

Section VI.

Clinical Monitoring and Follow-Up for Tuberculosis Treatment

Monthly Clinical Evaluation

All Class III and Class V patients, as well as Class IV patients on multidrug treatment, should receive at least monthly clinical evaluations by the treating physician and nurse to monitor response and adherence to treatment and to assess for adverse reactions. (See p. 103, Figure VI-1 and p. 105, Table VI-1.)

Physician Assessment

The following should be assessed and discussed with individuals receiving anti-TB treatment and documented in the clinic medical record:

- 1. Signs and symptoms of TB for response to treatment.** All patients should be evaluated for signs and symptoms of TB during the physical examination; if symptoms persist despite treatment, non-adherence or drug resistance should be suspected and frequent sputum specimens should be obtained for culture and drug-susceptibility testing.
- 2. Chest X-ray (CXR).** Patients who are initially culture negative should have a repeat CXR at 2 and 4 months to document response to treatment or the possibility of non-tuberculous lung disease. (See p. 114.)
- 3. Adherence to treatment.**
 - The physician should review directly observed therapy (DOT) records if the patient is receiving DOT. Patients who are prescribed intermittent DOT who are less than 80% compliant should be switched to a daily DOT regimen.
 - Patients on self-administered treatment should be instructed at the first visit to bring the last-issued medication bottles to follow-up visits. Pills should be counted by the physician or nurse, and the information recorded in the patient's chart.
- 4. Medication side effects and adverse reactions.** Adverse reactions from specific medications should guide the physician's decision regarding the physical exam and laboratory evaluation. (See p. 208, Appendix I-A and p. 210, Appendix I-B, for details and recommended monitoring parameters.)
- 5. Physical examination.** The nature and extent of the physical exam depends on the patient's symptoms and site of disease (e.g., evaluation of lymph node size, medication side effects). Taking a medical history at each follow-up visit is important to guide the exam, as patients may not reveal certain symptoms or events unless asked.
- 6. Laboratory tests.** Previous sputum and other laboratory tests requested should be assessed for availability of results to use in treatment decisions. Patients should be told whether their tests show improvement in or a deterioration of their condition and the effect of either on their treatment.

Note: Abnormal test results should be addressed as soon as received, independent of the date of the monthly follow-up visit.

- **Sputum..** Induced sputum should be obtained monthly for smear and culture in patients with drug-susceptible pulmonary disease. For patients with isoniazid- and rifampin-susceptible TB, there is no need to examine sputum monthly once culture conversion is documented (i.e., 2 negative cultures taken at least 2-4 weeks apart).

If sputum specimens remain smear positive for acid-fast bacilli (AFB) after documented culture conversion to negative, continue to collect sputum specimens at least monthly until smear converts. Clinical correlation is recommended. Sputum should be collected from all patients at the end of treatment to document cure.

- For patients who are initially smear positive and are being managed as outpatients, specimens should be collected every 1 to 2 weeks until smear converts to negative. This will allow timely decision-making about when patients may be allowed to leave their home, receive visitors or return to work or school.
- More frequent specimens are unnecessary except on rare occasions when a patient who is already smear or culture negative develops a newly positive AFB smear; in such cases, 2 to 3 specimens may be collected in a week's time as part of clinical reassessment. The specimen collection procedure should also be reviewed to ensure that the result is not falsely positive. Once smears have become negative for AFB on 2 to 3 consecutive specimens, monthly specimens are adequate until culture conversion is documented.
- For hospitalized patients, frequent specimens for smear conversion are vital to determine when airborne isolation can be discontinued or when patients can be safely discharged to the community or a long-term facility (if they are not eligible to be discharged while still AFB smear positive). Daily specimens are unnecessary; specimens should be taken every 3 to 7 days since smear conversion can take many weeks and median time to conversion for most patients is 4 weeks. However, once smears turn negative, specimens can be collected more frequently. Smear conversion is defined as having 3 consecutive negative AFB sputum smear in specimens collected over at least 48 to 72 hours.

- Specimens do not need to have cultures performed every week; cultures can be performed on all initial specimens collected for diagnostic purposes and on specimens taken 2 weeks apart—even for patients with multidrug-resistant TB (MDR-TB). However, if failure or relapse is suspected because smear or culture has reverted to positive after initial conversion, the specimens taken for reassessment should all have cultures done as well. In addition:

- All patients should have a sputum sample taken 1 to 2 weeks before the end of the intensive phase to assess risk of relapse or treatment failure, and to assess eligibility for rifapentine. (See p. 46.)
- More frequent specimens should be taken if the patient is nonadherent to the treatment regimen, there are signs of relapse or the patient is prescribed a nonrifamycin or nonisoniazid regimen. At the end of treatment, a sputum specimen should be taken to document cure; a negative sputum culture at the end of treatment is the only conclusive evidence that the patient has been cured.
- If the patient has isoniazid and/or rifampin-resistant TB, sputum cultures should be examined monthly until the end of treatment (see p. 84), and then evaluated post-treatment according to the guidelines on p. 115.

Sputum should be collected in the clinic setting via induction. Natural sputum collection should be done only in cases where the patient is homebound, has difficulty reaching the clinic or is unable to produce induced sputum during the day. Susceptibility testing on the most recent positive *Mycobacterium tuberculosis* (*M. tb*) culture should be requested if cultures remain positive after 4 months of treatment or if the individual fails to improve clinically.

Physicians who would like to arrange for more frequent susceptibility testing for selected patients should call the New York City Department of Health and Mental Hygiene Bureau of Laboratories at (212) 447-6745.

Figure VI-1

Therapy Evaluation Timeline for Previously Untreated Tuberculosis Patients with Drug-Susceptible Active Disease¹

Months	0	1	2	3	4	5	6	7	8	9	
Regimen I²											
Isoniazid ^{3,4}	→										
Rifampin ⁴	→										
Ethambutol ^{5,6}	→										
Pyrazinamide ⁵	→										
Regimen II²											
Isoniazid ³	→										
Rifampin	→										
Rifapentine ⁷	→										
Ethambutol ^{5,6}	→										
Pyrazinamide ⁵	→										
HIV Counseling and Testing	X					O					
Regular Monitoring											
Physician and Nurse Assessment	X	X	X	X	X	X	X	X	O	O	O
Sputum Smear and Culture ⁸	X	X	X	X	O		O	X	O	O	O
Nucleic Acid Amplification ⁹	X										
CXR¹⁰	X		O			O		X/O			X
Complete Blood Cell Count with Platelets	X		O	O	O	O	O	O	O	O	O
Liver Function Tests^{11,12}	X		O	O	O	O	O	O	O	O	O

- X = Recommended intervention
- O = As needed
- Regular treatment
- Continue treatment if pyrazinamide was not used in the intensive phase or if patient had a cavitary CXR and positive sputum culture at the end of the 2 months intensive phase of treatment
- If sputum cultures are positive at the end of 2-month intensive phase, continue rifapentine and isoniazid for a total of 7 months.

