



## CHAPTER 5: TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS DISEASE IN ADULTS

### INTRODUCTION

The overall goals of treatment of active tuberculosis (TB) disease are to cure the patient and to minimize the transmission of *Mycobacterium tuberculosis* (*M. tuberculosis*) to others. The New York City (NYC) Bureau of TB Control (BTBC) follows treatment guidelines as described in the *2016 Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA)*. Instances where BTBC practice differs from these recommendations have been noted in the text.



The most recent version of the ATS/CDC/IDSA treatment guidelines can be found online at: [www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid\\_ciw376.pdf](http://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf)

## TREATMENT REGIMENS AND DOSAGES FOR PULMONARY TUBERCULOSIS DISEASE

BTBC recommends that all individuals with signs and symptoms consistent with TB disease or confirmed TB disease receive treatment after specimens have been collected. Treatment is not to be delayed while waiting for confirmation by culture or drug-susceptibility test (DST) results. Before starting therapy, a complete medical evaluation including a history and physical evaluation, baseline complete blood count (CBC), blood chemistries (including assessment of kidney and liver function tests [LFT]), and chest imaging is performed. Viral hepatitis screening may also be performed, and other specimens may be obtained as indicated.

Any treatment regimen for active TB disease relies on the principle of using multiple antibiotics to which the bacterial isolate is either presumed or known to be susceptible. This approach reduces the likelihood of treatment failure and the acquisition of drug resistance. Treatment regimens are divided into an intensive phase and continuation phase. The shorter intensive phase, which usually lasts two months, includes treatment with more drugs than are used during the longer continuation phase, which is typically four to seven months. During each phase, the number of drugs used and/or the frequency of drug administration may vary. Most patients with TB disease are eligible for treatment with a standard six-month regimen.



**DIRECTLY OBSERVED THERAPY (DOT)** is the standard of care and ensures that patients complete an adequate course of treatment for TB. With DOT, a healthcare worker directly observes every dose of anti-TB medication taken by the patient.

Four options for DOT are offered free of charge by BTBC to any patient receiving care for TB disease in NYC, regardless of the provider caring for the patient:

1. **IN-PERSON CLINIC DOT:** patient comes to the clinic for observation
2. **COMMUNITY DOT:** BTBC staff meets the patient in their home or other agreed upon location in the community for observation
3. **LIVE VIDEO DOT:** patient is observed real-time through video conferencing software
4. **RECORDED VIDEO DOT:** patient records themselves ingesting their medication and securely transmits the video for observation

(See *Chapter 10: Case Management for Patients with Tuberculosis.*)

## STANDARD REGIMENS FOR TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS DISEASE

Because DST results for a patient's TB strain are not typically known at the time of treatment initiation, empiric treatment for TB is started with the assumption that a standard regimen will be effective for the majority of patients. If the specimen is smear-positive, nucleic acid amplification- (NAA) positive, and rpoB-negative, it is likely that the patient does not have multidrug-resistant TB (MDR-TB) and that this empiric regimen will be acceptable until further DSTs are known. The standard regimen for treating TB disease consists of a two-month intensive phase of four drugs: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB), taken daily followed by a four-month continuation phase of INH and RIF taken on

either a daily or intermittent basis. Under certain conditions, the continuation phase may be extended beyond four months (see *Duration of Treatment for Drug-Susceptible Pulmonary Tuberculosis Disease* later in the section).

- » Physicians can discontinue EMB before the end of the intensive phase if drug susceptibility testing and/or mutation analysis results show susceptibility to INH and RIF. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)
- » Individuals who cannot be evaluated for visual acuity or color vision are not routinely treated with EMB, but the other drugs and dosages in the regimen remain the same.
  - A fluoroquinolone (FQN) may be considered until final susceptibility results are available.
- » If clinical response is not adequate after two weeks (i.e., signs and symptoms persist), the addition of drugs to the regimen is considered, as drug resistance may be present. However, other possibilities including poor adherence to TB treatment, poor absorption of TB medication, or extensive disease are considered.
- » Pyridoxine (Vitamin B6) is often used in conjunction with INH to prevent side effects in the central and peripheral nervous system. (See *Table 5.3: The Use of Pyridoxine in Tuberculosis Treatment*.)
- » At the end of the intensive phase of treatment, EMB is stopped if not previously discontinued and PZA is discontinued unless drug resistance is suspected for the following reasons:
  - Mutation analysis or DST results show resistance to INH or RIF
  - Mutation analysis or DST results are not available and drug resistance is suspected due to a history of TB disease treatment or immigration from an area with high rates of drug resistance
  - If susceptibility results are not received, the lab should be contacted

**FOUR-MONTH REGIMEN WITH HIGH-DOSE RIFAPENTINE AND MOXIFLOXICIN:** A new four-month regimen is available for the treatment of drug-susceptible pulmonary TB. The regimen consists of a two-month intensive phase of INH, high-dose rifapentine (RPT), PZA, and moxifloxacin (MOX). The two-month continuation phase consists of INH, high-dose RPT, and MOX. (High-dose RPT is 1200 mg/day for a patient who weighs 50 kg or more.) DOT is recommended. Although the pill burden is high, this short regimen may be an advantage for some patients.

The four-month regimen is available to patients age 12 and older. The regimen should not be used during pregnancy or breastfeeding. Patients with human immunodeficiency virus (HIV) infection may use this treatment if receiving an efavirenz-based regimen for HIV.

associated with lower rates of relapse. BTBC does not recommend twice-weekly therapy in the continuation phase; in general, it may be considered for select patients who do not have human immunodeficiency virus (HIV) infection. Patients with HIV infection are treated with daily therapy in both the intensive and continuation phases due to higher rates of relapse and emergence of RIF-resistance.

