

## IV. TB DISEASE

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## 1. STANDARDS OF PUBLIC HEALTH PRACTICE

- IV-1. Medication for suspected or confirmed cases of TB disease is administered by directly observed therapy (DOT) and fully documented on the DOT sheet.
- IV-2. Each suspected or confirmed case of TB disease is evaluated in TB clinic by a clinician (physician or nurse practitioner) as soon as practicable, and at least within 10 days of the health department receiving the notification.
- IV-3. Initial treatment for each suspected or confirmed case of TB disease is administered by DOT for 14 days (including weekends and holidays), then may be given Monday-Friday by DOT as ordered by the TB clinician.
- IV-4. Treatment for active TB disease is completed within 12 months for patients whom 12 months of treatment or less is indicated.
- IV-5. Prior to the initiation of TB treatment (whenever possible), one (1) induced sputum is collected in TB clinic if the patient cannot easily mobilize an adequate (at least 2ml) natural sputum.
- IV-6. A series of three (3) natural sputum specimens is collected at least monthly until the patient's sputum cultures are negative for *Mycobacterium tuberculosis* (M. tb) for two (2) consecutive months.
- IV-7. Each drug susceptibility test (DST) result is included in the patient's medical record.
- IV-8. For each patient on the standard four (4) drug regimen, ethambutol (EMB) is discontinued when DST results show the M. tb strain is pansensitive.
- IV-9. Pyrazinamide (PZA) is administered as part of a multidrug TB regimen in the initial treatment phase (for at least eight (8) weeks).
- IV-10. Each patient with suspected TB disease is evaluated in TB clinic at least monthly by the TB clinician (physician or nurse practitioner).
- IV-11. Each patient dispositioned with confirmed TB disease (i.e., laboratory-confirmed, clinical, or provider verified) is evaluated by the TB clinician (physician or nurse practitioner) at least every two (2) months.
- IV-12. For each patient placed on treatment for suspected or confirmed TB disease, the treatment orders are documented in the medical record by the TB clinician: drug name(s), dosage, frequency of dose, DOT and planned duration of therapy.
- IV-13. Each TB/HIV co-infected patient has a documented baseline CD4+ count.
- IV-14. Each TB patient with diabetes mellitus has a documented baseline HgA1c.
- IV-15. Therapeutic drug monitoring (TDM) is obtained for each patient who remains culture-positive at two (2) months after initiation of therapy.
- IV-16. For each patient with suspected or confirmed TB disease, visual acuity and color discrimination testing is performed at each clinic visit and documented while patient is receiving EMB.
- IV-17. For each patient with suspected or confirmed TB disease receiving streptomycin or an aminoglycoside, clinical assessment for toxicity (Romberg testing and audiogram) is conducted at baseline and monthly.

**STANDARDS OF PUBLIC HEALTH PRACTICE (continued)**

- IV-18. For each patient with suspected or confirmed TB disease placed on a non-standard regimen, the regional TB program provides documentation of the TB clinician’s order and rationale to the TTBEF Central Office (C.O.) within two (2) business days.
- IV-19. Each order for discontinuation of respiratory isolation is consistent with the criteria established in the TTBEF Manual.

**2. CLINICAL EVALUATION**

**Medical Evaluation Components and Activities**

The TB clinician (physician or nurse practitioner) will perform a **complete** medical evaluation for patients with suspected or confirmed TB disease that includes the following (**Refer to Table IV-1**).

**Table IV-1: Medical Evaluation Components and Activities**

Medical Evaluation Component	Evaluation Activities
Medical history	<ul style="list-style-type: none"> <li>• Patient’s exposure to tuberculosis</li> <li>• Specific risk factors for TB infection</li> <li>• Clinical conditions associated with progression to TB disease once infected</li> <li>• Complete list of medications taken on a regular basis                             <ul style="list-style-type: none"> <li>○ Prescription</li> <li>○ Over-the-counter</li> <li>○ Herbal supplements</li> <li>○ Home or native remedies</li> </ul> </li> <li>• List of allergies and adverse reactions to medications</li> <li>• Presence of symptoms of TB disease (<b>Refer to Table IV-2</b>)</li> </ul>
Physician examination*	<ul style="list-style-type: none"> <li>• Weight and height</li> <li>• Complete vital signs</li> <li>• Skin assessment (jaundice)</li> <li>• Lymph nodes (adenopathy)                             <ul style="list-style-type: none"> <li>○ Swollen or tender</li> </ul> </li> <li>• Cardiopulmonary assessment</li> <li>• Abdominal assessment                             <ul style="list-style-type: none"> <li>○ Tenderness</li> <li>○ Liver abnormalities</li> <li>○ Ascites</li> </ul> </li> <li>• Extremities (edema)</li> <li>• Other stigmata of chronic liver disease</li> </ul>

Medical Evaluation Component	Evaluation Activities
Test for <i>M. tuberculosis</i> infection**	<ul style="list-style-type: none"> <li>• Documented positive tuberculin skin test (TST)</li> <li>• Documented positive interferon gamma release assay (IGRA) <ul style="list-style-type: none"> <li>○ QuantiFERON®-TB Gold In-Tube</li> <li>○ T-spot. TB®</li> </ul> </li> </ul>
Chest radiograph§	<ul style="list-style-type: none"> <li>• A posterior-anterior (PA) and lateral chest x-ray (CXR) initially on all patients presented to rule out active pulmonary or extrapulmonary disease. Arrangements can be made with local healthcare facilities to have over reads done at the request of the clinician</li> <li>• Children &lt;5 years will have both a PA and lateral CXR. All pediatric X-rays should be formally interpreted by a radiologist</li> <li>• Pregnant women who have a positive TST or IGRA should have a CXR (with appropriate shielding) as soon as feasible, even during the first trimester of pregnancy</li> </ul>
Bacteriologic examination of clinical specimens	<ul style="list-style-type: none"> <li>• All persons suspected of having TB disease (at any site) must have three (3) sputum specimens collected for acid fast bacilli (AFB) smear and culture (even if patient does not have symptoms consistent with pulmonary TB) to rule out pulmonary disease</li> <li>• Sputum specimens for AFB smear and culture will be collected during the first visit with a health department provider prior to initiation of TB treatment, when possible</li> <li>• If the patient cannot easily mobilize sputum for an adequate initial specimen (at least 2 ml), one induced sputum should be collected at the first TB clinic visit. Induced sputum is not required if the patient can naturally mobilize an adequate specimen</li> <li>• <b>Table IV-3</b> identifies specimens/procedures to aid in the diagnosis of TB</li> <li>• Natural sputum is needed if a positive culture is already known</li> </ul>
Drug-susceptibility testing (DST)	<ul style="list-style-type: none"> <li>• For patients with a positive culture for <i>M. tuberculosis</i> complex, the isolate should be tested for resistance to first-line TB drugs: isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA)</li> <li>• DST results direct clinicians to choose the appropriate drugs for treating each patient</li> <li>• Second-line DST to be performed in reference laboratories for those patients who: <ul style="list-style-type: none"> <li>○ Are contacts to patients with known drug resistance</li> <li>○ Have demonstrated resistance to first-line TB drugs</li> <li>○ Have positive cultures for <i>M. tuberculosis</i> complex for more than three (3) months after treatment initiation</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>• Each DST result is included in the patient’s medical record <b>(Standard of Public Health Practice IV-7)</b></li> </ul>
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\*The physical exam alone cannot be used to confirm or rule out TB disease but should be used in combination with other medical factors to make a diagnosis. The physical exam should be expanded if extrapulmonary TB is suspected.

\*\*A negative test for TB infection does not exclude a diagnosis of TB disease.

§Abnormalities seen on a CXR may be suggestive of, but are never diagnostic of, TB disease. Chest radiographs may be used to exclude pulmonary TB disease in a person with a normal immune system who has a positive TB test and who has no signs or symptoms of TB.

Reference:

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know, 2013.  
[http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf)

**Symptoms**

**Table IV-2** describes the symptoms of pulmonary and extrapulmonary TB disease.

**Table IV-2: Symptoms of Pulmonary and Extrapulmonary Disease**

Symptoms of Pulmonary TB Disease	Symptoms of Extrapulmonary TB Disease
<ul style="list-style-type: none"> <li>• Cough (≥ 2-3 weeks) with or without sputum production</li> <li>• Hemoptysis (coughing up blood)</li> <li>• Chest pain</li> <li>• Loss of appetite</li> <li>• Unexplained weight loss</li> <li>• Night sweats</li> <li>• Fever</li> <li>• Fatigue</li> </ul>	<ul style="list-style-type: none"> <li>• TB of the kidney (blood in urine)</li> <li>• TB meningitis (headache or confusion)</li> <li>• TB of the spine (back pain)</li> <li>• TB of the larynx (hoarseness)</li> <li>• Loss of appetite</li> <li>• Unexplained weight loss</li> <li>• Night sweats</li> <li>• Fever</li> <li>• Fatigue</li> </ul>

**Table IV-3: Specimens and Procedures in the Diagnosis of TB**

Specimen/Procedure	
Sputum	<ul style="list-style-type: none"> <li>• If specimen is collected by a provider outside of the HD ensure and document in the medical record, that an initial specimen/isolate is sent to the Tennessee Department of Health, Division of Laboratory Services for:               <ul style="list-style-type: none"> <li>○ Acid-fast bacilli (AFB) smear and culture</li> <li>○ Drug-susceptibility testing (DST)</li> <li>○ Genotyping (isolate sent to reference labs for testing)</li> </ul> </li> <li>• An induced sputum for AFB smear and culture is to be obtained and/or attempted at the first visit to TB clinic, unless a positive culture for <i>M. tuberculosis</i> complex is known or the patient can easily mobilize an adequate (at least 2ml) natural sputum               <ul style="list-style-type: none"> <li>○ Deep sputum-producing coughing may be induced by inhalation of an aerosol of warm, sterile 3% hypertonic saline                   <ul style="list-style-type: none"> <li>▪ Induced sputum is very watery and resembles saliva</li> <li>▪ Must be at least 2 ml in volume to be an adequate specimen</li> <li>▪ Specimen must be labeled as “induced sputum” on the laboratory requisition</li> </ul> </li> <li>○ Airborne precautions must be observed (<b>Refer to Module XI: Infection Control</b>)</li> </ul> </li> <li>• Natural (coughed) sputums are to be collected on three (3) consecutive days, collected 8-24 hours apart with at least one being an early morning specimen               <ul style="list-style-type: none"> <li>○ Early morning specimens are preferred when collected on consecutive days</li> <li>○ Observe airborne precautions (<b>Refer to Module XI: Infection Control</b>)</li> <li>○ Instruct the patient that sputum is the material brought up from the lungs, not the mucus from the nose or throat (saliva)</li> <li>○ Unsupervised patients are less likely to provide an adequate specimen; therefore, sputum collection should be observed when possible</li> </ul> </li> <li>• A health department provider(s) will pick up sputum specimens from the patient’s home and transport the specimens to the health department for shipment. Patients <b>must not</b> mail the specimens. It is the responsibility of the health care worker to ensure that the Clinical Laboratory Improvement Amendments (CLIA) regulations are met and specimens are labeled appropriately:               <ul style="list-style-type: none"> <li>○ Correct date of collection is on the requisition</li> <li>○ Two (2) patient identifiers are on the specimen tube</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ Specimen tube is tightly sealed to prevent leakage</li> <li>○ All specimens must arrive at the Tennessee Department of Health, Division of Laboratory Services within seven (7) calendar days from the date of collection</li> <li>○ <b>Write out the county name</b> on the lab requisition (no abbreviations, there are too many counties with the same initials)</li> </ul>
Bronchoscopy	<ul style="list-style-type: none"> <li>● Allows visualization of the inside of the airways in the lungs</li> <li>● Useful for specimen collection, especially if previous results have been non-diagnostic and/or the TB diagnosis is in doubt</li> <li>● May be useful if TB is among several other differential diagnoses being considered</li> <li>● Should be avoided in patients with suspected or confirmed TB disease or postponed until the patient is deemed non-infectious by three (3) negative AFB sputum smear results</li> <li>● Should never be substituted for sputum collection, but rather be used as an additional diagnostic procedure (if needed)</li> <li>● Should be performed under airborne infection isolation (AII)/negative pressure</li> </ul>
Gastric lavage	<ul style="list-style-type: none"> <li>● Used to obtain a specimen for AFB culture when a patient cannot produce adequate sputum (e.g., children &lt;5 years of age)</li> <li>● Requires hospitalization</li> <li>● Performed in the morning before the patient gets out of bed or eats (overnight respiratory secretions are swallowed and pool in the stomach)</li> <li>● Specimens should be transported to the lab immediately</li> </ul>
Urine	<ul style="list-style-type: none"> <li>● Mid-stream specimen voided early in the morning should be submitted</li> <li>● Specimen bottle must be ½ full</li> <li>● Prior to obtaining specimen, consult laboratory staff for further instructions on collecting and handling</li> </ul>
Spinal fluid	<ul style="list-style-type: none"> <li>● Collected at a facility/hospital</li> </ul>
Aseptically collected biopsy	<ul style="list-style-type: none"> <li>● Usually collected in a facility/hospital setting</li> <li>● May include tissue, pleural fluid, bronchial washing, pus, joint fluid, laryngeal swab, etc.</li> <li>● Arrangements must be made with the specialist performing the procedure in advance so that the specimen is submitted immediately for AFB smear and culture. <b>The specimen cannot be placed in formalin.</b></li> </ul>

References:

1. Tennessee Department of Health TB Elimination Program (TTBEP) practice
2. Tennessee Department of Health, Division of Laboratory Services practice
3. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. 2013.  
[http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf) (adapted)

**Assessment of Infectiousness**

**Table IV-4** outlines the non-infectiousness and infectiousness of persons with suspected or confirmed TB disease.

**Table IV-4: Infectiousness\* of People Known to Have or Suspected of Having TB Disease**

<b>Factors Associated with non-infectiousness</b>	<b>Factors Associated with Infectiousness</b>
No cough	Presence of a cough
No cavity in the lung	Cavity in the lung
No acid-fast bacilli on sputum smear	Acid-fast bacilli on sputum smear
Extrapulmonary (non-pulmonary) TB disease	TB disease of the lungs, airway or larynx
Receiving adequate treatment for 2 weeks or longer	Not receiving adequate treatment
Not undergoing cough-inducing procedures	Undergoing cough-inducing procedures (e.g., bronchoscopy, sputum inductions and administration of aerosolized medications)
Negative sputum cultures	Positive sputum cultures

\*Infectiousness depends on variety of factors. Clinicians should consider all of these factors when determining whether a TB patient should be considered infectious.

Reference:

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know, 2013.  
[http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf)

**Airborne Precautions (Respiratory Isolation)**

TB airborne precautions should be initiated for any patient who has:

- Signs or symptoms of TB disease (suspected TB disease) **or**
- Who has documented infectious TB disease and remains infectious in spite of treatment

Persons who have or are suspected of having infectious TB disease should be placed in an area away from other patients, preferably in room that has been designated for isolation of persons with suspected or known infectious TB disease and, if possible, an airborne infection isolation room. **Refer to Table IV-4 for factors associated with infectiousness and non-infectiousness.**

### **3. TB Suspect**

**“Suspect” Case of TB**—a patient that:

- Is suspected by a clinician of having active TB disease; and
- Is undergoing a medical evaluation by a clinician that includes at least the following elements:
  - Complete medical history
  - Physical examination by the clinician
  - Chest radiography (including for individuals with suspected extrapulmonary TB disease)
  - Appropriate diagnostic tests for TB disease; **and**
- Is started on an appropriate multi-drug regimen for TB disease, even if final diagnostic data (e.g., sputum, bronchial wash, or biopsy culture results) are pending.

Reference:

1. CDC. Report of Verified Case of Tuberculosis: Self-Study Modules. 2009. <http://www.cdc.gov/tb/programs/rvct/InstructionManual.pdf>

### **4. DIAGNOSIS OF TB DISEASE**

#### **Laboratory-Confirmed**

Laboratory criteria for diagnosis of TB disease

- Isolation of *M. tuberculosis* from a clinical specimen, **OR**
- Demonstration of *M. tuberculosis* complex from a clinical specimen by nucleic acid amplification test (NAAT), **OR**
- Demonstration of acid-fast bacilli (AFB) in a clinical specimen when a culture has not been or cannot be obtained, or is falsely negative or contaminated.