1. This chart applies only to patients whose isolates are found to be drug-susceptible. If drug resistance is documented, consult an expert in its management. To obtain treatment information and susceptibility results, call 212-788-4162 during business hours.
2. Pending the results of drug-susceptibility testing, begin all patients on the first four anti-TB medications listed, unless there are absolute contraindications.
3. Pyridoxine hydrochloride (vitamin B6) 10-25 mg with each dose of isoniazid may decrease peripheral neuritis and CNS effects. See Table III-4.
4. In the continuation phase, isoniazid and rifampin should be given for only 2 months if initial cultures are negative, for a total of 4 months of treatment. The continuation phase should last for 4 months (a total of 6 months of treatment) if initial cultures were positive but susceptibility results are not available.
5. Pyrazinamide and ethambutol can be discontinued at the end of the intensive phase of treatment for all patients with culture negative TB and for those patients with culture positive TB for whom drug-susceptibility is not available, unless drug resistance is strongly suspected, or the patient has been treated in the past.
6. During treatment with ethambutol, monitor visual acuity and color vision monthly.
7. Use rifapentine for pansensitive noncavitary pulmonary TB patients who have received at least isoniazid, rifampin, and pyrazinamide for the 2 month intensive phase of therapy. Rifapentine should not be used in HIV-positive patients, children under 12 years of age, pregnant women, and patients who are sputum AFB-smear positive after 2 months of treatment. It should not be used to treat extrapulmonary TB.
8. Initially at least 3 sputa for AFB smear and culture should be collected over 48 to 72 hours in order to maximize bacteriologic diagnosis. Most patients (e.g., patients on DOT, patients adherent to the treatment regimen, and patients with isoniazid and rifampin-susceptible TB) need monthly sputum tests only until cultures become negative – documented by 2 negative cultures taken 2-4 weeks apart. To document cure, a sputum test should be obtained at the end of treatment. If drug resistance is suspected or documented, seek expert consultation.
9. Nucleic acid amplification testing should be performed on the first sputum that is AFB smear positive and on selected smear negative specimens if the clinical suspicion of TB is high.
10. Obtain CXR after 2 and 4 months to document response to treatment if initial cultures are negative. CXR should be obtained at the end of treatment for all patients as a baseline in the event of suspected relapse in the future.
11. Baseline liver function tests (LFTs) should be done for all patients.
12. Monthly LFTs should be done in patients:
 - Whose baseline LFT results were abnormal;
 - Who are HIV seropositive, regardless of baseline LFT results;
 - Who have a history of heavy alcohol ingestion, liver disease, or chronic hepatitis, regardless of baseline LFT results;
 - Who are pregnant or postpartum (up to 2-3 months after delivery) and are currently taking isoniazid and/or rifampin, regardless of baseline LFT results;
 - Who currently inject drugs or who have documented chronic hepatitis B or C infection, regardless of LFT results;
 - Who are taking hepatotoxic medications

- **Liver function tests**

- Baseline liver function tests (LFTs) and a complete blood count (CBC) including platelets and chemistry panel including creatinine, should be obtained for all patients.
- Monthly LFTs should be done on patients who meet one or more of the following criteria:
 - Have abnormal baseline LFT results
 - Are HIV-positive, regardless of baseline LFT results
 - Have a history of heavy alcohol ingestion, liver disease or chronic hepatitis, regardless of baseline LFT results
 - Are pregnant or postpartum (up to 2-3 months after delivery) who are currently taking isoniazid and/or rifampin, regardless of baseline LFT results
 - Currently inject drugs or have documented chronic hepatitis B or C infection, regardless of baseline LFT results
 - Are treated with second-line medications that may be hepatotoxic (e.g., ethionamide) or with medications that may be hepatotoxic but are unrelated to TB treatment
 - In patients older than 35 years of age, periodic LFTs should also be performed (i.e., 1 and 3 months).

- **Additional Tests.** Other relevant laboratory values should be obtained at appropriate intervals according to the medications used and side effects present. For example, renal function and hearing may be affected by the aminoglycosides and capreomycin; uric acid values are affected by pyrazinamide. (Note: an increase in uric acid is not an indication to discontinue pyrazinamide, as long as the patient remains asymptomatic.) Thyroid function tests should be performed for patients on para-aminosalicylic acid or ethionamide.

HIV counseling and testing should be offered to all patients if HIV status is unknown

7. Formulation of a plan of care based on evaluation of current status.

- Because several medical providers may be involved in the care of one patient, it is important to outline a plan of care that details reasons for decisions, names and dosages of medications, planned length of treatment, etc. in order to ensure continuity of care.
- This plan should be communicated to non-Bureau of Tuberculosis Control (BTBC) providers on a regular basis.
- Changes in treatment plans should be communicated to all providers in a timely manner.

8. Medication orders (to be written on the medication order sheet). Medication must be prescribed on a specific medication order form and be clearly written. To prevent errors, non-standard abbreviations should not be used on the medication order form and the physician's name must be printed along with the signature. A "Hold Medication" order should not be used, as it is not time-specific— a medication should be discontinued, and then restarted when indicated. All medication orders should be time limited. Changes in medication orders due to adverse reaction should be flagged and/or communicated to the nurse who is to execute the order.

Eligible patients should be started on intermittent therapy with DOT, especially after the 2-month intensive phase.

9. Review of non-TB medications. In 1992, New York State amended Section 63.6 of the New York State Education Law, requiring that all medications a patient takes must be reviewed with the patient and noted in his or her medical record at each visit. In addition, a patient must be notified of potential drug interactions to any anti-TB medications that are prescribed in the BTBC.

