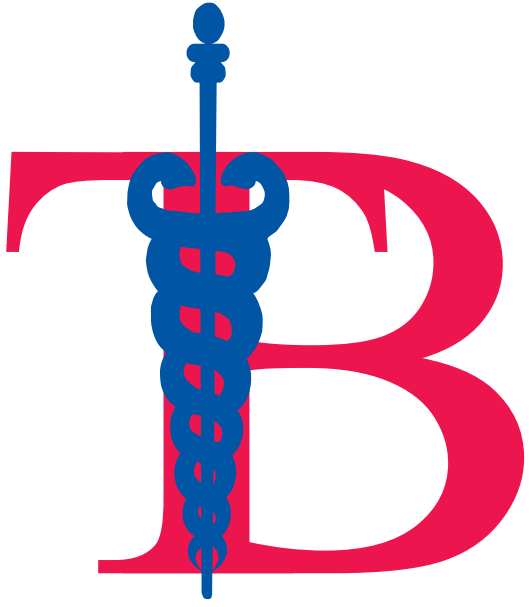
Georgia Tuberculosis Reference Guide



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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, the Centers for Disease Control and Prevention, the Infectious Disease Society of America, the New York City Department of Health, and the Atlanta TB Prevention Coalition. This edition contains updated recommendations on the treatment of latent tuberculosis infection and treatment of 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
- Georgia DHR, Division of Public Health TB Program: 404-657-2634

Sincerely,

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Acknowledgement

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ABBREVIATIONS

AFB:	Acid-Fast Bacilli
AIDS:	Acquired Immunodeficiency Syndrome
BCG:	Bacillus Calmette-Guerin
CAP:	Capreomycin
CBC:	Complete Blood Count
CNS:	Central Nervous System
CXR:	Chest X-Ray
DOPT:	Directly Observed Preventive Therapy
DOT:	Directly Observed Therapy
EMB:	Ethambutol
HIV:	Human Immunodeficiency Virus
IM:	Intramuscular
INH:	Isoniazid
IV:	Intravenous
KM:	Kanamycin
LFT:	Liver Function Test
LTBI:	Latent Tuberculosis Infection
MDR:	Multidrug Resistant
NRTI:	Nucleoside Reverse Transcriptase Inhibitor
NNRTI:	Non-nucleoside Reverse Transcriptase Inhibitor
PAS:	Para-aminosalicylic Acid
PI:	Protease Inhibitor
PO:	*Per os* (Oral)
PPD:	Purified Protein Derivative
PZA:	Pyrazinamide
RFB:	Rifabutin
RIF:	Rifampin
SM:	Streptomycin
TST:	Tuberculin Skin Test
TU:	Tuberculin Unit

Table of Contents

I. Classification System for Tuberculosis

Class O: *No TB Exposure—Not Infected*

No history of exposure. Negative reaction to the tuberculin skin test.

Class I: *TB Exposure—No Evidence of Infection*

History of exposure (contact to a case of TB) and negative reaction to the tuberculin skin test.

Class II: *TB Infection—No Disease*

Positive reaction to the tuberculin skin test, no clinical or radiographic evidence of TB, and/or negative bacteriologic studies (if done).

Class III: *Current TB Disease*

Clinical, bacteriological, and/or radiographic evidence of current tuberculosis. This is established most definitively by isolation of *M. tuberculosis*.

Class IV: *Previous TB Disease*

History of episode(s) of TB, or abnormal but stable radiographic findings, positive reaction to the tuberculin skin test, negative bacteriologic studies (if done) and no clinical or radiographic evidence of current disease.

Class V: *TB Suspected*

Diagnosis pending. Patient should not remain in this category for more than three months.

II. Epidemiology

- **Worldwide**, TB is the second leading cause of death due to an infectious disease. HIV is number one. TB is also the main cause of death in persons with HIV/AIDS worldwide (although not in the United States).

- The World Health Organization (WHO) estimates that there are more than 8 million new cases of TB disease and more than 2 million deaths due to TB each year.

- One-third of the world's population harbors *Mycobacterium tuberculosis* (i.e., 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 **United States** 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 have been 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.

- From 1992 through 2003, there has been a 41% decrease in the number of cases, as TB control was strengthened

nationally. In 2003, the U.S. reported 14,871 new cases (5.1 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.

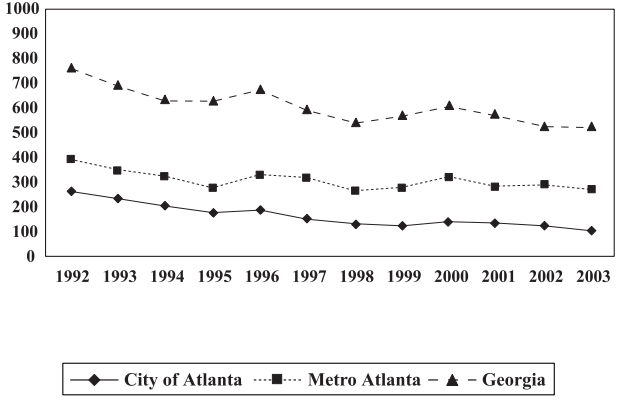
- TB is not evenly distributed among the U.S. population. Cases occur disproportionately in urban areas, in conditions of poverty and over-crowding, and among racial and ethnic minorities and foreign-born persons. In 2003, 51% of U.S. cases occurred among foreign-born persons (28% in Georgia).

- The average lifetime risk of developing active TB following TB infection, if no treatment of latent TB infection is received, is approximately 10% (5% in the first two years after tuberculin skin test conversion [new infection] and 5% in the remaining lifetime). 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 in HIV+ patients with LTBI).

- The state of **Georgia** has had TB rates higher than the U.S. average for the last quarter of a century. In 2003, Georgia had 526 new cases (6.0 per 100,000 population).

- The city of Atlanta has rates of TB more than seven (7) times the national average.
- More than half (54%) of TB cases in Georgia occurred in the 8-county metropolitan Atlanta area.

Number of TB Cases
City of Atlanta, Metro Atlanta*, Georgia
1992 – 2003



*8 county metro Atlanta

III. Tuberculin Skin Testing

Mantoux tuberculin skin testing is the standard method of identifying persons infected with *M. tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used. Tuberculin skin tests should be administered and read by trained healthcare personnel.

A. Administering and Reading the Skin Test

The tuberculin skin test (TST) is administered by injecting 0.1 ml of 5 tuberculin units (TU) of 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 (universal) 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).

Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG, although currently no FDA-approved method can reliably distinguish tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterial infections. A positive test 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 medical conditions that increase the risk for disease (Section IV, B).

B. Criteria for Tuberculin Positivity, by Risk Group

Reaction ≥ 5 mm of induration

- Human immunodeficiency virus (HIV)- positive persons
- Recent contacts of 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 mo. or more)

Reaction ≥ 10 mm of induration

- Recent immigrants to the U.S. (within the last 5 yrs) from high prevalence countries
- Injecting drug users
- Residents and employees of the following high-risk congregate settings: prisons and jails, nursing homes,

hospitals, residential facilities for persons with HIV/AIDS and homeless shelters

- Mycobacterial laboratory personnel
- Persons with the following clinical conditions that place them at risk of progression from infection to disease: silicosis, diabetes, chronic renal failure, leukemias and lymphomas, carcinoma of the head, neck or lung, weight loss of $\geq$ 10% of ideal body weight, gastrectomy, and jejunoileal bypass
- Children less than 5 yrs of age or infants, children, and adolescents exposed to adults at high-risk
- Recent conversion (increase of $\geq$ 10 mm of induration within the past 2 years)

Reaction $\geq$ 15 mm of induration

- Persons with no risk factors for TB
- Persons who are otherwise at low risk and are tested at the start of employment, a reaction of $\geq$ 15 mm is considered positive

C. Chest radiography

Persons with a newly documented positive tuberculin skin test should have a chest x-ray performed to assure that they do not have active tuberculosis disease. After an initial negative chest x-ray, **no routine follow-up chest x-rays are necessary**. Persons with a positive tuberculin skin test should be educated about the signs and symptoms of TB disease and instructed to consult with a physician if these symptoms occur.

D. Anergy Testing

Anergy testing is not recommended for routine use in persons who are infected 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. Recommendations for treatment of LTBI in some persons with negative tuberculin skin tests, regardless of anergy test results, are outlined in Section IV.

E. Two-Step Testing and the Booster Reaction

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

Two-step testing is recommended for employees or residents in institutional settings (such as health care workers or correctional institution employees) who will undergo routine, serial tuberculin screening, and for whom it is important to distinguish between new infection and 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 undergo annual or semi-annual tuberculin testing, two-step testing is required for only the first test, to establish a baseline negative test. Subsequent tuberculin testing should be only one test.

F. QuantiFERON-TB®

In 2001, the FDA approved a new diagnostic test for LTBI called the QuantiFERON-TB test or QFT. CDC has published guidelines for the use of QFT in selected populations [MMWR 2003; 52(RR-2):15-18]. QFT is a whole blood gamma interferon release assay that is an in vitro diagnostic aid that measures a component of cell mediated immune reactivity to *M. tuberculosis*. At the present time, QFT is not widely available for use in the diagnosis of LTBI. Newer generation QFT tests which use TB-specific antigens are under development. New and improved diagnostic tests for LTBI are needed given the limitations of the TST.