#### **Clinical Case**

In the absence of laboratory (bacteriological) confirmation, TB disease may also be diagnosed by meeting all of the following clinical criteria:

- A positive tuberculin skin test (TST) or positive interferon gamma release assay (IGRA) for *M. tuberculosis*; **and**
- Other signs and symptoms compatible with tuberculosis (TB) (e.g., abnormal chest radiograph, abnormal chest computerized tomography scan or other chest imaging study, or clinical evidence of current disease); **and**
- Treatment with two or more anti-TB medications; **and**
- A completed diagnostic evaluation.

#### **Provider Verification**

Even in the absence of laboratory confirmation and unmet clinical criteria (clinical case definition), the TB physician may feel strongly that the diagnosis is *M. tuberculosis*. Whenever possible, a final disposition should be made by the TB physician for each TB suspect within eight (8) weeks of the initial report of the individual to the health department. For the purposes of TB surveillance, disposition options include “TB disease,” “TB infection,” or “not a case” of TB

disease or TB infection. If the patient’s disposition cannot be determined at the end of this timeframe, consideration should be given to whether the patient has “provider-verified” TB disease. If so, please submit the Provider Verified Form PH-4079 with the TB physician’s signature and assessment of clinical and radiographical progress on page 2, along with appropriate medical records, to the TTBEF C.O. All Provider Verified Forms are reviewed by the State TB Medical Officer prior to reporting a “provider-verified” TB case to CDC. **(Refer to Tool IV-4: Request for Confirmation- TB Case Verified by Provider Form PH-4079).**

### **Mycobacteria Tuberculosis Complex (MTC)**

There are many species of mycobacteria that are part of the larger *Mycobacteria tuberculosis* (Mtb) complex that can cause TB disease. They include:

- M. tuberculosis
- M. bovis
- M. africanum
- M. microti
- M. canetti
- M. caprae
- M. pinnipedii
- M. mungi

### **Mycobacteria Other Than Tuberculosis**

The diagnosis, treatment and follow-up of disease in individuals infected with *Mycobacteria Other Than Tuberculosis (MOTT)* are not the responsibility of the Tennessee TB Elimination Program (TTBEP). Persons with other mycobacterial diseases should be referred to their private provider(s). The TTBEP funds cannot be utilized for the follow-up or treatment of any medical condition other than tuberculosis.

## **5. TREATMENT OF TB DISEASE**

The prescribing physician, whether in the public or private sector, has the responsibility to:

- Prescribe an appropriate drug regimen and document the treatment plan to include the length of treatment
- Collaborate with the public health manager to ensure successful completion of therapy with the correct number of directly observed therapy (DOT) weeks and DOT doses
- Monitor adherence and toxicity throughout treatment

Oversight of TB treatment may be shared between the public health department and other providers/organizations including:

- Private physicians
- Community health centers
- Migrant health centers
- Correctional facilities
- Hospitals
- Hospices
- Long-term care facilities
- Homeless shelters

The health department TB provider or regional health officer will communicate directly with the patient's other health care provider(s) to ensure that all aspects of the patient's treatment regimen and management of the plan of care are clearly established. Providers are strongly encouraged to refer patients with suspected or confirmed TB to the regional public health TB physician for clinical management.

The health department is ultimately responsible to:

- Ensure appropriate diagnostic evaluation
- Provide treatment services by directly observed therapy (DOT)
- Establish an adherence plan with incentives and enablers
- Monitor the results of TB treatment
- Assure completion of therapy for TB disease

### **Patient Education and Decision-Making**

Patient education will be provided (oral and written, if available) in the patient's preferred language at each clinic or home/facility visit.

Patients must be given opportunities to ask questions and discuss issues and barriers to their care. The TB case manager must be cognizant of the patient's cultural background. The TB case manager is to provide education to the patient on the following topics:

- TB medications
  - Medication for suspected or confirmed cases of TB disease is administered by DOT and fully documented on the DOT Sheet (**Standard of Public Health Practice IV-1**). (**Refer to Module VI. Medication Administration**)
  - Drug, dosage, frequency, and medication adverse effects
  - Ensure that patient is not taking multivitamins that contain iron, or antacids which contain calcium, aluminum and magnesium within two (2) hours of taking TB medications as these medications prevent absorption of some TB medications.
  - Explain that TB medications are absorbed in the stomach and alcohol may prevent absorption of the medications
- When to seek medical attention (**Refer to Module V. Case Management**)
  - Phone numbers of staff to call for assistance after hours
- Consequences of not taking the medications as prescribed
  - Risk of ongoing TB transmission to others
  - Treatment failure
  - Relapse
  - Development of drug resistance

**NOTE:** If patient adherence to the treatment plan is in jeopardy, discuss with the regional health officer before discussing possible measures with the patient. Discussion of legal measures should not be part of routine patient education.

- Isolation and infection control measures
  - Patient is willing to remain isolated in the home except for health-care associated visits until the patient has negative sputum smear results
  - No infants or children less than 5 years of age or persons with immunocompromising conditions are present in the household unless they have been evaluated and started on preventative therapy (Refer to **Discontinuation of Airborne Precautions Respiratory Isolation** pg. 51)
  - Instruct to cover their mouth and nose when coughing or sneezing
  - Sleep alone and not in a room with other household members
  - Refrain from having visitors in the home until they are noninfectious

**Regimen Options**

Currently, there are 10 drugs approved by the FDA for the treatment of TB disease (**Refer to Table IV-5**).

**Table IV-5: Anti-TB Drug Currently Used in the United States**

Drug Class	Anti TB Drugs	Comments
First-line drugs	Isoniazid (INH)	INH, RIF, PZA, and EMB form the core of initial treatment regimen
	Rifampin (RIF)	
	Pyrazinamide (PZA)	
	Ethambutol (EMB)	
	Rifabutin (RBT)*	May be used as a substitute for RIF in the treatment of all forms of TB caused by organisms that are known or presumed to be susceptible to this agent
	Rifapentine (RPT)	May be used once weekly with INH in the continuation phase of treatment for HIV-negative patients with non-cavitary, drug- susceptible pulmonary TB who have negative sputum smears at completion of the initial phase of treatment
Second-line drugs	Streptomycin (SM)	<ul style="list-style-type: none"> <li>• SM was formerly considered to be a first-line drug and in some instances is still used in the initial treatment</li> <li>• Increasing prevalence of SM resistance in many parts of the world has decreased its overall usefulness</li> </ul>
	Cycloserine	These drugs are reserved for special situations such as drug intolerance or resistance
	Capreomycin	
	p-Aminosalicylic acid (PAS)	
	Levofloxacin*	
	Moxifloxacin	
	Gatifloxacin*	
	Amikacin/Kanamycin*	
Ethionamide		

\*Not approved by the U.S. Food and Drug Administration for use in the treatment of tuberculosis

References:

1. CDC. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. MMWR 2000; 49 (No. RR-17). <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf> (adapted)

**Initial and Continuation Phase**

**Table IV-6** outlines the difference phases of TB treatment.

**Table IV-6: TB Treatment Phases**

Phase	Purpose	Treatment
Initial phase	<ul style="list-style-type: none"> <li>• Kills most of the tubercle bacilli during the first 8 weeks of treatment, but some bacilli can survive longer</li> <li>• Prevents the emergence of drug resistance</li> <li>• Determines the ultimate outcome of the regimen</li> </ul>	<p>Initial 2-month treatment regimen</p> <ul style="list-style-type: none"> <li>• Includes four drugs in the treatment (usually INH, RIF, PZA, and EMB)</li> <li>• EMB can be discontinued if DST sensitive to all drugs</li> <li>• PZA to continue x 8 weeks in initial phase</li> <li>• Each of the drugs plays an important role for short-course regimens with high cure rates.               <ul style="list-style-type: none"> <li>○ INH and RIF allow for short-course regimens with high cure rates.</li> <li>○ PZA has potent sterilizing activity, which allows further shortening of the regimen from 9 to 6 months.</li> <li>○ EMB helps to prevent the emergence of RIF resistance when primary INH resistance is present.</li> </ul> </li> <li>• Multiple drugs are needed to prevent the development of drug-resistant TB disease</li> </ul>
Continuation phase	<ul style="list-style-type: none"> <li>• Kills remaining tubercle bacilli (after initial phase)</li> <li>• If treatment is <b>not</b> continued long enough, the surviving bacilli may cause TB disease in the patient at a later time</li> </ul>	<p>An additional 4 or 7 months of treatment</p> <ul style="list-style-type: none"> <li>• 4 months is used for majority of patients</li> <li>• 7 months is recommended only for persons               <ul style="list-style-type: none"> <li>○ Who have drug-susceptible cavitary or extensive pulmonary TB disease and whose sputum culture obtained at the time of completion of 2 months of treatment is positive</li> <li>○ Whose initial phase of treatment did <b>not</b> include PZA</li> </ul> </li> </ul>
Treatment completion	<p>Defines the number of doses ingested within a specified timeframe</p> <p>Duration depends on</p> <ul style="list-style-type: none"> <li>• Drugs used</li> <li>• Drug susceptibility test results of the isolate</li> <li>• Patient's response to therapy</li> </ul>	<p>Most patients with previously untreated pulmonary TB disease can be treated with either a:</p> <ul style="list-style-type: none"> <li>• 6-month regimen (preferred) containing INH, RIF, and initially PZA</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• 9-month regimen containing INH and RIF</li> </ul>

## Reference:

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know, 2013.  
[http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf) (adapted)

## Selection of Treatment Regimen

- The decision to initiate combination anti-tuberculosis chemotherapy is based on epidemiologic information, clinical, pathological, and radiographic findings.
- There are four recommended regimens for treating patients with TB disease caused by drug-susceptible organisms. Each regimen has an initial two (2) month treatment followed by a continuation phase of either four (4) or seven (7) months.
- The standard treatment regimen for all patients with previously untreated tuberculosis should consist of a two (2) month initial phase of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB).
  - For each patient with suspected or confirmed TB disease placed on a non-standard regimen, the regional TB program provides documentation of the TB clinician's orders and rationale to the TTBEPC.O. within two (2) business days (**Standard of Public Health Practice IV-18**).
  - The assigned TB case manager will notify and fax or scan the supporting documentation to the TTBEPC.O. so that arrangements with the Tennessee State Pharmacist can be made to have the medication shipped to the regional/metro health department pharmacy.
- The initial phase may be given daily throughout (regimens 1 and 4 in **Table IV-7**) or daily for two (2) weeks then twice weekly for six (6) weeks (regimen 2 in **Table IV-7**). While current CDC/ATS/IDSA guidelines recommend that treatment can be given three (3) times weekly throughout (regimen 3, given a "B" rating—**Refer to Table IV-7**), TTBEPC recommends that this regimen should generally be used only for select patients, such as those who are not initially infectious (do not require respiratory isolation) and patients with end-stage renal disease who receive therapy after dialysis.
- Initial treatment for each suspected or confirmed case of TB disease is administered by DOT for 14 days (including weekends and holidays), then may be given Monday-Friday by DOT as ordered by the TB clinician (**Standard of Public Health Practice IV-3**).
- Because of the relatively high proportion of patients with TB disease caused by organisms that are resistant to INH, two (2) drugs are necessary in the initial phase for the six (6)-month regimen to be maximally effective.
- If INH cannot be used (resistance or intolerance), a six (6)-month regimen using RIF, PZA and EMB throughout treatment is nearly as efficacious as an INH-containing regimen.
- Alternatively, RIF and EMB for 12 months may be used, preferably with PZA during at least the initial two (2) months.
- If RIF cannot be used, INH, EMB and a fluoroquinolone should be given for a minimum of 12-18 months supplemented with PZA during at least the first two (2) months.
- EMB should be given in the initial phase of four (4) drug regimen (**Refer to Table IV-7**) until drug susceptibility is determined. EMB is discontinued when DST results show that the M. tb strain is pansensitive (**Standard of Public Health Practice IV-8**).

- Pyrazinamide (PZA) is administered as part of a multidrug regimen in the initial treatment phase (for at least eight (8) weeks) (**Standard of Public Health Practice IV-9**). If PZA cannot be included in the initial phase of treatment, the initial phase should consist of INH, RIF and EMB given daily for two (2) months (regimen 4 in Table IV-6) and treatment will be extended for seven (7) more months. Examples of circumstances in which PZA may be withheld include:
  - severe liver disease
  - active gout
  - pregnancy
  - drug resistance to PZA
- An injectable agent may also be included for the initial two-three (2-3) months for patients with extensive disease or to shorten the duration of treatment (e.g. to 12 months).
- Levofloxacin, moxifloxacin, and gatifloxacin may be useful in alternative regimens, but the potential role of a fluoroquinolone and the optimal length of therapy have not been defined.
- In situations where multiple first-line agents cannot be used because of intolerance, regimens based on the principles described for treating MDR-TB can be used.

Treatment orders are documented in the medical record by the TB clinician. These orders include (**Standard of Public Health Practice IV-12**):

- Drug name(s)
- Dosage
- Frequency of dose
- DOT
- Planned duration of therapy

Reference:

1. CDC. Treatment of Tuberculosis: American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR 2003; 52 (No. RR-11). <http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf>

**Table IV-7: Drug Regimens for Pulmonary TB in Adult Cases by Drug-Susceptible Organisms\***

Regimen	Initial		Continuation Phase			
	Drugs	Interval and Doses±§	Regimen	Drugs	Interval and Doses±§	Range of Total Doses
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) <b>or</b> 5 days/week for 40 doses (8 weeks) <sup>¶</sup>	1a	INH RIF	7 days/week for 126 doses (18 weeks) <b>or</b> 5 days/week for 90 doses (18 weeks)	182-130 (26 weeks)
			1b <sup>#</sup>	INH RIF	2 days/week for 36 doses (18 weeks)	92-76 (26 weeks)
			1c <sup>**</sup>	INH RPT	1 day/week for 18 doses (18 weeks) <sup>¶</sup>	74-58 (26 weeks)
2	INH RIF PZA EMB	7 days/week for 14 doses (2 weeks), then 2 days/week for 12 doses (6 weeks) <b>or</b> 5 days/week for 10 doses (2 weeks), <sup>¶</sup> then 2 days/week for 12 doses(6 weeks)	2a <sup>#</sup>	INH RIF	2 days/week for 36 doses (18 weeks) <sup>¶</sup>	62-58 (26 weeks)
			2b <sup>**</sup>	INH RPT	1 day/week for 18 doses (18 weeks) <sup>¶</sup>	44-40 (26 weeks)
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 weeks)	3a	INH RIF	3 times weekly for 54 doses (18 weeks) <sup>¶</sup>	78 (26 weeks)

Regimen	Initial		Continuation Phase			
	Drugs	Interval and Doses±§	Regimen	Drugs	Interval and Doses±§	Range of Total Doses
4	INH RIF EMB	7 days/week for 56 doses (8 weeks) <b>or</b> 5 days/week for 40 doses (8 weeks) <sup>¶</sup>	4a	INH RIF	7 days/week for 217 doses (31 weeks) <b>or</b> 5 days/week for 155 doses (31 weeks) <sup>¶</sup>	273-195 (39 weeks)
			4b <sup>#</sup>	INH RIF	Twice weekly for 62 doses (31 weeks) <sup>¶</sup>	118-102 (39 weeks)

\*For more information on strength and recommendation and quality of supporting evidence, refer to CDC. Treatment of Tuberculosis: American Thoracic Society, CDC, and Infectious Disease Society of America. MMWR 2003; 52 (No. RR-11) <http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf>

±When DOT is used, drugs may be given 5 days/week and the necessary doses adjusted accordingly.

§Patients with cavitation on initial chest X-ray and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase.

¶Patients on regimens given less than 7 days a week should receive DOT.

#Regimens given less than 3 times a week are **not** recommended for HIV-infected patients with CD4+ counts less than 100.

\*\*Used only for HIV-negative patients with negative sputum smears at completion of 2 months of therapy and who do **not** have cavitation on initial chest X-ray. For patients started on this regimen and found to have positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

#### References:

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know, 2013. [http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf) (adapted)

### **Intermittent Therapy Recommendations**

Intermittent TB therapy is the administration of TB medications by DOT either twice weekly (2 days/week) or thrice weekly (3 days/week) instead of daily (7 days/week or 5 days/week).