If there has been no change in the use of non-TB medications from previous visit(s), the documentation in the medical record should read: "no change in medication status." If the patient reports using new medications, if there has been a change in dosage or if any medications have been discontinued, the physician should:

- (1) Enter the name and dosage of the medication(s) in the medical record

Table VI-1

Common Adverse Reactions to First- and Second-Line Anti-Tuberculosis Medications*

Adverse Reaction	Symptoms and Signs	Usual Drug Responsible
Audiovestibular manifestations	Hearing loss, vertigo, new-onset tinnitus	Aminoglycosides, capreomycin
Blood sugar abnormalities	Dizziness, sweating, fainting, poor response to infections	Fluoroquinolones, pyrazinamide, rifampin
Dermatitis	Itching, rash, hives, fever, petechial rash	Pyrazinamide, rifampin, rifapentine, isoniazid (rarely, ethambutol, rifabutin or injectable agents)
Gastritis	Anorexia, nausea, vomiting, epigastric pain	Rifampin, rifapentine, pyrazinamide, rifabutin
Hematologic manifestations	Leucopenia, thrombocytopenia, anemia, eosinophilia	Rifampin, rifabutin, rifapentine, isoniazid, linezolid, capreomycin
Hepatitis	Anorexia, nausea, vomiting, jaundice, abdominal pain	Isoniazid, rifampin, rifapentine, pyrazinamide; rarely ethambutol, rifabutin
Hypothyroidism	Fatigue, weight gain, sluggish reflexes, depression	Para-aminosalicylic acid, ethionamide
Joint and tendon manifestations	Gout-like manifestations, systemic lupus erythematosus-like manifestations; tendinopathies	Pyrazinamide, isoniazid, fluoroquinolones, rifampin
Neurological and psychiatric manifestations	Headaches, depression, agitation, suicidal ideation	Isoniazid, fluoroquinolones, cycloserine
Peripheral neuropathy	Numbness or paresthesias of feet or hands	Isoniazid, linezolid
Renal manifestations	Hematuria, azotemia	Aminoglycosides, capreomycin, rifampin, rifapentine
Visual manifestations	Vision loss and color blindness, uveitis	Ethambutol, rifabutin, rifapentine, linezolid

* This is not a comprehensive list of adverse reactions. Please consult the drug's package insert, *Physicians Desk Reference* or other reference pharmaceutical texts for more information.

- (2) Determine whether the new non-TB medication(s) might interact with the anti-TB medications the patient is currently taking
- (3) Discuss potential drug-to-drug interaction(s) with the patient and document this discussion in the medical record.

Nurse Assessment

The nurse is responsible for performing a monthly nursing assessment of the patient. Nurses should document the following in the clinic medical record:

- Vital signs
- Signs and symptoms of TB disease (for patients with latent tuberculosis infection [LTBI] diagnosis)
- Symptoms of improvement (diseased patients)
- Assessment of adherence
- Monitoring of medication side-effects and adverse reactions, including:
 - Visual acuity testing and Ishihara's color vision testing for patients taking ethambutol
 - Hearing tests for patients receiving injectable agents
 - Check of patient's sclera and nail bed for signs of jaundice
- Review patient's knowledge of medication and dosage, potential side-effects and adverse reactions, and instruct the patient about what to report to the physicians
- Review the physician's plan of care with the patient
- Reinforce need for adherence to treatment and follow-up visit

- Review of non-TB medications
- Ensure that all physician orders were followed
- Perform/facilitate referrals for follow-up of abnormal findings

Management of Adverse Reactions

Anti-TB medications can cause a variety of adverse reactions, summarized on p. 105, Table VI-1; p. 208, Appendix I-A; and p. 210, Appendix I-B.

Dermatitis

Several anti-TB agents can cause rash, including all of the first-line agents; however, the most common culprit in our experience is pyrazinamide (followed by rifampin and isoniazid). Rifampin and the fluoroquinolones can also cause photosensitivity.

History and Examination

- The patient should be questioned about exposure to other medications or skin preparations, environmental contact, etc., that may be responsible.
- HIV-positive patients are subject to a variety of dermatologic diseases (either directly or indirectly related to HIV infection) and to other medications used for therapy or prophylaxis. Consultation with an appropriate infectious disease service or dermatology clinic may be required.
- The patient should be examined for evidence of unrelated skin disease (scabies, contact dermatitis, childhood exanthema, acne, etc.).

Follow-Up

- If the dermatologic reaction is severe and no other cause is found, anti-TB medications should be discontinued promptly and the patient should be examined each week until the skin reaction disappears.
- Patients with a severe dermatologic reaction (e.g., exfoliative dermatitis), or with dermatitis associated with severe systemic reactions should be referred for hospital admission for treatment and the establishment of either a new anti-TB regimen or a rechallenge regimen, under daily surveillance as an inpatient.
- If the drug reaction is mild, the physician may attempt to treat the patient with

antihistamines and topical steroids while continuing TB treatment. Clinical discretion is recommended.

Restarting Anti-TB Medications

- In cases managed in the chest center, rechallenge is appropriate after the skin reaction clears or subsides. It may not be possible to identify the specific causative agent by the characteristics of the skin reaction. Thus, it is appropriate to restart the most important member of the regimen (either isoniazid or rifampin) first, before trying pyrazinamide or ethambutol. (Note: In at least one study, pyrazinamide was found to be a major cause of skin reactions; most reactions occur within the first 4 weeks of treatment.)
- Single daily doses of isoniazid or rifampin should be given alone for 3 days with instructions to discontinue promptly if a reaction recurs. The patient should be examined in 3 to 4 days and in addition:
 - If there is no reaction, an alternate drug (rifampin or isoniazid) should be added with similar instructions. The patient should be re-examined in 3 to 4 days.
 - If the skin reaction does not recur or if it is not severe, ethambutol should be added (if this drug was part of the initial regimen). If there is no reaction to ethambutol, the regimen of isoniazid, rifampin and ethambutol can be continued and pyrazinamide discontinued on the presumption that this caused the skin reaction.
- Treatment should be continued with the original regimen minus the causative agent. A longer period of treatment may be required if the causative agent was isoniazid or rifampin, or pyrazinamide during the initial 2 months of treatment. For patients who are HIV-positive or who have extensive pulmonary or disseminated TB, a single, new drug, such as an injectable agent or a fluoroquinolone, should be added to regimens that lack isoniazid or rifampin. (See p. 83). The new drug should be continued for the duration of therapy. (In such instances, the addition of a single agent to a successful regimen does not violate the rule of “do not add a single drug to a failing regimen.”)
- The same principles of management apply to patients who experience dermatologic reactions while taking “retreatment” regimens for MDRTB.

Hepatitis

Several anti-TB medications can cause hepatotoxicity, which varies from adaptive responses to severe injury. In addition, concomitant use of TB medications increases the risk of developing drug-induced liver damage. Despite these risks, the benefits of TB treatment to the individual far outweigh the risks.

