reliable evidence of *M. tuberculosis* infection. Because of the

low probability of infection, a false-positive result is more likely. In such situations, the likelihood of *M. tuberculosis* infection and of disease progression should be reassessed, and the initial test results should be confirmed. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis. For such persons, an alternative is to assume, without additional testing, that the initial result is a false positive. This becomes somewhat complex because of the lack of a "gold standard" diagnostic test for LTBI. For healthy persons who have a low risk for both infection and progression, discounting an isolated positive result as a false positive may be reasonable. This will increase detection specificity and decrease unnecessary treatment.

- In persons with **discordant test results** (i.e., one positive and the other negative), decisions about medical or public health management require individualized judgment in assessing the quality and magnitude of each test result (e.g., size of induration and presence of blistering for a TST; and the TB Response, Nil, and Mitogen values for an IGRA), the probability of infection, the risk for disease if infected, and the risk for a poor outcome if disease occurs. Patients who are at high risk for progression to active TB when LTBI is present (e.g., persons living with HIV, those scheduled to begin a TNF-α inhibitor, children < 5 years) should be assumed to have LTBI if one diagnostic test is positive (even if there are discordant results). For persons who have received BCG and who are not at increased risk for a poor outcome if infected, TST reactions of < 15 mm in size may reasonably be discounted as false positives when an IGRA is negative. In other situations, inadequate evidence ex-

ists on which to base recommendations for dealing with discordant results. Consultation with a TB expert should be considered when discordant results are present.

- Persons with a positive diagnostic test for LTBI who have active TB excluded, should be considered for treatment of LTBI. Treatment of LTBI is recommended for those at increased risk of progression to active TB disease (see Table 3). Treatment regimens for LTBI are described in the following pages.

H. Reporting of Pediatric Positive Tests for LTBI

Latent TB infection (LTBI) in children indicates recent transmission of TB in the community. Also, young children who are infected with TB are at high risk of progressing to TB disease. Because of the extreme importance of identifying children who have been exposed to and infected with TB, **LTBI in a child less than 5 years old is a notifiable disease in the state of Georgia**. Cases may be reported electronically at http://sendss.state.ga.us, by calling 1-866-782-4584, or by calling your local health department.

III. Treatment of Latent TB Infection (LTBI)

Treatment of LTBI is recommended for persons who are at increased risk for developing active TB disease. Those at increased risk for developing active TB disease following infection with *M. tuberculosis* are outlined in Table 3 and include persons living with HIV, those who are immunosuppressed and/or receiving immunosuppressive therapy (or scheduled to receive immunosuppressive therapy including TNF-α inhibitors), close contacts of persons with infectious active TB (e.g., pulmonary TB), others who are thought to have recent infection with *M. tuberculosis* (e.g., persons who have had a conversion from a negative to a positive diagnostic test for LTBI within the previous 2 years), immigrants and refugees from high TB burden countries, and children at risk who are < 5 years old. The risk of serious disease, including miliary or disseminated TB and tuberculous meningitis, is highest among persons living with HIV, especially if they have advanced HIV/AIDS. Infants, the elderly, and patients with other causes of severe immunosuppression are also at increased risk for disseminated TB disease. Treatment for LTBI should be started only if clinical and radiographic evaluations exclude active TB disease. Persons with LTBI who are considered to be at high risk for developing active TB (see Table 3) should be offered (and encouraged to take) treatment for LTBI irrespective of age.

A. Treatment Regimens

Treatment regimens for LTBI are outlined in Table 4. Several different LTBI treatment regimens are recommended by CDC.

These include:

1. **Rifampin.** Rifampin for 4 months is a preferred CDC treatment regimen for the treatment of LTBI among persons presumed to be infected with drug-susceptible TB (INH and rifampin susceptible) and is the regimen of choice for the treatment of LTBI among persons thought to be infected with INH-resistant strains. Rifampin is also preferred by many clinicians and public health clinics because of the shorter duration of therapy compared to INH. Rifampin has less hepatotoxicity compared to INH for the treatment of LTBI. Rifampin for 4 months has been shown to be non-inferior to 9 months of INH for the treatment of LTBI in a randomized controlled trial. In addition, rifampin was associated with higher completion rates and fewer adverse effects compared to INH. Rifampin has a large number of drug -drug interactions (as discussed on page 78) including warfarin, oral contraceptives, azole antifungals, and HIV antiretroviral therapy. Other medications that a person with LTBI is taking is an important consideration when determining whether rifampin or other LTBI regimens which include rifampin or other rifamycins can be prescribed. Drug-drug interactions between rifamycins and antiretroviral therapy are regularly updated by the U.S. Department of Health and Human Services (https://aidsinfo.nih.gov/guidelines/html/4/ adult-and-adolescent-opportunistic-infection/0).

2. **INH plus Rifapentine (3HP).** A short course regimen of **weekly** INH plus rifapentine for 12 weekly doses is another CDC-preferred regimen for the treatment of LTBI (due to

presumed infection with drug-susceptible *M. tuberculosis*) in adults as well as children ≥ 2 years of age. In 2011, CDC first recommended 3HP for the treatment of LTBI and that it be by directly observed therapy [DOT]. However, based on recent studies and updated data, CDC revised guidelines for the use of 3HP in 2018 and expanded the patient populations for which this regimen could be used and included an option for self-administration of the 3HP regimen. CDC recommendations for 3HP in the treatment of LTBI include:

- use of 3HP in adults and persons aged 2–17 years with LTBI;
- use of 3HP in persons who are living with HIV with LTBI including those with AIDS and taking antiretroviral medications with acceptable drug-drug interactions with rifapentine*; and
- use of 3HP by directly observed therapy (DOT) or self-administered therapy (SAT) in persons aged ≥ 2 years. Per CDC recommendations, "the health care provider should choose the mode of administration (DOT versus SAT) based on local practice, individual patient attributes and preferences, and other considerations, including risk for progression to severe forms of TB disease" (MMWR 2018; 67:723-72).

The 3HP is regimen is NOT recommended for pregnant women, children < 2 years old, persons living with HIV who are on antiretroviral drugs that have significant drug-drug

*https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/ overview

interactions with rifapentine, or patients infected with **suspected** INH-resistant, rifampin-resistant, or MDR isolates. Other potential disadvantages of the 3HP regimen in addition to the drug-drug interactions due to rifapentine (similar to those seen with other rifamycin drugs such as rifampin) include cost of medications that are greater than most alternatives; the need to take numerous pills simultaneously (10 pills once weekly compared with two or three pills daily for other regimens for most adults); and the association with a systemic drug reaction or influenza-like syndrome that can include syncope and hypotension (although the risk of hospitalization is low, 0.1% in published studies).

3. **Isoniazid (INH).** In the new CDC 2020 LTBI treatment guidelines, 6 or 9 months of daily INH is a recommended alternative regimen for the treatment of LTBI (due to presumed infection with drug susceptible M. tuberculosis) as shown in Table 4. A regimen of 6 months of daily INH is strongly recommended for HIV-negative adults and children of all ages and conditionally recommended for HIV-positive adults and children of all ages; INH daily for 9 months is conditionally recommended for adults and children of all ages, both HIV-negative and HIV-positive. One practical approach for the use of INH for LTBI is to aim for a 9 month regimen with the goal of completion of at least 6 months. INH can be given daily (e.g., by self-administered therapy) or twice weekly (if given by directly observed therapy) as outlined in Table 5. INH should be used for the treatment of LTBI when there are serious potential drug-drug interactions with rifampin or other rifamycins.

4. **Isoniazid (INH) plus Rifampin.** A regimen of 3 months of daily INH plus daily rifampin is a CDC conditionally recommended regimen for the treatment of LTBI in adults and children of all ages. Because this regimen contains rifampin, clinicians must closely review other medications that a person with LTBI is on to assess whether there are drug-drug interactions that would prohibit the use of this regimen (as discussed above for rifampin).

Table 4. Recommendations for regimens to treat latent tuberculosis infection

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
		Conditional	Low (HIV positive)
Alternative	6 mos isoniazid given daily	Strong§	Moderate (HIV negative
		Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

Abbreviation: HIV = human immunodeficiency virus

* *Preferred:* excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens, and therefore higher effectiveness. *Alternative:* excellent efficacy but concerns regarding longer treatment duration, lower completion rates, and therefore lower effectiveness.

† No evidence reported in HIV-positive persons.

§ Strong recommendation for those persons unable to take a preferred regimen (e.g., due to drug intolerability or drug-drug interactions).

Table 5. Dosages for recommended LBTI treatment regimens

Drug	Duration	Dosage and age group	Frequency	Total doses
Isoniazid* and rifapentine†	3 mos	**Adults and children aged ≥ 12 yrs** Isoniazid: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum Rifapentine: 10 - 14.0 kg, 300 mg 14.1 - 25.0 kg, 450 mg 25. 1 - 32.0 kg, 600 mg 32.1 - 49.9 kg, 750 mg ≥ 50.0 kg, 900 mg maximum **Children aged 2 - 11 yrs** Isoniazid*: 25 mg/kg; 900 mg maximum Rifapentine†: see above	Once weekly	12
Rifampin¶	4 mos	**Adults:** 10 mg/kg **Children:** 15 - 20 mg/kg** **Maximum dose:** 600 mg	Daily	120
Isoniazid* and rifampin¶	3 mos	**Adults** Isoniazid*: 5 mg/kg; 300 mg maximum Rifampin¶: 10 mg/kg; 600 mg maximum **Children:** Isoniazid*: 10 - 20 mg/kg†† ; 300 mg maximum Rifampin¶: 15 - 20 mg/kg; 600 mg maximum	Daily	90

(Table 5 continued)

Drug	Duration	Dosage and age group	Frequency	Total doses
Isoniazid*	6 mos	**Adults:** 5 mg/kg **Children:** 10 - 20 mg/kg†† **Maximum dose:** 300 mg	Daily	180
		Adults: 15 mg/kg **Children:** 20 - 40 mg/kg†† **Maximum dose:** 900 mg	Twice weekly§	52
	9 mos	**Adults:** 5 mg/kg **Children:** 10 - 20 mg/kg†† **Maximum dose:** 300 mg	Daily	270
		Adults: 15 mg/kg **Children:** 20 - 40 mg/kg†† **Maximum dose:** 900 mg	Twice weekly§	76

* Isoniazid is formulated as 100-mg and 300-mg tablets.
† Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.
§ Intermittent regimens must be provided via directly observed therapy (i.e., a health care worked observes the ingestion of medication).
¶ Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.
** The American Academy of Pediatrics acknowledges that some experts use rifampin at 20 - 30 mg/kg for the daily regimen when prescribing for infants and toddlers. (**Source:** American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829-53).
†† The American Academy of Pediatrics recommends an isoniazid dosage of 10 - 15 mg/kg for the daily regimen and 20 - 30 mg/kg for the twice-weekly regimen.

Adapted from MMWR Recomm Rep 2020; 69(1):1-11.

Table 6. LTBI Treatment Drug Adverse Reactions

Drug	Adverse Reactions	Monitoring	Comments
Isoniazid (INH)	**Gastrointestinal (GI) upset,** hepatic enzyme elevations, hepatitis, peripheral neuropathy, mild effects on central nervous system (CNS), drug interactions	Order baseline hepatic chemistry blood tests (at least AST or ALT) for patients with the following specific conditions: HIV infection, liver disorders, post-partum period (≤3 months after delivery), regular alcohol use, injection drug use, or use of medica-tions with known possible inter -actions. [some providers prefer to obtain baseline tests on all adults]. **Repeat measurements** if: * baseline results are abnormal * client is at high-risk for adverse reactions * client has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption. Pyridoxine can prevent isoniazid-induced peripheral neuropathy.

(Table 6 continued)

Drug	Adverse Reactions	Monitoring	Comments
Rifampin (RIF) and Rifapentine (RPT)	**Orange discoloration of body fluids (secretions, tears, urine),** GI upset, drug interactions, hepatitis, thrombocytopenia, rash, fever, influenza-like symptoms**, hypersensitivity reaction*** **Many drug-drug interactions**	Complete blood count (CBC), platelets and liver function tests. **Repeat measurements** if: * baseline results are abnormal * client has symptoms of adverse reactions **Prior to starting RIF or RPT:** need to carefully review all medications being taken by the patient with LTBI and ensure there is no contraindication to the use of that medication and RIF or RPT.	Hepatitis risk increases with age and alcohol consumption. Rifampin monotherapy is associated with lower risk of hepatotoxicity compared to INH monotherapy for patients being treated for LTBI. Need to carefully review for possible drug-drug interactions prior to starting RIF or RPT and ensure there are no contraindications to these agents prior to using them for the treatment of LTBI.

Table 6 continues on next page.

(Table 6 continued)

Drug	Adverse Reactions	Monitoring	Comments
Isoniazid plus rifapentine (3HP)	See adverse effects associated with isoniazid alone and a rifamycin alone (see above)	See above recommendations for isoniazid and rifamycin drugs	Approximately 4% of all patients using 3HP experience flu-like or other systemic drug reactions, with fever, headache, dizziness, nausea, muscle and bone pain, rash, itching, red eyes, or other symptoms. Approximately 5% of persons discontinue 3HP because of adverse events, including systemic drug reactions; these reactions typically occur after the first 3–4 doses, and begin approximately 4 hours after ingestion of medication.