The standard of care in Tennessee is to use a daily (7 days/week including weekends and holidays) anti-TB regimen, during at least the first 14 days treatment, then 5 days/weeks until considered non-infectious, whichever date is later. This is particularly important in the following circumstances:

- Recurrent TB disease (relapse or re-infection)
- Treatment failure (as defined by ATS/CDC)
- Chronic liver disease (elevated baseline liver enzymes, viral hepatitis, cirrhosis, etc.)
- Risk for malabsorption syndromes (e.g., poorly controlled diabetes, Crohn's disease, inflammatory bowel disease, gastrectomy, HIV/AIDS infection, alcoholism, etc.)
- Multi-drug resistance (MDR TB) or poly-drug resistance

Certain patients are more likely to risk relapse, delayed response to therapy and/or treatment failure. Consider the following before initiating intermittent therapy:

- Patients with an unknown HIV status or confirmed HIV-positive status should not be placed on once weekly (1day/week) or twice-weekly (2 days/week) treatment regimens. The TTBEP recommends a daily (7 days/week or 5 days/week) throughout the initial phase; if adequate clinical response, thrice-weekly (3 days/week) therapy is acceptable during the continuation phase.
- TB cases with cavitation on chest radiograph and/or delayed culture conversion (beyond the Initial phase of two (2) months) should not be placed on intermittent therapy within the continuation phase.

TTBEP recommends consultation with the TTBEP Medical Director for exceptions to these recommendations.

### **TB Disease Treatment Regimens for Specific Situations**

#### **Pediatrics (Refer to Table IV-8)**

- DOT must always be utilized when treating children
- Children commonly develop primary TB disease which generally affects the middle and lower lung
- Because tuberculosis in infants and young children is more likely to disseminate, **treatment should be started as soon as the diagnosis is suspected.** In Tennessee, this early implementation of treatment is recommended for:
  - Children < 5 years of age **and**
  - Asymptomatic children with:
    - Positive PPD-tuberculin skin test **and**
    - Abnormal chest radiograph, including:
      - Atelectasis

- Parenchymal infiltrate
  - Nodules
  - Hilar adenopathy
- Children and adolescents with adult-type pulmonary tuberculosis should be started on the standard four-drug regimen
- The TTBEF recommends prescribing infants, children and adolescents with suspected or confirmed TB disease the same treatment regimen as prescribed to adults
- In cases of suspected drug-resistant tuberculosis in a child or when a source case isolate is not available, specimens should be obtained from the child for microbiologic evaluation, including:
  - Early morning gastric aspiration
  - Bronchoalveolar lavage
  - Biopsy
- Because it is difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis, it may be necessary to rely on the drug susceptibility tests obtained from the presumed source case to aid in the treatment regimen selection for the child
- In general extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. Some exceptions may require longer treatment duration, such as:
  - Disseminated tuberculosis (9-12 months of therapy recommended)
  - Tuberculosis meningitis (9-12 months of therapy recommended)
- The American Academy of Pediatrics recommends that HIV-infected children and adolescents with pulmonary TB disease be treated with at least three (3) TB medications for a minimum of nine (9) months
- If the prescribed TB medication comes in a suspension form, follow the regional/metro pharmacist recommendations for administration of medication, proper storage and expiration date
- When epidemiological circumstances suggest an increased probability of INH resistance, EMB can be used safely at a dose of 15 mg/kg/day, even in children too young for routine eye screening
- Streptomycin or amikacin can be used as the fourth drug, when necessary
- Pyridoxine is recommended only for children and adolescents who are being treated with INH and who have:
  - nutritional deficiencies
  - symptomatic HIV infection
  - infants who are breastfeeding

The TTBEF Medical Director is available to provide consultation on pediatric cases upon request.

**Table IV-8. Recommended Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents**

Infection or Disease Category	Regimen	Remarks
Pulmonary and extrapulmonary (except meningitis)	2 months of INH, RIF, PZA, and ethambutol daily or twice weekly, followed by 4 months of INH and RIF* by DOT** for drug-susceptible <i>Mycobacterium tuberculosis</i>	If possible drug resistance is a concern, some experts recommend a 3-drug regimen (INH, RIF, and PZA)  If hilar adenopathy only, a 6-month course of INH and RIF is sufficient
Meningitis	2 months of INH, RIF, PZA and an aminoglycoside or EMB or ethionamide, once a day, followed by 7-10 months of INH and RIF, once a day or twice a week (9-12 months total) for drug-susceptible <i>M. bovis</i>	For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin or capreomycin can be used instead of streptomycin

\*Medications should be administered daily for the first 2 weeks to 2 months of treatment and then can be administered 2-3 times per week by DOT.

\*\*If initial chest radiograph shows cavitary lesions and sputum after 2 months of therapy remains positive, duration of therapy is extended to 9 months.

Reference:

1. American Academy of Pediatrics. Tuberculosis. In: Pickering LK, editor. Red book report of the Committee on Infectious Diseases, 29<sup>th</sup> edition. Elk Grove Village, IL: American Academy of Pediatrics, 2012: 745 (adapted).

## Pregnant Women

- Untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than treatment of TB disease. Therefore, treatment of TB disease in pregnant women should be initiated whenever the probability of maternal disease is moderate to high
- Initial treatment regimen should consist of INH, RIF, and EMB. Although all of these drugs cross the placenta, they do not appear to have teratogenic effects
- PZA may safely be used during pregnancy and is recommended by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD). If PZA is **not** included in the initial treatment regimen, the minimum duration of therapy is nine (9) months.
- Streptomycin is the only anti-TB drug documented to have harmful effects on the human fetus (congenital deafness) and **should not** be used.
- Kanamycin, amikacin, and capreomycin presumably share this toxic potential for harmful effects on the human fetus and **should not** be used.
- The fluoroquinolones have been associated with arthropathies in young animals; therefore, they should be avoided if possible in pregnant women.
- There is not enough data to adequately determine the risk of other second-line agents.
- For pregnant women with MDR-TB, treatment should only be provided with consultation from the TTBEF Medical Director and other TB experts. Many of the medications currently used for treatment of MDR-TB may be harmful to the fetus.
- **Breastfeeding should not be discouraged for women being treated with the first-line anti-tuberculosis agents** (unless they are HIV+) because the small concentrations of these drugs in breast milk do not produce toxicity in the nursing newborn. Conversely, drugs in breast milk should not be considered to serve as an effective treatment for TB disease or TB infection in a nursing infant.
- Pyridoxine (B<sub>6</sub>) supplementation (50 mg daily) is recommended for all women taking INH who are either pregnant or breastfeeding.
- Pyridoxine (B<sub>6</sub>) supplement is recommended for breastfeeding infants whose mothers are taking INH.

## HIV-Infected Persons

- In patients with symptoms and signs of TB, a negative chest radiograph result does not exclude TB disease.
- The TB physician should consult with the patient's HIV specialist in the treatment of HIV-related tuberculosis due to the potential interact of anti-retroviral medications with the anti-tuberculosis medications, and due to patient's other possible co-morbid conditions.
- The TTBEF Medical Director should be consulted for HIV-infected women who are pregnant and for children co-infected with HIV.
- Prior to the initiation of therapy, HIV-infected patients with suspected or confirmed TB disease should be carefully evaluated for underlying liver disease, substance abuse, psychiatric disorders, other factors that may influence non-adherence, or intolerance to or toxicity of therapy.

- HIV-infected TB patients are to be initiated on a four (4)-drug treatment regimen unless contraindications exist. Every effort should be made to use a rifamycin-based regimen for the entire course of therapy in co-infected patients.
- The treatment regimens listed in **Table IV-7** are effective for TB patients living with HIV, with two exceptions (due to the increased risk of developing acquired drug resistance):
  - Once-weekly administration of INH and RPT in the continuation phase **should not** be used in any HIV-infected patient; and
  - Patients with advanced HIV (CD4+ counts <100) must be treated with daily or three (3) times/weekly therapy in both the initial and continuation phase.
- Patients with HIV co-infection who have drug-susceptible TB must be treated for a minimum of six (6) months.
- HIV+ adults with culture-negative tuberculosis must be treated for six (6) months.
- Patients with a cavity noted on the initial chest radiograph or positive cultures despite two (2) months of TB medication with strict DOT, must be treated for a minimum of nine (9) months to prevent treatment failure or relapse.
- The TTBEF recommends therapeutic drug monitoring (TDM) early (within the first eight (8) weeks) in the initial phase for all TB patients who are co-infected with HIV.

For TB patients with a new diagnosis of HIV (at the time of TB diagnosis), **Table IV-9** outlines the timeframes for starting HIV therapy.

**Table IV-9: Timeframe to Start HIV Therapy in TB/HIV Co-Infected Patients**

CD4+ Count and/or Clinical Status at Time of TB Diagnosis	ART Initiation
<50 cells/mm <sup>3</sup>	Within 2 weeks of starting TB therapy
≥50 cells/mm <sup>3</sup> with severe clinical disease*	Within 2-4 weeks of starting TB therapy
≥50 cells/mm <sup>3</sup> without severe clinical disease*	Within 8-12 weeks of starting TB therapy
Pregnant, any CD4+ count	As early as feasible
MDR or XDR-TB, and CD4+ count	Within 2-4 weeks of confirmation of drug resistance and start of 2 <sup>nd</sup> -line therapy

\*Severe clinical disease: low Karnofsky score, low body mass index, low hemoglobin, low albumin, organ system dysfunction, or disseminated/widespread TB disease.

Reference:

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services, 2013. <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0> (adapted)

Differences with the Rifamycins and their uses:

- Rifampin can be given with the following antiretrovirals:
  - All nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
  - Selected non-nucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz **only**

- Integrase inhibitor, raltegravir
- Rifampin **should not** be used with the following:
  - All protease inhibitors
  - Nevirapine, etravirine, rilpivavine (NNRTIs): efavirenz **only**
  - CCR5 antagonist, maraviroc
- Rifabutin (RBT) can be substituted for rifampin (RIF) and used with:
  - Protease inhibitors: atazanavir (with ritonavir boosting), darunavir (with ritonavir boosting), fosamprenavir (with ritonavir boosting), lopinavir/ritonavir (Kaletra). When RBT is given in combination with protease inhibitors, the dose of RBT needs to be reduced as outlined in **Table IV-10**.
  - NRTIs (e.g., zidovudine, lamivudine, emtricitabine, tenofovir, abacavir).
  - Selected NNRTI: efavirenz; the dose of RBT should be increased to 450 mg daily or 600 mg 3 times/week when administered with efavirenz
- Rifapentine (RPT) **should not** be used in patients with HIV co-infection for the treatment of TB disease.

**Table IV-10: Dosage Adjustments for ART and Rifamycins when Used in Combination**

	Rifampin (RIF)	Rifabutin (RBT)
<b>NNRTI</b>		
Efavirenz (EFV)	RIF no change (600 mg) EFV: no change (600 mg qhs) **Some clinicians increase EFV to 800 mg/d for patients >60 kg**	RBT: increase to 450 mg/d or 600 mg/tiw EFV: no change (600 mg qhs)
<b>Boosted PI</b>		
ATV/r DRV/r LPV/r FPV/r	DO NOT USE	RBT: decrease to 150 mg/d or 300 mg/tiw PIs: no change
<b>Integrase Inhibitor</b>		
Raltegravir (RAL)	RIF: no change (600 mg) RAL: increase to 800 mg bid	RBT: no change (300 mg) RAL: no change (400 mg bid)

Reference:

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services, 2013.  
<http://aidsinfo.nih.gov/ContentsFiles/AdultandAdolescentGL.pdf>. Section J-14.

Occasionally, patients with HIV-related tuberculosis may experience a temporary exacerbation of signs, symptoms, or radiographic manifestations of TB while receiving anti-tuberculosis treatment. This clinical or radiographic worsening (paradoxical reaction) occurs in HIV-infected

patients with active tuberculosis and is thought to be the result of immune reconstitution as a consequence of effective anti-retroviral therapy. Signs and symptoms may include:

- high fevers
- lymphadenopathy
- expanding central nervous system lesions
- worsening of chest radiographic findings
- The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other etiologies, particularly tuberculosis treatment failure.
- Non-steroidal anti-inflammatory agents may be useful for symptomatic relief. For severe paradoxical reactions, prednisone (1-2 mg/kg/day for 1-2 weeks, then gradually decreasing doses) may be used, although there are no data from controlled trials to support this approach.

### Renal Insufficiency and End-Stage Renal Disease

- TB physician should consult with the patient's nephrologist.
- Standard TB regimen doses are given unless there is patient intolerance.
- Renal insufficiency complicates the management of TB disease because some anti-tuberculosis medications are cleared by the kidneys (e.g., EMB).
- RIF and INH are metabolized by the liver, so conventional dosing may be used in the setting of renal insufficiency.
- For patients undergoing hemodialysis, administration of all anti-tuberculosis medications after dialysis is preferred. Arrangements may be made in advance with the hemodialysis HCW to administer DOT post-hemodialysis.
- Alteration in dosing of anti-tuberculosis medications is commonly necessary in patients with renal insufficiency and end-stage renal disease (ESRD) requiring hemodialysis.
- Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using therapeutic drug monitoring (TDM).
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, to avoid medication toxicity.
- The dosage of anti-tuberculosis medications **should not** be decreased because the peak serum concentrations may be low and smaller doses may decrease drug efficacy. Instead, the dosing interval of anti-tuberculosis medications should be increased.
- Based on creatinine clearance, most anti-tuberculosis medications can be given 3 times a week (3 days/week) immediately after hemodialysis.
- A longer interval between doses is recommended for PZA and EMB.

### Hepatic Disease

- The treatment of TB disease in patients with unstable or advanced liver disease is problematic. The TTBE Medical Director is available for consultation upon request.
- Consider regimens with fewer potentially hepatotoxic agents in patients with advanced or unstable liver disease due to their greater likelihood of drug-induced hepatitis. The

implications of drug-induced hepatitis with marginal hepatic reserve are potentially serious, even life-threatening.

- In all patients with pre-existing liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury.
- INH, RIF and PZA all can cause hepatitis that may result in additional liver damage in patients with pre-existing liver disease.
- If the serum AST is more than three (3) times the upper limit of normal (ULN) prior to the initiation of treatment (and the elevation is not thought to be caused by TB), several treatment options exist:
  - RIF, EMB, and PZA given for 6 months, avoiding INH
  - INH and RIF given for 9 months, supplemented by EMB until INH and RIF drug susceptibility tests are confirmed, thereby avoiding PZA.
- For patients with severe liver disease, a regimen with only one (1) hepatotoxic agent (generally, RIF plus EMB), could be given for 12-18 months depending on the extent of the disease and the response to treatment. This regimen should preferably be used with another agent, such as a fluoroquinolone, for the first two (2) months; however, there are no data to support this recommendation.
- In the setting of severe unstable liver disease, a regimen with no hepatotoxic agents may be necessary. Such a regimen might include SM, EMB, a fluoroquinolone and another second-line oral drug. There are no data to provide guidance as to the choice of agents, the duration of treatment, or to indicate the effectiveness of such a regimen. Expert opinion suggests that a regimen of this sort should be given for 18-24 months.

#### Diabetes and TB

- The TB clinician should consult with the patient's medical provider for diabetes during the course of TB treatment to optimize glycemic control.
- Poorly controlled diabetes may accelerate development of extensive TB disease. The TTBEF recommends obtaining a baseline hemoglobin A1c level initially and as ordered by the TB clinician. (**Standard of Public Health Practice IV-14**)
- Extensive TB disease may exacerbate symptoms of hyperglycemia in a patient with diabetes.
- People with diabetes who are diagnosed with TB disease have a:
  - 2-3 times higher risk of TB complications compared to people without diabetes
  - Higher risk of death during TB treatment
  - Higher risk of TB relapse after treatment
- Treat diabetics with suspected or confirmed TB disease (drug susceptible) with the standard four-drug therapy during the initial phase, and continue INH and RIF during the continuation phase.
- Due to the elevated risk of INH and/or RIF malabsorption in diabetic patients, the TTBEF strongly recommends daily anti-TB treatment in both the initial and continuation phases.