**TABLE 5.1:** Drug regimens for pulmonary tuberculosis disease caused by drug-susceptible organisms

INTENSIVE PHASE		CONTINUATION PHASE <sup>1,2,3</sup>		NOTES
Drugs	Interval and Duration	Drugs	Interval and Duration	
INH RIF PZA EMB	7 days/week for 56 doses (8 weeks)	INH RIF	7 days/week for 126 doses (18 weeks) --- or --- 3 days/week for 54 doses (18 weeks with DOT) <sup>4</sup>	<ul style="list-style-type: none"> <li>This is the standard regimen for drug-susceptible TB disease</li> </ul>
INH RIF EMB	7 days/week for 56 doses (8 weeks)	INH RIF	7 days/week for 217 doses (31 weeks) <sup>3</sup> --- or --- 3 days/week for 93 doses (31 weeks with DOT) <sup>3,4</sup>	<ul style="list-style-type: none"> <li>This regimen without PZA is the appropriate regimen for pregnant patients unless MDR-TB is suspected</li> </ul>
INH RPT PZA MOX	7 days/week for 56 doses (8 weeks)	RPT MOX INH	7 days/week for 63 doses (9 weeks)	<ul style="list-style-type: none"> <li>High-dose RPT: patients who weigh 50 kg or more receive RPT 1200 mg/day</li> </ul>

Adapted from: Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis.* 2016 Oct 1;63(7):e147-e195.

1. Biweekly treatment regimens during the continuation phase are not recommended due to high rates of relapse
2. For missed doses, extend treatment to make up the doses
3. Patients with a positive culture at 2 months of treatment should receive a 7-month continuation phase regimen (31 weeks; either 217 doses daily or 93 doses 3 times per week)
4. Not recommended for patients with HIV infection

**Abbreviations Used:** CXR=chest radiograph; DOT=directly observed therapy; EMB=ethambutol; HIV=human immunodeficiency virus; INH=isoniazid; MDR-TB=multidrug-resistant TB; MOX=moxifloxacin; PZA=pyrazinamide; RIF=rifampin; RPT=rifapentine

## INTERMITTENT REGIMENS

Intermittent therapy (i.e., regimens given on a schedule other than daily) is effective for most patients with drug-susceptible TB disease, is offered under DOT, and is only recommended by BTBC in the continuation phase of therapy. Intermittent therapy is easier to administer and may be preferred by patients compared to daily therapy. BTBC does not recommend intermittent therapy during the intensive phase of treatment. Missed doses can lead to treatment failure, relapse, and acquired drug resistance. Patients with treatment adherence less than 80% are placed on daily DOT until it is established that they can be placed on intermittent DOT.

Thrice-weekly intermittent therapy during the continuation phase is preferred to twice-weekly therapy, as it is associated with lower rates of relapse. BTBC does not recommend twice-weekly therapy in the continuation phase; in general, it may be considered for select patients who do not have HIV infection. Patients with HIV infection are treated with daily therapy in both the intensive and continuation phases due to higher rates of relapse and emergence of RIF-resistance.

Once an appropriate regimen has been identified, appropriate dosing is vital to successful treatment outcomes. See *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis* for details regarding doses of primary medications used in the treatment of TB disease. Dose will be affected by the frequency of administration: daily or three times per week.

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## DURATION OF TREATMENT FOR DRUG-SUSCEPTIBLE PULMONARY TUBERCULOSIS DISEASE

**CULTURE-POSITIVE PULMONARY DISEASE:** The standard six-month treatment for drug-susceptible TB consists of a two-month intensive phase followed by a four-month continuation phase. Certain patients with culture-positive pulmonary disease have a higher rate of relapse with the standard six-month regimen and benefit from longer treatment. An extended seven-month continuation phase is prescribed for the following:

- Patients who have positive sputum cultures after two months of therapy, regardless of chest radiograph (CXR) results
- Patients whose treatment regimen did not include PZA in the intensive phase or who have PZA-resistant TB
- Patients with extensive disease or a cavitary CXR who have poor response to treatment
- Patients with HIV infection who are not on antiretroviral therapy (ART) during TB treatment

**CULTURE-NEGATIVE PULMONARY DISEASE:** Clinically-confirmed or culture-negative pulmonary TB disease in patients without HIV infection can be treated successfully in four months, as the initial bacillary load is lower. As a result, for patients whose initial sputum cultures are negative, the intensive phase of treatment is followed by a two-month continuation phase of INH and RIF if drug resistance is not suspected. If the patient has received treatment for TB disease in the past or comes from an area with high rates of drug-resistant TB (DR-TB), INH, RIF, PZA, and EMB are prescribed for the full four months.

## TREATMENT OF EXTRAPULMONARY TUBERCULOSIS DISEASE

Although the treatment regimens for extrapulmonary disease are the same as for pulmonary disease, a few extrapulmonary sites of disease are routinely treated for longer periods of time in the continuation phase, regardless of culture results. (See *Table 5.2: Treatment of Extrapulmonary Tuberculosis Disease.*) Empiric treatment is more commonly prescribed for extrapulmonary TB disease, as the patient's specimens are more likely to be culture-negative or not sent for culture. The patient's clinical response is considered when determining length of treatment and regimens are individualized accordingly.

## SPECIAL CONSIDERATIONS FOR CENTRAL NERVOUS SYSTEM TUBERCULOSIS DISEASE

Central nervous system (CNS) TB can have devastating effects on morbidity and mortality, and as such, empiric treatment is started promptly while awaiting results of AFB smears and cultures. Treatment is identical to the standard intensive phase regimen for pulmonary TB disease. Treatment is similar for adults and children. Some experts recommend higher doses of RIF to penetrate the blood-brain barrier. Ethionamide (ETA) is usually preferred over EMB in children when an oral agent is used, as it is well-tolerated and has increased penetration into the CNS. (See *Chapter 7: Diagnosis and Treatment of Pediatric Tuberculosis Disease.*)

The continuation phase for CNS TB consists of a regimen of INH and RIF for seven to 10 months as long as there is no suspected or confirmed drug resistance. INH, RIF, and PZA penetrate the blood-brain barrier efficiently. EMB and injectable agents penetrate only when the meninges are inflamed. As penetration of some drugs into the cerebrospinal fluid (CSF) is poor, patients will most likely benefit from treatment regimens at the higher end of recommended dose ranges. Some experts advocate the addition of PZA during the continuation phase, as CSF concentrations of RIF are low and PZA readily penetrates the CNS; however, there are no clinical trials to support this approach.

Corticosteroids are routinely recommended when treating any patient with CNS TB, especially when treating a patient with a symptomatic tuberculoma, or any patient with CNS TB disease that has a decreased level of consciousness. Corticosteroids improve survival in individuals with severe disease and may reduce neurologic morbidity as well. If corticosteroids are used in a patient with a tuberculoma, dosages and tapering are similar as those for meningeal TB. Expert consultation with a neurologist is utilized as necessary. Corticosteroids are only given if the patient is on anti-TB therapy. Expert opinion on the optimal dosage for steroids varies; however, BTBC recommends dexamethasone or prednisone be given as follows:

**DEXAMETHASONE:** In adults, the initial dose is 12 milligrams (mg)/day. The initial dose is given for three weeks and then gradually decreased during the next three to five weeks. Neurologists should be consulted as needed.