Certain drugs provoke various physiologic adaptive responses in the liver, which may lead to asymptomatic transient elevations of alanine aminotransferase (ALT; formerly known as serum glutamate pyruvate transaminase [SGPT]) or induction of the microsomal enzymes; these rarely lead to hepatic damage. However, certain toxins such as alcohol can interfere with the adaptation processes and augment injury. Concomitant use of other known hepatotoxic agents should be avoided if possible during anti-TB treatment, especially in patients with underlying liver disease.

An increase in serum ALT is more specific for hepatocellular injury than an increase in aspartate aminotransferase (AST-serum glutamic oxaloacetic transaminase [SGOT]), which can also signal abnormalities in muscle, heart or kidney. Populations used to set standard values in the past probably included individuals with occult liver disease, whose exclusion has led to decreases in the upper limit of normal for LFTs. Transaminases tend to be higher in men and in people with greater body mass index. Levels may vary as much as 45% on a single day, with the highest levels occurring in the afternoon, or 10% to 30% on successive days. ALT and AST elevation may occur after exercise, hemolysis or muscle injury.

History and Examination

- Individuals taking anti-TB medication who develop symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice) should be instructed to discontinue all medications promptly and be examined by a physician; have LFTs and a viral hepatitis screen sent immediately.
- In some patients, rifampin or pyrazinamide may cause gastritis with symptoms similar to those of hepatitis. In these patients, LFTs remain normal or stable despite symptoms (see p. 110).

Follow-Up

- If symptoms disappear promptly and LFTs are normal, drug-induced hepatitis is unlikely. Another cause for symptoms should be suspected. Depending upon the nature, duration and severity of symptoms, a decision should be made about further diagnostic study.
- If the LFTs are abnormal (AST or ALT is 3 to 5 times the upper limit of normal) or if serum bilirubin is elevated, with or without symptoms, drug-related hepatitis should be strongly suspected and all anti-TB medication(s) should be discontinued.
- The patient should be examined and have LFTs repeated at least weekly. If symptoms persist for more than 2 weeks without anti-TB medication(s), or if LFTs continue to worsen, the physician should suspect progressive drug-related hepatitis or an unrelated cause of hepatitis. Depending upon the severity of the hepatitis, as indicated by clinical findings and LFTs, hospitalization may be necessary for closer observation and therapy.

Restarting Anti-TB Medications

- If there is strong evidence that the symptoms are not related to hepatitis or anti-TB medication, the entire regimen should be reinstated promptly and the individual followed closely for the recurrence of symptoms.
- If the patient has extensive pulmonary, meningeal or disseminated TB; has HIV infection; or lives in a congregate setting or with young children or immunosuppressed persons, the institution of a new regimen with a lesser potential for hepatotoxicity (e.g., streptomycin, ethambutol, fluoroquinolone) may be indicated even before liver enzymes return to normal.
- For all other patients, anti-TB treatment should be withheld until symptoms disappear and LFTs are normal or have declined and plateaued. During this time, the patient should be followed closely with weekly LFTs; it is then appropriate to rechallenge with a single daily dose of one of the drugs in the prior regimen.
- If hepatitis is caused by any of the drugs in the anti-TB regimen, isoniazid is most likely to be responsible, followed by pyrazinamide, rifampin and ethambutol (in this order).

- Although the specific cause of hepatitis cannot be identified by the pattern of LFT abnormality, rifampin is usually implicated if the pattern is cholestatic (bilirubin and alkaline phosphatase elevated and out of proportion, with little or no changes in ALT, to enzyme elevations). In contrast, isoniazid, rifampin or pyrazinamide may be the cause if the pattern is hepatocellular, with enzymes elevated and out of proportion to bilirubin or alkaline phosphatase. Ethambutol very rarely causes hepatitis.
- In some cases, the treating physician may not want to lose a rifamycin in the treatment regimen. Rifabutin rechallenge may be acceptable with close follow-up of patients.

Cholestatic pattern. If the initial pattern of hepatitis is cholestatic, the patient should be rechallenged with a standard daily dosage of isoniazid and ethambutol after LFTs return to normal or decline to 2 times the upper limit of normal and plateau. The patient should be examined weekly, with LFTs repeated at each visit.

If LFTs remain stable after 1 week of isoniazid and ethambutol, and the patient is asymptomatic, pyrazinamide should be added to the regimen. If there are no subsequent signs of hepatotoxicity, rifampin-induced hepatitis should be assumed, and the patient should be treated with isoniazid, ethambutol and pyrazinamide. Capreomycin or an appropriate aminoglycoside, as well as a fluoroquinolone, should be considered for addition to the regimen (see p. 87).

Hepatocellular pattern. If the pattern is hepatocellular, it is appropriate to rechallenge first with the agent least likely to have been responsible—ethambutol alone for a period of 1 week—after LFTs return to normal or decline and plateau. The patient should be instructed to stop the medication immediately if symptoms of hepatitis occur. The patient should be examined weekly, with LFTs repeated at each visit.

- If LFTs remain stable after 1 week of ethambutol and the patient is asymptomatic, rifampin should be added at the usual dosage, and ethambutol continued. The patient should be followed carefully at weekly intervals as previously.