G. Reporting of Pediatric Positive TSTs

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, a positive TST in a child less than 5 years old is now 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.

IV. Treatment of Latent TB Infection (LTBI)

Targeted tuberculin testing for LTBI is a strategic component of TB control that identifies persons at high risk for developing TB and who would benefit by treatment of LTBI, if detected. Persons at increased risk for developing TB include those who have had recent infection with *M. tuberculosis* and those who have clinical conditions that are associated with an increased risk for progression from LTBI to active TB (pages 12-14). Targeted tuberculin testing programs should be conducted only among groups at high risk and discouraged in those at low risk. Infected persons who are considered to be at high risk for developing active TB should be offered treatment of LTBI irrespective of age. Based on the sensitivity and specificity of the purified protein derivative (PPD) tuberculin skin test and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive tuberculin reaction: ≥5 mm, ≥10 mm, and ≥15 mm of induration (pages 12-14).

Among those with a positive tuberculin skin test, active tuberculosis disease must be ruled out (i.e., by a negative chest radiograph) prior to initiation of therapy for LTBI. Isoniazid (INH) or 9 months is the preferred therapy for the treatment of LTBI in adults and children. A six month regimen of INH is an alternative regimen in HIV-seronegative adults. Rifampin for 4 months is an alternative regimen (e.g., for treatment of LTBI among persons infected with INH-resistant strains). Because of the marked increase risk of toxicity (compared to INH), rifampin plus pyrazinamide [2 month short course regimen] is NOT recommended for the treatment of LTBI although these drugs remain an important component of a multidrug regimen in the treatment of active TB disease. Recommended regimens, dosages, length of therapy and number of doses for LTBI therapy are listed in the tables on page 14-15 and page 18-19.

A. Candidates for Treatment of LTBI

CATEGORY OF PERSON TESTED	TST < 5 mm
Child < 5 years and recent contact*	TREAT
HIV-infected and recent contact*	TREAT
Immunosuppressed and recent contact*	TREAT
HIV-infected	Do Not Treat
Immunosuppressed persons	Do Not Treat
Recent contact of TB case	Do Not Treat
Fibrotic changes on chest X-ray	Do Not Treat
Recent arrival from endemic country	Do Not Treat
Injection drug user	Do Not Treat
Resident/Employee institutional setting	Do Not Treat
Mycobacteria lab personnel	Do Not Treat
High-risk clinical conditions†	Do Not Treat
Child < 5 years	Do Not Treat
Persons < 18 exposed to high-risk adults	Do Not Treat
No risk factors (TST discouraged)	Do Not Treat

*Recent contacts of an active TB case who are initially TST-negative should have the TST repeated 12 weeks after the last exposure to the TB Case. LTBI treatment can be discontinued after second negative TST **in children**.

†Silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head and neck or lung), weight loss of ≥10% ideal body weight, gastrectomy, jejunoileal bypass.

NOTE: CXR *MUST* RULE OUT ACTIVE DISEASE BEFORE BEGINNING TREATMENT FOR LTBI

TST ≥ 5 mm	TST ≥ 10 mm	TST ≥ 15 mm
TREAT	TREAT	TREAT
TREAT	TREAT	TREAT
TREAT	TREAT	TREAT
TREAT	TREAT	TREAT
TREAT	TREAT	TREAT
TREAT	TREAT	TREAT
TREAT	TREAT	TREAT
Do Not Treat	TREAT	TREAT
Do Not Treat	TREAT	TREAT
Do Not Treat	TREAT	TREAT
Do Not Treat	TREAT	TREAT
Do Not Treat	TREAT	TREAT
Do Not Treat	TREAT	TREAT
Do Not Treat	TREAT	TREAT
Do Not Treat	Do Not Treat	Consider Treatment**

Pregnancy: Treat LTBI during pregnancy if either HIV-infected or recent *M. tuberculosis* infection (recent converter).

Contraindications to treatment of LTBI include: INH - history of INH-induced severe hepatitis, rash, neuropathy or presence of severe liver disease.

** See section A, page 12.

B. Recommended Drug Regimens for the Treatment of LTBI in Adults

Drug	Interval and Duration	Adult Dosage (maximum)
INH*	Daily for 9 months	5 mg/kg (300 mg)
	Twice-weekly for 9 months by DOT	15 mg/kg (900 mg)
INH*	Daily for 6 months	5 mg/kg (300 mg)
	Twice-weekly for 6 months by DOT	15 mg/kg (900 mg)
RIF	Daily for 4 months	10 mg/kg (600 mg)

Abbreviations: INH=isoniazid, RIF=rifampin, PZA=pyrazinamide, NRTIs=nucleoside reverse transcriptase inhibitors, NNRTIs=non-nucleoside reverse transcriptase inhibitors, DOT=directly observed therapy, mos.=months
Pregnancy: INH regimens preferred for pregnant woman.

RIF/PZA for 2 months is not recommended for treatment of LTBI due to increased risk of hepatotoxicity.

Criteria for Completion	Comments
270 doses within 12 mo. 76 doses within 12 mo.	**Preferred regimen for all persons.** In HIV-infected patients, INH may be administered concurrently with NRTIs, protease inhibitors, or NNRTIs. **DOT must be used with twice-weekly dosing.**
180 doses within 9 mo. 52 doses within 9 mo.	Offer if preferred or alternate regimens not feasible. **Not indicated for persons with HIV infection** or fibrotic lesions. Not indicated for children. **DOT must be used with twice-weekly dosing.**
120 doses within 6 mo.	For persons who are contacts of patients with INH-resistant, RIF susceptible TB or as an alternative regimen in adults.

Children: The only recommended treatment regimen for LTBI in children is INH for 9 months, daily 10 mg/kg or twice-weekly 20-40 mg/kg by DOT. HIV-infected children, and children who are breastfeeding, should have routine monitoring of liver enzymes and should receive pyridoxine (vitamin B6) supplementation daily 1-2mg/kg per day.

*Pyridoxine (vitamin B_6) should be used (25 mg daily or 50 mg twice-weekly) with INH for adults.

C. Monitoring of Patients on Treatment for LTBI

For all patients:

- Initial clinical evaluation
- Follow-up clinical evaluations at least monthly if receiving INH or RIF alone
- Include careful questioning about side effects and a brief physical examination checking for evidence of hepatitis or other side effects
- Educate patients about side effects associated with LTBI treatment
- Advise patient to stop treatment and promptly seek medical evaluation if these occur
- If side effects occur, evaluate promptly and change treatment as indicated
- CDC guidelines state routine monthly monitoring of liver function tests not generally indicated with INH or RIF-only treatment unless risk factors present for increase risk of hepatotoxity. We recommend baseline liver function tests (LFTs) in all adults. Consider monthly AST testing in adults.
- In the absence of liver disease or HIV infection, children on LTBI do not need monthly AST monitoring.

Indications for regular monthly monitoring of LFTs:

- Abnormal AST at baseline
- HIV infection

- Pregnancy
- First three months postpartum
- Chronic liver disease (including HCV infection)
- Regular alcohol use
- Patients on other drugs which are potentially hepatotoxic
- Advanced age

Medication should be stopped and patients evaluated if:

- Transaminase levels > 3 times upper limit of test in presence of symptoms of adverse events
- Transaminase levels > 5 times upper limit of test in asymptomatic patient

Pyridoxine (Vitamin B_6) 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 and children who are breastfeeding. For healthy individuals on a normal diet, pyridoxine is optional. However, we prefer to give pyridoxine to all patients on INH.

USPHS/IDSA EVIDENCE BASED RATING SYSTEM FOR THE STRENGTH OF TREATMENT RECOMMENDATIONS AND QUALITY OF EVIDENCE

Strength of the recommendation

A. Preferred; should generally be offered
B. Alternate; acceptable to offer
C. Offer when preferred or alternative regimens cannot be given
D. Should generally not be offered
E. Should never be given

Quality of evidence supporting the recommendations

I. At least one randomized trial with clinical end points
II. Clinical trials that either are not randomized or were conducted in other populations
III. Expert opinion

SUMMARY OF LTBI TREATMENT GUIDELINES

Drugs	Duration (mo)	Interval	Rating (Evidence) HIV-	HIV+
Isoniazid	9	Daily	A (II)	A (II)
		Twice weekly	B (II)	B (II)
Isoniazid	6	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampin	4	Daily	B (II)	B (III)
*Rifampin-pyrazinamide	2	Daily	D (II)	D (II)
	2-3	Twice weekly	D (III)	D (III)

MMWR 2003;52: 735-739

* Our Recommendation is:
DO NOT USE RIF-PZA for LTBI

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

In deciding how to treat persons with latent TB infection which may be due to an MDR-TB strain, the following four questions should be considered. A TB specialist 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 is much less likely to be newly infected.

- **How likely is it that the patient is infected with an MDR-TB strain?** A TST-positive infant of a parent with 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 infants and persons who are HIV infected or otherwise immunocompromised.