** Hypersensitivity reaction to rifamycins (rifampin or rifapentine): reactions may include a flu-like syndrome (e.g. fever, chills, headaches, dizziness, musculoskeletal pain), thrombocytopenia, shortness of breath or other signs and symptoms including wheezing, acute bronchospasm, urticaria, petechiae, purpura, pruritus, conjunctivitis, angioedema, hypotension or shock. If moderate to severe reaction (e.g. thrombocytopenia, hypotension), hospitalization or life-threatening event: Discontinue treatment. If mild reaction (e.g. rash, dizziness, fever): Continue to monitor patient closely with a low threshold for discontinuing treatment. A flu-like syndrome appears to be the most common side effect profile leading to discontinuation of the 3HP regimen.*

B. Monitoring of Patients on Treatment for LTBI

For all patients (based on CDC recommendations):

- Evaluate for active TB disease both before and during treatment of LTBI.
- Inform the patient or parents or legal guardians about possible adverse effects of the LTBI treatment regimen and instruct them to seek prompt medical attention when symptoms of possible adverse reaction first appear; particularly drug hypersensitivity reactions, rash, hypotension, or signs of thrombocytopenia (see Table 6).
- Conduct monthly evaluations to assess treatment adherence and adverse effects, with repeated patient education regarding adverse effects at each visit.
- For those on self-administered therapy, never dispense more than one month of therapy (and no refills). Include careful questioning about side effects and a brief physical examination checking for evidence of hepatitis or other side effects during each visit.
- Order baseline hepatic chemistry blood tests (AST or ALT) for patients with the following specific conditions: HIV infection, liver disorders, postpartum period (≤ 3 months after delivery), regular alcohol use, injection drug use, or use of medications with known possible interactions. (We prefer to obtain a baseline laboratory chemistry profile including a hepatic chemistry blood test on all adult patients starting LTBI therapy.)

- In the absence of liver disease or HIV infection, children on LTBI therapy do not need monthly ALT or AST monitoring.
- Conduct blood tests at subsequent clinical encounters for patients whose baseline testing is abnormal and for others at risk for liver disease. Discontinue the LTBI treatment regimen if a serum AST concentration is ≥ 5 times the upper limit of normal in the absence of symptoms or ≥ 3 times the upper limit of normal in the presence of symptoms.
- In case of a possible severe adverse reaction, discontinue the LTBI regimen immediately and provide supportive medical care. Conservative management and continuation of LTBI therapy under observation can be considered in the presence of mild to moderate adverse events as determined by the health care provider.

Indications for regular monthly monitoring of LFTs:

- Abnormal ALT (or AST) at baseline
- HIV infection
- Pregnancy
- First three months postpartum
- Chronic liver disease (including hepatitis C virus [HCV] infection)
- Regular alcohol use
- Injection drug use

- Patients on other drugs which are potentially hepatotoxic
- Advanced age

Medication should be discontinued, and patient evaluated if:

- Transaminase levels (i.e., ALT or AST) > 3 times upper limit of normal in the presence of symptoms of adverse events
- Transaminase levels (i.e., ALT or AST) > 5 times upper limit of normal in an asymptomatic patient

Pyridoxine (Vitamin B6) should be used (25-50 mg/day) with INH for persons with conditions in which neuropathy is common (e.g., HIV, diabetes, alcoholism, malnutrition) as well as pregnant women and persons with a seizure disorder to prevent isoniazid-associated neuropathy. It should be given to all HIV-infected persons, all children, and women who are breastfeeding. For healthy individuals on a normal diet, pyridoxine is optional. However, we prefer to give pyridoxine to all patients on INH. Pyridoxine (at 25 mg per day) is also recommended for children on INH.

C. Contacts of MDR-TB Cases (i.e., cases resistant to at least isoniazid and rifampin)

There are no results from randomized controlled trials to guide therapy for persons with LTBI thought to be infected with MDR-TB strains. Several studies are ongoing which should provide more guidance in the future. In deciding how to treat persons with LTBI which may be due to infection with an MDR-TB strain, the following four questions should be considered. **A TB special-**

ist should be consulted in the management of contacts to MDR-TB cases.

- ***How likely is it that a patient is newly TB infected?*** A patient with a documented positive prior TST (or another diagnostic test such as an IGRA) is much less likely to be newly infected.
- ***How likely is it that the patient is infected with an MDR-TB strain?*** An infant with a positive diagnostic test for LTBI (TST or IGRA) whose parent has active MDR-TB is highly likely to be infected with MDR-TB. In contrast, a health care worker with a positive TST and no known source case may have a low probability of being MDR-TB infected.
- ***How likely is the patient to develop active TB?*** Those at highest risk include persons living with HIV or otherwise immunocompromised and children < 2 years of age.
- ***What is the drug-susceptibility pattern of the source patient's isolate?*** Treatment of LTBI must be tailored to the susceptibility pattern of the source patient's isolate. When the source patient is known to have isoniazid-resistant TB, rifampin may be used for treatment of LTBI. As noted above, there are no current evidence-based guidelines for the treatment of LTBI when an individual is thought to be infected with an MDR-TB strain. In some cases of MDR-TB or XDR-TB, no LTBI regimen is available.

IV. Laboratory Diagnosis of Active Tuberculosis

A. Considerations

1. Active TB diagnosis is usually pursued by mycobacterial acid -fast bacilli smear ("AFB smear"), mycobacterial culture ("AFB culture"), nucleic acid amplification tests, radiological exam, and histopathology.

2. Phenotypic drug-susceptibility testing is optimal for patient care and genotyping is paramount for tuberculosis control. Both tests require an isolate from a positive culture. Thus, adequate samples for mycobacterial culture should be obtained whenever possible.

3. Diagnostic samples can be collected after TB treatment initiation among patients with life-threatening disease or other compelling indications for immediate TB treatment (Figure 1).

4. TST and/or IGRA are negative in 10-30% of patients with active TB. **Thus, a negative TST and/or IGRA do not rule out active TB.**

5. The sensitivity of each test (smear, culture, and nucleic acid amplification) differs by sample source (e.g., sputum vs. cerebrospinal fluid).

6. ATS/CDC/IDSA guidelines for Diagnosis of Tuberculosis in Adults and Children are a comprehensive source for labora-

tory tests for TB diagnosis [Lewinsohn *et al.* Clinical Infectious Diseases, 2017].

B. Selected Diagnostic Test Characteristics

1. AFB smear
    - Turnaround time is usually < 1 day.
    - AFB positive smears are not specific for Mycobacterium tuberculosis. Non-tuberculous mycobacteria can also lead to positive AFB smears.
2. AFB culture
    - Most laboratories use both solid and liquid culture media.
    - Growth can be detected as late as 8 weeks in either media.
    - Average time to culture positivity in solid cultures is 3–4 weeks and 10–14 days in liquid media.
    - Positive cultures are required for phenotypic drug-susceptibility testing and genotyping.
3. Nucleic acid amplification test (NAAT)
    - Turnaround time is usually < 1 day if the laboratory is able to run the test frequently.
    - Several FDA and non-FDA approved NAATs are available and performance characteristics are variable.

- Cepheid Xpert MTB/RIF ("Xpert MTB/RIF") and Hologic Amplified Mycobacteria Tuberculosis Direct ("MTD") NAATs are endorsed by ATS/IDSA/CDC guidelines.
- A positive AFB smear with negative Xpert MTB/RIF or MTD NAAT usually indicates presence of non-tuberculous mycobacteria in the sample.
- Xpert MTB/RIF also tests for genotypic evidence of rifampin susceptibility.

4. Histopathology
    - Necrotizing granulomas in the appropriate clinical scenario should prompt strong consideration for TB.
    - Necrotizing granulomas are an immune reaction to TB antigens and therefore are less likely to occur among immunosuppressed patients.
    - Absence of histopathological signs of inflammation should prompt concern for inadequate sampling.

C. Laboratory Diagnosis of Pulmonary Tuberculosis

1. Immunocompromised patients are less likely to have typical CXR findings. **A normal CXR does not rule out active pulmonary TB.**

2. A minimum of two AFB smears is generally recommended for persons with suspected pulmonary TB. The overall sensitivity of AFB smear for pulmonary TB is 50% to 70%, and the

sensitivity is reduced among immunosuppressed and pediatric patients.

3. First morning sputum specimens have increased sensitivity and at least one first morning specimen should be obtained.

4. The sensitivity of ATS/IDSA/CDC endorsed NAATs for smear-negative and smear-positive TB are approximately 67% and 96% respectively. **A negative NAAT performed on a smear-negative sample does not rule out TB,** whereas a negative NAAT performed on a smear-positive sample usually indicates presence of non-tuberculous mycobacteria.

5. For patients with suspected pulmonary TB who are unable to produce good quality sputum (defined as > 3 ml of sputum), consider obtaining induced sputum sample (using 3% NaCl aerosol) for smear, culture, and NAAT samples.

6. Consider obtaining bronchoscopy with transbronchial biopsy for smear, culture, NAAT, and histopathology: a) for patients with suspected pulmonary TB when sputum induction fails to produce good quality samples; b) when empiric TB treatment is unacceptable (e.g., high-risk for MDR TB); and/or c) when bronchoscopy is indicated to investigate alternative diagnosis (e.g., lung cancer).

7. **Bronchoscopy is an aerosol-generating procedure, and infection control measures for airborne pathogens should be observed.**

8. Consider obtaining post-bronchoscopy sputum sample for smear and culture.

9. Children are more likely to have paucibacilliary disease and are often unable to produce good quality sputum specimens. However, clinicians should pursue microbiological TB diagnosis when feasible. Gastric aspirate when appropriately performed has yield > 50%. Instruct patients to fast overnight. Commensal non-tuberculous mycobacteria are present in the GI tract and a positive AFB smear should be interpreted with caution.
(https://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-guide-gastric-aspirate-procedure)

D. Laboratory Diagnosis of Extrapulmonary Tuberculosis

1. **Patients with suspected extrapulmonary TB** should always be evaluated for concomitant pulmonary TB with at least CXR and sputum smear and culture.

2. **Tissue biopsies are aerosol-generating procedures, and infection control measures for airborne pathogens should be observed in cases of suspected TB.**

3. Sensitivity of smear, culture, and NAAT tests are generally reduced for extrapulmonary samples compared to sputum samples.

4. NAATs can be performed in extrapulmonary samples. However, NAATs are not FDA-approved for extrapulmonary samples, and negative results should be interpreted with caution. Extra-pulmonary samples are more likely to contain

PCR inhibitors, and clinicians should discuss test validity (i.e., positive-control results) with laboratory.

5. **Diagnostic tests have low sensitivity for central nervous system TB.** Cerebrospinal fluid AFB smear sensitivity is very low (< 5%), and culture and Xpert MTB/RIF both have sensitivity < 70%.

6. Pleural tissue histopathological exam sensitivity is > 70%, whereas pleural fluid and pleural tissue smear sensitivity are < 10% and < 40%, respectively. Pleural fluid and pleural tissue culture sensitivity are < 70%.
7. Fine needle aspiration (FNA) is as an appropriate diagnostic test for suspected TB lymphadenitis. However, excisional biopsy has higher yield and should be pursued when FNA results are negative and suspicion for TB remains high.

8. Consider obtaining adenosine deaminase (ADA) pleural, pericardial, peritoneal, or meningeal fluid in addition to smear, culture, and NAAT. However, ADA result should be interpreted with caution as sensitivity and specificity are highly influenced by cut-off values and anatomical sample source.

E. Rapid Molecular Drug Susceptibility Tests (DST)

1. All patients with culture-confirmed TB should have phenotypic DST performed. However, these tests are limited by a long turnaround time.

2. Several genotypic DST are available, and the Xpert MTB/RIF is the mostly commonly used in the U.S. with turnaround time < 1 day.

Xpert MTB/RIF sensitivity and specificity for rifampin-resistant TB is > 92% and 99%, respectively. However, given the low incidence of rifampin resistance in the U.S., Xpert MTB/RIF positive predictive value is low. Pre-test probability for rifampin resistance is increased among patients with prior TB treatment and patients with prolonged stay in high burden TB countries. A test result indicating rifampin resistance should prompt consultation with a TB expert **(see Appendix).**

V. Treatment of Current (Active) Disease Therapy

A. Considerations

1. The **provider (or public health program)** is responsible for prescribing an appropriate regimen *and* ensuring that treatment is completed successfully. **Proven or suspected active TB must be reported to the local health department at the time treatment is initiated.** The health department can assist with (or assume responsibility for if the clinician prefers) managing the TB treatment. The TB program can also provide access to TB experts throughout the state. **Contact information for TB coordinators in each county is found in the Appendix and at https://dph.georgia.gov/public-health-districts**

2. **The decision to initiate treatment for active TB is often (appropriately) made prior to the confirmation of the diagnosis. Numerous factors are considered in making this decision and are outlined in Figure 1 on page 54.**

3. Early or immediate reporting to the county health department or state TB program is indicated for:

   - Suspected or documented drug resistance
   - Patients with molecular test indicating rifampin resistance
   - Patients with prior treatment for active TB

- Patients failing treatment for active TB
- Life-threatening illness from suspected (or documented) active TB (i.e., meningitis or ICU admission)

4. **Directly Observed Therapy (DOT) to ensure adherence and treatment completion is the standard of care for all patients with active TB. DOT** is managed by the county public health department. A variety of approaches to DOT, including Video-DOT, are employed by our TB program. The Georgia DPH TB Control Program provides patient-centered care for all patients. Treatment is tailored and supervised based on each patient's clinical *and* social circumstances. TB treatment is most successful within a comprehensive framework that addresses both clinical *and* social issues of relevance to the patient.

5. Drug susceptibility testing should be performed on initial *M. tuberculosis* isolates in ALL cases. Drug susceptibility testing and AFB cultures are performed by the Georgia Public Health Laboratory (Phone: 404-327-7945 or 404-327-7946).

6. The best way to measure the effectiveness of therapy for pulmonary TB is to monitor patients bacteriologically through sputum examination *at least monthly* until two consecutive negative cultures are obtained. We recommend obtaining monthly sputum examinations throughout the course of therapy. **For patients with pulmonary TB, it is essential to obtain a culture at the time when 2 months of therapy have been completed– "the 2-month culture."**

7. Patients being treated for uncomplicated pulmonary TB do not require frequent chest x-rays; bacteriologic examination is far more important than monitoring chest radiographs.

8. If a patient's sputum cultures remain positive beyond 2 months of therapy, the possibility of drug-resistant disease, malabsorption, or patient non-adherence to taking medications as prescribed should be considered. Drug susceptibility testing studies should be repeated, and care should be reviewed with experts.

9. Adjust weight-based doses as weight changes.

B. Standard Therapy for Current (Active) Disease

1. Initiate therapy with a 4-drug regimen as shown in Table 7 on page 52.

   Any patient who is started on treatment for suspected or proven active TB (even while still in the hospital) should be reported to local public health authorities at the time treatment is started.