**PREDNISONE:** In adults, corticosteroid dosages that are equivalent to 40 to 60 mg/day of prednisone are recommended with gradual tapering over six to eight weeks.

**TABLE 5.2:** Treatment of extrapulmonary tuberculosis disease

SITE OF DISEASE	LENGTH OF THERAPY <sup>1</sup>	CONSIDERATIONS
<b>CNS (including Tuberculoma and Meningeal)</b>	9-12 months	If corticosteroids are used, dosages should be tapered (see <i>Special Considerations for Central Nervous System Tuberculosis Disease</i> ) Intracranial tuberculoma can be treated for a minimum of 9-12 months or longer depending on clinical response. Consultation with a neurologist is recommended.
<b>Cutaneous</b>	6 months	Patients require consultation with a dermatologist
<b>Disseminated</b>	6-9 months	More common in children younger than 5 years of age; at least 9 months of treatment recommended. In adults, 6 months of treatment may be considered, depending on sites and clinical response. Corticosteroids may be useful for treating respiratory failure due to disseminated TB and/or TB meningitis
<b>Genitourinary</b>	6 months	Surgical indications for renal TB include: intractable pain; persistent hematuria; persistent urinary tract infections due to obstruction; or a nonfunctioning or poorly functioning kidney. All patients with renal TB require consultation with a urologist Female genital tract TB may require surgical intervention for residual large tubo-ovarian abscesses. Infertility is a complication of TB disease of the female genital tract and gynecological consultation is routinely pursued
<b>Gastrointestinal</b>	6 months	Patients require consultation with a gastroenterologist or surgeon as appropriate
<b>Lymphatic</b>	6 months	Most commonly affects cervical or supraclavicular lymph nodes, although any lymph node can be involved. Even with lymph node excision, chemotherapy is indicated
<b>Pleural</b>	6 months	The routine use of steroids is not recommended.
<b>Pericardial</b>	6 months	The routine use of corticosteroids is not recommended. Corticosteroids are recommended only in patients at a higher risk of complications (i.e., large pericardial effusions, high levels of inflammatory cells or markers in pericardial fluid, or early signs of constriction). Pericardiectomy or creation of a pericardial window is indicated if there is chronic constriction with adverse hemodynamic consequences (cardiac tamponade)
<b>Peritoneal</b>	6 months	Anyone with confirmed diagnosis of peritoneal TB or signs and symptoms consistent with peritoneal TB is referred to an appropriate GI center or hospital for further evaluation
<b>Skeletal</b>	6-9 months	Joint instability may require surgical intervention prior to the completion of treatment, so most patients with skeletal TB disease require consultation with an orthopedist during TB treatment. For extensive disease, treatment can be extended to 9 months.

Adapted from: Blumberg HM, Burman WJ, Chaisson RE, et al; American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med.* 2003 Feb 15;167(4):603-62.

1. Length of treatment may be extended based on clinical judgment.

**Abbreviations Used:** BTBC=Bureau of Tuberculosis Control; CNS=central nervous system; GI=gastrointestinal; TB=tuberculosis

## USE OF PYRIDOXINE (VITAMIN B6) IN TUBERCULOSIS TREATMENT

Pyridoxine is often used in conjunction with certain anti-TB medications to prevent side effects in the peripheral nervous system. (See *Table 5.3: The Use of Pyridoxine (Vitamin B6) in Tuberculosis Treatment.*)

**TABLE 5.3:** The use of pyridoxine (Vitamin B6) in tuberculosis treatment

DRUG	B6 DOSE	CONSIDERATIONS
INH	25 mg daily (may be self-administered if patient is on intermittent DOT) --- or --- 50 mg three times per week, if INH given at 900 mg three times per week --- or --- If patient develops peripheral neuropathy, discontinue INH and continue pyridoxine (25 mg daily) until symptoms abate	Indicated for children on meat- and milk-deficient diets and for breast-feeding infants on INH. Also advised for patients with: <ul style="list-style-type: none"> <li>• HIV infection</li> <li>• Malnourishment (more than 10% below ideal body weight or any wasting disease)</li> <li>• Diabetes</li> <li>• Cancer</li> <li>• Chronic renal disease</li> <li>• Pregnancy</li> <li>• Alcoholism</li> <li>• Pre-existing peripheral neuropathy or taking medications that cause peripheral neuropathy</li> <li>• Chronic liver disease</li> <li>• Other immunosuppressive conditions</li> </ul>
CS*	50 mg for each 250 mg of CS to a maximum of 200 mg pyridoxine daily	Required for all patients taking CS

\*CS is usually reserved for the treatment of drug-resistant TB.

**Abbreviations Used:** CS=cycloserine; DOT=directly observed therapy; HIV=human immunodeficiency virus; INH=isoniazid; mg=milligrams

## DETERMINATION OF TREATMENT COMPLETION

TB treatment guidelines recommend that treatment is considered complete when 100% of the prescribed doses have been taken. At BTBC, a medical consultant reviews each TB case for treatment completion and, based on clinical judgment, makes a final determination if patients with less than 100% adherence have completed treatment. Clinical judgment is informed by site and extent of disease, radiological findings, sputum culture-positivity at two months of treatment, and drug-susceptibility results. While 100% treatment adherence is always desired, BTBC as a program considers 80% ingested doses of the total prescribed doses to be complete.