- **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. In some cases, no LTBI regimen is available.

V. Treatment of Current (Active) Disease Therapy (Classes III & IV)

A. Considerations

1) The **provider (or public health program if this is the site of treatment)** is responsible for prescribing an appropriate regimen ***and*** ensuring that treatment is completed successfully. It is strongly recommended that TB treatment be undertaken in consultation with a physician who is well versed and experienced in its management.

2) In general, **initiate therapy with a four drug regimen** (INH, RIF, PZA, EMB) as described on pp. 30-31 (Table 3). Treatment regimens are rated using the USPHS/IDSA evidenced-based system (see Table 3). A number of different treatment options are available as outlined in Table 3 and discussed in further detail below.

3**) DIRECTLY OBSERVED THERAPY (DOT) IS THE STANDARD OF CARE FOR ALL PATIENTS WITH TUBERCULOSIS TO FACILITATE ADHERENCE AND COMPLETION OF THERAPY.** DOT can be given by the county public health department.

Patient-centered care (also called enhanced DOT) is encouraged for all patients. Treatment is tailored and supervision 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.

4) 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). Repeat susceptibility testing should be performed on *M. tuberculosis* isolates for patients who do not respond to therapy or who have a positive culture after two months of therapy.

5) 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 after two months of therapy.**

Patients with cavitary pulmonary TB who have a positive sputum culture after two months of therapy are at increased risk for relapse after six months of therapy; a positive culture after two months of therapy impacts recommendations for the total length of therapy. Patients being treated for uncomplicated pulmonary TB do not require frequent chest x-rays; bacteriologic examination is far more important than monitoring chest films.

6) If a patient's sputum cultures remain positive beyond two months of therapy, the possibility of drug-resistant disease, malabsorption, or patient failure to take medications as prescribed should be considered. Drug susceptibility studies should be repeated, and if not already on directly observed therapy (DOT), such patients should be placed on DOT.

7) Adjust weight-based doses as weight changes.

8) For patients with drug susceptible pulmonary tuberculosis, treatment should be extended from 6 months to 9 months for patients who have cavitary disease on their initial CXR *and* a positive sputum culture after 2 months of therapy.

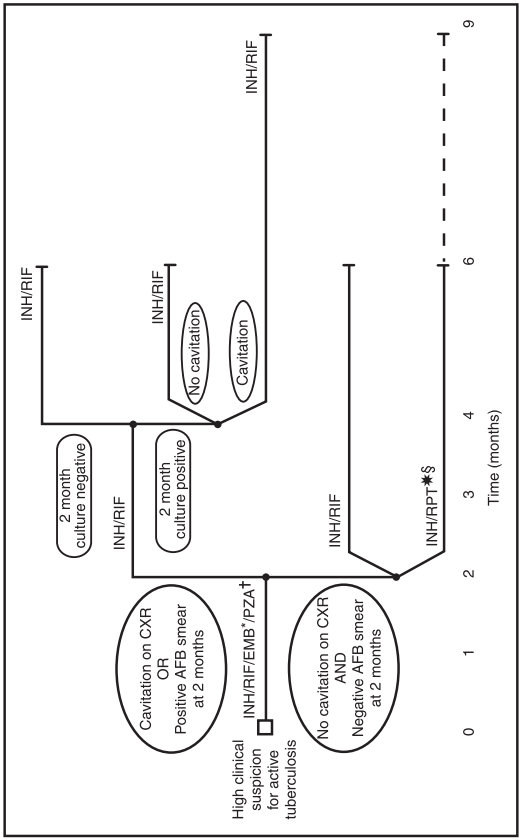
9) A treatment algorithm for TB is shown in Figure 1, on pp. 24-25.

B. Standard Daily Therapy for Current (Active) Disease

All patients should initially be started on a 4-drug regimen (INH, RIF, PZA, EMB) unless there are contraindications to any of the drugs or the patient is pregnant (pregnant patients may be started on a 3 or 4 drug regimen based on certain circumstances which are discussed further on page 63). See Table 1 on the pages 26-27 for maximum doses for children and adults.

Treatment regimens are listed in Table 3, pp. 30-31. Therapy consists of an **initiation phase** and a **continuation phase**. The initiation phase generally consists of 4-drug regimen given daily or 5 times per week per DOT; a thrice weekly option by DOT also exists. The initiation phase is followed by a continuation phase. For drug susceptible disease, this can consist of daily, 5 times per week or twice weekly therapy by DOT [see Table 3]. 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. See Figure 1, pp. 24-25.

Figure 1. Treatment algorithm for tuberculosis.



Patients in whom tuberculosis is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at the time of completions of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months treatment). If the patient has HIV infection and the CD4+ cell count is <100/µl, the continuation phase should consist of daily or three times weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once weekly isoniazid and rifapentine, or daily or twice weekly isoniazid and rifampin, to complete a total of 6 months (bottom). Patients receiving isoniazid and rifapentine, and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months).

* EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance.

† PZA may be discontinued after it has been taken for 2 months (56 doses).

✷ RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis.

§ Therapy should be extended to 9 months if 2-month culture is positive.

CXR = chest radiograph; EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

Adapted from: MMWR 2003;52(RR-11):1-77

Recommended four drug therapy for the initial treatment of TB in children (C) and adults (A), with maximum [MAX] doses:

Table 1: First Line Medications

Drug	Daily Dose [MAX]	Twice Weekly Dose* [MAX]
Isoniazid (INH) PO, IM or IV	**C**:10mg/kg **A**:300mg [300mg]	**C**:20-40mg/kg **A**:15mg/kg [900mg]
Rifampin (RIF) PO or IV	**C**:10-20mg/kg **A**:10mg/kg [600mg]	**C**:10-20mg/kg **A**:10mg/kg [600mg]
Rifabutin PO	**A:**5mg/kg [300mg]	**A:**5mg/kg [300mg]
Pyrazinamide (PZA) PO	**C**:15-30mg/kg **A**:25 mg/kg [2gm]	**C**:50 mg/kg **A**:50 mg/kg [2 gm]
Ethambutol (EMB) PO	**C**:15-25mg/kg **A**:15-25mg/kg	**C**:50mg/kg **A**:50mg/kg

*These regimens should be given by DOT only.

Table 1: First Line Medications

Thrice Weely Dose* [MAX]	Adverse Reactions
C:20-40 mg/kg [900 mg] **A**:15 mg/kg [900 mg]	Hepatic enzyme elevation; hepatitis; peripheral neuropathy; CNS effects: rash
C:10-20 mg/kg **A**:10 mg/kg [600]	Orange discoloration of secretions and urine (occurs in all patients); GI upset; hepatitis; immune mediated toxicity (e.g., thrombocytopenia, renal failure); flu-like symptoms; many drug interactions; rash
A:5mg/kg [300mg]	Similar to Rifampin; less drug interactions
C: 50-70 mg/kg **A**: 50-70 mg/kg [3 gm]	GI upset; hepatitis; hyperuricemia; arthralgias
C&A: 25-30mg/kg	Optic neuritis

SUGGESTED DOSAGES FOR
EMB AND PZA ON TABLE 2, P. 29

Notes

Table 2. Suggested pyrazinamide doses, using whole tablets, for adults weighing 40–90 kilograms.

	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	1,000 (18.2-25.0)	1,500 (20.0-26.8)	2,000† (22.2-26.3)
Thrice weekly, mg (mg/kg)	1,500 (27.3-37.5)	2,500 (33.3-44.6)	3,000† (33.3-39.5)
Twice weekly, mg (mg/kg)	2,000 (36.4-50.0)	3,000 (40.0-53.6)	4,000† (44.4-52.6)

* Based on estimated lean body weight.
† Maximum dose regardless of weight.

Suggested ethambutol doses, using whole tablets, for adults weighing 40–90 kilograms.

	Weight (kg)*		
	40–55	56–75	76–90
Daily, mg (mg/kg)	800 (14.5-20.0)	1,200 (16.0-21.4)	1,600† (17.8-21.1)
Thrice weekly, mg (mg/kg)	1,200 (21.8-30.0)	2,000 (26.7-35.7)	2,400† (26.7-31.6)
Twice weekly, mg (mg/kg)	2,000 (36.4-50.0)	2,800 (37.3-50.0)	4,000† (44.4-52.6)

* Based on estimated lean body weight.
† Maximum dose regardless of weight.

Adapted from: MMWR 2003;52(RR-11):1-77

Table 3. Drug regimens for culture-positive pulmonary

Initial phase			Continuation	
Regimen	Drugs	Interval and dose♦ (minimal duration)	Regimen	Drugs
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	1a 1b 1c❄	INH/RIF INH/RIF INH/RPT
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk), ¶ then twice weekly for 12 doses (6 wk)	2a 2b❄	INH/RIF INH/RPT
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	4a 4b	INH/RIF INH/RIF

Definition of abbreviations: EMB = Ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifamentine.

✶ Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.