   Therapy consists of an **initiation phase** and a **continuation phase**.

   The **initiation phase** generally consists of a 4-drug regimen given daily or 5 times per week per DOT. An option for twice weekly therapy by DOT after the initial 2 weeks of daily therapy ("Denver regimen") also exists but is only rarely appropriate. This option should **NOT** be used for patients with

HIV infection, cavitary pulmonary TB, disseminated TB, vertebral TB or for patients who have co-morbid medical conditions such as diabetes mellitus, end-stage renal disease, or liver disease.

The initiation phase is followed by a **continuation phase**. For drug susceptible disease, this can consist of daily, 5 times per week or thrice weekly by DOT (see Table 7). For patients with HIV co-infection, in the continuation phase, twice-weekly therapy is contraindicated because of increased risk of relapse with rifampin-resistant disease; in such cases therapy should be given daily (or 5 times per week) or thrice weekly by DOT. In general, daily therapy is preferred throughout for patients with HIV co-infection or other immune-compromising conditions. **See Figure 1 on page 54**.

See Tables 8 and 9, 10, 11, 12 on pages 56–62 for dosing recommendations for adults and children.

2. For patients with pulmonary tuberculosis, sputum specimens should be obtained at a minimum on a monthly basis until two consecutive specimens are culture negative (some obtain monthly specimens throughout the course of therapy). **As discussed above, the 2-month culture is a critical data-point**.

3. Twice-weekly therapy is not recommended for use in the continuation phase by us and is contraindicated for treatment of persons living with HIV.

4. Rifampin has many drug-drug interactions and may accelerate clearance of drugs metabolized by the liver including

methadone, coumadin, glucocorticoids, estrogens, oral hypoglycemic agents, anticonvulsants, fluconazole, voriconazole, itraconazole, cyclosporin, and protease inhibitors. Rifabutin can be used as a first line drug in place of rifampin for patients who are receiving medications, especially antiretroviral drugs, that have unacceptable interactions with rifampin.

- Women taking RIF (or rifabutin) should use a barrier birth control method (and not rely on hormone contraceptives alone).

5. Dose-counting: Although TB treatment regimens are generally described in terms of **"months"** of treatment, it is important that each patient receives an adequate **number** of doses. **Thus, treatment completion is defined by number of doses actually taken as well as duration of treatment.** The number of doses required for each regimen is listed in Table 7 on page 52.

6. Follow-up after completion of therapy is generally not needed for patients who have had a satisfactory and prompt bacteriologic response and who have completed observed therapy with a 6- or 9-month INH- and RIF-containing regimen. Patients should be informed to seek prompt medical evaluation if symptoms reappear. Many authorities would continue to follow patients who are HIV-infected or who had drug-resistant isolates.

Precautions

- Daily intake of alcohol increases the risk of hepatitis for patients taking INH.
- Never add a single drug to a failing regimen.
- **Directly observed therapy (DOT) is the standard of care for administering treatment of active TB, and such treatment should be supervised and coordinated by the local health department**. For any patient on self-administered therapy, dispense only a 1-month supply of medicine at a time.

C. Special Clinical Situations

1. Dosing for TB medications in adults with renal impairment is shown in Table 13 on page 63.
2. Therapy for TB in clinical situations for which standard TB therapy may not be tolerated or may be ineffective is shown in Tables 14 and 15 on pages 64-68.

Table 7. Recommended Regimens for Treatment of Adults and Children with Drug-Susceptible TB Pulmonary TB

Option	Total Duration (Months)	Initial Phase		Continuation Phase		Comments
		Drugs	**Interval & Dose # (minimal duration)**	Drugs	**Interval & Dose # (minimal duration)**	
1	6^	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily DOT for 40 doses **(8 wks)**	Isoniazid Rifampin Vitamin B6 Isoniazid Rifampin	**1a**. Daily DOT for 90 doses **(18 wks)** **OR** **1b.** Thrice-weekly DOT for 54 doses **(18wks)** **OR**	Regimen must be given by DOT. Continue ethambutol until susceptibility to isoniazid and rifampin is demonstrated.
2*	6	Isoniazid Rifampin Pyrazinamide Ethambutol Vitamin B6	Daily DOT for 10 doses **(2 wks),** then twice-weekly DOT for 12 doses **(6 wks)**	Isoniazid Rifampin Vitamin B6	**2a.** Twice-weekly DOT for 36 doses **(18 wks)**	We do not recommend this regimen. If used, it must be given by DOT. Include ethambutol in initial phase. After the initial phase, continue ethambutol until susceptibility to INH and rifampin is demonstrated.

Table 7 Notes

NOTE: 1 Daily DOT = 5 days/week (Monday through Friday). **Self-administered** doses **(including those on weekends)** will not be counted toward the total doses.

NOTE 2: Regimen 1a is the preferred regimen for patients with newly diagnosed TB.

NOTE 3: Pyridoxine (Vitamin B_6) 25 - 50 mg/daily should be added to all regimens that include isoniazid (INH) in adults to prevent development of INH-induced peripheral neuropathy. For patients with pre-existing peripheral neuropathy, increase pyridoxine dose to 100 mg/day unless there is abnormal renal function.

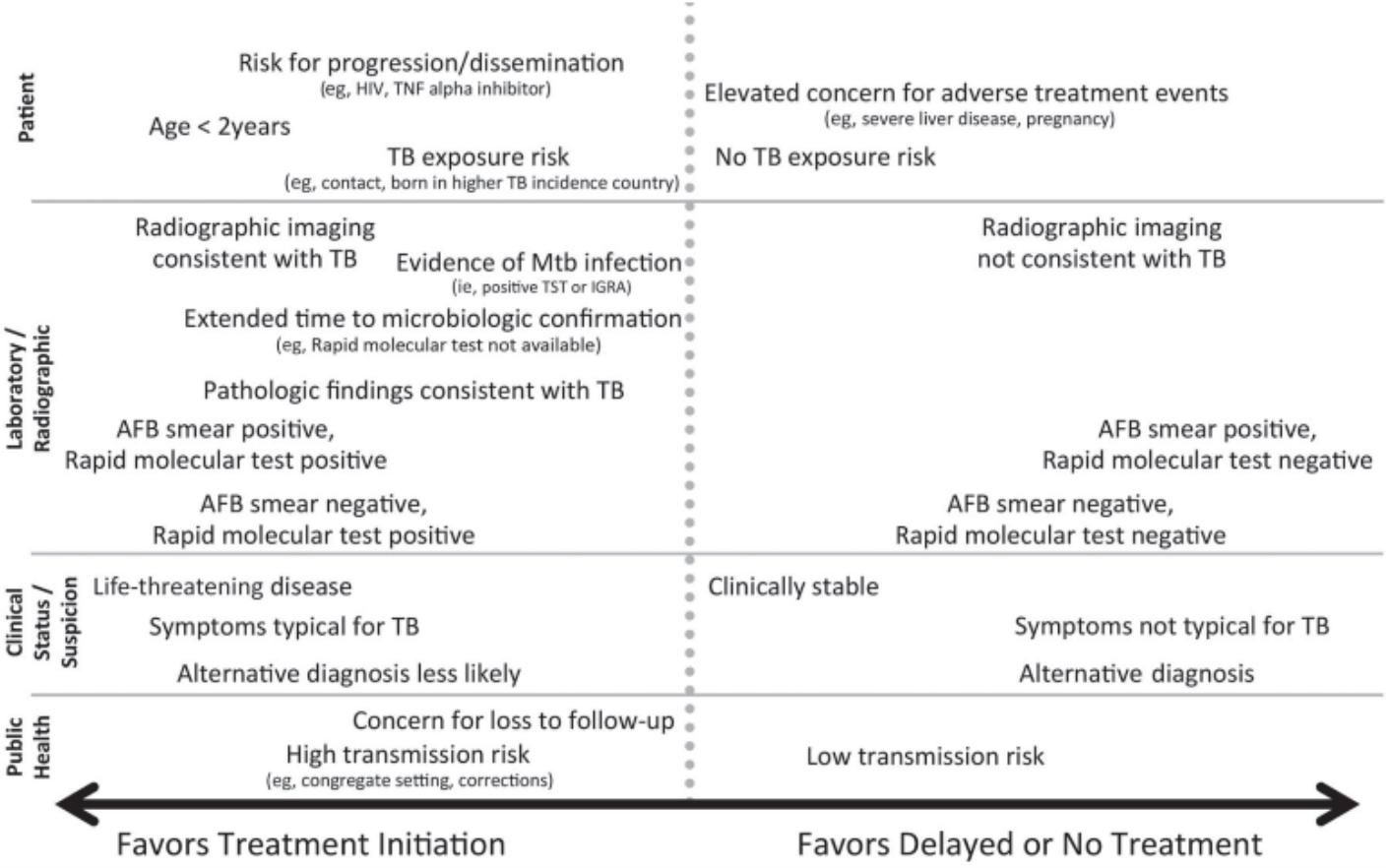
^NOTE: Duration of therapy for patients with drug-susceptible TB should be extended to 9 months (31 weeks continuation phase, 39 weeks total) for patients who have cavitary pulmonary TB and remain sputum culture positive after 2 months of therapy. Many experts would extend therapy to 9 months for all patients with HIV/TB, especially those slow to convert to negative cultures or not on effective HIV treatment.

***NOTE: Option 2 should NOT be used for patients with HIV infection, cavitary pulmonary TB, disseminated TB, vertebral TB or for patients who have co-morbid medical conditions such as diabetes mellitus, end-stage renal disease or liver disease.**

NOTE: Split dosing should be avoided.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interaction.

Figure 1. Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation)



Abbreviations: AFB, acid-fast bacilli; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; Mtb, Mycobacterium tuberculosis; TNF, tumor necrosis factor; TST, tuberculin skin test.

Clinical Infectious Diseases, Volume 63, Issue 7, 01 September 2016, Pages 853–867, https://doi.org/10.1093/cid/ciw566

Figure 1. Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation)

Abbreviations: AFB, acid-fast bacilli; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; Mtb, Mycobacterium tuberculosis; TNF, tumor necrosis factor; TST, tuberculin skin test.

Table 8. First-Line TB Drugs: Dosing for Adults (ages 16 and over) Directly Observed Therapy (DOT) is mandatory

Drugs	Adult Dose based on body weight in kilograms (kg)*			Adverse Reactions
	Daily	Thrice-Weekly	Twice-Weekly	
Isoniazid	300 mg	900 mg	900 mg	• Gastrointestinal (GI) upset • Liver enzyme elevation • Hepatitis • Peripheral neuropathy • Mild effects on central nervous system • Drug interactions
Rifampin	600 mg	600 mg	600 mg	• Orange discoloration of body fluids and secretions • Drug interactions • GI upset • Hepatitis • Bleeding problems • Influenza-like symptoms • Rash • Uveitis (rifabutin only)
Rifabutin	300 mg	Not recommended	Not recommended	

(Table 8 continued)

Drugs	Adult Dose based on body weight in kilograms (kg)*			Adverse Reactions
	Daily	Thrice-Weekly	Twice-Weekly	
Pyrazinamide**	40-55 kg: 1000 mg 56-75 kg: 1500 mg 76+ kg: 2000 mg	40-55 kg: 1500 mg 56-75 kg: 2500 mg 76+ kg: 3000 mg	40-55 kg: 2000 mg 56-75 kg: 3000 mg 76+ kg: 4000 mg	• GI upset • Joint aches • Hepatitis • Rash • Hyperuricemia • Gout (rare)
Ethambutol**	40-55 kg: 800 mg 56-75 kg: 1200 mg 76+ kg: 2000 mg	40-55 kg: 1200 mg 56-75 kg: 2000 mg 76+ kg: 2800 mg	40-55 kg: 1600 mg 56-75 kg: 2400 mg 76+ kg: 4000 mg	• Optic neuritis

*Formula used to convert pounds to kilograms: Divide pounds by 2.2 to get kilograms.

Example: Patient weighs 154 pounds ÷ 2.2 = 70 kilograms.

** Calculate pyrazinamide and ethambutol doses using actual body weight. Pyrazinamide and ethambutol dosage adjustment is needed in patients with estimated creatinine clearance less than 50 ml/min or those with end-stage renal disease on dialysis.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

Table 9. PEDIATRIC DOSAGE - ISONIAZID IN CHILDREN (birth to 15 years)

Child's Weight (lbs)	Child's Weight (kg)	Daily Dose (mg) 10 – 15 mg/kg PO	Twice-weekly Dose (mg) 20 – 30 mg/kg PO
6 – 10	3 – 4.5	50	100 mg PO
11 – 14	5.0 – 6.0	50	150 mg PO
14.5 – 18	6.5 – 8.0	100	200 mg PO
18.5 – 21.5	8.5 – 9.5	100	250 mg PO
22 – 24	10.0 – 11	150	300 mg PO
25 – 29	11.5 – 13	150	350 mg PO
29.5 – 32	13.5 – 14.5	200	400 mg PO
33 – 35	15 – 16	200	450 mg PO
36 – 40	16.5 – 18.	250	500 mg PO
40.5 – 43	18.5 – 19.5	250	550 mg PO
44 – 48	20 – 21.5	300	600 mg PO
48.5 – 51	22 – 23	300	650 mg PO

(Table 9 continued)

Child's Weight (lbs)	Child's Weight (kg)	Daily Dose (mg) 10 – 15 mg/kg PO	Twice-weekly Dose (mg) 20 – 30 mg/kg PO
52 – 54.5	23.5 – 24.5	300	700 mg PO
55 – 57.5	25 – 26	300	750 mg PO
58 – 62	26.5 – 28	300	800 mg PO
62.5 – 65	28.5 – 29.5	300	850 mg PO
66 +	30 +	300	900 mg PO

NOTE: Isoniazid tablets come in 50 mg, 100mg, 300 mg sizes and can be crushed for oral administration. Isoniazid tablets are also scored.

Isoniazid Syrup (50mg/5ml) should not be refrigerated. It contains sorbitol and will cause diarrhea. It should be used only when crushed tablets cannot accommodate the situation. (keep at room temperature).