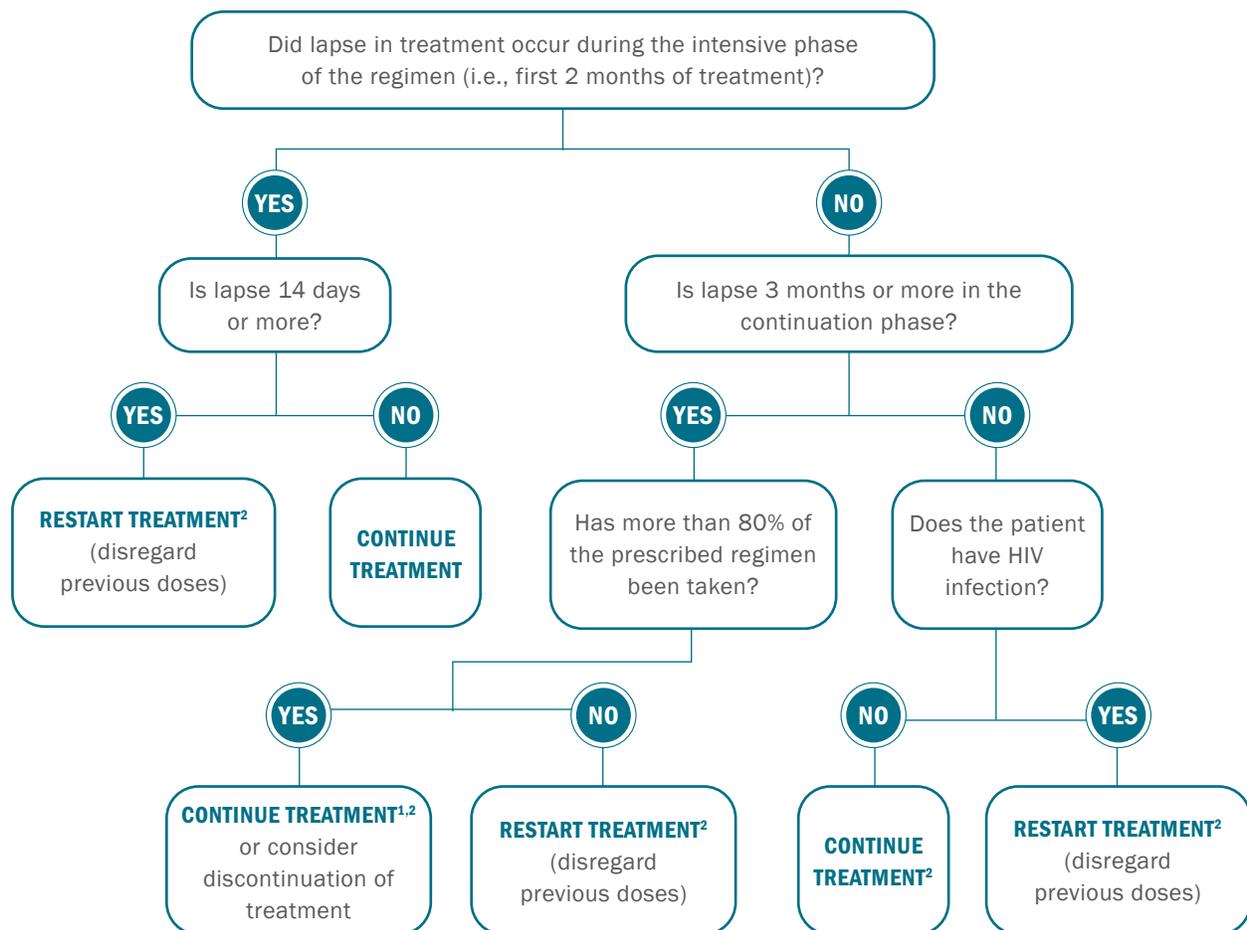
Treatment may be lengthened if all prescribed doses have not been taken within an optimal timeframe. For details regarding the number of doses of medication by regimen and optimal treatment durations, see *Table 5.1: Drug Regimens for Pulmonary Tuberculosis Disease Caused by Drug-Susceptible Organisms* and *Table 5.2: Treatment of Extrapulmonary Tuberculosis Disease.*

### INTERRUPTED OR INCOMPLETE TREATMENT

If a patient has had interrupted or incomplete treatment, a decision regarding whether to continue the originally prescribed regimen (increasing the duration of treatment to complete the required number of doses) or to completely restart the treatment regimen is made. For managing interruption in treatment, see *Figure 5.1: Reinstitution of Interrupted or Incomplete Anti-Tuberculosis Treatment*.

Continuous treatment is more crucial in the intensive phase of treatment because the number of organisms is highest in the beginning of treatment. A short lapse in treatment in the continuation phase would have less of an impact than the same lapse in the intensive phase, as there are fewer persistent organisms to kill. If more than 80% of the prescribed doses were taken before a lapse in treatment, the regimen may not need to be extended or restarted.

**FIGURE 5.1:** Reinstitution of interrupted or incomplete anti-tuberculosis treatment



1. Decision to continue treatment is based on clinical factors including length of treatment, length of relapse, AFB smear, CXR results, and other clinical risk factors including immunosuppression

2. Collect specimen and submit for laboratory testing for TB prior to restarting or continuing treatment

Abbreviations Used: AFB=acid-fast bacilli, CXR=chest radiograph; HIV=human immunodeficiency virus; TB=tuberculosis

In patients with HIV infection or other immunosuppressive conditions, the mycobacterial load can rebound rapidly, even with a short lapse in treatment. In such patients, consideration is given to restarting or extending treatment.

Clinical judgment is used to determine if a lapse in treatment is significant and if additional specimens should be collected and sent for repeat testing for TB. If there is a new positive culture, a new DST is obtained in order to inform clinical and public health management.



**If there is a lapse in treatment, additional specimens should be collected and sent for repeat testing for TB.**

### RESTARTING TREATMENT AFTER A SIGNIFICANT LAPSE

If there has been a significant lapse in treatment, a complete clinical evaluation is performed prior to restarting treatment, including a CXR and collection of sputum samples for AFB smear and culture and cultures with molecular and conventional DSTs. For management of treatment lapse, see *Figure 5.1: Reinstitution of Interrupted or Incomplete Anti-Tuberculosis Treatment*.

If the newly collected specimen is culture-positive, treatment is restarted and previous doses are disregarded. Susceptibility testing on culture-positive specimens following a lapse in treatment is requested from the laboratory, even if the previous isolates were drug-susceptible.

DOT is instituted if the patient is not currently receiving DOT. Every attempt is made to ensure that the patient completes a continuous course of TB treatment. If the patient has infectious TB, referral should be made for regulatory evaluation.

### TREATMENT FAILURE

Treatment failure is considered in patients with worsening clinical status or CXR due to TB. Treatment failure is defined as a positive TB culture any time after four months of appropriate TB treatment.