† Definition of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

♦ When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

tuberculosis caused by drug-susceptible organisms

Phase	Range of total doses (minimal duration)	Rating ✶ (evidence) †	
Interval and dose ♦§ (minimal duration)		HIV-	HIV+
Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk) ¶	182 – 130 (26 wk)	A (I)	A (III)
Twice weekly for 36 doses (18 wk)	92 – 76 (26 wk)	A (I)	A (II) ⌘
Once weekly for 18 doses (18 wk)	74 – 58 (26 wk)	B (I)	E (I)
Twice weekly for 36 doses (18 wk)	62 – 58 (26 wk)	A (II)	B (II) ⌘
Once weekly for 18 doses (18 wk)	44 – 40 (26 wk)	B (I)	E (I)
Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
Seven doses per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk) ¶	273 – 195 (39 wk)	C (I)	C (II)
Twice weekly for 62 doses (31 wk)	118 – 102 (39 wk)	C (I)	C (II)

§ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly] continuation phase.

¶ Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is AIII.

⌘ Not recommended for HIV-infected patients with CD4+ cell counts < 100 cells/µl.

❄ Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

Adapted from: MMWR 2003;52(RR-11):1-77

C. Therapy for Patients with Drug Resistance or Drug Intolerance: The following medications should only be used in consultation with a physician with expertise in the management of drug-resistant TB.

Table 4: Second-Line Medications

Drug	Daily Dose	[MAX]
Streptomycin (SM): IM	**C**:20-40mg/kg **A**:15 mg/kg	[1gm]
Levofloxin: PO Moxifloxacin: Gatifloxacin: PO	**A**:750 mg **A**:400 mg **A**:400 mg	
Amikacin: IV, IM, Kanamycin (KM)	**C**:15-30 mg/kg/d **A**: 15 mg/kg/d	
Capreomycin (CM): IM/IV	**C**:15-30 mg/kg **A**:15 mg/kg	[1gm]
Ethionamide: PO	**C**:15-20 mg/kg **A**:500-1000 mg	[1gm]
Cycloserine (CS): PO	**C**:15-20 mg/kg **A**:250-1000 mg	[1gm]
Para-amino-salicylic acid (PAS): PO	**C**:150 mg/kg **A**:150 mg/kg	[12 gm]
Clofazimine: PO	**C**:50-200 mg; **A**:100-300 mg	

* First line medication; can be substituted for EMB in initial regimen.

Note: In the treatment of drug resistant disease, always use at least 3 drugs to which the organism is likely to be susceptible. **Never add a single drug to a failing regimen.** Intermittent dosing of second-line medications is not recommended.

Adverse Reaction
Ototoxicity (hearing loss, vestibular dysfunction); renal toxicity
GI upset; dizziness; hypersensitivity; headaches Contraindicated in children
Auditory, vestibular & renal toxicity
Auditory, vestibular & renal toxicity; hypokolemia; hypomagnesemia; eosinophilia
GI upset; hepatotoxicity; hypothyroidism; metallic taste; bloating
Psychosis; seizures; headache; depression; other CNS effects (give 50 mg Vitamin B_6/250mg of CS)
GI upset; hypersensitivity; hepatotoxicity; sodium load; drug interactions
Orange/brown skin discoloration; GI complaints

Table 5: 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 malformation)	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-salicylic 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 asssociated with hearing impairment and/or other toxicity.
Do Not Use: Associated with premature labor, congenital malformations or teratogenicity.

NOTES: Table 5: 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 5 presents a consensus of published data and recommendations. Although detailed teratogen 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 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 pages 44-45 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.

D. 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 taken as well as duration of treatment. The number of doses required for each regimen is listed in Table 3, pp. 30-31.

E. Regimen Options for the Preferred Initial Treatment of Children and Adults with Tuberculosis

1) **Initiate therapy with a 4-drug regimen as shown in Table 3**. For each of the options shown, a TB medical expert should be consulted if the patient is symptomatic or is AFB smear or culture positive after two months.

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).

3) For pulmonary TB, obtaining sputum for AFB culture at the time of completion of the initial phase (e.g., 2 months) is critical and emphasized in order to identify patients at risk for relapse.

4) Extended treatment (to 9 months) is recommended for patients with drug-susceptible pulmonary TB who have cavitary disease on their initial CXR and a positive sputum culture after 2 months of therapy. [AIII]

5) Twice weekly therapy in the continuation phase is contraindicated for patients with HIV infection who have low CD4 counts (<100 cell/µl). [EII].

6) Newer rifamycins, rifabutin and rifapentine should be considered first-line drugs and can be used in place of rifampin in special situations: rifabutin for patients who are receiving medications, especially antiretroviral drugs, that have unacceptable interactions with rifampin; and rifapentine along with INH in highly selected patients who meet specified criteria in a once-a-week continuation phase.

   Rifapentine (RPT): May be used as a primary drug in combination with INH in a once-weekly continuation phase for highly-selected patients (i.e., HIV seronegative adults, non-cavitary TB) as noted in Table 3. [BI for HIV seronegative patients]. This regimen should NOT be used in HIV seropositive patients [EI] and is not recommended for children. The weekly dose of rifapentine is 10 mg/kg per week [600 mg maximum] plus INH 15 mg/kg per week [900 mg maximum].

7) Routine follow-up is generally not needed after completion of therapy for patients who have had a satisfactory and prompt bacteriologic response and who have completed a 6 or 9 months of an 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.
- The reliability of oral contraceptives is effected in patients being treated with RIF. Alternate contraceptive measures should be recommended.
- RIF will decrease the activity of methadone and a number of other drugs (e.g., coumadin, anticonvulsants, fluconazole, protease inhibitors). An increase in methadone (often of 50% more) is needed to prevent drug withdrawal. Dosage adjustment of the interacting drugs is recommended.
- Carefully monitor renal function in patients receiving SM, amikacin, KM or capreomycin.
- In persons > 60 years of age, the daily dose of SM should be limited to 10 mg/kg (max dose = 750 mg).
- Never add a single drug to a failing regimen.
- Dispense only a 1-month supply of medicine at a time for patients on self-administered therapy (**strongly consider DOT for all patients)**.

F. Drug Resistance

1. **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. Second line regimens often represent the patient's last best hope for being cured. Inappropriate management can have life threatening consequences.

2. **Directly observed therapy is the standard of care for all patients with drug-resistant TB.**

3. For treatment of suspected or confirmed drug resistance, select at least three and if possible 4-5 drugs, to which the patient has never been exposed and to which the organism is known or likely to be susceptible. With suspected or proven MDR-TB, regimens which include 4 to 6 drugs are recommended. **A single drug should *never* be added to a failing regimen or to one which has failed in the past.**

Table 6 provides suggestions for potential regimens for the treatment of drug resistant TB:

- For patients with only **INH resistance**, treat with RIF, PZA, EMB for a minimum of 6 months.

- For patients with only RIF resistance, treat with INH, EMB, a fluoroquinolone and PZA for a minimum of 12 months. An injectable agent (e.g., amikacin, streptomycin or capreomycin) may be included for the first 2-3 months of treatment for patients with extensive disease.

- MDR-TB (i.e., resistance to at least INH *and* RIF) presents difficult treatment problems. Treatment must be individualized and prolonged, based on medication history and drug susceptibility results; **seek expert consultation**. Regimens are often 24 months in duration (at least 12 months after culture conversion is documented). Surgery may be beneficial in selected patients and improve cure rates for MDR-TB patients if the bulk of the disease can be resected.

Table 6. Potential regimens for the management of

Pattern of drug resistance	Suggested regimen	Duration of treament (mo)
INH (± SM)	RIF, PZA, EMB (an FQN may strengthen the regimen for patients with extensive disease)	6
INH and RIF (± SM)	FQN, PZA, EMB, IA, ± alternative agent	18-24
INH, RIF (± SM), and EMB or PZA	FQN (EMB or PZA if active), IA, and two alternative agents	24
RIF	INH, EMB, FQN, supplemented with PZA for the first 2 months (an IA may be included for the first 2-3 months for patients with extensive disease)	12-18

Definition of abbreviations:
BMRC = British Medical Research Council; EMB = ethambutol;
FQN = fluoroquinolone; IA = injectable agent; INH = isoniazid;
PZA = pyrazinamide; RIF = rifampin; SM = streptomycin.
FQN = Fluoroquinolone; most experience involves ofloxacin, levofloxacin, or ciprofloxacin.

patients with drug-resistant pulmonary tuberculosis.