Table 10. PEDIATRIC DOSAGES - RIFAMPIN IN CHILDREN (birth to 15 years)

DOSE for either daily or twice weekly therapy

Child's Weight (lbs)	Child's Weight (kg)	Dose (mg) 10 – 20 mg/kg
15 – 32	7 – 14.5	150 mg
33 – 48.5	15 – 22	300 mg
49 – 65	22.5 – 29.5	450 mg
66 +	30 +	600 mg

Table 11. PEDIATRIC DOSAGES - ETHAMBUTOL IN CHILDREN (birth to 15 years)

Ethambutol is available in 100mg and 400 mg tablets

Child's Weight (lbs)	Child's Weight (kg)	Daily Dose (mg) 15 – 25 mg/kg
11 – 15	5 – 7	100 mg
16 – 31	8 – 14	200 mg
32 – 44	15 – 20	300 mg
45 – 55	21 – 25	400 mg
56 – 67	26 – 30.5	500 mg
68 – 76	31 – 34.5	600 mg
77 – 87	35 – 39.5	700 mg
88 – 121	40 – 55	800 mg
122 – 165	56 – 75	1200 mg
166 +	76 +	1600 mg

Table 12. PEDIATRIC DOSAGES - PYRAZINAMIDE IN CHILDREN (birth to 15 years)

Pyrazinamide is available in 500 mg tablets which are scored and can be cut in ½.

Child's Weight (lbs)	Child's Weight (kg)	Daily Dose (mg) 30 – 40 mg/kg	Twice Weekly Dose (mg) 50 – 70 mg/kg
13 – 23	6 – 10.5	250 mg	500 mg
24 – 26	11 – 12	250 mg	750 mg
27 – 31	12.5 – 14	500 mg	1000 mg
32 – 41	14.5 – 18.5	500 mg	1250 mg
42 – 47	19.0 – 21.5	750 mg	1250 mg
48 – 54	22.0 – 24.5	750 mg	1500 mg
55 – 63	25 – 28.5	1000 mg	1750 mg
64 – 67	29 – 30.5	1000 mg	2000 mg
68 – 80	31 – 36.5	1250 mg	2000 mg
81 – 93	37 – 42.5	1500 mg	2000 mg
94 – 106	43 – 48.5	1750 mg	2000 mg
107 +	49 +	2000 mg	2000 mg

Table 13. ANTITUBERCULOSIS ANTIBIOTICS IN ADULT PATIENTS WITH RENAL IMPAIRMENT

NOTE: Drug adjustments are based on the creatinine clearance (CrCl) which can be estimated as follows:

$$\frac{(140\text{-age in yrs})(\text{Ideal body weight in kg}) \text{ for men (x 0l85 for women)}}{(72)\ (\text{serum creatinine, mg/dL})}$$

Ideal body weight for men: 50 kg + 2.3 kg per inch over 5 feet
Ideal body weight for women: 45.5 kg + 2.3 kg per inch over 5 feet

Drug	*Usual Dose (UD) Normal Renal Function*	*CrCl 30-90*	*CrCL <30 or Hemodialysis*	*Peritoneal Dialysis*
INH	300 mg/day	UD	UD	Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.
Rifampin	600 mg/day	UD	UD	
Ethambutol	15-25 mg/kg/day	UD	20-25 mg/kg/dose thrice weekly	
Pyrazinamide	25 mg/kg d (max 2 gm/day).	UD	25-35 mg/kg/dose thrice weekly	
Levofloxacin	750 mg/day	UD	750-1000 mg/dose thrice weekly	
Moxifloxacin	400 mg/day	UD	UD	
Amikacin	15 mg/kg/daily or thrice weekly	UD	15 mg/kg/dose thrice weekly	
Linezolid	600 mg/day	UD	UD	

- Standard doses are given unless there is intolerance.
- The medications should be given after hemodialysis on the day of hemodialysis.
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
- In patients with 30–50 mL/min creatinine clearance, standard doses are used by experts, but measurement of serum concentrations 2 and 6 hours after timed administration can be used to assist with optimizing drug dosages.

Based on Nahid et al. Clin Infect Dis 2016;63(7):e147–95, Table 11

Table 14. Antituberculosis medications which may be used for patients who have contraindications to or intolerance of first line agents or who require IV therapy during acute or critical illness

Medication: Route(s)	Dosing (A for adults, C for children)	Adverse Reactions
Levofloxacin: PO/IV Moxifloxacin: PO/IV	A: 750 mg daily C: 15 – 20 mg/kg daily Max dose 750 mg A: 400 mg daily C: no established dose	GI upset, dizziness, hypersensitivity, Headaches, QT prolongation, tendon rupture (rare), arthralgia, increased risk for aortic dissection/rupture, hypo/hyperglycemia
Linezolid: PO/IV	A: 600 mg (once daily) C: 10 mg/kg/dose every 12 hours (max dose 600 mg)	Myelosuppression, GI upset, optic and peripheral neuropathy (may be irreversible)
Amikacin: IV	A: 10 to 15 mg/kg/day 5-7 days per week or 3 times per week C: 15 to 30 mg/kg/day (max dose 1 gram) 5-7 days per week or 3 times per week	Auditory, vestibular and renal toxicity

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Table 15. Clinical Situations for which standard therapy cannot be given or is not well-tolerated or may not be effective: Potential Alternative Regimens (Dosing and/or Drugs) [1]

Clinical Situation	Concerns raised	Regimen	Comments
Critical illness requiring vasopressors	Poor gut medication absorption	IV rifampin ≥ 10 mg/kg daily PO pyrazinamide UD PO ethambutol UD Consider adding at least two of following agents IV isoniazid UD[2,3] IV levofloxacin or moxifloxacin UD IV linezolid UD [4] IV amikacin UD [5]	Oral medications are generally poorly bioavailable among critically ill patients. Patients receiving sedation are unable to report isoniazid or linezolid-induced neuropathies nor aminoglycoside-induced otovestibular toxicity
Proven or suspected meningeal TB	Rapidly progressive and often fatal. High plasma levels needed to achieve adequate CNS penetration. High index of suspicion necessary; microbiological diagnostic tests have low yield.	IV rifampin ≥ 10 mg/kg daily PO or IV [2] isoniazid UD PO pyrazinamide UD PO ethambutol UD (adults) PO ethionamide (children) Consider adding IV levofloxacin or moxifloxacin UD in lieu of ethambutol	Rifampin has poor CNS penetration but is an essential drug for meningeal TB treatment. Isoniazid, pyrazinamide, levofloxacin, and moxifloxacin have excellent CNS penetration. Ethambutol has poor CNS penetration. Early use of fluoroquinolones has been associated with improved outcomes among patients with isoniazid-resistant meningeal TB
Patient age 75 years or greater [6]	Increased risk for pyrazinamide-induced hepatotoxicity	Can consider rifampin, isoniazid, and ethambutol without pyrazinamide when drug-susceptibility is known and/or patient has low burden of disease	3-drug regimens may increase risk of failure or acquired drug-resistance.

(Table 15 continued)

Clinical Situation	Concerns raised	Regimen	Comments
Disseminated TB with concern for poor absorption from gut [6]	Disseminated TB is associated with gut edema which decreases po medication bioavailability	Standard 4-drug regimen Consider increasing po Rifampin dose (15 to 20 mg/kg daily, minimum 600 mg) Consider IV rifampin and IV isoniazid [1] for inpatients.	Consider obtaining TB drug levels in ensure po dosing achieves at least minimum levels
Patient receiving medications via nasogastric or PEG tube [6]	Tube feeds may decrease TB drug bioavailability	No change in standard TB regimen	Hold tube feeds ≤2 hours prior and ≥1 hour after TB drug intake. Longer intervals are needed if quinolone-containing regimens are given with divalent-cation containing tube feeds
Baseline elevation of liver enzymes [6]	Consider limiting number of hepatotoxic drugs for patients with baseline ALT>3x UNL and/or advanced liver disease. Order of hepatotoxicity: PZA>INH>RIF	1-RIF/INH/EMB +/- FQN 2-RIF/EMB/FQN +/- LZD or AG 3-EMB/FQN +/- LZD or AG	Consider baseline liver enzyme elevation could be due to hepatic TB 3-drug regimens may increase risk of failure or acquired drug-resistance.
Acute hepatitis after starting standard therapy [6]	TB drug-induced hepatotoxicity Stop TB drugs if ALT>3x UNL and patient symptomatic or ALT >5x UNL regardless of symptoms	Sequential re-introduction of TB drugs once ALT <2x UNL. (1) Rifamycin x 5-7 days (2) Isoniazid x 5-7 days (3) Ethambutol x 5-7 days (4) Need and choice of 4th agent depends on burden of disease and drug-susceptibility pattern.	Pyrazinamide is often the culprit and effective regimens can be designed without this drug. Rifamycins are the drugs most important for sterilizing activity (i.e., cure) in TB treatment. Consider adding a 4th drug if patient has high burden of disease.

Abbreviations: UD, usual dose; UNL, upper normal limit.

TABLE 15 NOTES

1-Some of these recommendations differ or are not addressed by 2016 ATS/CDC/IDSA drug-susceptible TB guidelines. Drug-susceptibility testing for second-line drugs should be requested if these agents are used.

2-Limited availability

3-Associated with peripheral neuropathy. Add B6 ≥50 mg/daily

4-Associated with irreversible peripheral and optic neuritis. Add B6 ≥ 50 mg/daily

5-Associated with otovestibular toxicity

6-These recommendations are meant for patients with known drug-susceptible TB or at low risk for drug-resistant TB

D. Drug Resistance

Seek expert consultation for all patients with suspected or proven drug-resistant TB. Treatment of TB caused by drug-resistant organisms should be done by or in close consultation with an expert in the management of these difficult situations. INH-resistant TB is the most common form of drug-resistant TB (with a global prevalence of >10%). Newly updated ATS/CDC/IDSA recommendations for the treatment of drug-resistant TB recommend the addition of later generation fluoroquinolones (i.e., levofloxacin or moxifloxacin) to rifampin, pyrazinamide, and ethambutol for the treatment of INH-resistant TB, although there are limited data on the benefit of the addition of the fluoroquinolone in these circumstances. Multidrug-resistant (MDR)-TB is defined as resistance to at least INH and rifampin. New and repurposed anti-TB drugs included in treatment regimens have provided new options for the treatment of MDR-TB. As noted, consultation with an expert is required for MDR-TB and other drug-resistant TB cases. Second line treatment regimens often represent the patient's last best hope for being cured. Inappropriate management can have life-threatening consequences . See Appendix and/or website for making contact with an appropriate expert in your county:

https://dph.georgia.gov/district-health-directors

E. Monitoring Patients on Therapy for Response and Adverse Events

1. Response to Treatment

a. For patients with pulmonary TB, obtain sputum for AFB smear and culture at least monthly until two consecutive sputum samples are culture negative. Some authorities prefer to obtain monthly AFB sputum smear and cultures throughout the course of therapy.

b. Patients with cavitary pulmonary TB who have a positive 2 -month sputum culture are at increased risk for relapse if treated with only 6 months of therapy. If the **2-month culture** remains positive or if symptoms do not resolve, request repeat drug susceptibility testing to evaluate for acquired drug resistance. Additionally, review information related to treatment adherence. For any patient receiving self-administered therapy (this should be very rare as DOT is our standard of care) who has a positive 2-month culture, DOT should be initiated.

c. For patients with drug susceptible disease who have **positive 2-month culture and have cavitary disease on their initial CXR,** the continuation phase should be increased to 7 months so that they receive a total of 9 months of therapy.

d. Factors to be considered in deciding whether to prolong treatment in patients with <u>either</u> cavitation on initial CXR or a positive culture after 2 months of therapy (but not

both) include being more than 10% underweight at diagnosis, having HIV infection or having extensive involvement on CXR.

e. HIV testing should be performed on all persons diagnosed with TB.

2. Monitoring for Adverse Reactions

a. Obtain the following baseline measurements to detect any abnormality that would complicate the regimen or necessitate its modification:

- Hepatic enzyme (e.g., AST) level, bilirubin, serum creatinine, complete blood count and platelet count.
- Baseline visual acuity (if EMB is used)
- Baseline audiometry (if Amikacin is used).
- CD4 count and HIV viral load for patients with HIV infection.

b. Patients with epidemiologic risk factors for hepatitis B or C (e.g., injection drug use, birth in Asia or Africa, HIV infection) should have serologic tests for these viruses performed.

c. All patients should be seen at least monthly and questioned about potential adverse reactions. If symptoms suggesting drug toxicity occur, appropriate laboratory testing should be performed to confirm or exclude such toxicity. Patients should be instructed to report symptoms of hepatitis (which can be induced by INH, RIF and/or

PZA) immediately. Such symptoms include nausea, loss of appetite, vomiting, jaundice (dark urine, yellow skin), malaise, unexplained fever for ≥ 3 days, or abdominal tenderness. If patients have jaundice or symptoms of liver disease, discontinue medications immediately and consult a specialist.

d. Routine monthly laboratory monitoring is generally not required for those with normal baseline and no underlying disease. Monitor hepatic enzymes monthly if baseline levels are elevated, and for those with HIV infection, history of alcoholism, chronic liver disease, concomitant use of other drugs which can cause hepatotoxicity, or pregnancy. At least 20% of patients will have elevated hepatic enzymes; asymptomatic elevation less than five times the upper limit of normal is not an indication to stop treatment in asymptomatic patients. If patients have jaundice or symptomatic liver disease, discontinue medications immediately and consult a specialist

e. Patients receiving EMB should be questioned regarding visual disturbances at monthly intervals; monthly repeat testing of visual acuity and color vision is recommended for patients receiving an EMB dose exceeding 15–20 mg/kg (recommended range) and for patients receiving EMB for more than two months.

f. Pyridoxine will usually prevent INH-induced neurotoxicity (peripheral neuropathy).

g. Hyperuricemia may occur in patients on PZA but acute gout is uncommon. Asymptomatic hyperuricemia is not an indication for discontinuing the drug.

F. TB and HIV

HIV is the most important risk factor for active TB disease and TB-related mortality. TB is one of the few co-infections occurring in HIV-infected persons which is transmissible, curable and preventable. Importantly, HIV is a risk factor for active TB across all CD4 count levels.