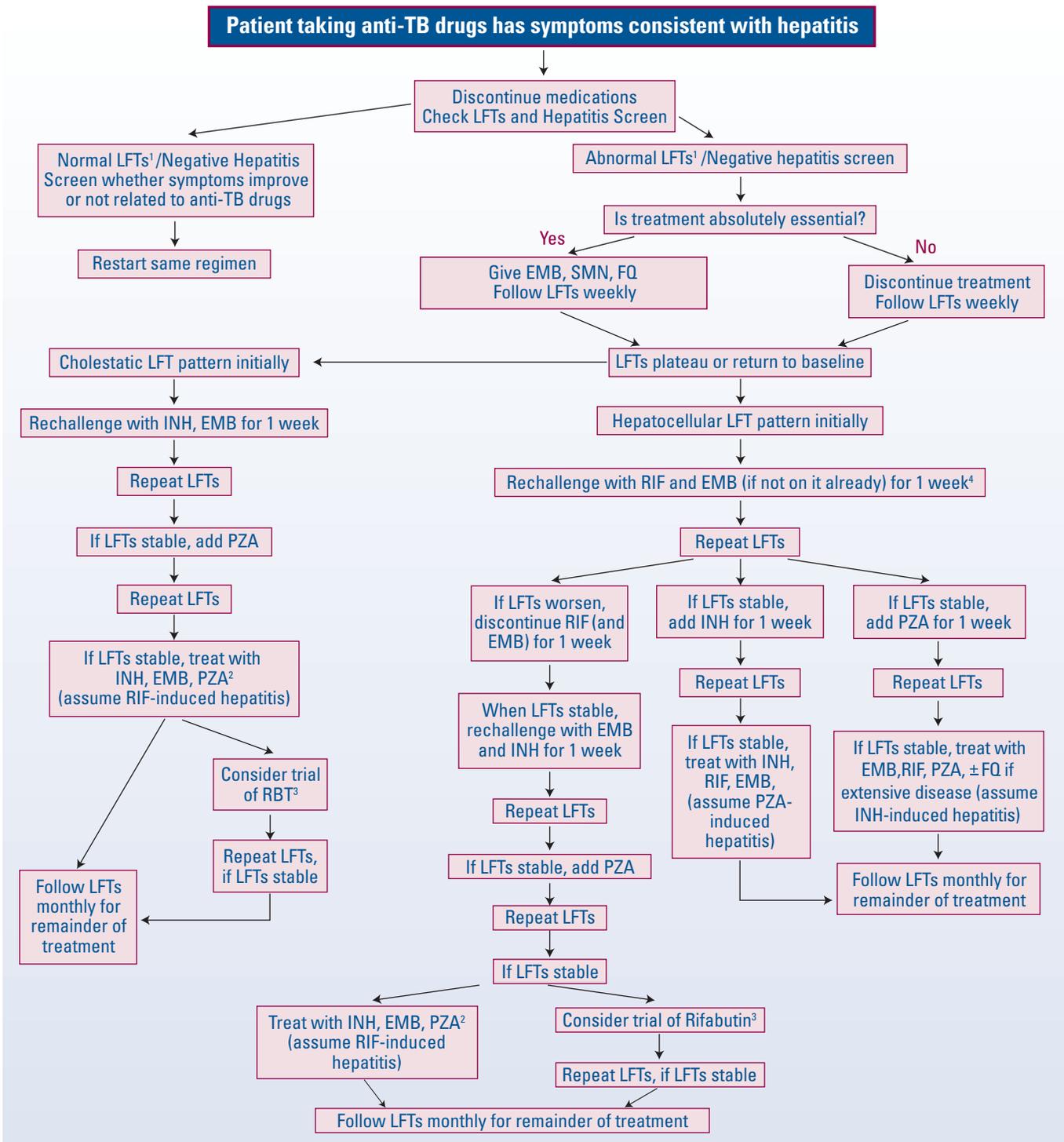
- If LFTs remain stable after 1 week of ethambutol and rifampin, pyrazinamide should be added to the regimen of ethambutol and rifampin. If there are no subsequent signs of hepatotoxicity, isoniazid-induced hepatitis should be assumed, and the patient should be treated with ethambutol, rifampin and pyrazinamide.
- If LFTs worsen after 1 week of ethambutol and rifampin, these medications should be stopped. LFTs should be allowed to return to normal or to decline and plateau, the patient should then be rechallenged with isoniazid and ethambutol.
- If LFTs remain stable after 1 week of isoniazid and ethambutol, pyrazinamide should be added to the regimen. If there are no subsequent signs of hepatotoxicity, rifampin-induced hepatitis should be assumed, and the patient should be treated with isoniazid, ethambutol and pyrazinamide. Capreomycin or an appropriate aminoglycoside, and in selected cases a fluoroquinolone, should be considered for the regimen (see p. 87).

The recommendations for restarting anti-TB medications in patients with drug-induced hepatitis are summarized on p. 109, Figure VI-2.

- Rechallenge with pyrazinamide may be hazardous in patients who tolerate the reintroduction with rifampin and isoniazid. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months. Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide rechallenge.
- Patients who start treatment with a new regimen because of hepatitis should have monthly LFTs for the remainder of treatment.
- Individuals who cannot take either isoniazid or rifampin should be treated with a retreatment regimen—usually pyrazinamide, ethambutol and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin, given for 18 to 24 months. (See p. 88.)

Figure VI-2

Restarting Anti-TB Medications in Patients with Drug-Induced Hepatitis



Abbreviations: EMB – Ethambutol; FQ – fluoroquinolone; INH – isoniazid; LFTs – liver function tests; PZA – pyrazinamide; RIF – rifampin; RBT – rifabutin; SMN – streptomycin

1. Abnormal LFTs are ≥ 3 times the upper limit of normal with symptoms or ≥ 5 times the upper limit of normal without symptoms.
2. Capreomycin or an appropriate aminoglycoside, and in selected cases a fluoroquinolone, should be considered for the regimen (see Section V-B). Treatment needs to last for 18 months unless rifabutin is added successfully. An alternate shorter regimen is isoniazid, streptomycin and pyrazinamide, all given for 9 months.
3. There may be times when rifabutin may be tried in an attempt to decrease duration of treatment from 18 months to 6-9 months.
4. Some clinicians may prefer to challenge with ethambutol and rifampin sequentially rather than simultaneously.

- Similar principles of management apply to cases of hepatitis induced by “reserve drugs,” (e.g., para-aminosalicylic acid, rifabutin and, rarely, fluoroquinolones).

Non-Drug Related Hepatitis

Hepatitis from various causes is a common co-morbidity in TB patients. Refer to p. 61 for further details on how to manage such patients.

Gastritis

Almost any medication can cause gastric irritation in susceptible individuals. Of the first-line anti-TB medications, rifampin most often causes gastritis, although pyrazinamide is responsible in some instances. Because rifampin is the most important member of combined chemotherapy, every effort should be made to reintroduce this drug once gastric symptoms resolve.

History and Examination

- Because the symptoms of gastritis (anorexia, nausea, vomiting and epigastric distress) may be due to drug-related hepatitis, LFTs must be done on all individuals who present with such symptoms.

Follow-Up

- Anti-TB medications should be discontinued in symptomatic patients. If LFTs are normal or unchanged from baseline and symptoms persist for 4 to 5 days without medication, unrelated gastrointestinal disease (e.g., peptic ulcer disease, gastritis due to another cause, etc.) should be suspected and appropriate referral made for diagnostic study.

Restarting Anti-TB Medications

- If the individual is taking isoniazid, rifampin, pyrazinamide and ethambutol, rifampin is the most likely cause of gastric symptoms. After symptoms subside, it is appropriate to renew treatment with isoniazid, pyrazinamide and ethambutol.
- If gastric symptoms return, pyrazinamide should be suspected as the cause and treatment should be attempted with isoniazid, rifampin and ethambutol.