- Persons with diabetes are at increased risk of peripheral neuropathy and should receive vitamin B6 daily to help prevent INH-induced neuropathy.
- PZA and EMB dosages may need adjusting for diabetics with renal impairment. The TTBEF recommends obtaining a serum creatinine level initially and as ordered by the TB clinician.
- Due to increased risk of malabsorption of some TB medications, the TTBEF recommends early (within the first eight (8) weeks) therapeutic drug monitoring (TDM) for INH and RIF for all diabetics with newly-diagnosed TB disease.
- Consider extending TB treatment to nine (9) months for persons with diabetes, especially those patients with cavitary disease or delayed sputum clearance. Patients with diabetes have relative immune suppression and often a higher burden of TB disease.
- PZA and EMB need adjustment for renal impairment in diabetics. May need to consider checking serum creatinine.
- RIF raises blood glucose levels even in a non-diabetic patient, and also activates the CYP450 enzyme system. Blood levels of sulfonylureas and thiazolidinediones are significantly lowered by RIF. As a result, blood glucose control in patients with diabetes may worsen during the treatment of TB disease. For this reason, the frequency of communication and collaboration between the clinicians managing the patient's TB disease and diabetes is essential.
- Many patients with diabetes are on statins, as well as the thiazolidinediones, which carry a risk of hepatotoxicity. The TTBEF recommends monitoring liver enzymes initially and monthly during the treatment of TB disease.

#### References:

1. World Health Organization (WHO). Tuberculosis & Diabetes 2011.  
[http://www.who.int/tb/publications/diabetes\\_tb.pdf](http://www.who.int/tb/publications/diabetes_tb.pdf)
2. Francis J. Curry International TB Center. *Draft Interim* USAPI Standards for the Management of Tuberculosis and Diabetes (PITCA Ratified 12-01-2010) 2010.  
[http://www.download.thelancet.com/journals/landia/article/PIIS2213-8587\(14\)70230-X/fulltext](http://www.download.thelancet.com/journals/landia/article/PIIS2213-8587(14)70230-X/fulltext)
3. Heartland National TB Center. Rifamycins and Anti-Diabetic Agents: Drug-Drug Interactions. 2012.  
[http://www.heartlandntbc.org/assets/products/Rifamycins%20and%20Anti-Diabetic%20Agents\\_2012.pdf](http://www.heartlandntbc.org/assets/products/Rifamycins%20and%20Anti-Diabetic%20Agents_2012.pdf)

#### Extrapulmonary TB Disease

- The primary goal of the TB program is to provide effective treatment and case management to all persons with suspected or confirmed TB disease, regardless of infectiousness or site of involvement. By ensuring completion of an adequate course of TB treatment, the TB program can prevent extrapulmonary tuberculosis from hematogenously becoming pulmonary (and potentially infectious) tuberculosis, and the individual patient's morbidity and mortality will be greatly reduced.

- As a general rule, the principles used for the treatment of pulmonary TB disease apply to patients with extrapulmonary TB.
- A six (6) month regimen is recommended for patients with extrapulmonary disease unless the organisms are known or strongly suspected to be resistant to first-line drugs.
- If PZA cannot be used in the initial phase, the continuation phase must be increased to seven (7) months.
- Prolongation of therapy must be considered for patients with tuberculosis in any site that is slow to respond. Consultation with the TTBE Medical Director is recommended if treatment is expected to extend > 12 months.
- Patients who have TB of the central nervous system are recommended to complete 9-12 months of treatment.

Most experts recommend corticosteroids to be used as additional therapy for patients with TB meningitis and pericarditis:

- Adults:
  - 60 mg/day of prednisone (or the equivalent dose of prednisolone) given for 4 weeks, followed by
  - 30 mg/day for 4 weeks
  - 15 mg/day for 2 weeks, and finally
  - 5 mg/day for the 11th and final week
- Children:
  - Doses proportionate to their weight, beginning with approximately 1 mg/kg body weight and decreasing the dose as described for adults.

**Table IV-11** outlines the duration of treatment for cases of extrapulmonary TB

**Table IV-11 Duration of Treatment for Extrapulmonary TB**

Site of Disease	Length of Treatment (months)
Lymph node	6
Bone and joint	6-9
Pleural disease	6
Pericarditis	6
Central nervous system (including meningitis)	9-12
Disseminated disease	6
Genitourinary	6
Peritoneal	6

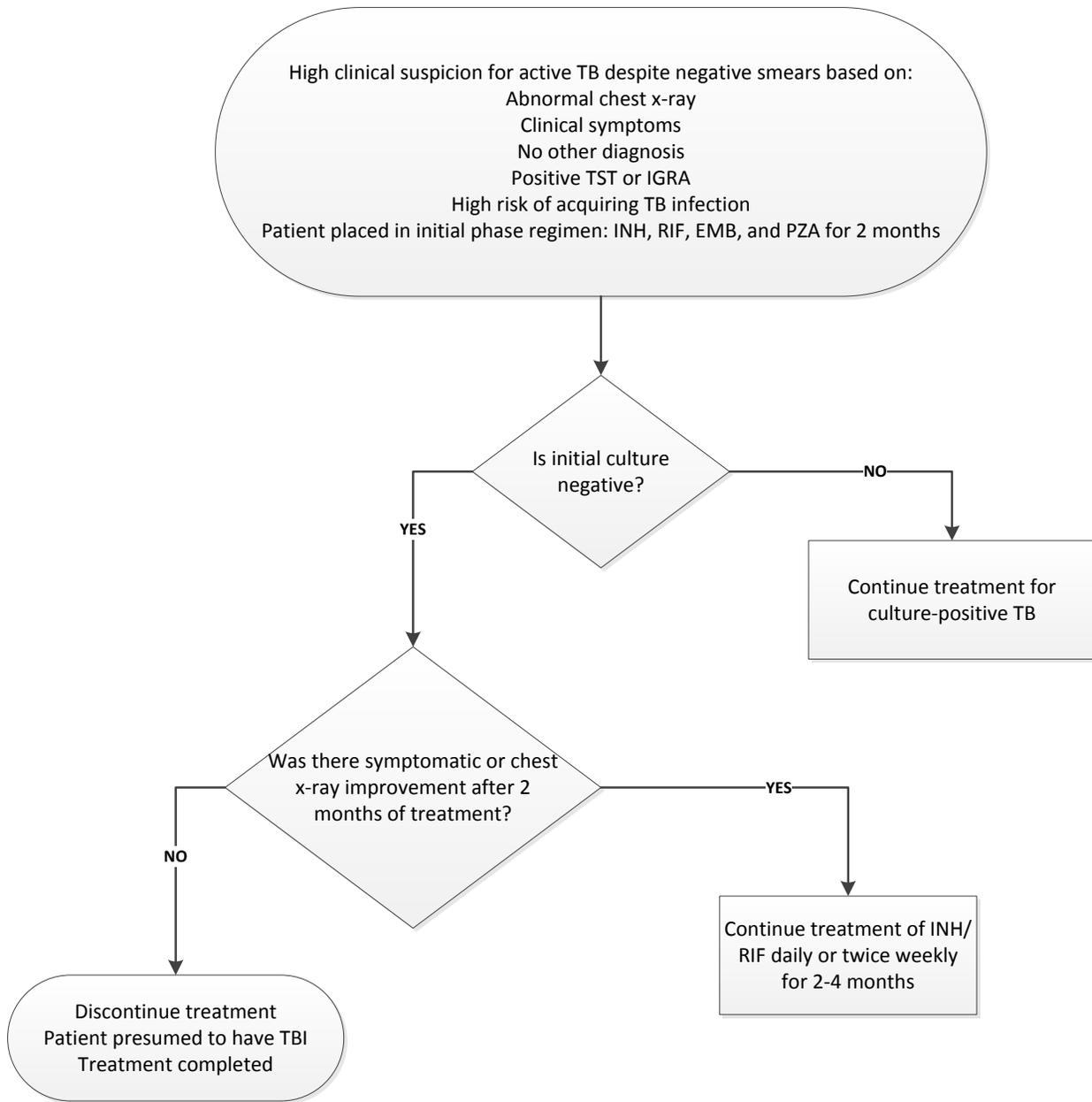
Reference:

1. CDC. Treatment of Tuberculosis: American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR 2003; 52 (No. RR-11). <http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf> (adapted)

Culture-Negative Pulmonary Tuberculosis and Radiographic Evidence of Prior Pulmonary Tuberculosis (Refer to Figure IV-1)

- Failure to isolate *M. tuberculosis* from persons with suspected pulmonary TB based on clinical features and chest radiographic examination does not exclude a diagnosis of active tuberculosis. Alternative diagnoses must be considered carefully and further appropriate diagnostic studies undertaken in persons with apparent culture-negative tuberculosis.
- A diagnosis of tuberculosis can be strongly inferred by the clinical and radiographic response to anti-tuberculosis treatment when the following are performed:
  - Careful clinical re-evaluation must be performed after two (2) months of effective therapy to determine if there has been a response attributable to anti-tuberculosis treatment
  - PA and lateral chest radiographs must be repeated two (2) months after treatment was initiated
- If clinical and/or radiographic improvement is noted and no other etiology is identified, continue treatment for active tuberculosis. Treatment regimens in this circumstance include:
  - One of the standard six (6) month chemotherapy regimens, or
  - INH, RIF, PZA and EMB for two (2) months followed by INH and RIF for two (2) additional months (four (4) months total).
- If there has been no clinical or radiographic improvement, further evaluation for other diagnoses is needed and discontinuation of therapy may be indicated. Ensure that failure to improve cannot be attributed to:
  - non-adherence
  - inadequate therapy (e.g., low serum drug concentration, drug-drug interactions, etc.)
  - development of resistance prior to stopping therapy
- Occasionally, patients who are being evaluated for pulmonary tuberculosis will be found to have positive AFB smears but negative cultures. There are several potential explanations for this occurrence:
  - Possibly the acid-fast bacilli (AFB) organisms are non-tuberculous mycobacteria (NTM) and difficult to culture, or
  - They are non-viable tubercle bacilli and are the result of laboratory or processing error (e.g., specimen put in formalin).
- The approach taken in such cases should be individualized, based on clinical and radiographic findings. If suspicion of tuberculosis is high and the patient has positive AFB smears, even with negative cultures, he/she should be treated as if the culture is positive using one of the recommended regimens.

**Figure IV-1: Treatment for Culture-Negative TB**



Reference:

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. 2013.  
[http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf)

## Drug Resistance

- Mono-resistant TB (resistance to only one TB drug—especially INH) and poly-resistant TB (especially INH and SM) are increasingly common in certain populations in Tennessee.
- Multidrug-resistant TB (MDR TB) is defined as TB disease resistant to at least INH **and** RIF.
- MDR TB can only be proven by drug-susceptibility testing.
- Patients with MDR TB are at a higher risk for treatment failure and further acquired drug resistance. **Patients with MDR TB must be reported to the TBEP Medical Director.**
- Drug-resistant TB disease can develop in two different ways:
  - Primary resistance: occurs in persons who are initially exposed to and infected with resistant organisms
  - Secondary resistance: acquired resistance which develops during TB therapy because of:
    - Treatment with an inadequate regimen
    - Not taking TB regimen as prescribed
    - Drug malabsorption
    - Drug-drug interactions leading to low serum levels
- Drug resistance in a patient with newly-diagnosed TB disease may be suspected on the basis of:
  - Previous treatment
  - Contact with a known drug-resistant case
  - Time spent in a region in which drug resistance is common
- Patients with strains of *M. tuberculosis* resistant to both INH and RIF (multidrug-resistant) are at high risk for the following:
  - Treatment failure
  - Relapse
  - Further acquired resistance
  - Death
- A single new drug must **never** be added to a failing regimen.
- In patients with MDR organisms resistant to first-line drugs, in addition to INH and RIF, regimens employing four (4) to six (6) drugs that are new to the patient and to which the isolate shows in vitro susceptibility appear to be associated with better results.
- Patients with multidrug-resistant organisms must receive the highest priority for DOT, which should be administered either in the hospital, home, or other facility.
- The use of drugs to which there is demonstrated in vitro resistance is **not** encouraged because there is little or no efficacy of these drugs and alternative medications may be available.
- Resistance to RIF is associated in nearly all instances with cross-resistance to RBT and RPT.
- There is no cross-resistance between SM and the other injectable agents amikacin, kanamycin, and capreomycin (although resistance to all may occur as independent

events); cross-resistance between amikacin and kanamycin is not universal but frequently seen.

- Resistance to PZA is uncommon in the absence of resistance to other first-line drugs; if mono-resistance to PZA is observed, consideration must be given to the possibility that the disease is caused by *M. bovis*, not *M. tuberculosis*.
- Intermittent therapy should not be used in treating TB disease caused by drug-resistant organisms, except perhaps for injectable agents after the Initial phase (usually two to three (2 to 3) months) of daily therapy.
- Some patients with extensive pulmonary MDR tuberculosis may require surgical resection after several months of intensive chemotherapy. Discussion and arrangements for this option must be made with the TTBEF Medical Director.
- Patients with MDR will need 18-24 months of treatment past culture conversion.

Management of patients with drug-resistant TB disease is based on the following guidelines:

- Patients with MDR TB usually require hospitalization for PICC line insertion and to begin a MDR treatment regimen which includes an injectable/intravenous (IV) medication.
  - TB case manager must consult with the TTBEF C.O. to make necessary discharge arrangements and to establish contracts with facilities and HCWs that will be needed to provide IV therapy in the home. (**Refer to Tool IV-3 Case Managing the TB Patient Receiving Contracted Vendor Services**)
  - All discharge plans should be completed prior to hospital discharge.

Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs.

For dosage and frequency of MDR TB medication, refer to “Drug-Resistant Tuberculosis: A Survival Guide for Clinicians” 2<sup>nd</sup> edition. Francis J. Curry National Tuberculosis Center, 2011. <http://www.currytbcenter.ucsf.edu/drtb/>

**Table IV-12** identifies potential regimens for the management of patients with drug-resistant pulmonary tuberculosis.

**Table: IV-12: Potential Regimens for the Management of Patients with Drug-Resistant Pulmonary Tuberculosis**

Pattern of Drug Resistance	Suggested Regimen	Duration of Treatment	Comments
INH ( $\pm$ SM)	RIF, PZA, EMB (a fluoroquinolone may strengthen the regimen for patients with extensive disease)	6 months	IN BMRC trials, 6-month regimens have yielded $\geq 95\%$ 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 six (6) months (Rating BII). Fluoroquinolones were not employed in BMRC studies, but may strengthen the regimen for patients with more extensive disease (Rating BII). INH should be stopped in cases of INH resistance.
INH and RIF ( $\pm$ SM)	Fluoroquinolone (FQN), PZA, EMN, injectable agent (IA) $\pm$ alternative agent	18-24 months	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. Re-sectional surgery may be appropriate.
INH, RIF ( $\pm$ SM) and EMB or PZA	FQN (EMB or PZA if active), IA, and two alternative agents	24 months	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.

Pattern of Drug Resistance	Suggested Regimen	Duration of Treatment	Comments
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)	9-12 months	Daily and three times weekly regimens of INH, PZA, and SM given for nine (9) mos 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 months should be effective (Rating BII). But for more extensive disease and/or to shorten duration (e.g., to 12 months), an injectable agent may be added in the initial 2 months of therapy (Rating BIII).