As soon as treatment failure is determined, three new consecutive daily sputum samples or other appropriate specimens are sent for smear, culture, and susceptibility testing. Susceptibility testing is requested on the most recent positive TB culture to determine if new drug resistance has developed.

Patients who are clinically stable may be maintained on their current anti-TB regimen (“holding regimen”) until DST results are available to guide the choice of medications.

Patients who are clinically deteriorating are given at least two to three new anti-TB medications to which the strain is likely to be susceptible. **A single drug is never added to a failing regimen**, as this can promote further drug resistance. When susceptibility results are available, the regimen is modified accordingly.

DOT is instituted if the patient is not currently receiving it. If treatment adherence is suspected to be an issue, refer for regulatory evaluation (See *Chapter 10: Case Management for Patients with Tuberculosis*).

## TREATMENT OF COEXISTING TUBERCULOSIS DISEASE AND HUMAN IMMUNODEFICIENCY VIRUS

Patients who are diagnosed with TB disease and HIV concurrently are started on antiretroviral treatment (ART) early in the TB treatment course. Waiting to initiate ART until after the completion of TB treatment leads to increased all-cause mortality. Patients with severe immunosuppression, especially those with a CD4 count < 50/cubic millimeter (mm<sup>3</sup>), should begin ART within two weeks of starting TB therapy. All other TB patients with HIV infection, including patients with CNS TB disease, should start ART within eight to 12 weeks of starting TB treatment.

Although introducing ART early in the TB treatment course leads to a higher rate of immune reconstitution inflammatory syndrome (IRIS), early treatment of HIV offers a clear survival advantage. The only exception to this guidance is for patients with confirmed CNS TB or signs and symptoms consistent with CNS TB. A brisk immune response after starting ART in a patient with CNS TB can result in cerebral edema and a poor outcome. ART may need to be delayed in patients with CNS TB based on clinical judgment. (See section *Immune Reconstitution Inflammatory Syndrome*.)

Given the challenges of managing drug interactions and overlapping toxicities, TB providers carefully coordinate the treatment of patients with TB disease and HIV in consultation with HIV experts. Close attention is paid to the possibility of TB treatment failure, ART treatment failure, IRIS, development of drug resistance, and unique and synergistic overlapping adverse effects for all drugs used. As new ART drugs are developed and more information becomes available, recommendations for the use of these drugs with anti-TB medications will change.

For drug-susceptible TB, a rifamycin-containing anti-TB regimen can be safely administered with most ART. In some situations, rifabutin (RBT) can be substituted for RIF to decrease drug-to-drug interactions and is considered equally as effective as RIF. Daily treatment with DOT during the intensive and continuation phase is recommended. (See *Table 5.4: Treatment Adjustments in TB Patients Receiving a Rifamycin Who are Human Immunodeficiency Virus-Infected and Taking Antiretroviral Agents*.)

If an INH-resistant, RIF-susceptible organism is isolated, it is essential to try to adjust the ART regimen so that a rifamycin can be used. Otherwise the patient will need treatment with a regimen used for MDR-TB.

### COMBINATION THERAPY FOR HUMAN IMMUNODEFICIENCY VIRUS

Drug-to-drug interactions between rifamycins and ART regimens containing two protease inhibitors (PI), two non-nucleoside reverse transcriptase inhibitors (NNRTI), or both a PI and an NNRTI have not been well studied. It is not recommended to use ART regimens that contain more than one PI (with the exception of ritonavir-boosted regimens), or a PI and an NNRTI, simultaneously with a rifamycin-containing regimen for the treatment of TB disease.

**TABLE 5.4:** Treatment adjustments in TB patients receiving a rifamycin who are human immunodeficiency virus-infected and taking antiretroviral agents<sup>1,2</sup>

CLASS OF ANTIRETROVIRAL AGENT	SELECT DRUGS WHOSE CONCENTRATIONS ARE SUBSTANTIALLY DECREASED BY RIFAMYCINS	TREATMENT ADJUSTMENT
Protease Inhibitors (PI)	<ul style="list-style-type: none"> <li>• Lopinavir/ritonavir (Kaletra®)</li> <li>• Darunavir/ritonavir (Prezista®)</li> <li>• Atazanavir (Ritovaz®)</li> <li>• Atazanavir/ritonavir</li> </ul>	<ul style="list-style-type: none"> <li>• RBT is preferred with PIs</li> <li>• For ritonavir-boosted regimens, RBT is given at 150 mg daily</li> <li>• Double-dose lopinavir/ritonavir can be used with RIF but toxicity is increased</li> <li>• In young children, double-dose lopinavir/ritonavir given with RIF results in inadequate concentrations of the antiretrovirals               <ul style="list-style-type: none"> <li>- Super-boosted lopinavir/ritonavir is advised (if available) by some experts</li> </ul> </li> <li>• RIF should not be used with PIs except double-dose lopinavir/ritonavir or super-boosted lopinavir/ritonavir</li> </ul>
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)	<ul style="list-style-type: none"> <li>• Nevirapine (Viramune®)</li> <li>• Efavirenz (Sustiva®)</li> <li>• Rilpivirine (Edurant®)</li> <li>• Emtricitabine, rilpivirine, TDF (Complera®)</li> <li>• Etravirine (Intelence®)</li> <li>• Doravirine (Pifeltro®)</li> </ul>	<ul style="list-style-type: none"> <li>• RIF decreases exposure to all NNRTIs</li> <li>• If nevirapine is used with RIF, lead-in nevirapine dose of 200 mg daily is omitted and 400 mg daily nevirapine dosage is given</li> <li>• With RIF, many experts advise that efavirenz be given at standard dosage of 600 mg daily, although FDA recommends increasing efavirenz to 800 mg daily in persons greater than 60 kg</li> <li>• Rilpivirine cannot be given with RIF or RPT</li> <li>• Etravirine is not given with RIF, but can be used with RBT at usual dosing</li> <li>• Nevirapine can be used with RBT at usual dosing</li> <li>• Efavirenz and RBT use requires dose increase of RBT to 600 mg daily, as such RIF is preferred</li> <li>• Complera® can only be given with RBT; an additional 25 mg tablet of rilpivirine once per day is taken concomitantly with Complera® and with a meal for the duration of the RBT co-administration</li> <li>• Doravirine is contraindicated with RIF</li> <li>• Doravirine can be given with RBT. The dose of Doravirine is increased to 100 mg twice daily with RBT</li> </ul>
C-C chemokine receptor type 5 inhibitors (CCR5)	<ul style="list-style-type: none"> <li>• Maraviroc (Selzentry®)</li> </ul>	<ul style="list-style-type: none"> <li>• Maraviroc cannot be used with RIF; however, RBT can be used</li> </ul>