Persons with HIV infection may have diminished (or absent) tuberculin skin test reaction and/or negative IGRA because of immunosuppression. Therefore, tuberculin reactions of $\geq$ 5 mm of induration are considered indicative of TB infection in an HIV-infected individual (see page 7). Standard IGRA cut-offs apply for patients with HIV despite reduced sensitivity of IGRA test among patients with HIV.

Because HIV status is a critical factor in the treatment of TB, HIV counseling and testing should be offered to all patients with proven or suspected active TB disease.

The clinical presentation of TB in a person living with HIV may differ from that in persons without HIV. Apical pulmonary disease with cavitation, a classic finding in immunologically competent persons, is less common among persons living with HIV, especially among those with low CD4 counts. HIV-infected patients may present with infiltrates in any lung zone and/or with mediastinal

or hilar lymphadenopathy. Extrapulmonary and disseminated TB are common among HIV-infected TB patients.

Treatment for Individuals with TB & HIV

1. The treatment of TB in persons living with HIV is similar to that for patients without HIV infection. However, intermittent therapy should be avoided, and twice-weekly regimens are contraindicated.

2. Persons living with HIV with active TB disease should be initiated on a 4-drug treatment regimen (INH, RIF (or Rifabutin), PZA and EMB) and pyridoxine as outlined in Table 7 on page 52, unless contraindications to medication exist. The use of antiretroviral therapy and TB medications is discussed on page 84. Persons living with HIV with drug-susceptible TB disease generally respond well to standard anti-TB drugs.

3. **Patients with HIV co-infection who have drug-susceptible TB disease should be treated for a minimum of 6 months with antituberculosis therapy. Duration of therapy should be prolonged for patients with delayed or slow response to therapy.** Persons living with HIV with TB disease should be monitored closely for clinical and bacteriological response. **Many experts extend treatment duration to 9 months for all patients with HIV**, but prolonged treatment beyond 6 months is especially recommended for patients who do not achieve HIV viral suppression during TB treatment and/or are slow to respond to therapy, including patients who remain culture positive after two months of therapy. Because

patient adherence to therapy is critical for good outcomes, DOT is the standard of care and is strongly recommended for all patients with active TB including persons living with HIV.

4. Persons living with HIV with TB disease should be monitored very closely during therapy as they appear to have a greater frequency of adverse reactions to anti-TB drugs.

5. HIV viral load should be monitored very closely during TB therapy given drug-drug interactions. Viral load should be measured prior to antiretroviral therapy (ART) initiation and within 2–4 weeks but no later than 8 weeks after ART initiation. An HIV viral load should be measured every 3 months among patients with stable ART regimen and suppressed viral load.

6. After treatment for TB disease is completed, patients should be reminded that if symptoms reappear, they should seek prompt medical evaluation.

G. Antiretroviral Therapy (ART) and Treatment of Persons Living with HIV with Active Tuberculosis Disease

Treatment of persons living with HIV with active TB disease should be carried out in consultation with a physician who has experience in the use of rifamycin drugs and antiretroviral agents. Recommendations on the treatment of TB in combination with antiretroviral therapy continue to evolve, and it is important to check for updated guidelines:

https://aidsinfo.nih.gov/guidelines

Antiretroviral therapy (ART) improves outcomes for persons living with HIV and decreases HIV-related mortality. Patients in the United States with tuberculosis disease who are HIV co-infected commonly have advanced HIV/AIDS with low CD4 counts and high plasma HIV RNA levels; all TB patients with HIV co-infection should receive treatment for HIV with ART.

***Timing of* ART.** Multiple studies have demonstrated the benefits of ART initiation among people living with HIV during TB treatment, including a reduction in mortality. However, the use of ART among persons living with HIV with active TB disease is complicated by overlapping toxicity profiles of some antituberculosis and antiretroviral drugs; complex drug-drug interactions; and the occurrence of 'paradoxical" or immune reconstitution inflammatory syndrome (IRIS). There are certain situations where ART therapy should be delayed. A study of people living with HIV with TB meningitis found that early ART was associated with an increase in severe adverse events and no mortality benefit. Thus, timing of ART initiation in HIV-TB patients should take into account both the degree of immune suppression and site of disease (see Table 16). Patients who are already on ART at the time of TB diagnosis, generally should be continued on the ART treatment (though ART regimen may need to be adjusted).

***Choice of* ART.** Because of the potential for significant drug interactions and overlapping toxicities, the choice of ART among persons living with HIV who have active TB disease should be made only after direct communication between HIV and tuberculosis care providers. Any change in either the TB medications or the ART regimen should be immediately shared between the 2 providers.

There are clinically important drug-drug interactions between the rifamycins (e.g., rifampin, rifabutin) and some of the antiretroviral drugs, especially integrase and protease inhibitors. The rifamycins are inducers of the cytochrome P450-3A (CYP3A) system in the liver and thereby decrease serum concentrations of drugs metabolized by this system including integrase and protease inhibitors. Rifampin is a potent inducer of the CYP3A, while rifabutin is a less potent inducer. Rifampin cannot be given with most protease inhibitors because it results in low serum levels of these drugs. Rifabutin has less of an effect and therefore can be used with certain protease inhibitors as described below. Rifampin and rifabutin can be given with certain integrase inhibitors.

The protease inhibitors also affect rifamycin metabolism and because the rifamycin metabolism is retarded by these drugs, the dose of rifabutin needs to be reduced in order to avoid rifabutin related toxicity.

Despite these drug-drug interactions, a rifamycin (rifampin or rifabutin) should ALWAYS be included in the treatment regiment for drug susceptible TB among persons living with HIV.

Rifampin can be given with the following antiretrovirals:

- MOST Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (e.g., zidovudine, lamivudine, emtricitabine, tenofovir disoproxil fumarate (TDF), abacavir). Tenofovir alafenamide (TAF) is not currently recommended for use in combination with rifamycins.
- SELECTED Non-nucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz only (all others are contraindicated for

coadministration with rifampin).

- Selected Integrase inhibitors: raltegravir and dolutegravir. The dose of raltegravir must be increased to 800 mg *bis in die* (twice daily) (BID) and dose of dolutegravir must be increased to 50 mg BID for patients on rifampin. Neither drug requires a dosing change when used with rifabutin.

Rifampin should **NOT** be used with the following:

- Tenofovir alafenamide (TAF)
- Protease inhibitors
- Nevirapine, etravirine, rilpivarine (NNRTIs)
- Bictegravir, elvitegravir

A summary of preferred treatment options for patients with tuberculosis disease who are HIV infected is shown in Tables 18 and 19. For additional information refer to updated HHS guidelines, visit: https://aidsinfo.nih.gov/guidelines

Table 16. When to start HIV therapy

HHS Panel Recommendations on treatment of Tuberculosis Disease with HIV co-infection: Timing of Antiretroviral Therapy (ART) Initiation relative to TB treatment	
CD4 count and/or clinical status at time of TB diagnosis	ART initiation
< 50 cells/mm3**	within 2 weeks of starting TB therapy.
≥ 50 cells/mm3**	by 8 to 12 weeks of starting TB therapy
Pregnant, any CD4 count	As early as feasible

** EXCEPTION: tuberculous meningitis. To avoid life-threatening CNS immune reconstitution inflammatory syndrome (IRIS), persons living with HIV and tuberculous meningitis should not be started on ART until AFTER 8 weeks of TB therapy

Above based on guidelines developed by the Department of Health and Human Services (DHHS) Panel on Guidelines for Use of Antiretroviral Agents for Adults and Adolescents and Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal Transmission in the United States, last reviewed and updated April 15, 2019 (https://aidsinfo.nih.gov/guidelines).

Table 17. What to start: Choice of TB therapy and Antiretroviral Therapy (ART) when treating co-infected patients

Principle: Despite drug interactions, a rifamycin (rifampin or rifabutin) should be included in TB regimens for patients receiving ART, with dosage adjustment if necessary (see Table SMR11 for dosage adjustments).
Option 1: Rifabutin-based ART regimen: Integrase inhibitor and 2 NRTIs Preferred ART choices: RAL or DTG + TDF/FTC Alternative ART choices: DTG + ABC/3TC **Contraindicated medications: TAF, other integrase inhibitors (Bictegravir, Elvitegravir)** **NOTE:** Dolutegravir has higher barrier to resistance compared to raltegravir. Dolutegravir is preferred when there is high risk poor adherence.
Option 2: Rifampin-based ART regimen: Efavirenz and 2 NRTIs Preferred ART choices: Efavirenz (NNRTI) + (TDF/FTC) Alternative ART choices: Efavirenz + ABC/3TC **Contraindicated medications: TAF, other NNRTIs: Nevaripine, Doravirine, Etravirine, or Rilpivirine** **NOTE:** Efavirenz is not a preferred regimen for patients initiating ART. Integrase inhibitors DTG and RAL are preferred ART regimens for patients initiating ART but require BID dosing if used with rifampin. Efavirenz has low barrier to resistance making this regimen less suitable when there is high risk for poor adherence. Efavirenz is associated with neuropsychiatric side-effects. Screening for depression and suicidality is recommended prior to and during efavirenz-based regimens. Efavirenz + ABC/3TC is associated with higher rates of virologic failure when baseline HIV viral load is >100.000 copies/ml.
Option 3: Rifabutin-based (dose adjusted) ART regimen: boosted PI and 2 NRTIs Preferred ART choices: ATV/r or ATV/c + TDF/FTC DRV/r or DRV/c + TDF/FTC Alternative ART choices: ABC/3TC in place of TDF/FTC **Contraindicated medications: TAF** **NOTE:** PI's have high barrier to resistance. However, given rifabutin is given at half-dose when used with PI's adherence to ART should be closely monitored. Poor adherence to PI's while on rifabutin increases risk for rifampin resistance.

(Table 17 continued)

Option 4: Rifampin-based ART regimen: dose adjusted integrase inhibitor + 2 NRTIs Preferred ART choices: RAL (dose adjusted) or DTG (dose adjusted)+ TDF/FTC Alternative ART choices: DTG (dose adjusted) + ABC/3TC **Contraindicated medications: TAF, other integrase inhibitors (Bictegravir, Elvitegravir)** **NOTE:** Dolutegravir has higher barrier to resistance compared to raltegravir. Dolutegravir is preferred when there is high risk poor adherence.
Choice for Pregnant women with active TB and HIV infection: TB regimen: Rifabutin –based (dose adjusted) ART regimen: boosted PI (ARV/r or DRV/r) [2] **+** 2 NRTIs (TDF/FTC or ABC/3TC) **NOTE:** Preliminary data suggest that there is an increased risk of neural tube defects in infants born to women who were receiving DTG at the time of conception. DTG is contraindicated for pregnant women during first trimester and for women who are planning to become pregnant or are not using effective contraception. DTG is the preferred integrase inhibitor after first trimester [1].

NRTIs: nucleoside/-tide reverse transcriptase inhibitors
NNRTIs: non-nucleoside reverse transcriptase inhibitors
PIs: protease inhibitors
/r: boosted with ritonavir
/c: boosted with cobicistat
TDF: Tenofovir disoproxil fumarate
TAF: Tenofovir alafenamide
FTC: Emtricitabine
3TC: Lamivudine
ABC: Abacavir
ATV/r: Atazanavir/ritonavir
DRV/r: Daraunavir/ritonavir
RAL: Raltegravir
DTG: Dolutegravir

Above based on guidelines developed by the Department of Health and Human Services (DHHS) Panel on Guidelines for Use of Antiretroviral Agents for Adults and Adolescents and Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal Transmission in the United States, last reviewed and updated April 15, 2019 (http://aidsinfo.nih.gov/guidelines).

1-Data on integrase inhibitors and pregnancy outcomes is rapidly evolving and DHHS guidelines are frequently updated.
2-Cobicistat is currently not recommended for pregnant women.

Table 18. Dosage Adjustments for ART and Rifamycins when used in Combination

	Rifampin (RIF)	Rifabutin (RBT)
Integrase Inhibitor		
Dolutegravir (DTG)*	RIF: no change (600 mg) DTG: increase to 50 mg BID	RBT: no change (300 mg) DTG: no change (50 mg)
Raltegravir (RAL)	RIF: no change (600 mg) RAL: increase to 800 mg bid	RBT: no change (300 mg) RAL: no change (400 mg bid)
Boosted PI		
ATV/r or /c, DRV/r or /c, LPV/r or /c	DO NOT USE	RBT: decrease to 150 mg/d PIs: no change
NNRTI		
Efavirenz (EFV)	RIF no change (600 mg) EFV: no change (600 mg qhs)	DO NOT USE

* Preliminary data suggest that there is an increased risk of neural tube defects in infants born to women who were receiving DTG at the time of conception. DTG is contraindicated for pregnant women during first trimester and for women who are planning to become pregnant or are not using effective contraception. DTG is the preferred integrase inhibitor after first trimester.

NNRTIs: non-nucleoside reverse transcriptase inhibitors
PIs: protease inhibitors
ATV/r: Atazanavir/ritonavir
DRV/r: Daraunavir/ritonavir
LPV/r: Lopinavir/ritonavir
RAL: Raltegravir
DTG: Dolutegravir
/c : boosted with cobicistat

Table 18 is based on guidelines developed by the Department of Health and Human Services (DHHS) Panel on Guidelines for Use of Antiretroviral Agents for Adults and Adolescents and Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal Transmission in the United States, last reviewed and updated April 15, 2019
(http://aidsinfo.nih.gov/guidelines).

1-Data on integrase inhibitors and pregnancy outcomes is rapidly evolving and DHHS guidelines are frequently updated.

2-Cobicistat is currently not recommended for pregnant women.

H. Immune Reconstitution Inflammatory Syndrome (IRIS) Associated with Initiation of Antiretroviral Therapy During the Course of TB Therapy

The temporary exacerbation of TB symptoms and lesions after initiation of antituberculosis therapy—known as a paradoxical reaction or immune reconstitution inflammatory syndrome (IRIS)—has been described as a rare occurrence in HIV-negative patients after the initiation of antituberculosis therapy. These "paradoxical reactions" are thought to be due to immune reconstitution and can occur among persons living with HIV who are started on antiretroviral therapy early in the course of antituberculosis therapy. After initial clinical improvement, paradoxical worsening of disease (or IRIS) developed in up to 36% of HIV infected TB patients on ART compared with 7% of HIV co-infected patients treated for TB but who did not receive ART [Narita et al.].