**Reference:**

1. CDC. Treatment of Tuberculosis: American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR 2003; 52 (No. RR-11). <http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf> (adapted)

**Table IV-13** lists the protocol for giving streptomycin and other injectable TB drugs

**Table IV-13 Instructions for Giving Streptomycin and Other Injectable TB Drugs**

Equipment	Protocol
<ul style="list-style-type: none"> <li>• 5 ml syringe</li> <li>• 22 or 23 gauge 1' needle syringe to draw up medication</li> <li>• 1 ½ or 2 inch 23 gauge needle for injection</li> <li>• Bottle of streptomycin or other injectable TB drug</li> <li>• Bottle of sterile water, or 1 % Lidocaine</li> <li>• Alcohol swabs</li> <li>• Gloves</li> <li>• Gauze pad</li> <li>• Band-Aid</li> </ul>	<ol style="list-style-type: none"> <li>1. Draw the Streptomycin or other injectable into the 5 ml syringe using the 1 inch 22 or 23 gauge needle</li> <li>2. Draw 0.5 ml of appropriate diluent (sterile water or 1% lidocaine if ordered by the physician) into <b>the same</b> 5 ml syringe</li> <li>3. Holding the syringe in an upright position, change the 1 inch needle to a 1 ½ or 2 inch 23 gauge needle</li> <li>4. Discard the uncapped needle in a sharps container</li> <li>5. Wash your hands, put on gloves</li> <li>6. Have patient lie in a prone position and as relaxed as possible</li> <li>7. Select site in the upper outer quadrant of the gluteal area</li> <li>8. Clean the area with an alcohol swab</li> <li>9. Using your non-dominant hand to pull the skin downward or laterally to displace the tissue about 1 inch</li> <li>10. Insert the needle at a 90 degree angle quickly and deeply</li> <li>11. Aspirate for 5 to 10 seconds and look for blood to ensure that you have not hit a blood vessel (if blood appears start over)</li> <li>12. Inject the drug slowly at a rate of 10 seconds/ ml of medication</li> <li>13. Ensuring the needle is completely empty, withdraw the needle</li> <li>14. Release the skin to its original position</li> <li>15. Use a dry gauze to apply very gentle pressure to the puncture site, cover with Band-Aid if needed</li> <li>16. Never massage a Z-track injection site. This may cause irritation or force the drug into subcutaneous tissue</li> <li>17. Do not recap, bend or break needles</li> <li>18. Dispose of needles and syringes in a puncture-resistant container</li> </ol>

Reference:

Heartland National TB Center

<http://www.heartlandntbc.org/assets/products/flipbook/preview/Picture/AdministrationStreptomycin.php>

Precautions and limitations:

- As with other injectable medication, anaphylactic reactions can occur, though rarely, following the injection of streptomycin or other injectable antibiotic. For this reason, the following precautions should be observed:
  - Question the patient about any evidence of drug toxicity or allergic reaction to previous injections
  - Observe the patient for 15-30 minutes following each injection
  - Follow regional or local health department policies for treatment of anaphylaxis, in the event of an anaphylactic reaction
  - Report all anaphylactic reactions to the physician as soon as possible.
  - Document the problem in the patient’s record
- Do not place injections into a disabled limb. If there is decreased circulation, the medication absorption will be affected and an abscess formation can occur
- Never inject more than 5 ml of medication at a time when using the Z-track method. If a larger dose is ordered, divide it and inject it in to two separate sites
- Do not give a Z-track injection into skin that is lumpy, reddened, irritated, bruised, stained, or hardened
- Encourage the patient to walk about to enhance absorption of the medication
- Rotate the injection sites from one buttock to the other

**Medication Dosages**

**Table IV-14** through **Table IV-20** outline the dosage recommendations for the treatment of TB disease in adults and children

**Table IV-14: Dosage Recommendations for the Treatment of TB in Adults**

Drugs	Adult Dose based on Body Weight in Kilograms (kg)*		
	Daily	2 times/week	3 times/week
INH	300 mg (5 mg/kg Maximum Dose= 300mg)	900 mg (15 mg/kg Maximum Dose=900 mg)	900 mg (15 mg/kg Maximum Dose=900 mg)
RIF	600 mg (10 mg/kg Maximum Dose=600 mg)	600 mg (10 mg/kg Maximum Dose=600 mg)	600 mg (10 mg/kg Maximum Dose=600 mg)
RBT	300 mg (5 mg/kg Maximum Dose=300 mg)	300 mg (5 mg/kg Maximum Dose=300 mg)	300 mg (5 mg/kg Maximum Dose=300 mg)
PZA**	40-55 kg: 1000 mg	40-55 kg: 2000 mg	40-55 kg: 1500 mg
	56-75 kg: 1500 mg	56-75 kg: 3000 mg	56-75 kg: 2500 mg
	≥76 kg: 2000 mg	≥76 kg: 4000 mg	≥76 kg: 3000 mg
EMB**	40-55 kg: 800 mg	40-55 kg: 2000 mg	40-55 kg: 1200 mg
	56-75 kg: 1200 mg	56-75 kg: 2800 mg	56-75 kg: 2000 mg
	≥76 kg: 1600 mg	≥76 kg: 4000 mg	≥76 kg: 2400 mg

\*To convert pounds to kilograms: divide pounds by 2.2

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

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

Reference:

1. Georgia Department of Public Health. Georgia Tuberculosis Reference Guide. 2014.  
<https://dph.georgia.gov/sites/dph.georgia.gov/files/TB-Pub-GATBReferenceGuide2014.pdf>

**Table IV-15: Commonly Used Drugs for Treatment of Tuberculosis in Infants, Children, and Adolescents**

Drug	Dosage Forms	Daily Dosage, mg/kg	Twice a Week Dosage, mg/kg per Dose	Maximum Dose	Adverse Reactions
Ethambutol	Tablets 100 mg 400 mg	20	50	2.5 g	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Isoniazid <sup>a</sup>	Scored tablets 100 mg	10-15 <sup>b</sup>	20-30	Daily, 300 mg	Mild hepatic enzyme elevation, hepatitis <sup>b</sup> , peripheral neuritis, hypersensitivity
	300 mg			Twice a week, 900 mg	
	Syrup 10 mg/mL				Diarrhea and gastric irritation caused by vehicle in the syrup
Pyrazinamide <sup>a</sup>	Scored tablets 500 mg	30-40	50	2 g	Hepatotoxic effects, hyperuricemia, arthralgia, gastrointestinal tract upset
Rifampin <sup>a</sup>	Capsules 150 mg 300 mg Syrup formulated capsules	10-20	10-20	600 mg	Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus, oral contraceptives may be ineffective

<sup>a</sup> Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (greater than 50 kg) daily doses of each drug. Rifater, available in the United States, is a capsule containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Isoniazid and rifampin also are available for parenteral administration.

<sup>b</sup> When isoniazid in a dosage exceeding 10 mg/kg/day is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

Reference:

1. American Academy of Pediatrics. Tuberculosis. In: Pickering LK, editor. Red book report of the Committee on Infectious Diseases, 29<sup>th</sup> edition. Elk Grove Village, IL: American Academy of Pediatrics, 2012: 745 (adapted).

**Table IV-16: Pediatric Dosage—INH in Children (Birth to 14 years)**

Child's Weight in lbs	Child's Weight in kg	Daily Dose (mg) 10-15 mg/kg PO	Twice-Weekly Dose (mg) 20-30 mg/kg PO
<6	<3	Refer to current Red Book	
6-10	3-4.5	50	100 mg PO
11-14	5.0-6.0	50	150 mg PO
14.5-18	6.5-8.0	100	200 mg PO
18.5-21.5	8.5-9.5	100	250 mg PO
22-24	10.0-11	150	300 mg PO
25-29	11.5-13	150	350 mg PO
29.5-32	13.5-14.5	200	400 mg PO
33-35	15-16	200	450 mg PO
36-40	16.5-18	250	500 mg PO
40.5-43	18.5-19.5	250	550 mg PO
44-48	20-21.5	300	600 mg PO
48.5-51	22-23	300	650 mg PO
52-54.5	23.5-24.5	300	700 mg PO
55-57.5	25-26	300	750 mg PO
58-62	26.5-28	300	800 mg PO
62.5-65	28.5-29.5	300	850 mg PO
≥66	≥30	300	900 mg PO

**NOTE:** Isoniazid tablets are available in 50 mg, 100 mg and 300 mg sizes and can be crushed for oral administration. Isoniazid tablets are also scored. Isoniazid Syrup (50mg/5ml) should not be refrigerated. It contains sorbitol and may cause diarrhea. The isoniazid syrup should only be used when crushed tablets cannot accommodate the situation (keep at room temperature).

**Reference:**

1. Georgia Department of Public Health. Georgia Tuberculosis Reference Guide. 2014.  
<https://dph.georgia.gov/sites/dph.georgia.gov/files/TB-Pub-GATBReferenceGuide2014.pdf>

**Table IV-17: Pediatric Dosage—RIF in Children (Birth to 14 years)—Dose for Either Daily or Twice Weekly Therapy**

Child's Weight in lbs.	Child's Weight in kg	Dose (mg) 10-20 mg/kg
<15	<7	Refer to current Red Book
15-32	7-14.5	150
33-48.5	15-22	300
49-65	22.5-29.5	450
≥66	≥30	600

NOTE: RIF comes as 150 mg or 300 mg capsules.

Reference:

1. Georgia Department of Public Health. Georgia Tuberculosis Reference Guide. 2014.  
<https://dph.georgia.gov/sites/dph.georgia.gov/files/TB-Pub-GATBReferenceGuide2014.pdf>

**Table IV-18: Pediatric Dosage—EMB in Children (Birth to 14 years)**

Child's Weight in lbs	Child's Weight in kg	Daily Dose (mg) 15-25 mg/kg
<11	<5	Refer to current Red Book
11-15	5-7	100 mg
16-31	8-14	200 mg
32-44	15-20	300 mg
45-55	21-25	400 mg
56-67	26-30.5	500 mg
68-76	31.34.5	600 mg
77-87	35-39.5	700 mg
88-121	40-55	800 mg
122-165	56-75	1200 mg
≥166	≥76	1600 mg

Note: EMB is available in 100 mg and 400 mg tablets.

Reference:

1. Georgia Department of Public Health. Georgia Tuberculosis Reference Guide. 2014.  
<https://dph.georgia.gov/sites/dph.georgia.gov/files/TB-Pub-GATBReferenceGuide2014.pdf>

**Table IV-19: Pediatric Dosage—PZA in Children (Birth to 14 years)—**

Child's Weight in lbs	Child's Weight in kg	Daily Dose (mg) 30-40 mg/kg	Twice Weekly Dose (mg) 50-70 mg/kg
<13	<5	Refer to current Red Book	
13-23	5-10.5	250 mg	500 mg
24-26	11-12	250 mg	750 mg
27-31	12.5-14	500 mg	1000 mg
32-41	14.5-18.5	500 mg	1250 mg
42-47	19.0-21.5	750 mg	1250 mg
48-54	22.0-24.5	750 mg	1500 mg
55-63	25-28.5	1000 mg	1750 mg
64-67	29-30.5	1000 mg	2000 mg
68-80	31-36.5	1250 mg	2000 mg
81-93	37-42.5	1500 mg	2000 mg
94-106	43.48.5	1750 mg	2000 mg
≥107	≥49	2000 mg	2000 mg

Note: PZA is available in 500 mg tablets, which are Scored and Can Be Cut in half

Reference:

1. Georgia Department of Public Health. Georgia Tuberculosis Reference Guide. 2014.  
<https://dph.georgia.gov/sites/dph.georgia.gov/files/TB-Pub-GATBReferenceGuide2014.pdf>

**Treatment Interruptions**

- When interruptions in therapy occur, the physician must decide whether to restart a complete course of treatment or simply to continue as intended originally. This decision depends on whether the interruption occurred during the initial or the continuation phase of therapy.

- Continuous treatment is more important in the initial phase of therapy when there is the highest bacillary population and the chance of developing drug resistance is greatest.
- During the continuation phase, the number of bacilli is much smaller and the goal of therapy is to kill the persisting organisms.

If interruption in treatment occurs during the course of treatment, follow the recommendations below:

#### During the Initial Phase

**Figure IV-2** outlines treatment interruptions during the initial phase. If the interruption occurs during the initial phase, the following guidelines apply:

- Lapse is for  $\geq 14$  days—restart treatment from the beginning
- Lapse is for  $< 14$  days—continue treatment to complete planned total number of doses (as long as all doses are completed within three (3) months)
- If any doses are missed during the first 14 days — continue daily (including weekends and holidays) medications to complete the 14 days

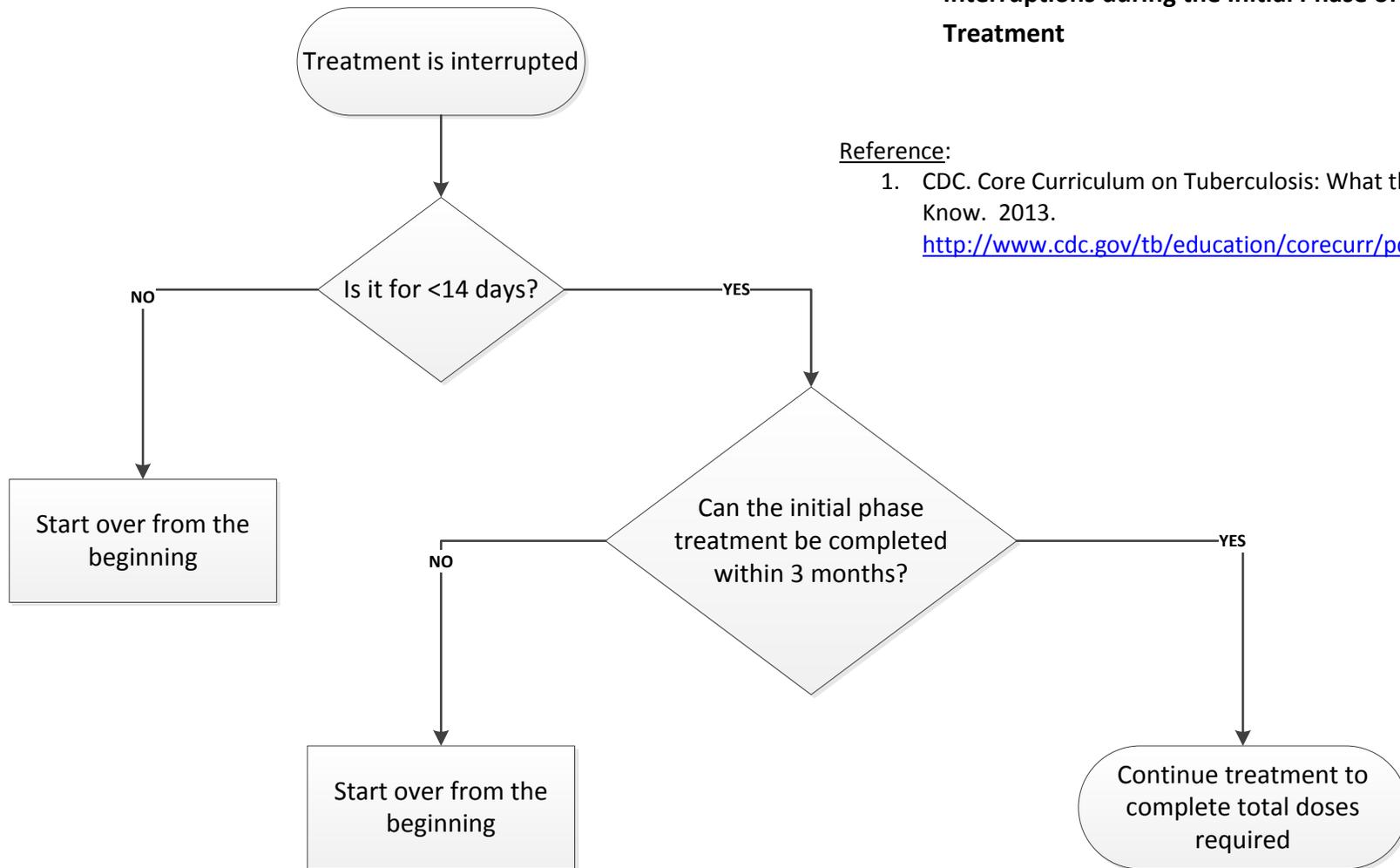
#### During the Continuation Phase

**Figure IV-3** outlines treatment interruptions during the continuation phase (80% rule). If the interruption occurred during the continuation phase, the following guidelines apply. If the patient received:

- $\geq 80\%$  of doses and sputum was acid-fast bacilli (AFB) smear negative on initial testing—further therapy may not be necessary
- $\geq 80\%$  of doses and sputum was AFB smear positive on initial testing—continue therapy
- $< 80\%$  of doses and lapse is less than three (3) months in duration—continue therapy until all doses are completed (full course)
- $< 80\%$  of doses and lapse is greater than 3 months in duration—restart therapy from the beginning of initial phase.