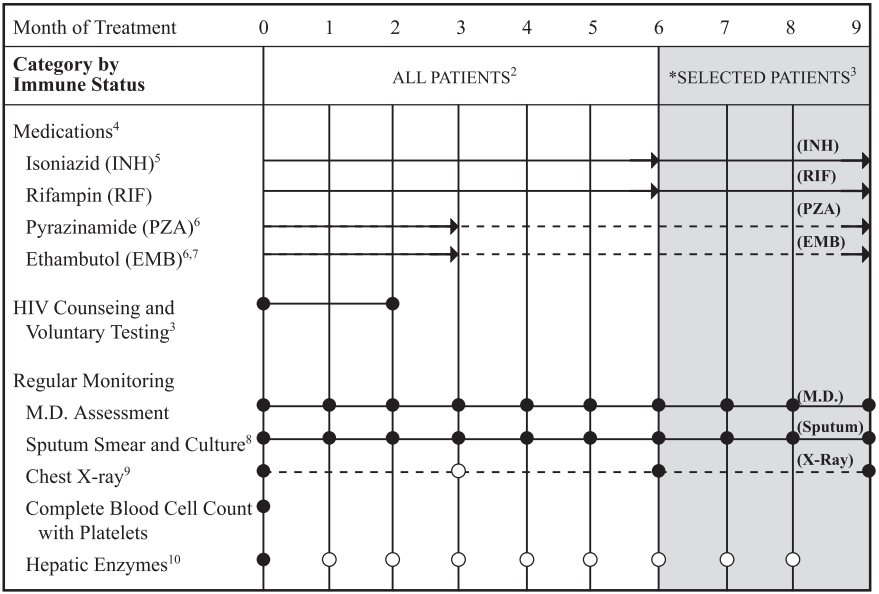
Comments
In BMRC trials, 6-mo regimens have yielded ≥95% success rates despite resistance to INH if four drugs were used in the initial phase and RIF plus EMB or SM was used throughout. Additional studies suggested that results were best if PZA was also used throughout the 6 mo (Rating BII). Fluoroquinolones were not employed in BMRC studies, but may strengthen the regimen for patients with more extensive disease (Rating BIII). INH should be stopped in cases of INH resistance (see text for additional discussion).
In such cases, extended treatment is needed to lessen the risk of relapse. In cases with extensive disease, the use of an additional agent (alternative agents) may be prudent to lessen the risk of failure and additional acquired drug resistance. Resectional surgery may be appropriate (see text).
Use the first-line agents to which there is susceptibility. Add two or more alternative agents in case of extensive disease. Surgery should be considered (see text).
Daily and three times weekly regimens of INH, PZA, and SM given for 9 mo. were effective in a BMRC trial (Rating BI). However, extended use of an injectable agent may not be feasible. It is not known if EMB would be as effective as SM in these regimens. An all-oral regimen for 12–18 mo. should be effective (Rating BIII). But for more extensive disease and/or to shorten duration (e.g., to 12 months), an injectable agent maybe added in the initial 2 mo. of therapy (Rating BIII).

IA = Injectable agent; may include aminoglycosides (streptomycin, amikacin, or kanamycin) or the polypeptide capreomycin.

Alternative agents = Ethionamide, cycloserine, p-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, linezolid.

Adapted from: MMWR 2003;52(RR-11):1-77

Table 7: Therapy Timeline for Previously Untreated Tuberculosis Patients with Active Disease[1]



[1] All initial isolates of *M. tuberculosis* should have drug-susceptibility testing performed. **This chart applies <u>only</u> to patients whose isolates are found to be drug susceptible.** If drug resistance is documented, consult a physician expert in its management.

[2] Pending the results of susceptibility testing, begin all patients on all four of the anti-TB medications listed, unless there are absolute contraindications.

[3a] Patients with cavitary tuberculosis on initial chest x-ray and culture positive after 2 mo. of treament should receive 9 months of therapy because of high risk of relapse.

[3b] HIV counseling and testing should be encouraged for all TB patients, ideally at the first or second clinical visit. Patients known or suspected to be HIV+ with drug susceptible disease should be treated for a minimum of 6 months. Patients who are slow to respond to therapy or culture positive after 2 months should be treated for a total of 9 months.

[4] Ideally every TB patient should receive every dose of anti-TB medication on a program of directly observed therapy (DOT). Call your local Health Department for help in arranging DOT for your patient.

[5] Pyridoxine (Vitamin B6), 25-50 mg with each dose of INH can be given to prevent INH-induced peripheral neuropathy. Pyridoxine should be given to all patients who are pregnant, malnourished or who use alcohol.

[6] Continue PZA until a) at least eight weeks of therapy have been given, *and* b) laboratory results document susceptibility to INH and RIF. EMB should be continued until susceptibility to INH and RIF is documented.

[7] During treatment with EMB, monitor visual acuity and color vision monthly.

[8] Regular monitoring of sputum AFB smears and mycobacteriology cultures is essential. Examine sputum at least monthly until conversion to negative culture; some prefer to obtain monthly sputum exminations throughout the course of therapy. If drug resistance is documented, seek expert consultation.

[9] Obtain chest x-ray after three months to document response to treatment if initial cultures are negative.

[10] Monitor hepatic enzymes monthly if baseline levels elevated or history of alcoholism or liver disease. At least 20% of patients will have elevated hepatic enzymes: asymptomatic elevation less than five times the upper limit of normal is **<u>not</u>** an indication to stop treatment. If patients have jaundice or symptomatic liver disease, discontinue medications immediately and consult a specialist.

* Extend therapy for 3 additional months (total 9 months) in patients who have cavitary disease on initial CXR and are still culture positive after 2 months of therapy because of high risk of relapse (regardless of HIV status).

ANTITUBERCULOSIS ANTIBIOTICS IN

Note: Drug adjustments are based on the patient's creatinine clearance

$$\frac{(140\text{-age})\ (\text{Ideal body weight in kg})}{(72)\ (\text{serum creatinine, mg/dL})}$$ for men (x 0.85 for women)

Drug	Usual Dose (UD) Normal Renal Function	CrCl 25-50
INH	300 mg/d	UD
Rifampin	600 mg/d	UD
Ethambutol	15-25 mg/kg/d	15mg/kg/d
Pyrazinamide	25 mg/kg/d (max 2.0 gm/d)	UD
Levofloxacin	750 mg/d	500 mg/d
Ciprofloxacin	750 mg BID	750 mg/d
Ofloxacin	400 mg BID	400 mg/d

UD = usual dose
HD = hemodialysis
PD = peritoneal dialysis
CrCl = creatinine clearance (ml/min)
d = day

*All four first-line drugs (INH, RIF, PZA, EMB) may be adminstered thrice weekly after HD to facilitate DOT.

ADULT PATIENTS WITH RENAL IMPAIRMENT

which can be estimated as follows:
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

CrCl 10-25	CrCl <10	Hemodialysis*	Peritoneal Dialysis
UD	UD	UD	UD
UD	UD	UD	UD
15 mg/kg q 36°	15 mg/kg q 48°	15-25 mg/kg thrice weekly	15-25 mg/kg thrice weekly
20 mg/kg/d	25 mg/kg thrice weekly	25-30 mg/kg thrice weekly after HD	25 mg/kg thrice weekly
250 mg/d	250 mg/d	250 mg/d	250 mg/d
750 mg/d	500 mg/d	500 mg/d	500 mg/d
400 mg/d	300 mg/d	200mg BID	200mg/d

G. Drug Monitoring

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. As discussed above, it is essential to obtain a sputum culture after two months of therapy to assess risk of relapse.

c. After two months of therapy, if cultures remain or convert to positive or if symptoms do not resolve, obtain new specimens for culture and drug susceptibility testing. Such patients should be reviewed for drug resistant disease and failure to adhere to the prescribed treatment regimen. For patients receiving self-administered therapy, if cultures do not convert to negative after two months of therapy, DOT should be initiated.

d. Patients with drug susceptible disease who are culture positive at 2 months 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.

e. Factors to be considered in deciding whether to prolong treatment in patients with either 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.

f. HIV testing should be offered to 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, platelet count and uric acid level (if PZA is used).
   - Baseline visual acuity (if EMB is used)
   - Baseline audiometry (if SM is used).
   - CD4 count 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 $\geq$ 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. Monitoring tests are frequently required for patients on second line drugs (based on the particular drugs being used).

g. Pyridoxine will usually prevent INH-induced neurotoxicity (peripheral neuropathy). The indications and use of pyridoxine are described on p. 17.

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

i. Drug Interactions:

- INH and phenytoin (Dilantin) increase the serum concentrations of both drugs. Follow phenytoin levels closely.
- RIF may accelerate clearance of drugs metabolized by the liver including methadone, coumadin, glucocorticoids, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, ketoconazole, fluconazole, cyclosporin, and protease inhibitors.
- Women taking RIF should use a birth control method other than oral contraceptives or contraceptive implant (e.g., Norplant).

H. TB and HIV

If a patient is infected with *M. tuberculosis*, HIV infection is a very important risk factor for development of active TB disease. TB is one of the few diseases occurring in HIV-infected persons that is transmissible, curable and preventable.

Persons with HIV infection may have diminished tuberculin skin test reactions because of immunosuppression. Therefore, tuberculin reactions of $\geq$ 5 mm of induration are considered indicative of TB infection in an HIV-infected individual (see p. 7).

Anergy among persons with HIV infection is common, especially among those with very low CD4 counts.

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

The clinical presentation of TB in an HIV-infected person may differ from that in persons with relatively normal cellular immunity who develop reactivation TB. Apical pulmonary disease with cavitation, a classic finding in immunologically competent persons, is less common among HIV+ persons, 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.

1) **Treatment for Individuals with TB & HIV**
   The treatment of TB in persons with HIV infection is similar to that for patients without HIV infection. There are two important exceptions: 1) Once weekly INH-rifapentine in the continuation phase should NOT be used in any HIV-infected patient; and 2) twice weekly INH-RIF or INH-rifabutin should NOT be used for HIV-infected patients with CD4 counts <100/µl.