- If symptoms do not recur, rifampin may be introduced in most cases without the recurrence of gastric symptoms by modifying the pattern of administration, for example by giving all of the medication before bedtime, preceding the medication with a small meal or renewing rifampin with a smaller dose (300 mg) and increasing to 600 mg over a period of 1 to 2 weeks.

- If rifampin is identified as a cause of gastritis and a rifamycin-containing regimen is appropriate, rifabutin can be attempted.

- Antacids may be useful to help alleviate the symptoms of gastritis, but antacids may interfere with the absorption of isoniazid and fluoroquinolones. If used, antacids should be given 2 hours after isoniazid and a fluoroquinolone have been taken; prolonged use should be avoided. An H₂-blocker or a proton pump inhibitor may be tried. However, patients taking para-aminosalicylic acid granules should take them with acidic foods such as yogurt, applesauce or orange juice rather than with neutral foods such as milk.

- If gastritis is caused by pyrazinamide, it can be omitted from the regimen with less risk than omitting rifampin. If the patient has TB susceptible to isoniazid and rifampin, these 2 medications can be used for a total of 9 months.

Peripheral Neuropathy

Isoniazid may cause peripheral neuropathy, especially in individuals with a predisposing cause, such as alcoholism, diabetes, HIV infection or malnutrition. Pyridoxine usually, but not invariably, prevents the emergence of isoniazid-induced peripheral neuropathy. In rare instances, ethambutol can also cause peripheral neuritis.

History and Examination

- Isoniazid should be assumed to be the primary cause for paresthesias and numbness of the feet and hands (with or without peripheral motor weakness) in isoniazid-treated patients, even if other predisposing causes are present.

Follow-Up

- Isoniazid should be discontinued in patients with peripheral neuropathy and pyridoxine (25 mg per day) should be given until symptoms abate.
- The neuropathy usually subsides over weeks to months, when it is diagnosed early and isoniazid is promptly discontinued. However, neurologic injury may be irreversible if diagnosis is delayed and manifestations become severe; neurologic consultation should be obtained if the diagnosis is not clear.

Linezolid can also cause a peripheral neuropathy and optic neuritis. Vitamin B₆ may or may not help ameliorate the symptoms (see p. 94).

Joint Manifestations

- Isoniazid (and rarely, rifampin) can induce active systemic lupus erythematosus (SLE), especially in patients who have this disease in a subclinical stage. The patient may have only arthralgias or alopecia, or may present with a full-blown pattern of SLE, with arthritis and other systemic manifestations. The diagnosis requires clinical suspicion and positive antinuclear antibody (ANA) markers of SLE. Isoniazid must be discontinued, and these patients should be referred to an appropriate medical or rheumatology clinic. This syndrome has been reported with rifampin as well.
- Pyrazinamide invariably leads to increased levels of serum uric acid because it impairs renal excretion of uric acid; this symptom can be used as a measure of compliance. In rare situations, elevated serum uric acid induces typical bouts of gouty arthritis, especially in patients with a history of gout. Pyrazinamide should be discontinued in such instances, unless it is essential to the anti-TB regimen. Allopurinol can lower the baseline serum uric acid level, but it cannot lower serum uric acid levels that are elevated because of pyrazinamide.
- Hyperuricemia without symptoms of gout is not a reason for discontinuing pyrazinamide.

Renal Manifestations

Renal injury in patients treated for TB is most often due to aminoglycosides or capreomycin. Also, rifampin can cause acute or chronic nephritis (with or without symptoms), evidenced by proteinuria, hematuria and urinary white blood cells. In rare instances, acute or chronic renal failure can occur. Isoniazid and ethambutol are not known to cause renal disease, although the blood levels of ethambutol (and cycloserine, aminoglycosides and capreomycin) may become markedly elevated in patients with renal function impairment. Pyrazinamide is metabolized by the liver, but its metabolites may accumulate in patients with renal insufficiency. Potassium and magnesium losing nephropathy is common with the injectable agents, particularly capreomycin, and can usually be managed with oral supplements.

History and Examination

Urinalysis, blood urea nitrogen serum, creatinine and electrolytes, including magnesium, should be monitored serially in patients with underlying renal disease who are taking ethambutol, cycloserine, an aminoglycoside or capreomycin. Similar studies should be done promptly in any patient who has symptoms consistent with acute or chronic nephritis.

Follow-Up

For information on treatment and follow-up in patients with chronic renal failure, see p. 60.

Hematologic Manifestations

All first-line anti-TB agents can, in rare cases, lead to hematologic abnormalities. Leukopenia can be caused by rifampin, isoniazid, pyrazinamide and rarely, ethambutol. Rifampin is the most common cause of thrombocytopenia, although the other first-line drugs may depress platelets as well. A “flu-like syndrome” has been reported with rifampin, especially when it is used intermittently and has also been seen with rifabutin and rifapentine; it consists of an acute episode with fever, chills and muscle pain that may be associated with severe anemia, thrombocytopenia and leukopenia. Hemolytic syndromes and other types of anemia rarely occur. Eosinophilia is seen with capreomycin and

linezolid can cause pancytopenia and a hemolytic anemia. (See p. 94; p. 105, Table VI-1; and p. 210, Appendix I-B.)

Examination and Follow-Up

If a patient taking anti-TB drugs develops symptoms, signs or laboratory evidence of significant anemia, leukopenia or thrombocytopenia that cannot otherwise be explained, all anti-TB drugs should be discontinued and any non-TB medications that may cause the abnormality should be withheld. The patient should be referred promptly to his/her private physician and to a hematologist for consultation. Blood counts should be allowed to recover with sequential reinstitution of the medications least likely to have caused the hematologic abnormality.

Each medication should be reintroduced on a weekly basis with close follow-up of the CBC and differential. If the medication is absolutely necessary for the patient's regimen and the patient does not have evidence of hemolysis, growth factors, if available, may be used in consultation with a hematologist. In the case of rifampin-induced thrombocytopenia and leukopenia, rifabutin may be tried while following CBC every 1 to 2 weeks.

Visual Manifestations

Ethambutol-induced optic neuritis occurs only rarely, and usually resolves completely when ethambutol is discontinued. However, optic neuritis may progress to severe visual loss if diagnosed late. In general, optic neuritis occurs mostly with elevated serum levels of ethambutol; because the drug is cleared largely by renal excretion, individuals with impaired renal function, especially the elderly, are most susceptible, as are adult patients who receive doses of ethambutol greater than 15 mg/kg body weight per day. Toxic levels of rifabutin may cause uveitis, leading to visual disturbances. Linezolid can also cause optic neuritis.