Upon the patient resuming treatment, sputum cultures should be obtained and a repeat drug susceptibility test performed.

**Figure IV-2: Management of Treatment Interruptions during the Initial Phase of TB Treatment**

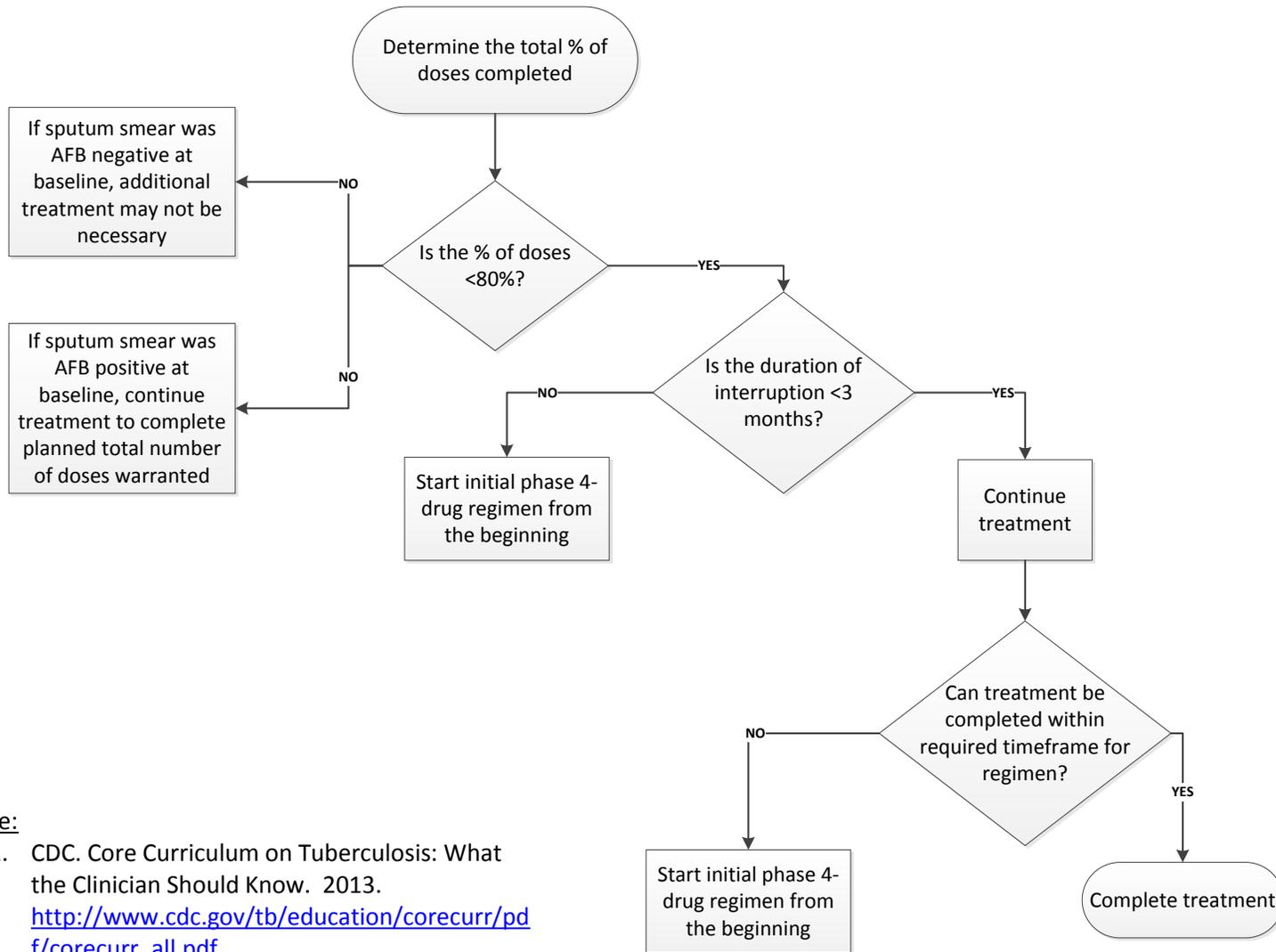


Reference:

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. 2013.

[http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf)

**Figure IV-3: Management of Treatment Interruptions during the Continuation Phase of TB Treatment**



Reference:

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. 2013. [http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf)

## **Clinical and Laboratory Monitoring**

### **TB Clinic Visits**

Each suspected or confirmed case of TB disease is evaluated in TB clinic by a clinician (physician or nurse practitioner) as soon as practicable, and at least within 10 days of the health department receiving notification (**Standard of Public Health Practice IV-2**). Following the initial medical evaluation, monthly TB clinic visits allow for timely medical evaluation to determine clinical and radiographic improvement, adverse effects to TB medications and adherence to the treatment regimen.

Each patient with suspected TB disease is evaluated in TB clinic at least monthly by the TB clinician (physician or nurse practitioner) (**Standard of Public Health Practice IV-10**).

Each patient dispositioned with confirmed TB disease (i.e., laboratory-confirmed, clinical, or provider-verified) is evaluated by the TB clinician (physician or nurse practitioner) at least every two (2) months (**Standard of Public Health Practice IV-11**) under the following conditions:

- Not infectious, **AND**
- Clinically and radiographically improving, **AND**
- Tolerating TB treatment regimen, **AND**
- Adherent to the TB treatment regimen

### **Visual Acuity (Snellen Chart) and Color Discrimination**

For each patient with suspected or confirmed TB disease, visual acuity and color discrimination testing is performed at each TB clinic visit and documented while the patient is receiving EMB (**Standard of Public Health Practice IV-16**) (**Refer to Tool IV-1 and Tool IV-2**).

- This assessment may be performed at a health care facility, health department, TB clinic or patient's residence prior to the initiation of the medication, and documented on the Drug Screening and Monitoring Record (PH-2040).
- Patients taking EMB must be assessed every month for possible visual disturbances, including blurred vision or scotomata, as well as performing the monthly visual acuity (Snellen chart) screening and color discrimination assessment.
- The physician should do gross visual field examinations and consider referring the patient for an ophthalmologic examination if changes in the patient's visual acuity are suspected or known to be occurring. The TB case manager may submit a Request for Prior Authorization Form (**Refer to Appendix E and F**) to the TTBEPCO if the TB physician orders an ophthalmology referral for a formal evaluation.
- EMB should be discontinued immediately and permanently if there are any signs of visual toxicity.

### **Auditory Monitoring**

For each patient with suspected or confirmed TB disease receiving streptomycin or an aminoglycoside, clinical assessment for toxicity (Romberg testing and audiogram) is conducted at baseline and monthly (**Standard of Public Health Practice IV-17**).

- Baseline and monthly audiogram testing while on an aminoglycoside (including streptomycin) may need to be provided by an outside healthcare facility. The TB case manager may submit a Request for Prior Authorization Form (**Refer to Appendix E**) to the TTBEF C.O. when arrangements are made for the audiogram to be performed.
- Follow-up auditory testing after completion of therapy is not generally required, but patients should be instructed to seek medical attention promptly if auditory deficits occur.

### Vestibular Monitoring

For each patient with suspected or confirmed TB disease receiving streptomycin or an aminoglycoside, clinical assessment for toxicity (Romberg testing and audiogram) is conducted at baseline and monthly (**Standard of Public Health Practice IV-17**). This assessment is used to monitor possible side effects of dizziness or vertigo from the aminoglycoside medication. To perform vestibular assessment:

- Ask patient:
  - How is your hearing? Do your ears feel full or “stuffy”?
  - How is your balance?
  - Are you weak?
  - Are you nauseated? (none, sometimes, all the time)
- Assess patient’s balance:
  - Observe for normal balance, teetering and/or falling
- Walking
  - Observe for normal gait, weaving and/or staggering
- Past pointing exercise
  - Patient sits facing you with his/her eyes closed
  - Have him/her point their fingers, then place your fingers below theirs
  - Hold your position, ask patient to raise both hands and return fingers to yours
  - Deviation right or left from target fingers is considered “past pointing”
- Romberg
  - Patient stands with feet together
  - Encircle the patient with your arms, but do not touch
  - Tell the patient “I will not let you fall”
  - Have patient close their eyes
  - Falling is a Romberg sign
- Heel-to-Toe Walking
  - Stand beside standing patient
  - Demonstrate walking heel-to-toe
  - Do it together (be prepared to catch patient)
  - Observe for jerkiness, falling and/or excess swaying (a small degree of hesitancy is acceptable)

### Laboratory Tests

The following lab tests are indicated for patients with suspected or confirmed TB disease prior to initiation of treatment:

- CMP and CBC with platelets
- HIV testing (if not already obtained), unless patient specifically chooses to “OPT OUT” of HIV testing
- Baseline hemoglobin A1c test for patients with diabetes mellitus (DM) (**Standard of Public Health Practice IV-14**)
- Baseline CD4+ test for patients with known HIV (**Standard of Public Health Practice IV-13**)
- Pregnancy test for females, if indicated
- Sputum collection

Other baseline monitoring may be considered on an individual basis for persons taking other medications or with chronic medical conditions.

The TB physician may order monthly laboratory monitoring to include:

- CBC with platelets and without differential
- CMP
- Sputum collection
- Other tests as clinically indicated

### Sputum Collection

Sputum collection is a critical diagnostic procedure for several reasons:

- Laboratory confirmation of pulmonary TB disease (AFB smear and M.tb culture)
- Drug sensitivity testing (DST)
- Genotyping, used to track and interrupt patterns of TB transmission
- Monitoring response to therapy

The following patients should have sputum specimens collected:

- Anyone with symptoms or otherwise suspected of having TB disease of the lungs, pleura, airways or larynx
- Persons with chest radiograph findings consistent with TB disease (current, previous, or healed TB)
- HIV-infected persons with any respiratory symptoms or signs suspicious for TB, regardless of chest radiograph findings
- Persons suspected of having pulmonary disease for which bronchoscopy is being considered
- Persons with suspected or confirmed extrapulmonary disease, regardless of chest radiograph findings

The TTBEF recommends that selection of “induced” versus “natural” (also described as “coughed”) sputum collection should be guided by two factors: (a) the patient’s ability to

easily mobilize an adequate natural sputum specimen; and (b) the clinical use of the information sputum analysis will provide.

- “Induced” sputum for AFB smear and culture—indications:
  - Initial diagnostic evaluation for persons with suspected TB disease who cannot easily mobilize an adequate natural sputum specimen
    - If biopsy is not indicated, induced sputum may provide a non-invasive alternative to bronchoscopy in some patients
  - Initial diagnostic evaluation for persons with suspected TB disease which is typically paucibacillary (few bacilli) (e.g., HIV infection, with minimal radiographic changes)
  - Any patient with suspected TB disease for whom drug resistant TB is a consideration during initial evaluation (primary resistance)
    - Patients with a history of previous treatment for TB disease or TBI, regardless of elapsed time
    - Patients from countries in which TB drug resistance is common
      - Symptomatic patients
      - B1/B2 class immigrants and refugees with a history of abnormal CXR—regardless of overseas sputum smear/culture results
    - Patients with delayed, inadequate, or unanticipated clinical response to an appropriate treatment regimen
  - Persons for whom emergence of drug resistant TB during treatment (secondary resistance) is a serious concern
    - Relapse
    - Treatment failure
- “Natural” sputum for AFB smear and culture—indications:
  - Initial diagnostic evaluation for patients who are able to easily mobilize an adequate sputum specimen
  - Routine monitoring of microbacteriological response to ongoing anti-TB therapy

Prior to initiation of TB treatment (whenever possible), obtain the following sputum specimens for AFB smear and culture from the patient: **(Standard of Public Health Practice IV – 5)**

- One (1) natural sputum in TB clinic (only if the patient can easily mobilize an adequate (at least 2 ml) natural sputum); **OR**
- One (1) induced sputum in TB clinic (have low threshold for obtaining by induction); **AND**
- Two (2) natural sputums at home (canisters to be picked up by a HCW for delivery to the State Lab)

Specimens should be:

- Collected on different days, 8-24 hours apart
- Early morning sputum collection (recommended)

Continue to obtain sputum specimens:

- Weekly
  - A set of three (3) natural sputum specimens on consecutive days every week for the first eight (8) weeks or while patient is on respiratory isolation, until sputum smear results convert to negative; **then**
- Monthly
  - A series of three (3) natural sputum specimens is collected at least monthly until the patient's sputum cultures are negative for M. tb for two (2) consecutive months (**Standard of Public Health Practice IV-6**). If patient remains smear and culture negative, sputum collection may be discontinued at the discretion of the TB physician.

Reference:

1. CDC, MMWR "Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, December 30, 2005/Vol. 54/N. RR-17.  
<http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf> (adapted)

Therapeutic Drug Level Monitoring

Therapeutic drug monitoring (TDM) measures the serum concentration of TB medications in the bloodstream at certain intervals after receiving a dose of medication. TDM may help the TB clinician assess whether a TB patient's slow or inadequate response to treatment may be due to:

- inadequate dosing
- malabsorption versus delayed absorption

**(Refer to Module. XII. Laboratory Aspects of TB for more information on TDM)**

TDM is obtained for each patient who remains culture-positive at two (2) months after initiation of therapy (**Standard of Public Health Practice IV-15**).

Patients for whom early (within the first 8 weeks) TDM should be considered include:

- History of TB treatment relapse or failure
- Diabetes mellitus (DM)
- History of alcohol abuse
- HIV, regardless of CD4 count
- Sputum smear positivity failing to convert within 30 days of initiating TB treatment

The TTBEF recommends TDM for diabetics with active TB disease, as follows:

- Poorly-controlled DM (HgbA1c  $\geq 9$ )- TDM within two (2) weeks of initiating daily HRZE
- Fairly-controlled DM (HgbA1c 7-9)- TDM within two (2) weeks of initiating daily HRZE
- Well-controlled DM (HgbA1c  $<7$ )- TDM within four (4) weeks of initiating daily HRZE depending upon clinical and microbiological response

The TB case manager should submit a Request for Prior Authorization Request form to the TTBEF C.O. prior to the drug levels being obtained. (**Refer to Appendix E**).

Prior to collection of drug levels, consider the following recommendations:

- Patient needs to be on daily anti-TB therapy.
  - If patient is receiving DOT two (2) days/week or three (3) days/week, the TB physician must write an order to change DOT frequency to daily, at a minimum of five (5) days/week.
- Patient must take three (3) consecutive days of TB medications.
- Obtain drug levels only on Monday, Tuesday, or Wednesday to give adequate time for shipping to the University of Florida Laboratory. (**NOTE:** You must confirm with the lab their availability during holiday weeks. The TTBEF recommends avoiding scheduling drug levels during holiday weeks, if possible.)
- If drawing levels on:
  - **Monday:** Patient will need DOT on Saturday, Sunday and Monday. A DOT worker will have to make a home visit on Saturday and Sunday. Patient cannot self-administer the weekend doses.
  - **Tuesday:** Patient will need DOT on Sunday, Monday and Tuesday. A DOT worker will have to go out Sunday to DOT. Patient cannot self-administer the weekend dose.
  - **Wednesday:** Patient will need DOT on Monday, Tuesday and Wednesday.
- After medication adjustment(s), repeat drug levels within 1-2 weeks only for medications with modified dosages.

#### Discontinuation of Airborne Precautions

Because culture and drug-susceptibility results are not usually known when the decision to **discontinue airborne precautions** is made, all patients with suspected TB disease must remain under airborne precautions until all three (3) standard criteria are met as shown below (**Refer to Table IV-20**). Each order for discontinuation of respiratory isolation should be consistent with the criteria established in this manual (**Standard of Public Health Practice IV-19**). Note that the criteria below differ between (A) patients with any AFB-positive sputum smears, and (B) patients with no AFB-positive smears. Also, criteria for discontinuation of airborne precautions are NOT synonymous with criteria for release of a patient with suspected or confirmed TB disease from a hospital to home or to a congregate setting.