2) HIV-infected patients with active TB disease should be initiated on a 4-drug treatment regimen (INH, RIF, PZA and EMB) and pyridoxine as outlined in Table 3 on pp. 30-31, unless contraindications to medication exist or the patient is on certain antiretroviral therapy which include protease inhibitors. The use of antiretroviral therapy and TB medications is discussed on p. 54. HIV-infected patients

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.** HIV infected patients with TB disease should be monitored closely for clinical and bacteriological response. Prolonged treatment beyond 6 months (e.g., to 9 months) is recommended for patients who are slow to respond to therapy, including patients who remain culture positive after two months of therapy. Because patient adherence to therapy is crucial for good outcomes, DOT is the standard of care and is strongly recommended for all HIV-infected patients with active TB.

4) HIV-infected patients should be monitored very closely during therapy as they appear to have a greater frequency of adverse reactions to anti-TB drugs. (Obtain a monthly AST.)

5) For patients with drug-resistant disease, if both INH and RIF are not included in the regimen, treatment should be continued for at least 18 months *and* at least 12 months after culture conversion. Directly observed therapy is essential for all patients with MDR-TB. **Seek expert medical advice** for all patients with MDR-TB.

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

I. Antiretroviral Therapy and Treatment of HIV Seropositive Patients with Active Tuberculosis Disease.

Treatment of HIV-infected patients with active TB disease who are on antiretroviral therapy or for whom this is planned, 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 continues to evolve and therefore it is important to check for new updated guidelines. (www.cdc.gov/nchstp/tb/TB_HIV_Drugs/TOC.htm)

The introduction of highly active antiretroviral therapy (HAART) has dramatically improved outcomes for HIV-infected patients and decreased HIV-related mortality. Patients in the United States with tuberculosis disease who are HIV-infected commonly have advanced HIV/AIDS with low CD4 counts and high plasma HIV RNA levels, and thus could potentially benefit from antiretroviral therapy. However, adherence to antiretroviral agents must be extremely high for there to be a sustained virologic response; the use of antiretroviral therapy among HIV-infected patients with tuberculosis is complicated by overlapping toxicity profiles of some antituberculosis and antiretroviral drugs; complex drug-drug interactions; and the occurrence of paradoxical or immune reconstitution reactions.

In order to prevent the occurrence of paradoxical or immune reconstitution reactions (see page 58), especially among patients with low CD4 counts, and because of potentially overlapping

toxicities, it is generally recommended not to start HAART (if the patient is stable) until the tuberculosis disease is substantially improved (e.g., after two months of antituberculosis treatment). The use of antiretrovirals among HIV-infected patients with tuberculosis requires close and frequent communication between tuberculosis and HIV care providers. The use of rifampin or other rifamycin drugs in combination with HAART is outlined on page 54. For additional information refer to updated CDC recommendations (MMWR 2004;53:37). [www.cdc.gov/nchstp/tb/TB_HIV_Drugs/TOC.htm].

There are clinically important drug-drug interactions between the rifamycins (e.g., rifampin, rifabutin) and some of the antiretroviral drugs, especially 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 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. The protease inhibitors also effect 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.

TB Therapy in the HAART Era

Option 1 – Rifampin based regimen plus HAART (no PI)

- Efavirenz (increase dose to 800 mg/day) plus 2 NRTIs (e.g., AZT/3TC)

Option 2– Rifabutin substituted for rifampin

- **PI** (e.g., indinavir, nelfinavir or amprenavir, fosamprenavir, lopinavir/ritonavir [Kaletra], atazanavir) plus 2 NRTIs. Dose of indinavir or nelfinavir should be increased to 1000 mg every 8 hours.
  – **Substitute rifabutin at lower dose (150 mg/day with the PIs above or 300 mg 3x/week) for indinavir, nelfinavir, amprenavir or fosamprenavir; 150 mg 3x/week or 150 mg every other day for atazanavir and Kaletra, or dual PI regimen that contains ritonavir.**
- **NNRTI (efavirenz)** plus 2 NRTIs
  – Increase dose of rifabutin to 400 mg/d or 600 mg 3x/week

Option 3 – Rifampin as part of standard regimen, no HAART

- Patient not candidate for HAART

Option 4 – TB regimen without rifampin/rifamycin drug

- Continue with HAART – no rifamycin [**Not recommended**]
- Short course therapy (e.g., 6 months) not possible; potentially worse outcome without rifamycin drug.

NNRTI - non-nucleoside reverse transcriptase inhibitor
NRTI - nucleoside reverse transcriptase inhibitor
Adapted from MMWR 2004;53:37 and Am J Resp Crit Care Med 2001;164:7-12.

Rifabutin can be substituted for rifampin in the antituberculosis regimen and used with:

- The protease inhibitors indinavir, nelfinavir, amprenavir, fos-amprenavir, atazanavir, lopinavir/ritonavir (Kaletra); or ritonavir [any dose] with saquinavir, indinavir, amprenavir, fos-amprenavir or atazanavir are used (TB Therapy in the HAART Era, Option 2). If rifabutin is substituted for rifampin in combination with protease inhibitors, the dose of rifabutin needs to be reduced as outlined on page 54 and in Table 8 (p. 57).
- Nucleoside reverse transcriptase inhibitors (e.g., zidovudine, stavudine, lamivudine, etc). There are no significant drug interactions between the NRTIs and rifamycins.
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz or nevirapine are used. The dose of rifabutin should be increased to 450 mg daily or 600 mg thrice weekly when administered with efavirenz.

Rifabutin should **NOT** be used in combination with the following antiretrovirals [see Table 8]:

- Saquinavir hard-gel capsules
- NNRTI drug delavirdine

Rifampin can be given with the following antiretrovirals:

- Nucleoside reverse transcriptase inhibitors (e.g., zidovudine, stavudine, lamivudine, etc). There are no significant drug interactions between the NRTIs and rifampin or other rifamycins.

- NNRTI efavirenz (TB Therapy in the HAART Era, Option 1). The dose of efavirenz should be increased to 800 mg/day when used with rifampin.

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

- Protease inhibitors including indinavir, nelfinavir, amprenavir, fos-amprenavir, and atazanavir. Rifampin can be used with ritonavir (600 mg twice daily) when it is used as a single PI as part of a HAART regimen but this approach is limited by the poor tolerability of full dose ritonavir. Rifampin can be used with dual PI therapy involving lopinavir or saquinavir plus ritonavir [see Table 8, p. 57].
- The NNRTI drug delavirdine.

Rifapentine, a long acting rifamycin, which is given once a week should **NOT** be used in patients with HIV co-infection because of the development of rifamycin resistant *M. tuberculosis* which occurred among HIV-infected patients with tuberculosis on rifapentine.

A summary of treatment options for patients with tuberculosis disease who are HIV-infected is shown in the table on page 54 labeled TB Therapy in the HAART Era and in Table 8, page 57.

Table 8. Treatment Options for HIV-Infected Patients.

	Rifabutin (RIFB)	Rifampin (RIF)
SINGLE PROTEASE INHIBITOR		
APV or fos-APV (Amprenavir, Agenerase, Lexiva)	RIFB 150mg/d or 300mg/tiw APV NC	DO NOT USE
ATV (Atazanavir, Reyataz)	RIFB 150mg/d or 300mg/tiw ATV NC	DO NOT USE
IDV (Indinavir, Crixivan)	RIFB 150mg/d or 300mg/tiw IDV 1,000mg/q8h	DO NOT USE
NFV (Nelfinavir, Viracept)	RIFB 150mg/d or 300mg/tiw NFV 1,000mg/q8h	DO NOT USE
RTV (Ritonavir, Norvir)	RIFB 150mg/qod or 150mg/tiw RTV NC	RIF & RTV NC
SQV (Invirase, Fortavase, Saquinavir)	DO NOT USE	DO NOT USE
DUAL PROTEASE INHIBITOR		
LPVr, IDVr, ATVr, APVr, SQVr	RIFB 150mg/qod or 150mg/tiw P.I. NC	RIF NC LPV 400mg or SQV 400mg + RTV 400mg bid
NNRTI		
EFV (Efaverenz, Sustiva)	RIFB 450mg/d or 600mg/tiw EFV NC	RIF NC EFV 800mg/d
NEV (Nevaripine, Viramune)	RIFB 300mg/d or 300mg/tiw NEV NC	DO NOT USE
DLV (Delaviridine, Rescriptor)	DO NOT USE	DO NOT USE

NC = No Change in Dose *tiw = three times per week*

r (dual protease inhibitor) = Ritonavir (used to boost levels)

LPVr = Kaletra (lopinavir/ritonavir) *qod = every other day*

(adapted from J. Lennox, M.D. and MMWR 2004;53:47)

J. Paradoxical or Immune Reconstitution Reactions Associated with Initiation of Antiretroviral Therapy During the Course of TB Therapy

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

Paradoxical or immune reconstitution reactions are characterized by fever, worsening infiltrates on chest radiograph and peripheral and mediastinal adenopathy. The paradoxical reactions are associated with increase reactivity on tuberculin skin testing and a significant reduction in HIV viral load. Patients with clinical findings that are compatible with an immune reconstitution reaction should have other diagnoses ruled out. These paradoxical or immune reconstitution reactions are usually 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 antituberculosis therapy and HAART) starting at a dose of prednisone or methyl prednisolone of 1 mg/kg per day and then tapering the therapy after 1 to 2 weeks of therapy.