Paradoxical or immune reconstitution manifestations depend on anatomical site of disease (e.g., headache in patient with meningeal TB). Additionally, IRIS can occur in an anatomical site of known disease and/or anatomical sites not previously known to be involved (e.g., lymph node suppuration in patient without previous adenopathy), a process known as "unmasking". Of note, patients with HIV can have > 1 opportunistic infection and unmasking reactions can occur that are from previously unsuspected infections (e.g., cryptococcal meningitis). The paradoxical reactions are associated with increased reactivity on tuberculin skin testing and a significant reduction in HIV viral load.

IRIS may be self-limited and can last 10 to 40 days. Mild to moderate reactions can be managed by reassurance and non-steroidal anti-inflammatory drugs. Severe reactions included those characterized by marked increase in adenopathy causing an anatomic problem (e.g., compromised breathing, swallowing or movement of the neck, or expanding central nervous system lesions) can be managed with corticosteroids (with continuation of the anti-tuberculosis therapy and ART) starting at a dose of prednisone at 1.25–1.5 mg/kg per day for 2 weeks and then tapering the therapy over a period of 6 to 12 weeks (or longer).

For persons living with HIV with active TB disease and at high risk for developing TB-associated immune reconstitution inflammatory syndrome (TB-IRIS), pre-emptive prednisone is now recommended as adjunctive therapy with the initiation of antiretroviral therapy. “High-risk” for IRIS is defined as CD4 count ≤ 100 cells/mm3 and starting ART within 30 days of initiating treatment for active TB. The prednisone regimen consists of 40 mg daily for 2 weeks followed by 20 mg daily for 2 weeks. Pre-emptive prednisone therapy for IRIS prevention should NOT be offered to patients with active hepatitis B infection, Kaposi sarcoma, rifampin-resistant TB, or with poor response to TB treatment.

I. Treatment of Extrapulmonary TB (Table 19)

The basic principles that underlie the treatment of pulmonary TB also apply to extrapulmonary forms of the disease. A 6-month course of therapy is recommended for treating tuberculosis in-

volving any site with the exception of the meninges for which a 9 – to 12-month regimen is recommended. Prolongation of therapy also should be considered for patients with tuberculosis in any site that is slow to respond. The addition of corticosteroids is recommended for patients with meningitis as it decreases mortality as discussed below.

Lymphatic and hematogenous TB are especially common among persons with HIV infection. Central nervous system involvement has been reported and may be difficult to diagnose when it occurs in conjunction with other opportunistic CNS infections.

To establish the diagnosis of extrapulmonary TB, a variety of specimens including pleural fluid, peritoneal fluid, pleural and peritoneal biopsy specimens, lymph node tissue, bone marrow, bone, blood, urine, brain, or cerebrospinal fluid may need to be obtained for mycobacterial culture.

Specimens must be examined microscopically and sent for AFB culture, but the inability to demonstrate AFB on smear and the absence of granuloma formation does not exclude the diagnosis of TB. Surgery may be necessary to obtain specimens for diagnosis and to treat such processes as constrictive pericarditis or spinal cord compression from Pott's disease. Evidence-based guidelines for the treatment of extrapulmonary TB and adjunctive use of corticosteroids are shown in Table 20 on pages 88-89.

J. Adjunctive Use of Corticosteroid Therapy (Table 19)

Adjunct corticosteroid therapy is indicated in the treatment of tuberculous meningitis as its use along with appropriate anti-

tuberculosis drugs is associated with a lower mortality. For patients with tuberculous meningitis, dexamethasone or prednisolone is recommended for a total of 6 to 8 weeks. An initial dose of 8 mg per day of dexamethasone for children < 25 kg and 12 mg per day for children > 25 kg and adults can be used. The initial dose is given for 3 weeks and then the dose should be tapered during the following 3 weeks. Adjunctive corticosteroids in treatment of pericardial tuberculosis did not reduce mortality, tamponade or constrictive physiology in a large randomized clinical trial and are thus no longer routinely recommended. Some experts would use corticosteroids in selected patients with TB pericarditis: those with large effusions and/or high levels of inflammation in pericardial fluid.

Table 19. Guidelines for Treatment of Extrapulmonary* Tuberculosis: Length of therapy and Adjunctive Use of Corticosteroids

Site	Length of therapy with standard regimen and normal host (months)	Corticosteroids	Steroid dosing A (adults) C (children)	Additional management considerations
Lymph node	6	Not recommended		Pursue microbiologic proof of diagnosis prior to starting Rx
Bone (non-vertebral) and joint	6 to 9	Not recommended		Extend to 12 months if hardware is present
Spine without meningitis	6 to 9	Not recommended for TB rx but may be indicated for cord compression		Most spine infection can be cured with medical Rx. Surgery indicated for relief of cord compression, progressive disease despite medical therapy, instability of the spine.
Spine with meningitis	9 to 12	Strongly recommended	A and C >= 25kg: 12 mg/day of dexamethasone x 3 weeks followed by 3-week taper C < 25kg: 8 mg /day of dexamethasone for 3 weeks followed by 3-week taper	
CNS tuberculosis including meningitis	9 to 12	Strongly recommended		Negative CSF culture or PCR test does NOT exclude this diagnosis Follow CSF profile for response to therapy
Pleural disease	6	Not recommended		Empyema may require decortication

(Table 19. continued)

Site	Length of therapy with standard regimen and normal host (months)	Corticosteroids	Steroid dosing A (adults) C (children)	Additional management considerations
Pericarditis	6	NO LONGER routinely RECOMMENDED		Consider steroids for patients at highest risk of later constriction: large pericardial effusions high levels of inflammatory cells or markers in pericardial fluid those with early signs of constriction
Disseminated disease	6	Not recommended		Obtain cultures from blood, urine and sputum in addition to clinically apparent sites of disease.
Genitourinary	6	Not recommended		
Peritoneal	6	Not recommended		

*ALWAYS EVALUATE for concomitant pulmonary involvement with respiratory samples for smear and culture (regardless of chest imaging findings).

Based on CID 2016:63 (1 October) • Nahid et al

VI. Pregnancy and TB

A. Treatment for LTBI and Risk Factors

A pregnant woman with a positive skin test and negative chest x-ray (a lead apron should cover the entire abdomen during x-ray) should be started on treatment for LTBI with INH (and B6) *immediately* if they have one or more of the following risk factors:

- Documented recent tuberculin skin test conversion;
- HIV infection not receiving antiretroviral therapy or those with HIV risk factors who refuse HIV testing;
- Close contact of patient with AFB smear-positive pulmonary TB.

Pyridoxine (25–50 mg/d) is recommended for all pregnant or nursing mothers who receive INH. All pregnant and immediate post-partum patients should have a baseline and monthly liver function tests (e.g., AST or ALT) performed while on therapy. Treatment of other pregnant positive reactors can be deferred until several months after the completion of pregnancy.

Among HIV-infected pregnant women on antiretroviral therapy, isoniazid preventive therapy is not recommended until after delivery (e.g., 3 months post-partum) unless they are close contacts of a known patient with active TB disease. This is due to recent study that demonstrated that he risks associated with initiation of isoniazid preventive therapy during pregnancy appeared to be greater than those associated with initiation of therapy during the postpartum period.

B. Treatment of Active TB in Pregnancy

TB disease discovered during pregnancy should be treated without delay. Because of the risk for tuberculosis to the fetus, treatment of TB in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. Three sputum samples should be submitted for examination. The outcome of the cultures and susceptibility test results will determine the regimen for continuation of treatment.

1. Drug Treatment in Pregnancy

a. The initial treatment regimen usually consists of INH, RIF and EMB; consideration should be given to including PZA.

b. Although detailed teratogenicity data are not available, PZA can probably be used safely during pregnancy and is recommended for use by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD). In some U.S. jurisdictions, PZA has not been routinely recommended. PZA should be included in the initial regimen for HIV seropostive women and for HIV seronegative women who are thought to be at high risk for drug resistant TB. If PZA is not included in the initial treatment regimen, the minimum duration of therapy is 9 months.

c. Pyridoxine (Vitamin B6) (25 mg/d) is recommended for all pregnant women taking INH.

d. ***Avoid:*** Aminoglycosides (e.g., streptomycin, amikacin) are contraindicated for all pregnant women because of po-

tential adverse effects on the fetus. Fluoroquinolones (e.g., levofloxacin, moxifloxacin) have been associated with arthropathies in young animals; therefore, they should be avoided if possible in pregnant women.

2. Breast Feeding

The small concentrations of first line TB drugs in breast milk do not have a toxic effect on nursing newborns and **breast feeding should not be discouraged.** Conversely, drugs in breast milk should not be considered to serve as effective treatment for disease or as treatment of LTBI in a nursing infant.

Table 20. Use of Anti-TB Medications in Special Situations: Pregnancy, Tuberculous Meningitis and Renal Failure

Drug	Safety in Pregnancy (1)	Central Nervous System Penetration (2)	Dosage in Renal Insufficiency (3)
Isoniazid	Safe (4)	Good (20-100%)	No change
Rifampin	Safe (isolated reports of mal-formation)	Fair, Inflamed meninges (10-20%)	No change
Pyrazinamide	Caution (1)	Good (75-100%)	Decrease dose/ Increase interval
Ethambutol	Safe	Inflamed meninges only (4-64%)	Decrease dose/ Increase interval
Aminoglycosides (Streptomycin, Kanamycin, Amikacin)	Avoid	Poor (5)	Decrease dose/ Increase interval (6)
Capreomycin	Avoid	Poor	Decrease dose/ Increase interval (6)
Levofloxacin, Moxifloxacin Gatifloxacin	Do not use	Fair (5-10%) Inflamed meninges (50-90%)	Decrease dose/ Increase interval (7)
Ethionamide	Do not use	Good (100%)	No change
Cycloserine	Avoid	Good (50-100%)	Decrease dose/ Increase interval
Para-amino-sili-cylic acid	Safe	Inflamed meninges only (50-100%)	Incomplete data
Clofazimine	Avoid	Unknown	Probably no change

Safe: Drug has not been demonstrated to have teratogenic effects.

Avoid: Limited data on safety or for aminoglycosides associated with hearing impairment and/or other toxicity.

Do Not Use: Associated with premature labor, congenital malformations or teratogenicity.

NOTES: Table 20 Special Situations

(1) As with all medications given during pregnancy, anti-TB drugs should be used with caution. The risk of TB to the fetus far outweighs the risk of medications. Pregnant patients with active TB should be treated. Data are limited on the safety of some anti-TB drugs during pregnancy. Table 20 presents a consensus of published data and recommendations. Although detailed teratogenic data is not available, PZA can probably be used safely for pregnant patients. Concentrations of anti-TB drugs in breast milk are low; treatment with these medications is not a contraindication to breastfeeding. (Conversely, medication present in breast milk is not sufficient to prevent or treat TB in the newborn.) Consult a medical expert when treating a pregnant patient who has TB. For treatment of LTBI, most authorities recommend beginning INH several months after delivery, unless the woman is at high risk for progression to active TB (e.g., recent TST or IGRA conversion, HIV-infected).

(2) Steroid treatment appears to improve outcome in TB meningitis, particularly in patients with altered mental status.

(3) If possible, monitor serum drug levels of patients with renal insufficiency. See page 71 for dosage.

(4) Supplement with pyridoxine (Vitamin B6) during pregnancy.

(5) Has been used intrathecally; efficacy not documented.

(6) Avoid aminoglycosides and capreomycin in patients with reversible renal damage, if possible.

(7) Fluoroquinolones may accumulate in renal failure and are poorly removed by dialysis. Dose adjustment indicated.

VII. Childhood Tuberculosis

The basic principles for treatment of TB disease and infection in children and adolescents are similar to adults. The objective of treatment is to kill the tuberculous bacilli in the shortest amount of time while preventing the development of resistance. Dosage adjustments of medications may often be required based on weight. When possible, crushed tablets or the mixed contents of capsules are preferred over suspensions that may be difficult to access and may contain fewer desirable additives.

Either TST or immunologic-based testing (IGRAs) may be used to aid in LTBI or TB disease diagnosis in immune competent children age 2 years or older. For children under 2 years of age, TST is preferred; however, if the child has a negative TST but is at high risk for TB disease or LTBI, then an IGRA may be performed. The involvement of a provider with expertise in management of children with tuberculosis infection or disease is beneficial in guiding diagnostic evaluation and treatment.

A. Management Considerations

1. TB disease in infants and children younger than 4 years of age is much more likely to disseminate; therefore, prompt evaluation and treatment should be started when the diagnosis is suspected.

2. Mycobacterial culture of respiratory specimens for children with suspected pulmonary TB is recommended. Acceptable specimens include induced sputa or early morning gastric

aspirates on 3 consecutive days for children who cannot produce sputa. In cases when the adult source case is known, it is acceptable to rely on the results of susceptibility tests of specimens from the adult source case to guide the treatment regimen. However, when the *M. tuberculosis* isolate from the presumed source patient is not available or in cases of suspected drug-resistant TB, obtaining induced sputa or early morning gastric aspirates from the young child should be performed. In certain situations, bronchoalveolar lavage or tissue biopsy may be considered.

3. Primary intrathoracic TB (parenchymal infiltration, hilar adenopathy, or both, in a child with evidence of tuberculosis exposure) should be treated in the same manner as pulmonary TB.

4. An empiric regimen of four drugs (INH, RIF, PZA, EMB) for 2 months and RIF and INH for the remaining 4 months when the possibility of drug resistance is low is recommended. A three-drug regimen (INH, RIF, PZA) can be used as initial therapy when the isolate (i.e., from source TB case) is known to be fully drug susceptible. Children and adolescents with "adult-type" tuberculosis consisting of cavitation and AFB positive sputum samples should receive a 4-drug regimen initially until susceptibility is proven. The persistence of cavitary lesions and/or a positive sputum culture after 2 months of therapy may warrant extension to a 9-month course of therapy.