**Table IV-20: Criteria for Discontinuation of Airborne Precautions**

<b>A. Patient with one (1) or more AFB-positive sputum smears</b>	<b>B. Patient with no AFB-positive sputum smears</b>
<ol style="list-style-type: none"> <li>1. At least three (3) consecutive AFB-negative sputum specimens collected at 8- to 24-hour intervals, with at least one (1) being an early morning specimen or, preferably, one induced sputum if patient cannot easily mobilize an adequate specimen (at least 2 ml); <b>AND</b></li> <li>2. Clinical improvement on anti-TB therapy; <b>AND</b></li> <li>3. Approved multi-drug anti-TB regimen, given by <u>DOT for a minimum of 14 consecutive days</u> (including weekends and holidays)</li> </ol>	<ol style="list-style-type: none"> <li>1. At least three (3) consecutive AFB-negative sputum specimens collected at 8- to 24-hour intervals, with at least one (1) being an early morning specimen or, preferably, one induced sputum if patient cannot easily mobilize an adequate specimen (at least 2 ml); <b>AND</b></li> <li>2. Clinical improvement while on anti-TB therapy; <b>AND</b></li> <li>3. Approved multi-drug anti-TB regimen, given by <u>DOT for a minimum of seven (7) consecutive days</u> (including weekends and holidays)</li> </ol>

Hospital Discharge to Home

Patients with suspected or confirmed TB disease are frequently sent home from the hospital after starting treatment even though they may still be infectious. Such patients can be discharged to home even if they do not have three consecutive AFB-negative sputum smears, if the following criteria are met:

1. Initial diagnostic work-up is completed (including specimens collected and analyzed for AFB; nucleic acid amplification testing, if appropriate; and mycobacterial culture set up; specimens sent to State Lab, if possible)
2. A discharge plan has been made in advance with the local health department TB program
3. The patient is on standard TB treatment, and DOT has been arranged
4. Clinically stable for discharge
5. Health department has confirmed that the patient has a home to go to, with appropriate medical/social support arrangements in place
6. All household contacts have been evaluated and there are **no infants or children <5 years of age, or persons with immunocompromising conditions are present in the household, unless** they have been evaluated and started on preventive therapy; in these cases, the regional/metro TB staff should consult with the TTBEF C.O. staff to consider alternative living arrangements until infants, children <5 years of age, and/or immunocompromised persons can be evaluated in TB clinic and preventive treatment initiated; and
7. The patient is willing to maintain respiratory isolation in the home except for TB clinic appointments (all other health-care associated visits should be deferred) until airborne precautions have been discontinued.

**NOTE:** The greatest risk to household contacts of an individual with active, infectious TB disease was prior to the patient's hospital admission, placement in respiratory isolation, and initiation of an adequate anti-TB treatment regimen. **(Refer to Module V Case Management, Responsibilities of the TB Case Manager for information on Housing Assistance during the Infectious Period).**

#### References:

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. 2013. [http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf) (adapted)

#### Hospital Discharge to a Congregate Setting

Persons with pulmonary TB who are homeless or will be discharged to a congregate setting (e.g., a jail, nursing home, respite care center, shelter, etc.) must be rendered non-infectious before they can be released from the hospital. The regional TB physician, regional health officer or the TTBEF Medical Director should be consulted prior to release.

1. Initial diagnostic work-up is completed (including specimens collected and analyzed for AFB; nucleic acid amplification testing, if appropriate; and mycobacterial culture set up; specimens sent to State Lab, if possible); also,
  - a. At least three (3) consecutive AFB-negative sputum specimens collected at 8- to 24-hour intervals, with at least one (1) being an early morning specimen or, preferably, one (1) induced sputum if patient cannot easily mobilize an adequate specimen (at least 2 ml)
  - b. Clinical improvement on anti-TB therapy
  - c. Approved multi-drug anti-TB regimen, given by DOT for a minimum of 14 consecutive days (including weekends and holidays) - even if three (3) consecutive AFB-negative sputum smears documented in less than 14 days
2. A discharge plan has been made in advance with the local health department TB program
3. The patient is on standard TB treatment, and DOT has been arranged
4. Clinically stable for discharge
5. Health department has confirmed in advance the acceptance of the patient by the congregate setting, assuring that appropriate medical/social support arrangements are in place
6. Appropriate transportation of the patient to the congregate setting is arranged
7. Appropriate written discharge documentation is provided in advance to medical and/or public health staff assuming responsibility for continuity of the medical care of the patient

Infectious patients who are discharged from the hospital without prior health department notification may present a threat to public health. For that reason, the TTBEF recommends that the TB clinician or regional health officer (or designee) notifies the hospital in a timely manner

of the proper procedures that must be followed prior to the discharge of any persons with suspected or confirmed TB disease.

Upon notification from a facility of a person with suspected or confirmed TB disease, the TB case manager will obtain all necessary information. Instruct the caller that once the health department has made any necessary arrangements for the patient (see criteria above), the TB case manager will then notify the hospital that discharge can occur.

When dealing with suspected or confirmed infectious, drug-resistant TB, even greater emphasis should be placed on strict adherence to infection control standards. Because the consequences of transmission of multi-drug resistant TB (MDR TB) are more severe, and there are no proven regimens for window prophylaxis or treatment of TBI attributable to MDR TB, it is appropriate to be more cautious about returning MDR TB patients back to their homes, schools, work sites, and congregate settings. Decisions regarding discharge of hospitalized patients with MDR TB or release of such patients from respiratory isolation should be made in consultation with the TTBEF Medical Director.

1. Particular care should be taken when considering if patients can return to settings where there are young children, immunocompromised individuals, and people who have not previously been exposed to the patient.
2. MDR TB patients are considered contagious as long as their sputum cultures remain positive. It is recommended that the patient remain under airborne precautions during the entire hospitalization or until culture conversion is documented, regardless of sputum smear results, and to not release MDR TB patients to congregate settings until their sputum cultures become consistently negative.
3. The World Health Organization (WHO) guidelines consider patients with MDR TB to be contagious until their sputum is consistently culture-negative, and forbids travel in public airplanes or other public transportation until consistently culture-negative status is documented.

For MDR TB patients, long-term hospitalization in a negative pressure room is exceedingly expensive. Safe options should be explored once the patient is medically stable **and** tolerating the full drug-resistant TB regimen. In some cases, management at home will not be possible while a patient is still potentially contagious due to the following:

- infants and children **<5 years** of age;
- persons with **immunocompromising** conditions;
- previously **unexposed** individuals living in the home; or
- physical layout or small space prevents the patient from having a private space for home isolation

In these cases, it is recommended for the regional/metro TB staff to consult with the TTBEF C.O. to consider alternative living arrangements.

On rare occasions it may be necessary to require isolation and quarantine procedures for patients who will not or cannot observe the previously mentioned reasonable airborne precautions. When necessary, the regional health officer may consider appropriate legal interventions (**Refer to Module XII Public Health Law and TB**).

#### References:

1. CDC. Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings. MMWR 2005; 54 (No. RR-17).  
<http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf>
2. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. 2013.  
[http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf) (adapted)
3. Francis J. Curry International TB Center. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians. 2011.  
[http://www.currytbcenter.ucsf.edu/drtb/docs/MDRTB\\_book\\_2011.pdf](http://www.currytbcenter.ucsf.edu/drtb/docs/MDRTB_book_2011.pdf)

#### Management of Treatment Relapse and Failure

Consultation should be obtained from the State TB Medical Director for recommendations on management for any patient with treatment relapse or failure.

#### Relapse

Relapse is defined by recurrent tuberculosis at any time after completion of treatment and apparent cure.

- All TB cases with potential relapse should be discussed in a timely manner with the TTBEF Medical Director.
- If relapse is suspected, rigorous efforts must be made to establish a diagnosis and to obtain microbiologic confirmation of the relapse to enable testing for drug resistance.
- Most relapses occur within the first 6-12 months after completion of therapy.
- In nearly all patients treated with rifamycin-containing regimens using DOT, relapses occur with organisms having the same drug-susceptibility pattern as the pre-treatment isolate.
- In patients who received self-administered therapy or a non-rifamycin based regimen and experience a relapse, the risk of acquired drug-resistance is substantial.
- The selection of empirical treatment for patients with relapse must be based on the prior treatment regimen and severity of disease.
  - For patients with tuberculosis that was caused by drug-susceptible organisms, who were treated under DOT, and who have early relapses, initiation of the standard four-drug regimen is appropriate until the results of drug susceptibility tests are available.
  - For patients who have life-threatening forms of tuberculosis, at least three (3) additional drugs to which the organisms are likely to be susceptible must be included.
  - For patients who experience relapse, it is prudent to infer that drug resistance is present for patients that:

- Did not receive TB medication by DOT
- Were not treated with a rifamycin-based regimen
- Are known or presumed to have had irregular treatment

### Treatment Failure

Treatment failure is the continued or recurrently positive cultures during the course of anti-tuberculosis therapy. Patients whose sputum cultures remain positive after **four (4)** months of treatment must be deemed treatment failures. The TB clinician should seek timely consultation with the TTBE Medical Director to determine the next step of the treatment plan.

- Possible reasons for treatment failure in patients receiving appropriate regimens include:
  - non-adherence to the drug regimen (the most common reason)
  - drug resistance
  - malabsorption of drugs
    - Ensure that the patient is not taking antacids or iron with medications
  - laboratory error
  - extreme biologic variation in response
- Patients with positive cultures after **three (3)** months of effective treatment must be evaluated carefully in order to identify the cause of the delayed culture conversion.
  - Patient must be re-evaluated in TB clinic by TB clinician
  - Induced sputum must be collected for *M. tuberculosis* and sent promptly to the Tennessee Department of Health, Division of Laboratory Services with a request for drug susceptibility testing to both first- and second-line anti-TB drugs
  - Therapeutic drug monitoring (TDM) should be performed to assess the adequacy of the current medication dosages
- A fundamental principle in managing patients with treatment failure is **never** to add a single drug to a failing regimen. This could lead to acquired resistance to the new drug. It is recommended to add at least two (2) and preferably three (3) new drugs to which susceptibility could logically be inferred in order to lessen the probability of further acquired resistance.
- If failure is likely due to drug-resistance and the patient is not seriously ill, an empirical re-treatment regimen could be started or administration of an altered regimen could be deferred until results of drug-susceptibility testing from a recent isolate is available.
- **Isolation must be maintained until the patient is no longer infectious.** The TTBE C.O. can assist with arrangements (housing or other special needs) for patients requiring prolonged isolation.

### Adverse Reactions to TB Drugs

**Table IV-21** summarizes common adverse reactions to TB drugs.

**Table IV-21: Common Adverse Reactions to TB Drugs**

Cause by	Adverse Reaction	Signs and Symptoms	Significance of Reaction*
Any drug	Allergic	<ul style="list-style-type: none"> <li>• Skin rash</li> <li>• Difficulty swallowing or breathing</li> </ul>	May be serious or minor
EMB	Eye damage	<ul style="list-style-type: none"> <li>• Blurred or changed vision</li> <li>• Changed color vision</li> </ul>	Serious
INH PZA RIF	Hepatic toxicity	<ul style="list-style-type: none"> <li>• Abdominal pain</li> <li>• Abnormal liver function test results</li> <li>• Dark urine</li> <li>• Fatigue</li> <li>• Fever for three (3) or more days</li> <li>• Flu-like symptoms</li> <li>• Lack of appetite</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Yellowish skin or eyes</li> </ul>	Serious
INH	Nervous system damage	<ul style="list-style-type: none"> <li>• Dizziness</li> <li>• Tingling or numbness around the mouth</li> <li>• Mental status changes</li> </ul>	Serious
	Peripheral neuropathy	<ul style="list-style-type: none"> <li>• Tingling sensation in hands and feet</li> </ul>	Serious
PZA	Stomach upset	<ul style="list-style-type: none"> <li>• Stomach upset</li> <li>• Vomiting</li> <li>• Lack of appetite</li> </ul>	May be serious or minor
	Gout	<ul style="list-style-type: none"> <li>• Abnormal uric acid level***</li> <li>• Joint aches</li> </ul>	Serious
RIF	Bleeding problems	<ul style="list-style-type: none"> <li>• Easy bruising</li> <li>• Slow blood clotting</li> </ul>	Serious
	Discoloration of body fluids	<ul style="list-style-type: none"> <li>• Orange urine, sweat, or tears</li> <li>• Permanently stained soft contacts</li> </ul>	Minor
	Drug interactions	<ul style="list-style-type: none"> <li>• Interferes with certain medications such as birth control pills, birth control implants, and methadone treatment</li> </ul>	May be serious or minor
	Sensitivity to the sun	<ul style="list-style-type: none"> <li>• Frequent sunburn</li> </ul>	Minor

\*Patients should stop medication for serious adverse reactions and consult a clinician immediately. Patients can continue taking medication if they have minor adverse reactions.

\*\*Asymptomatic elevated uric acid levels are expected with PZA treatment. Acute gouty arthritis, which is rare without pre-existing gout, is a contraindication to PZA use.

Source: Core Curriculum on Tuberculosis: What the Clinician Should Know. 6<sup>th</sup> ed. National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, Division of Tuberculosis Elimination. <http://www.cdc.gov/TB/education/corecurr/default.htm>

For adverse reactions to second-line drugs refer to <http://www.currytbcenter.ucsf.edu/tbdruginfo/docs/tbdruginfo2ndEd.pdf>.

**Bacteriologic Response to Treatment for Pulmonary TB Disease**

**Table IV-22** outlines bacteriologic response to treatment for pulmonary TB disease.

**Table IV-22: Response to Treatment for Pulmonary TB Disease**

Bacteriologic Status	Recommendations for Response to Treatment
Positive sputum cultures prior to treatment	<ul style="list-style-type: none"> <li>• Obtain specimens for culture at least monthly until three (3) consecutive specimens are negative on culture</li> <li>• Perform monthly sputum AFB smears and cultures on MDR TB patients for entire course of treatment</li> <li>• A repeat chest radiograph after two (2) months of treatment may be useful but is not essential</li> </ul>
Negative sputum cultures prior to treatment	<ul style="list-style-type: none"> <li>• Repeat chest radiograph at intervals based on clinical circumstances and differential diagnosis</li> <li>• If radiograph does not improve after patient has received two (2) months of treatment, abnormality may be due to:               <ul style="list-style-type: none"> <li>○ Previous (not current) TB disease</li> <li>○ Another reason</li> </ul> </li> </ul>
Cultures have not become negative after three (3) months of therapy	<ul style="list-style-type: none"> <li>• Re-evaluate for:               <ul style="list-style-type: none"> <li>○ Potential drug-resistant disease</li> <li>○ Potential failure to adhere</li> </ul> </li> </ul>
Cultures are still positive after four (4) months of treatment	<ul style="list-style-type: none"> <li>• Consider as having failed treatment and manage accordingly</li> </ul>

**References:**

1. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. 2013. [http://www.cdc.gov/tb/education/corecurr/pdf/corecurr\\_all.pdf](http://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf)

**Documentation of Completion of Therapy**

- Treatment for active TB disease is completed within 12 months for patients whom 12 months of treatment or less is indicated (**Standard of Public Health Practice IV-4**).
- TB case manager is to ensure that the correct number of DOT doses and weeks of treatment (per CDC definition) has been given to patient before treatment is discontinued.
- TB clinician will write final orders, with an explanation documented if treatment was prolonged from original written treatment plan.

- Patients do not require follow-up after completion of therapy but are to be instructed to seek care promptly if signs or symptoms of TB disease reoccurs.
- RVCT is to be finalized in TB PAM and a copy placed in patient's medical record.
- Appropriate disposition code is to be entered into PTBMIS.