In order to prevent the development of immune reconstitution reactions, it may be prudent to delay the initiation of antiretroviral agents until the patient has received two months of antituberculosis therapy and the tuberculosis disease is under better control.

K. Treatment of Extrapulmonary TB

The basic principles that underly the treatment of pulmonary TB also apply to extrapulmonary forms of the disease. A 6-month course of therapy is recommended for treating tuberculosis involving any site with the exception of the meninges for which a 9-12 month regimen is recommended. Prolongation of therapy also should be considered for patients with tuberculous in any site that is slow to respond. The addition of corticosteroids is recommended for patients with tuberculosis pericarditis and meningitis as it improves outcome and decreases mortality as discussed below.

Lymphatic and hematogenous TB are especially common among persons with HIV infection. Central nervous system (CNS) 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 9, page 61.

L. Adjunct Use of Corticosteriod Therapy

Adjunct corticosteroid therapy is indicated in the treatment of tuberculous meningitis and pericarditis as its use along with appropriate antituberculosis drugs is associated with a lower mortality. Corticosteroids are recommended as adjunctive therapy for tuberculous pericarditis during the first 11 weeks of antituberculosis therapy. Corticosteroids do not reduce the risk of development of constrictive pericarditis, however. For the treatment of adults with tuberculous pericarditis, 60 mg of prednisone should be given for 4 weeks, followed by 30 mg for 4 weeks, 15 mg for 2 weeks, and finally 5 mg for the 11th and final week. For patients with tuberculous meningitis, dexamethasone is recommended for a total of 6 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.

Table 9. Evidence-based* guidelines for the treatment of extrapulmonary tuberculosis and adjunctive use of corticosteroids in patients with drug susceptible disease in adults.

Site	Length of therapy (mo)	Rating (duration)	Corticosteroids	Rating (corticosteroids)
Lymph node	6	AI	Not recommended	DIII
Bone and joint	6–9	AI	Not recommended	DIII
Pleural disease	6	AII	Not recommended	DI
Pericarditis	6	AII	Strongly recommended	AI
CNS tuberculosis including meningitis	9–12	BII	Strongly recommended	AI
Disseminated disease	6	AII	Not recommended	DIII
Genitourinary	6	AII	Not recommended	DIII
Peritoneal	6	AII	Not recommended	DIII

* For rating system, see Table 3.

MMWR 2003;52(RR-11):1-77.

VI. Pregnancy

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 (300 mg daily) *immediately* if they have one or more of the following risk factors:

- Documented recent tuberculin skin test conversion;
- HIV infection 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 AST performed while on therapy. Treatment of other pregnant positive reactors can be deferred until several months after the completion of pregnancy.

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 (See Table 5, pp. 34-35)

a) The initial treatment regimen usually consists of INH, RIF and EMB; and 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 B_6) (25 mg/d) is recommended for all pregnant women taking INH.

d) ***Avoid:*** Aminoglycosides (e.g., streptomycin, kanamycin, amikacin) and capreomycin are contraindicated for all pregnant women because of potential adverse effects on the fetus. Fluoroquinolones (e.g., levofloxacin, ofloxacin, moxifloxacin, gatifloxacin, ciprofloxacin) have been associated with arthropathies in young animals; therefore, they should be avoided if possible in pregnant women. Because of lack of data, avoid ethionamide and cycloserine in pregnancy.

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.**

VII. Childhood Tuberculosis

The basic principles for treatment of TB in children and adolescents are essentially the same as adults. For children who receive LTBI therapy, a nine-month course is recommended. Dosage adjustments of medications are made based on weight.

Management Considerations

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

2) Primary intrathoracic TB (parenchymal infiltration, hilar adenopathy, or both, in a child with a significant tuberculin skin test reaction) should be treated in the same manner as pulmonary TB.

3) Because sputum specimens are less likely to be helpful in children, it may be necessary to rely on the results of cultures and susceptibility tests of specimens from the adult source case to "confirm" the diagnosis in the child and to guide the choice of drugs. In cases of suspected

drug-resistant TB or where adult isolates are not available, the aggressive pursuit of early morning gastric aspirates, bronchoalveolar lavage, or tissue diagnosis should be considered.

4) For the same reason, bacteriologic examinations are less useful in evaluating the response to treatment. Thus, clinical and radiographic examinations are of relatively greater importance in children. However, CXRs of children with hilar adenopathy may not become normal for two to three years after treatment. In this instance, a normal CXR is not a necessary criterion for discontinuing anti-TB drugs.

5) Some experts prefer to treat young children with an initial regimen of 3 drugs (INH, RIF, PZA) in the initial phase because the bacillary population is low (e.g., in primary disease). A three drug regimen can be used as initial therapy when the isolate is known to be fully drug susceptible. However, children and adolescents may develop "adult-type" tuberculosis with upper lobe infiltration, cavitation and sputum production. In such cases a 4-drug regimen should be given initially until susceptibility is proven. 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 the 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.

6) In general, extrapulmonary TB, including cervical adenopathy, can be treated with the same regimens as pulmonary TB (e.g., 6 months for drug-susceptible disease). Exceptions include disseminated (miliary) disease,

and meningitis for which 12 months of therapy is currently recommended.

7) Directly observed therapy is the standard of care for all children.

8) Management of the newborn infant whose mother or other household contact is suspected of having TB is based on individual considerations. Separation of the mother (or contact) and infant should be minimized, if possible. Differing circumstances and resulting recommendations are as follows:

i. *Mother or other household contact who has a positive tuberculin skin test reaction and no evidence of current disease.* If, after investigation, no evidence of active disease is found in the mother or extended family to whom the infant is exposed, the infant should be tested with a Mantoux test (5 TU PPD) at 4-6 wk of age and at 3-4 mo of age. Separation of mother and infant is not indicated. If the family cannot be tested promptly, consider administration of INH (10 mg/kg/d) to the infant until skin testing of family has excluded contact with a case of active TB.

ii. *Mother who has current disease and is judged to be noninfectious at delivery.* Investigation of household members and extended family is mandatory. A CXR and Mantoux test at 4-6 wk of age should be performed on the infant; if negative, test again at 3-4 mo and at 6 mo. Separation of mother and infant is not necessary if mother is adherent with therapy.

The infant should receive INH even if the tuberculin skin test is negative and the CXR does not suggest TB, since cell-mediated immunity of a degree sufficient to mount a significant reaction to tuberculin skin testing may only develop as late as 6 mo of age in an infant infected at birth. INH can be discontinued if the tuberculin skin test is negative at 6 mo of age and no active disease exists in family members. Examine the infant carefully at monthly intervals.

iii. *Mother who has active disease and is suspected of being infectious at the time of delivery.* The mother and infant should be separated until the mother is judged to be noninfectious. Otherwise, manage the same as when the disease is judged to be noninfectious to the infant at delivery (see p. 66).

iv. *Mother who has hematogenous spread of tuberculosis (e.g., meningitis, miliary disease, or bone involvement).* If mother has hematogenous spread of TB, congenital TB in the infant is possible. If the infant is suspected of having congenital TB, a tuberculin Mantoux skin test and CXR should be performed promptly and treatment of the infant for TB disease should begin at once. If clinical or x-ray findings do not support the diagnosis of congenital TB, the infant should be separated from the mother until she is judged to be noninfectious. The infant should be given INH until 6 months of age at which time the skin test should be repeated. If the skin test is positive, INH should be continued for a total of 9 months.

VIII. Tuberculosis and Nursing Homes

TB remains a problem in older individuals who were 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 tuberculin skin testing and chest x-rays for individuals who are tuberculin skin-test positive.

Since people over 50 years old may have diminished skin test reactivity, the two-step technique (see pp. 8-9) of tuberculin skin testing is recommended at admission. A "booster effect" has been noted in persons in whom DTH reaction to tuberculin may have waned over the years. In these situations, an initial tuberculin skin test may demonstrate a negative or only weakly positive 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.

Residents of nursing homes or long term care facilities whose baseline two-step skin tests are negative on admission should have repeat tuberculin testing when an exposure to a case of potentially infectious TB has occurred.

- Any person who converts a TST from negative to positive should be considered for treatment of LTBI

after active TB is ruled out (by chest x-ray at least and sputum specimens if indicated).

- Any resident with symptoms of TB regardless of TST results should have a chest x-ray 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, and annual testing thereafter. Employees who are TST positive at baseline should be evaluated for treatment for LTBI (see pages 11-18). Those with recent conversion should be strongly encouraged to take treatment for LTBI. Routine annual symptom screening for previously positive TST employees is recommended instead of an annual CXR.

IX. BCG Vaccination

Bacille Calmette-Guerin (BCG) is a vaccine that is used in many countries to primarily prevent disseminated TB disease in children. Because of variable effectiveness, *BCG is not generally recommended in the U.S.* All individuals who need to be screened, including those who have had BCG vaccination, should have a Mantoux tuberculin skin test with 5TU of PPD as part of targeted TB testing and evaluation or among a healthcare worker surveillance testing program.