   When clinical or epidemiologic circumstances suggest an increased probability of INH resistance, EMB can be used

safely at a dose of 15–20 mg/kg per day as a fourth drug, even in children too young for routine eye testing. Streptomycin, kanamycin or amikacin can also be used as a fourth drug when necessary. Either an aminoglycoside or ethionamide should be used as the fourth drug in cases of TB meningitis.

5. In general, extrapulmonary TB, including cervical adenopathy (scrofula), can be treated with the same regimen as pulmonary TB (i.e., 6 months for drug-susceptible disease). Exceptions include TB meningitis for which 12 months of therapy is currently recommended.

6. Directly observed therapy is the standard of care for all children. HIV testing should be performed on all individuals with TB disease (including children) as the treatment regimen (including need for antiretroviral therapy) is altered with HIV infection.

7. Clinical and radiographic examinations may be monitored for response to therapy. However, resolution of abnormal findings on chest radiography with pulmonary or intrathoracic lymphadenopathy may lag behind clinical response. Chest radiography is usually not performed at the conclusion of a successful course of treatment and should not be used as a criterion for discontinuing anti-TB drugs.

8. Management of the newborn infant whose mother or other caregiver is suspected of having TB is based on individual considerations. Separation of the mother (or caregiver) and

infant should be minimized, if possible. Differing circumstances and resulting recommendations are as follows:

a. ***Mother or other caregiver who has a positive tuberculin skin test or IGRA and normal chest radiography.*** If, after investigation, no evidence of active TB disease is found in the mother or caregiver to whom the infant is exposed, separation of mother or caregiver and infant is not indicated. These mothers may breastfeed their infants. Evaluation of all contacts should be performed to attempt to identify a source case.

b. ***Mother or other caregiver who has abnormal chest radiography suggestive of tuberculosis disease but is judged to be noninfectious at delivery.*** The situation in which a mother or caregiver's history, physical examination, and sputa examination do not suggest active disease may be considered to be a low risk exposure and the separation of mother/ caregiver and the infant is not necessary. The mother/caregiver should receive therapy and contacts should be evaluated with a TST or IGRA to attempt to identify a source case. The infant should be followed closely by a pediatric provider.

c. ***Mother who has active TB disease and is suspected of being infectious at the time of delivery***. The infant should be assessed for evidence of congenital tuberculosis and the mother/caregiver should be evaluated for HIV infection. A healthcare provider with expertise in the treatment of infants with congenital tuberculosis should be

consulted to assist with management of the infant's anti-TB regimen. If congenital tuberculosis is not suspected, the infant should receive INH (10 mg/kg/ dose) daily until the infant is 3 – 4 months of age when a TST should be placed. If the TST result is reactive, an evaluation for tuberculosis disease should be conducted. If TB disease is excluded, the infant should continue to receive INH until 9 months of age with monthly assessments to complete treatment for LTBI. If the TST at 3–4 months of age is nonreactive and the mother/ caregiver's adherence to therapy can be documented and is no longer infectious, the infant's INH may be discontinued.

For a mother/caregiver who has active TB disease and is infectious, the mother/caregiver and infant should be separated until the mother/caregiver and infant have received appropriate antituberculosis therapy. The mother/caregiver should wear a mask and follow appropriate infection control procedures until she/he has been judged to be noninfectious. The mother/caregiver should be separated from the infant in situations where infection with MDR TB is possible and/or adherence to therapy cannot be documented. BCG immunization may be considered for the infant in these situations. Women with tuberculosis disease who have received 2 weeks of appropriate therapy and who are not considered to be infectious may breastfeed. A healthcare provider with expertise in tuberculosis should be consulted to assist with recommendations in individual situations when a woman receiving antituberculosis therapy wishes to provide human milk to an infant.

VIII. Tuberculosis and Long-Term Care Facilities

TB remains a problem in older individuals who may have been infected many years ago and did not develop active disease at the time. Also, there is increasing documentation of outbreaks of TB occurring in nursing home residents when a patient with TB disease infects a population of older people who are newly exposed to that case.

TB control in nursing homes and long-term care facilities must begin with a careful assessment of TB status upon admission, including a diagnostic test for LTBI (TST or IGRA). For those with a positive diagnostic test for LTBI, an assessment and chest x-ray should be performed as described above to exclude active TB disease.

Since people over 50 years old may have diminished skin test reactivity, the two-step technique (see page 10) of tuberculin skin testing is recommended upon admission to the nursing home if the TST is the diagnostic test being performed to screen for LTBI. A "booster effect" with the TST has been noted in elderly persons in whom the delayed type hypersensitivity (DTH) reaction to tuberculin may have waned over the years. In these situations, an initial tuberculin skin test may demonstrate a negative reaction, but it boosts the immune system so that subsequent tuberculin skin tests may be increased in size and may be interpreted as positive. This "boosted" response is considered as the valid baseline for the individual and thought to represent latent TB infection (after active disease is excluded).

Residents of nursing homes or long-term care facilities whose baseline two-step skin tests are negative (or whose baseline IGRA is negative if the IGRA is being used to screen for LTBI) on admission should have repeat testing performed when an exposure to a case of potentially infectious TB has occurred.

- Any person who converts a TST or IGRA from negative to positive should be considered for treatment of LTBI after active TB is ruled out (by chest x-ray at a minimum and sputum specimen if indicated).
- Any resident with symptoms of TB regardless of TST (or IGRA) results should have a chest x-ray performed to evaluate for active TB disease.
- Treatment of active TB disease (Class III) is the same as that used for younger adults.

Employees of nursing homes or long-term care facilities should have two-step tuberculin testing when they start to work in the nursing home if the TST is used for testing of health care workers (if they have not had a TST in the year prior to initiating employment). The frequency of subsequent testing of healthcare workers is described on page 102. Employees who are TST (or IGRA) positive at baseline should be evaluated for treatment of LTBI (see pages 25–27). In addition, those with a recent TST conversion should be strongly encouraged to take treatment for LTBI after active TB is excluded. Routine annual symptom screening for previously positive TST employees is recommended instead of an annual CXR.

IX. BCG Vaccination

Bacille Calmette-Guerin (BCG) vaccine is one of the most commonly used vaccines in the world and is given in the vast majority of low- and middle-income countries. BCG is recommended in higher TB incidence areas because it has a documented protective effect against TB meningitis and disseminated TB in young children. It does not prevent primary infection and, more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community. The impact of BCG vaccination on transmission of *M. tuberculosis* is therefore very limited (or there is no impact). BCG has not impacted the global epidemiology of TB. Because of variable efficacy, *BCG is NOT recommended for use in the U.S.* BCG is not a contraindication to a TST but as noted there can be cross reactions between BCG and the TST. The primary advantage of IGRAs is that they do not cross react with BCG. Interpretation of a tuberculin skin test reaction is not changed for patients who have received BCG. A reaction of ≥ 10 mm (≥ 5mm in HIV-infected persons) of induration should be considered infection with *M. tuberculosis* because:

- Conversion rates after BCG vaccination are not 100%;
- The mean reaction size among BCG vaccines are often less than 10 mm (a large reaction is more likely to be due to infection with M. tuberculosis than BCG vaccination);
- Tuberculin sensitivity tends to wane considerably after BCG vaccination; and,

- BCG is usually given in high TB incidence countries, so assume that the reaction is from infection, not vaccination.

Since many BCG-vaccinated persons come from areas of high TB incidence, it is important that persons with a positive TST be evaluated for presence of TB disease and managed accordingly. Appropriate follow-up includes a careful medical history, CXR to rule out active TB disease, and evaluation for treatment of LTBI. An IGRA is the preferred LTBI test among individuals with a history of BCG vaccination but a TST is an acceptable test in BCG-vaccinated persons.

X. TB Infection Control: Hospital Isolation Procedures

Effective infection control efforts are essential in preventing nosocomial transmission of TB. A hierarchy of control measures is recommended to prevent TB transmission in health care facilities.

A. Administrative Controls

Administrative controls are most important and include measures to reduce the risk of exposure to persons with infectious TB; this includes careful screening, early identification and treatment of patients with TB. A high index of suspicion is critical. Patients with or at risk for TB need to be isolated upon admission (placed in a negative pressure airborne infection isolation [AII] room). Unsuspected patients with active TB disease and misdiagnosis (especially among HIV-infected patients who may have "atypical" or non-classical presentations) have led to nosocomial transmission at a number of hospitals (as well as at correctional institutions and other health care facilities).

Grady Memorial Hospital in Atlanta has prevented nosocomial transmission in large part by the effective use of administrative controls. Careful screening of patients and isolation of those at risk for TB have been accomplished by the introduction of an expanded respiratory isolation policy.

B. Surveillance for Health Care Workers

In general, the risk of occupational acquisition of TB is low among the large majority of US health care workers (HCWs) given the changing epidemiology of the disease in the U.S. The risk of TB exposure among most US-based health care workers (HCWs) is similar to the general population given the decreased TB incidence and improved hospital infection control measures in this country. Given the low risk among the vast majority of US HCWs, serial TB testing for US-based HCWs has been associated with a high rate of false-positive conversions. Therefore, CDC guidelines were updated in 2019 and no longer recommend routine serial testing for most US-based HCWs [MMWR Morb Mortal Wkly Rep 2019;68:439–44.]. Guidelines continue to recommend baseline screening and testing in addition to an individual TB risk assessment to aid in TB test interpretation. All HCWs should have baseline test for LTBI (unless documented to be previously TST or IGRA positive or documented to have had prior TB disease). Two-step tuberculin skin testing upon employment is recommended unless the HCW had a TST in the prior year. Updated guidelines suggest health care facilities may consider serial testing in selected situations, such professionals at increased risk for exposure or selected areas in the facility where transmission has occurred and/or infection control lapses occur and infectious patients were present. If serial testing of HCWs is needed, we recommend the use of the TST rather than an IGRA for reasons described above (see pages 19–21). HCWs should be educated about the basic concepts of TB transmission and pathogenesis, infection control practices, signs and symptoms of TB, and risk for TB exposure in the facility annually.

Following exposure, HCWs should be evaluated for signs and symptoms of TB. Those with a negative baseline test and no prior LTBI or TB should have a TST (or IGRA) performed. If the test is negative, a repeat test 8-10 weeks after the last exposure is recommended.

Any worker who develops symptoms of active TB disease or whose test for LTBI (TST or IGRA) converts to positive should be evaluated promptly. Health care workers with recent TB infection on the basis of a conversion to a positive test for LTBI (regardless of age) and no evidence of active disease should be encouraged to take treatment for LTBI (see pages 24–36).

Grady Hospital TB Isolation Policy

Criteria for Isolation	Length of Isolation
1. Active Pulmonary TB	Duration of hospitalization if less than 4 weeks; if >4 weeks must have clinical response, drug susceptibility data and 2 negative AFB sputum smears
2. "Rule Out" TB Any patient who has sputum for AFB collected or pulmonary TB is in the differential diagnosis.	Until 2 sputum AFB smears are negative
3. HIV+ patient admitted with abnormal CXR	Until 2 sputum AFB smears are negative

C. Environmental Controls

Patients admitted to health care facilities with suspected or confirmed TB should be placed in an airborne infection isolation (AII) room (i.e., negative pressure rooms with ≥ 6 air changes per hour; ≥ 12 for new construction); air from AII rooms should be exhausted directly to the outside or through a HEPA filter before being recirculated.

D. Personal Respiratory Protection

Appropriate respirator masks should be worn by health care workers when entering AII rooms or performing high risk procedures such as sputum induction and bronchoscopy. Use of a N-95 respirator by health care workers is the minimum level of protection required by OSHA.

XI. Community Tuberculosis Control

A. TB Surveillance in Georgia

TB is a reportable disease in Georgia. All Georgia physicians, laboratories, and other health care providers are required by law to immediately report clinical and laboratory–confirmed TB (including extrapulmonary) cases under their care to Georgia public health authorities. TB cases may be directly reported to a County Health Department, a District Health Office, or to the State TB Program and TB Epidemiology Section of the Georgia Department of Public Health (GDPH), which is responsible for the systematic collection of all reported TB cases in the state. Immediate reporting of TB cases enables public health staff to follow up with patients, administer directly observed therapy (DOT), monitor TB treatment until completion, evaluate and screen individuals exposed to a TB case, and control TB outbreaks.

Cases may be reported electronically through **SendSS** at http://sendss.state.ga.us, by calling 1-866-782-4584, or by calling the public health department in the county where the patient resides (see Appendix). Hospital infection control personnel, as well as public health nurses, outreach staff, epidemiologists, and communicable disease specialists involved in disease surveillance are encouraged to report TB through SendSS and register to become a SendSS user by logging into the system's Web site at: http://sendss.state.ga.us then selecting TB from the list of reportable diseases.

Public health authorities collect data about reported TB cases including demographic, clinical, risk factor, and contact infor-

mation, which are analyzed to describe the distribution of the disease among Georgia's population, identify high risk groups and TB clusters, describe trends in morbidity, mortality, drug resistance patterns, treatment outcomes, and infection rates among contacts to TB cases. The data are used at state and local levels to guide policy and decision making, set priorities for program interventions, evaluate program performance for the prevention and control of TB in Georgia, and educate key stakeholders and the general public on TB. Georgia's TB surveillance data are transmitted electronically to the U.S. Centers for Disease Control and Prevention (CDC) and become part of the national TB surveillance database.

Latent TB infection in young children (under age 5) is also reportable in Georgia. Young children with latent TB infection are at very high risk of developing active TB including TB meningitis. These children have, by definition, been recently exposed to an adult with contagious TB. And there are often additional young children who have also been exposed. Rapid public health response will address both of these concerns.

- **ALL Latent TB infection (LTBI) in children under 5 years of age** must be reported to the public health department in the county where the patient resides.
- **A source Case Investigation** will be conducted by the health department when LTBI is found in a child under 5 years old.