History and Examination

- The usual symptoms of optic neuritis are loss of visual acuity for small objects (newsprint, sewing, etc.) and/or impairment of red-green color discrimination.
- All patients started on ethambutol should have baseline visual acuity and red-green

color discrimination established at the initiation of therapy.

- All patients at risk for renal disease should have serum blood urea nitrogen and creatinine tested before treatment with ethambutol.
- Ethambutol should be avoided, or used with caution and with frequent monitoring of vision and renal function, in patients with:
 - Renal function abnormalities
 - Risk for renal function abnormalities (e.g., elderly patients and patients with diabetes or hypertension)
 - Patients with preexisting, non-correctable loss of vision
- Patients should be asked about visual changes at each follow-up visit and serial tests of visual acuity and color vision should be performed for early detection of signs of optic neuritis.
- If the patient already has red/green colorblindness at baseline and the use of ethambutol is necessary, the patient should be referred for specialized ophthalmologic evaluation to assess the degree of colorblindness; treatment decisions should be made in conjunction with the ophthalmologist.

Follow-Up

Ethambutol should be discontinued immediately if optic neuritis is suspected and the patient should be referred for ophthalmology consultation if the visual impairment does not reverse promptly. In some patients, visual impairment due to ethambutol may take months to resolve.

Audiovestibular Manifestations

History and Examination

- Patients receiving an aminoglycoside or capreomycin should have a baseline audiogram and a follow-up audiogram during the first and second months of treatment. The audiogram should be repeated every 2 months thereafter or repeated promptly if hearing loss is suspected.
- At each monthly examination, patients receiving an aminoglycoside or capreomycin should be asked about changes in hearing;

most patients will volunteer information about tinnitus or dizziness if these symptoms occur.

Follow-Up

- The aminoglycoside or capreomycin should be discontinued if hearing loss, vertigo or new-onset tinnitus occurs.
 - An ear examination should be done to exclude other sources of these symptoms, such as cerumen or otitis media.
 - An audiogram should be performed and the results compared with the baseline results in order to detect hearing loss.
 - If symptoms or any other evidence of hearing loss is suspected to be unrelated to the aminoglycoside or capreomycin, the patient should be referred to an otolaryngology clinic for consultation.

Restarting Anti-TB Medications

If significant hearing loss, new-onset tinnitus or vertigo is demonstrated and any of these reactions cannot be explained otherwise, the aminoglycoside or capreomycin should be eliminated from the regimen.

Drug Desensitization

Drug desensitization has been tried with most of the first-line agents with varying degrees of success. Rifampin has been the drug most commonly tried. Desensitization is done in a manner similar to penicillin desensitization, with incremental amounts of rifampin given to the patient until a full dose is tolerated. It should only be done in a monitored setting, such as the ICU, after consultation with the Bureau Director or Director of Medical Affairs.

Paradoxical Reactions, Non-HIV-Related

Paradoxical response is defined as the clinical worsening of pre-existing tuberculosis lesions or the development of new lesions after initial clinical improvement on effective antituberculous therapy. Paradoxical response occurs more commonly in patients with HIV coinfection (up to 30% in one series), but also occur in patients who are HIV negative (up to 10%) (see p. 56).

Etiology

The etiology of paradoxical reaction may be related to reversal of the immunosuppression caused by TB disease once antituberculosis therapy has been initiated. The rapid killing of bacilli may cause increased cytokine release, leading to a severe inflammatory response.

Diagnosis

- The diagnosis may only be made after secondary infection, non-compliance with therapy, drug resistance and adverse effects to medication have been excluded.
- In one review of 122 episodes of paradoxical response among patients who are HIV negative, 82% of reactions were associated with extrapulmonary tuberculosis, with a median time from initiation of anti-tuberculous therapy to paradoxical reaction of 60 days. The initial disease site from most common to least common was:

1. Disseminated
2. Central nervous system (CNS)
3. Pulmonary
4. Pleural
5. Lymph node
6. Abdominal
7. Osteoarticular

The paradoxical response occurred in the initial site of infection in 75% of episodes and when the paradoxical response occurred in another anatomical site, the most common site was the CNS (see p. 75).

- In another review among HIV negative patients, 25 (23%) of 109 patients with lymph node TB had paradoxical worsening of disease after a median of 46 days on anti-tuberculous therapy. Episodes lasted a median of 68 days and most patients had cervical lymphadenopathy at diagnosis. Manifestations of paradoxical worsening included expansion of lymphadenopathy or development of new nodes, often pronounced. Some severe cases were associated with sinus tract formation and respiratory compromise.

Treatment

- Many experts advocate the use of corticosteroids in the case of prolonged

or severe paradoxical reactions, although no randomized clinical trials have been done to assess the benefit. If corticosteroids are used, the usual dose is prednisone, 1 mg/kg per day, up to 60 mg/day, gradually tapered over several weeks. Recurrence with tapering is not uncommon.

- Surgical drainage may be indicated in the case of tense, painful lymphadenopathy with impending sinus tract formation. Any drainage should be sent for AFB smear and culture. The patient may need to be on airborne isolation pending the results of the AFB smear.
- The antituberculous regimen rarely needs to be changed once the diagnosis of paradoxical reaction has been established.

Reporting Adverse Events

- All serious adverse reactions to medications in patients followed in the BTBC chest centers must be reported on the DOHMH Reportable Occurrences Form. The form can be accessed

on the intranet at http://healthweb.health.nycnet/pdf/hca/Reportable_Occurrences_Form.pdf.

- The DOHMH Intranet has a detailed document on reportable occurrences at http://healthweb.health.nycnet/pdf/hca/Reportable_Occurrences_Guide.pdf
- A serious adverse reaction is any grade 3 or 4 adverse event that leads to temporary or permanent discontinuation of a drug. Below are general definitions of grades of toxicity. Further details can be found at <http://ctep.cancer.gov/reporting/ctc.html>.
- Any clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 adverse event. The BTBC Director of Medical Affairs and the Quality Assurance Coordinator should be notified and should receive a copy of the Reportable Occurrences Form. The patient should be followed until the adverse reaction is resolved or until transfer to another medical provider or facility has been confirmed.