**TABLE 5.4:** Treatment adjustments in TB patients receiving a rifamycin who are human immunodeficiency virus-infected and taking antiretroviral agents (*continued*)

CLASS OF ANTIRETROVIRAL AGENT	SELECT DRUGS WHOSE CONCENTRATIONS ARE SUBSTANTIALLY DECREASED BY RIFAMYCINS	TREATMENT ADJUSTMENT
Integrase Strand Transfer Inhibitors (INSTI)	<ul style="list-style-type: none"> <li>• Cabotegravir (Vocabria®)</li> <li>• Raltegravir (Isentress®)</li> <li>• Dolutegravir (Tivicay®)</li> <li>• Dolutegravir coformulated with abacavir and lamivudine (Triumeq®)</li> <li>• Elvitegravir (Vitekta®)</li> <li>• Elvitegravir co-formulated with cobicistat, tenofovir and emtricitabine (Stribild®), elvitegravir, cobicistat, emtricitabine, and TAF (Genvoya®)</li> <li>• Bictegravir/emtricitabine/TAF (Biktarvy®)</li> </ul>	<ul style="list-style-type: none"> <li>• Increase dose of raltegravir to 800 mg twice daily with RIF, although clinical trial data show similar efficacy using 400 mg twice daily</li> <li>• Dolutegravir dose is increased to 50 mg every 12 hours with RIF</li> <li>• Do not use RIF with elvitegravir</li> <li>• RBT can be used with all INSTIs except bictegravir/emtricitabine/TAF</li> <li>• Bictegravir/emtricitabine/TAF cannot be used with RIF and should not be used with RBT at this time</li> </ul>
Attachment inhibitors	<ul style="list-style-type: none"> <li>• Fostemsavir (Rukobia®)</li> </ul>	<ul style="list-style-type: none"> <li>• Fostemsavir should not be given with RIF and RPT</li> <li>• Potential weak interaction with RBT- additional action/monitoring or dosage adjustment is unlikely to be required</li> </ul>
Combination medicines	<ul style="list-style-type: none"> <li>• Cabotegravir/rilpivirine (Cabenuva®)</li> <li>• Dolutegravir/lamivudine (Dovato®)<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Cabotegravir/rilpivirine should not be given with RIF, RBT, or RPT</li> <li>• Dolutegravir/lamivudine can be given with RIF or RPT. Because the dose of dolutegravir is too low in Dovato, an additional dolutegravir 50 mg tablet, separated by 12 hours from Dovato, should be taken. This dose adjustment should be maintained for approximately 2 weeks after stopping RIF and RPT as the inducing effect may persist after discontinuation of a strong inducer.</li> <li>• Dolutegravir/lamivudine can be given with RBT</li> </ul>

Adapted From: Nahid P, Dorman SE, Alipanah N. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, Clin Inf Dis. 2016; NIH Office of AIDS Research Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV; and University of Liverpool HIV Drug Interaction Checker

1. Knowledge of the contraindications unique to each of the rifamycins is vital when prescribing TB treatment for HIV patients; RIF and RBT cross-react differently and must be used appropriately.
2. The list of antiretroviral medications included in this table is not comprehensive, as medications for the treatment of HIV are continuously changing. See the United States Agency for International Development list of approved antiretrovirals, University of California San Francisco's HIV InSite, and individual drug packaging for more information.
3. Close monitoring of HIV infection is recommended when dolutegravir/lamivudine is used with RIF and RBT.

**Abbreviations Used:** FDA=Food and Drug Administration; HIV=human immunodeficiency virus; INSTI=Integrase Strand Transfer Inhibitors; kg=kilograms; mg=milligrams; NNRTI=Non-nucleoside Reverse transcriptase inhibitors; PI=protease inhibitor; RBT=rifabutin; RIF=rifampin; RPT=rifapentine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

## SPECIAL DRUG INTERACTIONS WITH RIFAMYCINS

**COBICISTAT AND RIFAMYCINS:** Cobicistat (Tybost®) is not an ART, but a pharmacokinetic enhancer increasing the amount of other HIV medications in the blood, and is used in combination with other ART in several formulations:

- Darunavir and cobicistat (Prezcobix®)
- Atazanavir and cobicistat (Evotaz®),
- Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate (TAF) (Genvoya®),
- Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (TDF) (Stribild®)
- Darunavir, cobicistat, emtricitabine + TAF (Symtuza®)

Drug combinations that use cobicistat in combinations with other ART are not used concurrently with RIF. Regimens that contain cobicistat may be used with RBT, but the RBT dose is adjusted to 300 mg every other day or 150 mg per day.

**TENOFOVIR ALEFENAMIDE AND RIFAMYCINS:** TAF is being used increasingly in fixed-drug combinations in preference to TDF. TAF causes less bone resorption compared to TDF. However, there is a theoretical concern that the rifamycins will cause decreased absorption of TAF. Although there is some clinical evidence that TAF can be used with RIF, at this time, according to the package insert, TAF is contraindicated with rifamycins. There are currently five combination pills with TAF on the market:

- Emtricitabine/TAF/Elvitegravir/Cobicistat (Genvoya®)
- Emtricitabine/TAF (Descovy®)
- Emtricitabine/TAF/Rilpivirine (Odefsey®)
- Bictegravir/emtricitabine/TAF (Biktarvy®)
- Darunavir/cobicistat/emtricitabine/TAF (Symtuza®)

## REGIMENS FOR PREGNANT PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Treatment of HIV and active TB disease in pregnant patients is challenging. A basic principle is that patients should receive treatment for both HIV and TB disease during the pregnancy. ART should be initiated as early as possible for treatment of maternal HIV infection and to prevent maternal-child transmission. The care of any patient requiring treatment for both conditions during pregnancy is discussed in consultation with an expert.

## LENGTH OF THERAPY IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENTS

Recent guidelines suggest that recommended treatment regimens and length of therapy are similar for individuals with HIV infection who are on ART and those who do not have HIV infection. Patients not on

ART should have treatment extended. Short course therapy is possible if a standard rifamycin-containing regimen is used.