#### **4. Tools**

IV-1: Visual Acuity (Snellen chart)

IV-2: Color Discrimination Chart

IV-3: Case Managing the TB Patient Receiving Contracted Vendor Services

IV-4: Provider Verified Form (PH-4079)

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**Tool IV-1**  
**Snellen Eye Chart**

[http://www.visionsource.com/site/assets/files/1192/free\\_eye\\_chart.pdf](http://www.visionsource.com/site/assets/files/1192/free_eye_chart.pdf)

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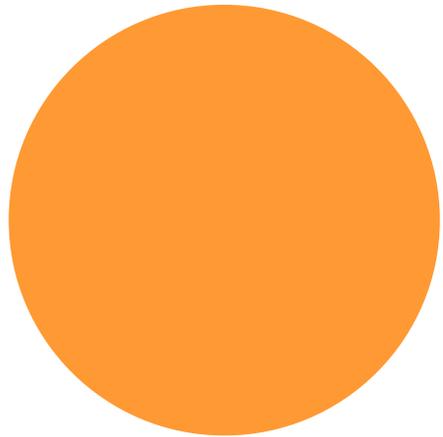
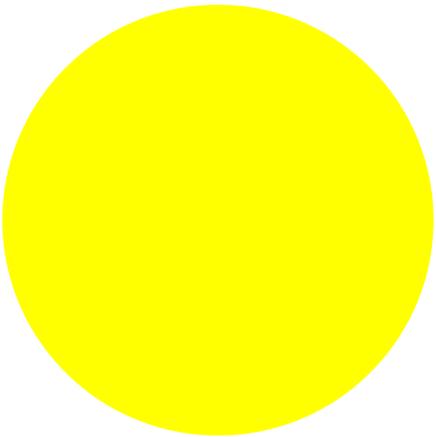
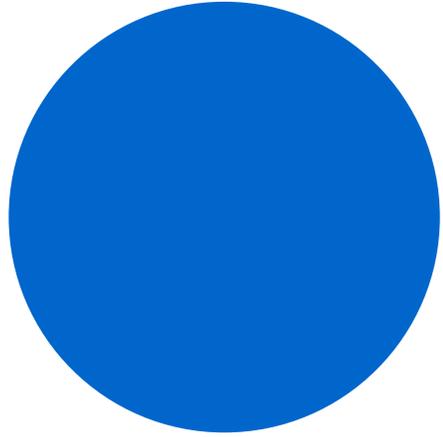
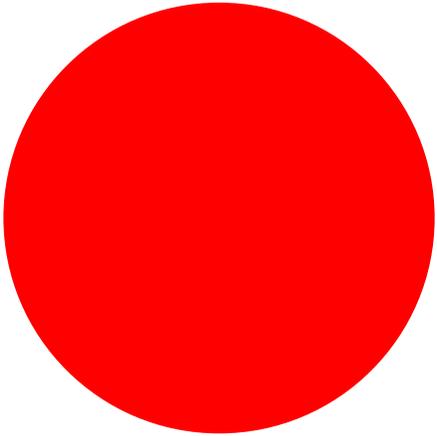
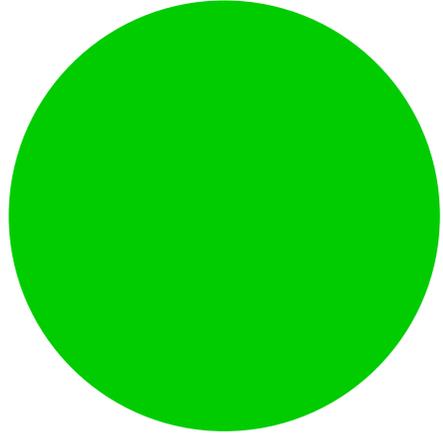
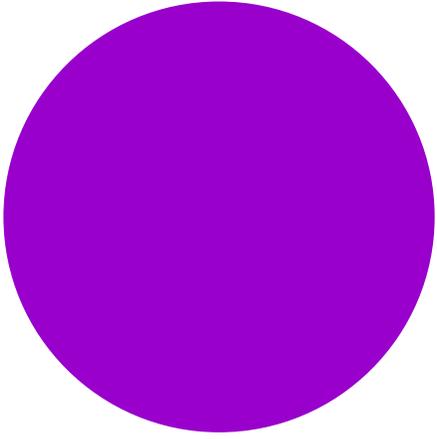
**Tool IV-2**  
**Color Discrimination Instructions and**  
**Chart**

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### **Color Discrimination Test**

1. The patient should be asked to identify the red and green colors from a series of six (6) colors.
2. If the patient can identify the red and green colors the notation on the patient's medical record should be: "Red-green color discrimination is normal." If the patient is unable to identify the colors, this should be noted in the record.
3. Loss of the ability to discriminate red and green colors should be called to the attention of the physician before medication is refilled.

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**Tool IV-3**  
**Case Managing the TB Patient Receiving**  
**Contracted Vendor Services**

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## Case Managing the TB Patient Receiving Contracted Vendor Services

When a person with suspected or confirmed TB disease is in a medical facility, the TB case manager should take an active role in the discharge planning. If there are anticipated needs for a service to be provided by a home health agency, an infusion supply company, or other contracted vendor upon discharge, the TB case manager will complete the *Prior Authorization Request (PAR)* form and submit the form, along with the TB physician's progress notes, to the TTBEPCentral Office (C.O.) Nurse Consultant for review and approval. Upon receiving the *PAR* and progress notes, the TTBEPCentral Office (C.O.) Nurse Consultant will negotiate a financial agreement with the vendor(s). Once the financial agreement(s) are in place, the TTBEPCentral Office (C.O.) Nurse Consultant will update the TB case manager, who is then responsible for case managing the plan of treatment for the patient. After notification by C.O., the TB case manager will then notify the facility that follow-up services are in place and the patient can be discharged from the facility at the appropriate time.

Home health services may be ordered for a TB patient upon discharge from a facility. These services will require a *Prior Authorization Request* and a *financial agreement* prior to patient's discharge. The home health services may provide skilled care to perform:

- Intravenous (IV) therapy
- Dressing changes to:
  - IV sites (i.e., PICC lines, portacaths)
  - Drain sites
  - Other sites related to TB disease
- Patient education

Infusion supply company services may be ordered for a TB patient upon discharge from a facility. These services would require a *Prior Authorization Request* and a *financial agreement* prior to patient's discharge. The infusion supply company may provide:

- Delivery of medication
- Delivery of supplies needed by the home health agency to provide treatment as ordered by the physician (outside provider or the TB physician)

When discharge plans include home health referrals and/or the need for an infusion supply company to provide medication and supplies, the TB case manager will ensure that the TTBEPCentral Office (C.O.) and vendors (i.e., home health agency, infusion supply company) receive all orders and notifications regarding the plan of treatment. The TB case manager will:

1. Obtain the home health referral orders from the discharge planner/social worker at the discharging facility
2. Notify the TTBEPCentral Office (C.O.) Nurse Consultant to begin financial arrangements with the appropriate vendor(s) by faxing or emailing the home health referral orders to the C.O.
3. Complete a *PAR* form and submit the form, along with the TB physician's progress notes, to the TTBEPCentral Office (C.O.) Nurse Consultant
4. Call the home health agency and coordinate plan of care upon discharge. Fax or email the home health referral orders. Ideally, the discharge planner/social worker at the facility will forward the home health referral to the home health company; however, in

order to ensure continuity of care, the TB case manager will send the home health referral orders to the vendor's contact person

5. Obtain orders for the medication(s) and supplies that are to be supplied by the infusion company
6. Notify the TTBEPC.O. Nurse Consultant to begin financial arrangements with the appropriate vendor(s) by faxing or emailing the medication orders to the C.O.
7. Complete a *PAR* form and submit the form, along with the TB physician's progress notes, to the TTBEPC.O. Nurse Consultant
8. Call the infusion supply company and coordinate plan of care upon discharge. Fax or email the physician's orders. Ideally, the discharge planner/social worker at the facility will send the physician's orders for the medication to the infusion supply company; however, in order to ensure continuity of care, the TB case manager will send the physician's orders to the vendor's contact person. (The home health agency may not routinely forward the physician's orders to the infusion supply company.)

The TB case manager will ensure that the home health agency, the infusion supply company, any other contracted service, and the TTBEPC.O. is aware of all changes to the plan of treatment, as well as the patient's status during the time of the contracted service, which may include:

- Date of discharge from facility
- Medication (dosage change, frequency change, hold or discontinue medication)
- Treatment plan (frequency of services, hold or discontinue services)
- Hospitalization(s)
- Patient contact information (new address, new telephone numbers)
- Payor source
- Death

Anytime there is a change in the plan of treatment, a new physician's order must be written (if not obtained from an outside provider) and submitted to each vendor providing a service and to the TTBEPC.O.

For **medication changes** (i.e., increase dose, decrease dose, change in frequency, hold or discontinue medication), the TB case manager will:

1. Obtain from the TB physician or an outside provider the new written medication order
2. Notify the TTBEPC.O. Nurse Consultant of the medication change(s)
3. Call and report changes to the vendor(s) providing a service (i.e., home health company, infusion supply company, other contracted vendor)
4. Fax or email the order to the vendor(s)'s contact person and to the TTBEPC.O. Nurse Consultant

If the patient is **hospitalized** during the time that vendor services are provided, the TB case manager will:

1. Notify the TTBEPC.O. Nurse Consultant of readmission to a facility
2. Complete a new *PAR*, if readmitted to a facility due to TB disease, and send the *PAR*, along with the TB physician's progress notes, to the TTBEPC.O. Nurse Consultant

3. Obtain from the TB physician or an outside provider the new written order to hold medication and/or services until further notice
4. Call and report the hospitalization to the vendor(s) providing a service (i.e., home health company, infusion supply company, other contracted vendor)
5. Fax or email the order to the vendor(s)'s contact person

Upon **discharge** from the facility, the TB case manager will:

1. Notify the TTBE C.O. Nurse Consultant of the patient's discharge date from the facility
2. Obtain from the TB physician or an outside provider the new written order for the home health referral and/or medication order(s) or to discontinue the vendor(s) service and/or medication supply
3. Call and report the patient's discharge to the vendor(s) providing a service (i.e., home health company, infusion supply company, other contracted vendor)
4. Fax or email the order to the vendor(s)'s contact person

If the patient **moves or has a telephone number change**, the TB case manager will:

1. Notify the TTBE C.O. of changes in the patient's contact information during the contracted service timeframe. If patient is moving to new region, follow the Intrastate Movement procedure in the TTBE Manual, Module VIII
2. Call and report the new contact information for the patient (i.e., new address, telephone number) as soon as possible, to the vendor(s) providing a service (i.e., home health company, infusion supply company, other contracted vendor)

If the patient has a change in the **payor source**, the TB case manager will:

1. Notify the TTBE C.O. of any changes in the payor source during the contracted service timeframe
2. Call and report the new payor source (i.e., insurance, PAR) to the vendor(s) providing a service (i.e., home health company, infusion supply company, other contracted vendor)

If the patient **expires**, the TB case manager will:

1. Notify the TTBE C.O. when the patient expires
2. Call and report the patient's expired status, as soon as possible, to the vendor(s) providing a service (i.e., home health company, infusion supply company, other contracted vendor)
3. Obtain death certificate and send a copy along with the complete medical record to the TTBE C.O. Nurse Consultant

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**Tool IV-4**  
**Request for Confirmation- *TB Case***  
***Verified by Provider* Form PH-4079**

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**TENNESSEE TB ELIMINATION PROGRAM**  
*Request for Confirmation – TB Case Verified by Provider*

Name (last, first, M.I.)	Date of Birth / /	Region / County	Form Received / /
Hospital or Other Facility	Meds Started / /	Meds Ended / /	Form Returned / /

**Date of initial clinical presentation:** \_\_\_/\_\_\_/\_\_\_      **Facility:** \_\_\_\_\_

**Presenting symptoms/signs:** \_\_\_\_\_

\_\_\_\_\_ **Date of symptom onset:** \_\_\_/\_\_\_/\_\_\_

**Pertinent medical history (34)\*:** (check all that apply)

\* reference to RVCT item number

- |   |   |   |
|---|---|---|
| <input type="checkbox"/> Diabetes mellitus    | <input type="checkbox"/> S/P gastrectomy        | <input type="checkbox"/> Inflammatory bowel disease             |
| <input type="checkbox"/> HIV+                 | <input type="checkbox"/> Head / neck cancer     | <input type="checkbox"/> Prolonged therapy with corticosteroids |
| <input type="checkbox"/> ESRD                 | <input type="checkbox"/> Leukemia / lymphoma    | <input type="checkbox"/> Immunosuppressive therapy              |
| <input type="checkbox"/> Silicosis            | <input type="checkbox"/> Sarcoidosis            | <input type="checkbox"/> Alcoholism / IVDA / non-IVDA (circle)  |
| <input type="checkbox"/> S/P organ transplant | <input type="checkbox"/> Other (specify): _____ |   |

**Additional risk factors (34):** (check all that apply)

- |   |  |
|---|--|
| <input type="checkbox"/> Contact of MDR-TB pt. (≤ 2 yrs.) | <input type="checkbox"/> Contact of infectious TB pt. (≤ 2 yrs.) |
| <input type="checkbox"/> Missed contact (≤ 2 yrs.)        | <input type="checkbox"/> Incomplete LTBI tx.                     |
| <input type="checkbox"/> Healthcare worker                | <input type="checkbox"/> Congregate setting employee / volunteer |
| <input type="checkbox"/> Other (specify): _____           |  |

**Pertinent social history:** (check all that apply)

- |  |   |
|--|---|
| <input type="checkbox"/> Born outside U.S. – specify country (12): _____;              | Arrival in U.S.: ___/___/___                                |
| <input type="checkbox"/> Homeless at time of diagnosis (27)                            | <input type="checkbox"/> Ever homeless (mo./yr.)            |
| <input type="checkbox"/> Incarcerated at time of diagnosis (28)                        | <input type="checkbox"/> Ever incarcerated > 24 hrs.        |
| <input type="checkbox"/> Jail – specify county: _____                                  | <input type="checkbox"/> Prison: _____                      |
| <input type="checkbox"/> Resident of long-term care facility at time of diagnosis (29) |   |
| <input type="checkbox"/> Nursing home  | <input type="checkbox"/> A&D treatment facility             |
| <input type="checkbox"/> Hospital-based facility                                       | <input type="checkbox"/> Mental health residential facility |
| <input type="checkbox"/> Other long-term care facility: _____                          |   |

**TST (23):** Date placed: \_\_\_/\_\_\_/\_\_\_      Result: \_\_\_\_\_ mm

**IGRA (24):** Date obtained: \_\_\_/\_\_\_/\_\_\_      Type:  QuantiFERON Gold     T-SPOT.TB  
 Result:  Positive     Negative     Indet.     Invalid

**HIV screen (26):** Date obtained: \_\_\_/\_\_\_/\_\_\_      Result:  Positive     Negative     Refused

**Primary site of suspected TB disease (16):** \_\_\_\_\_

**Initial clinical specimens:** (Circle if sputum I-induced vs. N-natural; MTD vs PCR)

<u>Collection date:</u>	<u>Anatomic source:</u>	<u>AFB result:</u>	<u>MTD / PCR result:</u>	<u>Culture result:</u>
___/___/___	_____ (I/N)	_____	_____	_____
___/___/___	_____ (I/N)	_____	_____	_____
___/___/___	_____ (I/N)	_____	_____	_____

**Initial CXR (22A):**

Date: \_\_\_/\_\_\_/\_\_\_      Result: \_\_\_\_\_

**Initial CT/other imaging (22B):**

Date: \_\_\_/\_\_\_/\_\_\_      Result: \_\_\_\_\_

<b>Name</b>	<b>Date of Birth</b> / /	<b>Region / County</b>	<b>Meds Started</b> / /
-------------	-----------------------------	------------------------	----------------------------

**Anti-TB medications:**

Medication name:	Dosage/frequency:	Date started:	Date stopped:
_____	_____	___/___/___	___/___/___
_____	_____	___/___/___	___/___/___
_____	_____	___/___/___	___/___/___
_____	_____	___/___/___	___/___/___
_____	_____	___/___/___	___/___/___

**Explanation for non-standard regimen, discontinuing a standard medication (HRZE) early, or addition of a non-standard drug to the regimen:** \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

**Physician to complete - summary/rationale for disposition as a “provider-verified TB case”:**  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Did **clinical** improvement occur with anti-TB therapy?  Yes  No

Did **radiological** improvement occur with anti-TB therapy?  Yes  No

Physician’s signature: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_

*TTBEP Central Office Use Only*

**Request for additional information:** \_\_\_\_\_  
 \_\_\_\_\_

**Summary of review by State TB Control Officer:** \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

**FINAL DISPOSITION:**  Clinical TB case  Provider-verified TB case  Not TB disease

**Recommendations:** \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

**TB Control Officer’s signature:** \_\_\_\_\_ **Date:** \_\_\_/\_\_\_/\_\_\_