B. TB Case Definitions for Public Health Surveillance

GDPH utilizes the 2009 Council of State and Territorial Epidemiologists (CSTE) case definition for tuberculosis (Position Statement 09-ID-65) that can be accessed at: https://wwwn.cdc.gov/nndss/conditions/tuberculosis/case-definition/2009/

Clinical case definition—A case that meets all of the following criteria:

- A positive tuberculin skin test or positive interferon gamma release assay for M. tuberculosis
- Signs and symptoms compatible with TB (abnormal chest imaging study or clinical evidence of current disease)
- Treatment with two or more anti-TB medications
- A completed diagnostic evaluation

Laboratory criteria for diagnosis:

- Isolation of M. tuberculosis complex on a culture from a clinical specimen, or
- Demonstration of M. tuberculosis complex from a clinical specimen by nucleic acid amplification test

Confirmed case: A case that meets the clinical case definition or is laboratory confirmed

C. Role of the Health Department

Health department staff are trained and experienced in contact investigation, provision of directly observed treatment of latent TB infection (LTBI) and directly observed therapy (DOT) for the treatment of patients with active disease. Physicians with expertise in treating TB are part of the health department team in each county. **DOT is the standard of care for all patients with TB disease in Georgia and is strongly recommended for all patients with tuberculosis to facilitate adherence and completion of therapy.**

Early reporting of suspected or confirmed TB cases is important for control of TB and is required by law. Reporting gives the clinician access to the resources of the public health department for assistance in case management and contact investigation and consultation with expert TB clinicians. Contact investigations are indicated to determine those who have been exposed to infectious TB patients so close contacts can be evaluated for evidence of active or latent TB and treatment provided as indicated.

Tuberculosis services (radiology, medical consultations, DOT, etc.) are available in every health district. All TB medications are provided by the state pharmacy free of charge.

D. Hospital Discharge Planning for Patients with Suspected or Proven TB

For TB control efforts, it is important that there be a smooth transition from the in-patient to the out-patient setting and close

cooperation and coordination of activities among the wide variety of organizations involved in TB patient care, education and TB control.

Minimum Criteria for discharge planning:

- Patients have been initiated on treatment with an appropriate anti-TB regimen (e.g., 4-drug regimen) and are medically ready for discharge.
- All TB patients have their discharge endorsed in the chart *prior to discharge* by the hospital social worker and **the local health department liaison**.

E. The U.S.-Mexico Binational Tuberculosis Referral Program (CureTB)

CureTB (www.curetb.org) is a referral and continuity of care program for tuberculosis patients and their contacts who travel between the United States and Mexico. Services are available for patients, their families and providers from any state in the United States or Mexico. CureTB also provides services for patients travelling to other countries.

CureTB facilitates and supports continuity of care for individuals with active tuberculosis disease and their contacts and provides linkages to ongoing care and follow-up for all referred patients. CureTB accepts referrals from health departments, correctional facilities, and other entities that diagnose or treat patients with tuberculosis.

The Binational Card is a tool to help mobile patients and their

families connect with CureTB when they arrive at their next destination. They can also give the card to their provider to connect with CureTB to obtain the latest clinical information. The card is easy to carry and has the CureTB 1-800 number, reachable from inside or outside the U.S.

To request binational cards

- Telephone: (619) 542-4013
- Email: curetb.hhsa@sdcounty.ca.gov

CureTB accepts referrals for:

- Persons with active Tuberculosis and those suspected of having TB
- Contact Notification
- Source Case Finding
- Clinical History Request

To Submit a CureTB Referral

You can submit a CureTB referral in three ways. Use a referral form and attach hard copies of relevant clinical information whenever possible. Visit the www.curetb.org website for additional information regarding the relevant clinical information for the different types of referral.

1. Fax: (619) 692-8020
2. Email: curetb.hhsa@sdcounty.ca.gov
3. Telephone: (619) 542-4013

XII. Alternative Housing Program for Homeless TB Patients in Georgia

The GA TB program has a contract with the American Lung Association of GA (ALAG) to provide alternative housing and basic necessities (meals, personal supplies, transportation, and social services) for patients without these resources.

Hundreds of tuberculosis patients have utilized the Alternative Housing Program since 1996. The Program utilizes inexpensive motels, trailers, duplexes, apartments and houses. The Health Departments provide DOT and transportation to TB and Ryan White clinic appointments. In 2005, ALAG began to extend its services to provide housing services for non-infectious clients in addition to infectious clients.

The plan to place homeless patients in area housing requires frequent communication among ALAG area hospitals, and county TB Clinics. In addition to the formal agreements between ALAG and rental establishments, letters of agreements are on file from all participating districts. These letters demonstrate a commitment to the Alternative Housing Program by each District TB Program. Monthly patient care reviews are mandatory to ensure that continuity of care is maintained and other needed services are being provided. A designated Outreach Worker (ORW) provide DOT and patient follow-up.

XIII. Georgia Department of Public Health (DPH) Community Guidelines for Respiratory Isolation of Patients With Active TB in the Community

In setting guidelines, the Georgia Department of Public Health (DPH) follows CDC recommendations that a stepwise approach be used to seek the least intrusive policy that is consistent with maintaining the health of the community. These guidelines provide a framework for clinical management of patients with TB. The management of each patient must be customized to the individual's circumstances, living environment, and compliance with TB therapy. The guidelines classify active TB cases into three grades of infectiousness and two grades of organism resistance. They recommend appropriate levels of housing options and degrees of respiratory isolation for each grade of infectiousness and resistance.

Infectiousness is graded by AFB smear, TB culture results, clinical improvement in response to medical therapy, and evidence of adherence with therapy.

Grades of Infectiousness:

Grade I: smear positive, culture positive
Grade II: smear negative, culture positive or unknown
Grade III: smear negative, culture negative

Smear negative = three consecutive negative sputum AFB smears on separate days.

Culture negative = three consecutive negative AFB cultures one week apart.

Drug susceptibility or drug resistance is based on the drug susceptibility testing results of the M. *tuberculosis* isolate recovered from the patient. TB isolates are considered fully susceptible if they have been shown to be susceptible to all first line anti-TB drugs. Resistant strains are those resistant to one or more anti-TB drugs.

Housing options include the home for patients who can return to a stable home and three levels of facilities for those without a stable home.

Levels of housing:

Level 1: Acute care hospital
Alternative Housing Program (smear positive, medically stable and clinical improving)

Level 2: Shelters that require negative smears; trained staff provide DOT, Alternative Housing Program (smear positive, medically stable and clinical improving)

Level 3: Shelters that require negative cultures; trained staff for DOT available

These categories of respiratory isolation, based on guidelines from the National Jewish Center for Immunology and Respiratory Disease, regulate patient activities and use of masks based on grade of infectiousness:

a. Activity defined by the Level 1 institution;

b. Home permitted provided that no new persons will be exposed in the home;

c. Wear mask to medical appointments, otherwise stay home;

d. Wear mask only when indoors around unexposed persons.

Per CDC guidelines, use simple surgical masks for patients. Isolation categories apply to patients with clinical improvement in response to medical therapy (e.g., resolution of fever, diminished cough, reduced number of organisms on AFB smear) and evidence of adherence with therapy. DOT is the standard of care for all TB patients in Georgia.

TB Infection Control in the Home

Patients with TB disease can be sent home even if they do not have two negative sputum smears, if the following criteria are met:

- A follow-up plan has been made with the local TB program;
- The patient is on standard TB treatment, and directly observed therapy (DOT) has been arranged;
- No infants or children less than 5 years of age or persons with immunocompromising conditions are present in the household; and
- The patient is willing to remain isolated in the home except for health-care associated visits until the patient has negative sputum smear results. Patients who have suspected or confirmed TB disease are more likely to have already transmitted TB infection to members of their household before their TB disease was diagnosed and treatment was started.

However, TB patients and members of their household should take steps to prevent the further spread of TB infection after they return home. Patients with TB disease should

- Be instructed to cover their mouth and nose when coughing or sneezing;
- Sleep alone and not in a room with other household members; and
- Refrain from having visitors in the home until they are noninfectious.

XIV. References

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XV. Appendix: District TB Coordinators (by district)

DISTRICT	COUNTIES		TB COORDINATOR
DISTRICT 1 UNIT 1 ROME	Bartow Catoosa Chattooga Dade Floyd	Gordon Haralson Paulding Polk Walker	**Stacy Henderson, Rn, BSN** *District TB Coordinator* Northwest Georgia Health District 1309 Redmond Road, NW Rome, Georgia 30165 **Phone:** (706) 802-5626 **Secondary Phone:** (706) 295-6827 **Fax:** (706) 295-6150 Stacy Henderson @dph.ga.gov
DISTRICT 1 UNIT 2 DALTON	Cherokee Fannin Gilmer	Murray Pickens Whitfield	**Tammy Bowling, RN, BSN** *District TB Coordinator* North Georgia Health District 1710 Whitehouse Court Dalton, GA 30720 **Phone:** (706) 529-5741 x12232 **Fax:** (706) 529-5752 Tammy.Bowling @dph.ga.gov

DISTRICT	COUNTIES		TB COORDINATOR
DISTRICT 2 GAINESVILLE	Banks Dawson Forsyth Franklin Habersham Hall Hart	Lumpkin Rabun Stephens Towns Union White	**Melinda Dolphyn, MPH** *District TB Coordinator* District 2 Public Health 1280 Athens St. Gainesville, GA 30507 **Phone:** (770) 718-5084 **Cell:** (678) 780-6176 **Fax:** (770)535-5958 Melindadolphyn @dph.ga.gov
DISTRICT 3 UNIT 1 COBB Back-up for TB Coordinator: **Mitzi Wyche** *Communicable Disease Specialist 3* **Phone:** (770) 514-2473 Mitzi.Wyche @dph.ga.gov	Cobb	Douglas	**Phyllistine Gardner** District TB Coordinator 1650 County Services Parkway SW Marietta, GA 30008 **Phone:** (770) 514-2343 (678) 697-5276 **Fax:** (770) 514-2801 Phyllistine.Gardner @dph.ga.gov

District TB Coordinators (by district)

DISTRICT	COUNTIES	TB COORDINATOR
DISTRICT 3 UNIT 2 FULTON	Fulton	**Tonya King, MPA** *District TB Coordinator* *Health Program Administrator* Medical and Preventative Services 10 Park Place South, SE Atlanta, Georgia 30303 **Phone:** **(**404) 613-1410 Tonya.King @fultoncountyga.gov
DISTRICT 3 UNIT 3 CLAYTON	Clayton	**Toni Miles, RN, BSN** *District TB Coordinator* Clayton County Board of Health Annex 685 Forest Parkway Forest Park, GA 30297 **Phone:** (678) 479-2222 **Mobile**: (678) 689-3120 **Fax:** (770) 603-4874 Toni.Miles@dph.ga.gov

DISTRICT	COUNTIES	TB COORDINATOR
DISTRICT 3 UNIT 4 GWINNETT	Gwinnett, Newton, Rockdale	**Suntana Ly, RN, BSN** *District TB Coordinator* Gwinnett County Public Health 455 Grayson Highway, Suite 400 Lawrenceville, GA 30046 **Phone:** (678) 442-6880 **Cell:** (678) 231-0701 **Fax:** (770) 339-4279 Suntana.Ly@gnrhealth.com ***(Also, Coordinator Contact)*** **Hoa Le** *Lead Case Manager* **Phone:** (678) 442-6880 **Cell:** (678) 414-7772

District TB Coordinators (by district)

DISTRICT	COUNTIES	TB COORDINATOR
DISTRICT 3 UNIT 5 DEKALB	DeKalb	**Juanita Martin** *TB Refugee Program Coordinator* DeKalb County Board of Health County Wide Services 445 Winn Way Decatur, GA 30031 **Phone:** (404) 294-3816 **Cell:** (404) 273-7676 **Fax:** (404) 297-7230 Juanita.Martin1@dph.ga.gov

DISTRICT	COUNTIES		TB COORDINATOR
DISTRICT 4 LAGRANGE	Butts Carroll Coweta Fayette Heard Henry	Lamar Meriwether Pike Spalding Troup Upson	**Melody Wegienka, RN** *District TB Coordinator* District Four Public Health Services 122–A Gordon Commercial Drive LaGrange, GA 30240 **Phone:** (706) 298-7764 **Cell:** (706) 616-2749 **Fax:** (706) 845-4294 Melody.Wegienka@dph.ga.gov
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District TB Coordinators (by district)

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DISTRICT	COUNTIES	TB COORDINATOR
DISTRICT 6 AUGUSTA ***Georgia State Medical Prison*** **Millie Reeves, PA** Augusta State Medical Prison 3001 Gordon Hwy. Grovetown, GA 30813 **Phone:** (706) 855-4823 **Mobile:** (706) 832-8396 **Fax:** (706) 855-4991 Mreeves@augusta.edu	Burke Columbia Emanuel Glascock Jefferson Jenkins Lincoln McDuffie Richmond Screven Taliaferro Warren Wilkes	**LeAnna Niki Crawford, RN, BSN** *District TB Coordinator* 950 Laney Walker Blvd. Augusta, GA 30901 **Phone:** (706) 721-5846 **Fax:** (706) 721-5845 Leanna.Crawford@dph.ga.gov

District TB Coordinators (by district)

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DISTRICT 7 COLUMBUS	Chattahoochee Clay Crisp Dooly Harris Macon Muscogee Marion	Quitman Randolph Schley Stewart Sumter Talbot Taylor Webster	**Sonja Tate, RN** *District TB Coordinator* Columbus Health Department 5601 Veterans Parkway Columbus, GA 31904 **Phone:** (706) 321-6244 **Fax:** (706) 321-6384 Sonja.Tate@dph.ga.gov **Main:** (706) 321-6300
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DISTRICT 9 UNIT 1 SAVANNAH/ BRUSWICK	Bryan Camden Chatham Effingham	Glynn Liberty Long McIntosh	**Jennifer Reimann, RN** *District TB Coordinator* TB Program/Coastal Health District 420 Mall Blvd. Savannah, GA 31406 **Phone:** (912) 644-5224 **Cell:** (912) 332-0875 **Fax:** (912) 349-2326 Jennifer.Riemann@dph.ga.gov

District TB Coordinators (by district)

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TB Hotline for Physicians
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CDC Division of TB Elimination
http://www.cdc.gov/tb/

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