In NYC, relapse rates are generally low for patients with HIV and TB. Regardless, if cultures remain positive after two months of rifamycin-based treatment, the therapy is extended to nine months.

## **IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME**

IRIS is an inflammatory response to TB antigens as the body's immune system recovers while on TB and HIV treatment. While IRIS may occur in patients without HIV infection, patients with HIV-associated TB disease who are started on ART regimens seem to be at a particularly increased risk of developing this syndrome.

Onset of IRIS may occur within a few weeks of starting ART, and coincides most closely with viral load decline. If IRIS occurs, the patient appears to clinically worsen, with the development of new manifestations of TB or worsening of existing signs and symptoms of TB. While early initiation of ART is recommended and decreases all cause-mortality, it could lead to an increased risk of IRIS.

The frequency of IRIS is estimated to be approximately 20% among patients with concurrent TB disease and HIV on treatment. IRIS occurs more often in patients with lower CD4 counts, extrapulmonary TB disease, disseminated TB disease, or with a shorter interval between TB treatment and subsequent ART treatment.

IRIS can manifest in a wide variety of sites, including cervical or mediastinal adenopathy, worsening infiltrates on CXR or enlarging CNS lesions. Fever may or may not be present. Patients may experience substantial morbidity due to IRIS even though the prognosis for survival is favorable. The course of IRIS can be brief or prolonged, with multiple recurrences and exacerbations. The diagnosis of IRIS is a diagnosis of exclusion and this relies on: negative culture of clinical samples; decrease in HIV viral load; and lack of other etiologies, such as relapse of TB disease, poor adherence to treatment, adverse effects of drugs, and worsening TB disease due to drug resistance or other infections.

Among patients with CD4 counts less than 100 mm<sup>3</sup>, prednisone treatment during the first four weeks after initiation of ART results in a lower incidence of TB-associated IRIS without evidence of an increased risk of severe infections or cancers (40 mg per day for 14 days followed by 20 mg for 14 days).

If IRIS develops, mild and moderate reactions can be managed by reassuring the patients or by prescribing non-steroidal anti-inflammatory agents. While standard treatment for severe IRIS is not well established, some experts advocate the use of corticosteroids, such as when lymphadenopathy may compromise respiration and swallowing, or the development of CNS mass lesions occurs. To treat IRIS, prednisone is prescribed at 50 mg to 80 mg daily for two to four weeks with tapering for six to 12 weeks or longer. In conjunction with the anti-TB regimen, the use of corticosteroids for short periods does not seem to adversely affect the outcome of the TB treatment.

## TREATMENT OF COEXISTING TUBERCULOSIS AND NONTUBERCULOUS MYCOBACTERIA

Nontuberculous mycobacteria (NTM) can cause disease in immunocompromised and immunocompetent patients. Severely immunosuppressed individuals, usually with HIV infection, can develop TB disease and disseminated *M. avium-intracellulare* (MAI) infection concurrently, and must be treated for both conditions. In immunocompetent patients, NTMs may overgrow *M. tuberculosis* in the laboratory. *M. tuberculosis* requires specific laboratory techniques. The decision to treat TB is made on a case-by-case basis. Drugs currently recommended to treat MAI are macrolides (clarithromycin and azithromycin), EMB, and the rifamycins (especially RBT). If RBT cannot be used due to drug interactions, fluoroquinolones (FQN) or parenteral amikacin (AK) have also been used. When treating concomitant MAI and TB disease, RBT is not used at the same time as RIF. If RBT is required for MAI treatment, RIF is replaced by RBT in the anti-TB regimen as well.

In general, patients with coexisting MAI and TB disease can be treated at a NYC Health Department TB clinic for both diseases until TB treatment is completed or TB disease is ruled out. Patients should also be followed up by another expert in the treatment of NTMs to ensure successful treatment outcomes. Following treatment completion for TB, the patient is referred to another provider if continued treatment for the NTM is warranted. BTBC does not treat patients with NTMs alone.

## TREATMENT REGIMENS FOR PREGNANT PATIENTS

Treatment for TB disease is initiated for any pregnant patient who has a positive TB culture and for whom there is a high clinical suspicion of TB disease based on symptoms, CXR, and clinical evaluation. For the latter group, treatment may be deferred until the end of the first trimester if the patient is very reluctant to take treatment and the following conditions are met:

- Sputum smears are AFB-negative
- Without HIV infection or other immunocompromising condition
- Without symptoms of TB disease (i.e., cough, fever, night sweats, weight loss)
- Without cavitory lesion on CXR

Treatment regimens for pregnant patients differ from standard treatment regimens in that PZA is avoided as the effect of PZA on the fetus has not been well established; however, PZA is included in the initial treatment regimen for patients with either HIV infection or a probable diagnosis of MDR-TB. Because PZA has been used extensively in pregnant patients internationally without apparent adverse effects, the World Health Organization (WHO) recommends PZA at all stages of pregnancy for all pregnant patients. If the patient has TB that is INH-resistant or intolerant to INH, PZA should be included in the regimen, as the benefit outweighs the risk.

## STANDARD REGIMEN FOR PREGNANT PATIENTS

The usual doses of INH, RIF, and EMB are used in the standard regimen unless there are absolute contraindications. (See *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis.*) If the patient has not been prescribed PZA during the intensive phase, treatment must be extended to nine months. For pregnant patients taking INH, pyridoxine 25 mg/day is given unless the patient is already taking a prenatal vitamin that contains the equivalent amount of pyridoxine.

If pregnancy is discovered while the patient is already on a standard four-drug regimen that includes PZA, and the patient is in the first trimester of pregnancy, the PZA can be stopped. If the first trimester has passed before the pregnancy is discovered, all four drugs are continued (EMB can be dropped if the TB isolate is drug-susceptible), in order to finish a two-month intensive phase of treatment. If the isolate is drug-susceptible and PZA was given during the two-month intensive phase, treatment can be shortened from nine to six months. Otherwise therapy should be continued for nine months.