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 vaccinees is 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 often given in areas where TB is endemic, so assume that the reaction is from infection, not vaccination.

Since many BCG-vaccinated persons come from areas of high TB prevalence, it is important that persons with significant reactions to the tuberculin skin test be evaluated for presence of disease and managed accordingly. Appropriate follow-up includes a careful medical history, CXR to rule out disease, and evaluation for treatment of LTBI.

Individuals with a history of BCG vaccination should have a tuberculin skin test performed when required for pre-employment, admission or periodic testing unless there is a documented history of a prior positive Mantoux tuberculin skin test reaction.

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. Unsuspected patients with TB 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, which has cared for approximately 150 patients with lab-confirmed TB disease each year over the past decade, 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

All health care workers should have baseline two-step tuberculin skin testing upon employment (unless *documented* to be previously TST positive) and at intervals determined by their

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 3 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 3 sputum AFB smears are negative
3. HIV+ patient admitted with abnormal CXR	Until 3 sputum AFB smears are negative

risk of exposure. The frequency of skin testing is determined by the risk assessment. For healthcare workers in *medium risk* settings (i.e., institutions with ≥ 200 beds and 6 or more TB cases per year or < 200 beds and ≥ 3 TB cases per year), testing should be done annually. For low risk settings (i.e., ≥ 200 beds and less than 6 TB cases or < 200 beds and < 3 TB cases per year), testing of healthcare workers should be done at baseline and then only if an exposure occurs but not on a routine basis. TB clinics and TB outreach programs should be considered medium risk. Any inpatient or outpatient setting with evidence of recent patient

to patient or patient to healthcare worker transmission of *M. tuberculosis* should be classified as *potential ongoing transmission* until appropriate control measures have been implemented and transmission ceases. This is a temporary classification which requires immediate interventions; healthcare workers in such settings should be tested every 3 months until transmission has been terminated.

Any worker who develops symptoms of TB or whose skin test result converts to positive should be evaluated promptly. Health care workers with a recent TST conversion (regardless of age) and no evidence of active disease should be encouraged to take treatment for LTBI (see pp. 11-18). Health care workers should be educated about the basic concepts of TB transmission and pathogenesis, infection control practices, and the signs and symptoms of TB.

C. Engineering Controls

Patients admitted to health care facilities with suspected or confirmed TB should be placed in an airborn infection isolation room (i.e., negative pressure rooms with $\geq$ 6 air changes per hour; $\geq$ 12 for new construction); air from isolation 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 isolation rooms or performing high risk procedures such as cough inductions and bronchoscopy. Use of the N-95 respirator mask is required by OSHA.

XI. Community Tuberculosis Control

A. Reporting Requirements

- In Georgia, the law requires ***all TB cases must be reported to the local county public health department***. This is the responsibility of the physician. At Grady Memorial Hospital, the TB Control Coordinator in the Epidemiology Department (404-616-3598) reports all patients with active disease to the local health departments for the physician. Any health care provider who is managing TB patients in non-health department settings must update the health department on the progress of each patient, including sputum results on a quarterly basis. Cases may be reported electronically at http://sendss.state.ga.us, by calling 1-866-782-4584, or by calling your local health department.

- **NEW:**

  ALL Latent TB infection (LTBI) in children under 5 years of age must be reported to the patient's local county public health department.

  A Source Case Investigation should be conducted by the health department when LTBI is found in a child under 5 years old.

B. 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. **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 it gives the clinician access to the resources of the public health department for assistance in case management and contact investigation. Contact investigations are indicated to determine those who have been exposed to infectious TB patients so tuberculin skin testing can be performed on close contacts and treatment of LTBI can be initiated for those who have been infected.

Role of the Health Department

- Identify and treat all persons with TB disease; ensure that patients complete appropriate therapy
- Provide Directly Observed Therapy (DOT)
- Provide laboratory services
- Identify and evaluate contacts to persons with infectious TB; offer therapy as appropriate
- Screen high-risk groups for TB infection; offer therapy as appropriate
- Collect and analyze data
- Provide training, education, and consultation

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.

C. Grady Hospital TB Discharge Policy

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.

To improve TB control efforts in Atlanta and protect the community from TB, a TB Discharge Policy has been developed for Grady Memorial Hospital. The standard requires that:

- Patients be discharged on an appropriate anti-TB regimen (e.g., 4 drug regimen)

- All TB patients have their discharge endorsed in the chart *prior to discharge* by the Hospital's TB social worker and the local health department liaison;

- All TB patients meet appropriate criteria for discharge according to the following policy:

Summary:
Grady Hospital TB Discharge Policy

Site & Patient Characteristics		Criteria
I.	Another Acute Care Hospital	Transfer anytime when stable
II.	Prison with Appropriate Isolation	Transfer when medically ready for discharge unless MDR-TB suspected
III.	Alternative Housing Program (GA DHR/ALAG)	Transfer when medically ready for discharge
IV.	Home	When medically ready for discharge **AND** the criteria shown in the chart on the following page are met:

Patient Characteristics	**Discharge Destination**	**Criteria (See Below)**
Known or suspected MDR-TB	Stable Home Unstable Home or Prison	Need A, B, C, D, H Cannot discharge to these sites
Cavitary or moderate infiltrate an/or/ positive initial respiratory AFB smear	Stable Home Unstable Home	Need A, B, C, H Need C, E, F, I or C, E, F, G
Minimal or no infiltrate & initial AFB respiratory smears ($\geq$3) were negative	Stable Home Unstable Home	Need A, B, & C Need C, E, & F
Non-respiratory TB closed site of infection (Pleural, etc.)	Stable Home Unstable Home	Need A, B, & C Need C, E, & F
Non-respiratory TB open site of infection (skin, etc)	Stable Home Unstable Home	Need, A, B, C, D Need C, D, E, & F
Positive smear now; previous pos. culture for non-TB Mycobacteria collected within 60 days	Stable Home Unstable Home	Need A, B, C, D, H Need C, D, E, & F
Situations Other Than Those Above	Stable Home Unstable Home	Need A, B, C, & D Need C, D, E, & F

Keys to Letters Defining Criteria:

A. Social service and county health department liaison have documented stable/appropriate home environment.
B. Arrangement is made and documented in the chart for follow-up visit by appropriate county health dept, clinic or other appropriate health care provider, as soon as possible and no longer than 10 week days after discharge. Patient (and/or family and/or significant other) are informed of arrangement.
C. Patient (and/or family and/or significant other) has received discharge teaching about the disease and about isolation, if appropriate.
D. Pulmonary or infectious diseases consult or hospital epidemiologist endorses in chart that disposition is appropriate.
E. Social service and the county health liaison document unstable home environment.
F. Patient has arrangement made and documented in chart for follow-up visit by county health dept, clinic or other appropriate health care provider, as soon as possible (no longer than 5 week days after discharge). Patient, family and/or significant other are informed of arrangement.
G. After 3 negative AFB smears.
H. Patient has good clinical response to initial anti-TB therapy and when medically stable: there will be no new persons exposed to the patient in the home who have not been in long-term contact with the patient prior to hospitalization; patient (and family or significant others, as applicable) agrees to and is assessed as likely to comply with isolation of the patient at home, until the patient is seen by the county health department
I. Patient accepted into Alternative Housing Program.

XII. DHR Community Guidelines for Respiratory Isolation of Patients with Active TB in the Community

In setting guidelines, the Georgia Department of Human Resources, Division of Public Health 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 TB patients. 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 sensitivity or drug resistance is based on the drug sensitivity of the patient's TB isolate. Sensitive isolates are those sensitive to all anti-TB drugs. Resistant strains are those resistant to one or more drugs.

Housing options include 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 (e.g., Madison House in Atlanta or some church shelters)

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 groups of unexposed people.

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.**

Patients must cover all coughs or sneezes with double tissues and dispose of the tissues directly into the toilet or into a paper or plastic bag before putting them in the trash.

All high risk contacts (i.e., immunocompromised individuals, inmates of correctional facilities, residents of long term care facilities, IVDUs, close contacts, children < 5 years of age) should be placed on treatment for latent TB infection for three months, unless otherwise contraindicated, regardless of results of skin testing and x-ray. If initial TST is negative, TST should be re-evaluated in three months.

NOTE: If patient is high risk for MDR-TB, manage as drug-resistant until susceptibility results are available and isolate is known to be drug susceptible. If at low risk for MDR-TB and clinically improving, patient can be managed with restrictions as for drug susceptible disease.

Infectiousness				Isolation Category	
Grade	Smear	Culture	Organism Resistance	No Stable Home	Stable Home
I	Positive	Positive	Drug Resistant	Level I (A)	Home (BC)
			Drug Sensitive	Level I (A)	Home (BC)
II	Negative	Positive or Unkown	Drug Resistant	Level I (A)	Home (BC)
			Drug Sensitive	Level 2 (D)	Home (BD)
III	Negative	Negative	Drug Resistant	Level 2,3	Home
			Drug Sensitive	Level 2,3	Home

XIII. References

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Notes

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