**AFB culture and pathological evaluation of the placenta is requested as part of the diagnosis process. This may help when evaluating the infant for the possibility of congenital TB.**

## ANTI-TUBERCULOSIS MEDICATIONS IN BREASTFEEDING MOTHERS

The small concentrations of anti-TB drugs in breast milk are not toxic to the nursing newborn. Therefore, breastfeeding is not discouraged for a mother without HIV who is planning to take, or who is taking, INH or other anti-TB medications. Furthermore, the low concentration of anti-TB medications in breast milk is not considered effective treatment for disease or for treatment for latent TB infection (LTBI) in a nursing infant. Mothers with HIV infection should not breastfeed because of the risk of HIV transmission to the infant. (See *Appendix I: The Use of Anti-Tuberculosis Drugs and Pregnancy, Breastfeeding, Tuberculosis Meningitis, and Renal and Hepatic Failure.*)

## TREATMENT REGIMENS FOR PATIENTS WITH CHRONIC RENAL FAILURE

In most patients with chronic renal failure, the regimens for TB treatment must be adjusted; the interval between conventional dosages should be lengthened instead of decreasing dosing. (See *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis.*) No dose adjustment is necessary for: INH, RIF, ETA, and para-aminosalicylic acid (PAS); however, a dose adjustment is required for PZA and EMB. In addition, both PZA and EMB are given after hemodialysis. Three times per week regimens are convenient and should be developed in coordination with the patient's hemodialysis schedule to ensure medications are given after hemodialysis.

There is very little information about how to dose patients who are on peritoneal dialysis. While there is some literature on intraperitoneal administration of anti-TB medications, BTBC recommends patients are dosed per hemodialysis dosing.

The following anti-TB medications are eliminated by the kidney and therefore require a dose adjustment:

- » Injectable agents can be used in 15 mg/kg doses, but only two or three times per week. The dose is administered immediately after hemodialysis in patients who are receiving maintenance hemodialysis. Levels of AK, if used, may be helpful in guiding therapy.
- » PZA can be used at the usual daily dose in patients with mild to moderate renal insufficiency. In patients with severe renal failure, however, a three times per week dose of 30 mg/kg (range 25 to 35 mg/kg) is recommended. The medication is given immediately after hemodialysis.
- » EMB and cycloserine (CS) are excreted primarily by the kidney, and excessive and toxic blood levels can occur in patients with chronic renal insufficiency. Both medications are avoided if possible. When either EMB or CS are used, drug levels should be monitored.
- » If EMB is essential to the regimen (e.g., in patients with MDR-TB), 20 to 25 mg/kg doses may be given 3 days per week, but visual acuity and color vision must be monitored closely.
- » CS is given immediately after hemodialysis at a dose of 250 mg or 500 mg three times per week.
- » FQNs undergo some degree of renal clearance that varies from drug to drug. Levofloxacin (LFX) at 750 to 1000 mg three times per week is adequate for treatment of TB in patients with chronic renal failure. Moxifloxacin (MFX) may be the preferred agent for patients with renal failure, as it is mostly cleared by the liver.

## **TREATMENT REGIMENS FOR PATIENTS WITH LIVER DISEASE**

Many anti-TB drugs are metabolized by the liver. Therefore, patients with underlying liver disease may be more likely to experience liver toxicity from these drugs. In most situations, it is not necessary to reduce the dosages of drugs that are metabolized by the liver (INH, RIF, PZA, and ETA). The administration of RIF with INH can increase the possibility of drug-induced hepatitis during therapy. Close monitoring of patients' liver function and signs and symptoms of toxicity should be more frequent, either biweekly or monthly.

- » If it is necessary to exclude one of these agents from the regimen because of elevated LFTs, INH is considered first. If INH is excluded, the patient may be treated with EMB, RIF, and PZA for six to nine months. (See *Table 6.2: Traditional Suggested Regimens for Treatment of Drug-Resistant Tuberculosis* in *Chapter 6: Treatment of Drug-Resistant Tuberculosis Disease in Adults*.)
- » If RIF is excluded, the duration of treatment will need to be prolonged to 12 to 18 months.
- » Depending on the severity of the hepatitis attributed to RIF, a trial of RBT is considered.
- » If the TB is drug-susceptible and PZA is the cause of the increased LFTs and excluded from the regimen, INH and the rifamycin are given for at least nine months.
- » A FQN can be added if PZA and/or INH is not used in the regimen.

Patients who have viral hepatitis may be difficult to treat because of the underlying hepatic disease and potential drug toxicities. For patients with chronic active hepatitis B, LFTs and hepatitis B deoxyribonucleic acid (DNA) are obtained. If elevated, a gastroenterologist or infectious disease specialist should be consulted regarding further testing and treatment; clinical and LFT monitoring should occur every two to four weeks. For patients with chronic hepatitis C, a hepatitis C viral ribonucleic acid (RNA) load should be obtained. If RNA viral load is elevated, the patient should be referred to a gastroenterologist for evaluation. In these patients, elevated LFTs may be indicative of underlying liver disease and may not be drug induced. In patients with acute liver failure, a regimen of non-hepatotoxic drugs, also known as a liver sparing regimen—such as an injectable agent, EMB, CS, and a FQN—should be used until the liver function improves. LFX is the preferred FQN to use in patients with hepatic insufficiency. MFX may be used with no change in dosage; however, it should be used with caution, especially in cases of severe hepatic insufficiency. A similar regimen can be used in patients with severe chronic liver disease who cannot tolerate INH or RIF. The duration of therapy depends on whether it is possible eventually to add INH and RIF to the regimen, and on the final regimen that is tolerated.

## **DRUG INTERACTIONS**

Clinically important drug interactions exist between TB medications and other medications, as well as TB medications and certain foods. It is important to be aware of these interactions to ensure quality and safety of care. (See *Appendix F: Potential Drug Interactions with Isoniazid and Rifamycin Medications* and *Appendix J: Recommendations for Patients to Assist with Taking Tuberculosis Medications*.) For interactions with specific drugs, providers may use online drug-to-drug interaction trackers, the electronic medical record, or UptoDate.

## **SUMMARY**

All individuals with a confirmed diagnosis of TB disease or signs and symptoms consistent with TB disease begin treatment promptly. Most forms of active TB disease can be treated with the standard six-month regimen. However, treatment regimens are adjusted based on DST results, both molecular and conventional, of a patient's positive culture or due to suspicion of drug resistance. Length of treatment may be adjusted based on site of disease. Completion of treatment is dependent on the number of uninterrupted doses taken in both the intensive and continuation phase. Expert consultation should always be sought for complicated TB treatment issues.

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