Grades of Toxicity

GRADE 1 Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required
GRADE 2 Moderate	Mild to moderate limitation in activity — some assistance may be needed; no or minimal medical intervention or therapy required
GRADE 3 Severe	Mark limitation in activity, some assistance usually required; medical intervention or therapy required, hospitalization possible
GRADE 4 Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Reclassification of Patients Suspected of Having Tuberculosis

All patients initially classified as TB Class V should be reclassified to the appropriate TB class within 4 months of the initiation of evaluation, for example:

- Patients initially classified as TB Class V should be reclassified as TB Class III if they have a positive *M. tb* culture.
- Patients initially designated as TB Class V who do not produce a positive culture for *M. tb* should be reclassified as TB Class III if they meet the following criteria:
 - Resolution of TB symptoms on TB treatment (e.g., cough, fever, sweats, weight loss, chest pains), if initially present, in a time course consistent with TB
 - Improvement of CXR on TB treatment (e.g., improvement or resolution of infiltrates, cavities and effusions) in a time course consistent with TB.

- Patients initially designated as TB Class V (High or Low) who are found to have a negative culture for *M. tb*, should be reclassified as TB Class IV if their CXR is stable after 2 and 4 months of treatment, and is consistent with “old TB.” **A non-TB diagnosis should also be considered.**
- Patients may only be considered Class III when they are classified as “countable” on the Tuberculosis Registry.
- All other TB Class V patients should be given an appropriate International Classification of Tuberculosis based on the test for TB infection result and clinical evaluation.
- In some cases, there may not be enough information to classify patients under the International Classification system; the patient should then be closed out as lost, moved or died, as applicable.

Case Closing and End-of-Treatment Evaluation

- At the end of treatment for pulmonary TB, a sputum culture and a CXR should be obtained.
- A notation should be made in the medical record that the patient has completed treatment and an order should be written indicating that the case should be listed on the TB Registry as completed treatment.
- All patients who complete treatment, except those requiring post-treatment evaluation (see below), should be discharged from the clinic.
- Each patient should be given a document stating that he or she has completed a course of treatment for TB disease.

Post-Treatment Evaluation

- Controlled trials of anti-TB treatment have shown conclusively that the risk of relapse is low in patients with TB susceptible to isoniazid, rifampin and pyrazinamide who complete an optimal treatment regimen. Post-treatment evaluation of patients in this category, therefore, is rarely productive and is not cost-effective. These patients, however, should be advised to return to the chest center for re-evaluation if, in the future, they develop symptoms suggestive of active pulmonary TB

(e.g., fever, night sweats, weight loss, malaise or prolonged cough, with or without sputum).

- Post-treatment evaluation is also not required for most patients who:
 - Have *M. tb* isolates resistant to isoniazid only but susceptible to rifampin, pyrazinamide and ethambutol
 - Have completed 6 months of treatment with all three medications, with or without a fluoroquinolone

Controlled trials have shown low relapse rates for these patients, comparable to rates for patients with isoniazid-susceptible strains.

- Recommendations for the frequency of post-treatment evaluation are summarized on p. 116, Table VI-2.

Candidates and Procedures for Post-Treatment Evaluation

Category 1 and 2 Patients

Certain patients are at greater risk for post-treatment relapse and should be re-evaluated periodically after they complete treatment. Patients in this category include the following:

Category 1. Patients with TB resistant to isoniazid and rifampin, regardless of the regimen used and the duration of treatment.

Category 2. Patients treated with a regimen that did not include rifampin or rifabutin because of resistance or adverse reactions to these drugs.

- Patients in these categories should be scheduled to return for re-evaluation every 4 months for 1 year and at 18 and 24 months. A CXR should be obtained at each visit and compared with the CXR obtained at the end of therapy. At each visit, a single sputum specimen should be obtained for smear and culture. A second appointment is not needed to present the results of the culture, but patients should be told that they will be contacted by telephone if the results are positive.
- If the smear is positive for AFB, the patient should be advised to return for 3 additional sputum specimens. If any specimen is culture positive for *M. tb*, the patient should return promptly for a complete clinical reevaluation and the reinstatement of appropriate therapy.

Table V1-2

Frequency of Post-Treatment Evaluation*

Category of Patient		Frequency of Post-Treatment Evaluation
1	Patients with TB resistant to isoniazid and rifampin (MDRTB)	4, 8, 12, 18 and 24 months**
2	Patients treated without rifampin or rifabutin	4, 8, 12, 18 and 24 months**
3	Selected patients treated with a self-administered regimen whose adherence to therapy is in doubt	At 4, 8 and 12 months**
4	Selected patients who have a history of previous treatment, but who (1) have no details available about the treatment, (2) have negative sputum cultures, (3) have significant changes on CXR consistent with TB, and (4) refuse preventive retreatment	At 4, 8 and 12 months**
5	Selected patients who have no history of previous treatment and who (1) have negative sputum cultures, (2) have significant changes on the CXR consistent with TB, and (3) refuse current treatment	At 4, 8 and 12 months**
6	Selected patients who (1) have a positive test for TB infection (2) have negative sputum cultures (3) have CXR that may be consistent with TB, but also with pulmonary disease other than TB (4) are treated empirically	Refer to general chest clinic if no response to treatment If no referral or patient refuses, re-evaluate with a CXR every 3-4 months for 1 year

Abbreviation: CXR=chest X-ray

* Patients who do not need re-evaluation include those with pan-susceptible TB who complete an optimal regimen and those who have mono-resistance to isoniazid, but who complete 6 to 9 months of treatment with at least rifampin, pyrazinamide and ethambutol.

**Evaluation should include a CXR and the collection of a sputum specimen for AFB smear and culture.

Categories 3, 4, 5 and 6

Patients in the following categories should also receive periodic post-treatment evaluation.

Category 3. Selected patients who were treated with a self-administered regimen and whose adherence to therapy is in doubt.

Category 4. Selected patients who have a history of previous treatment, but who:

- Have no details available about the treatment
- Have negative sputum cultures
- Have significant changes on CXR consistent with TB
- Refuse preventive retreatment

Category 5. Selected patients who have no history of previous treatment and who:

- Have negative sputum cultures
- Have significant changes on CXR consistent with TB
- Refuse current treatment

Patients in categories 3, 4 and 5 should be re-evaluated as described for categories 1 and 2, but only at 4, 8 and 12 months.

Category 6. Category 6 comprises patients who have a positive test for TB infection (TTBI), who have negative sputum cultures for TB and who are treated empirically because a lesion apparent on CXR is believed to be consistent with TB. It is always possible that the lesion is

not the result of TB and is caused by another disease. Lesions are especially important when they appear as a non-calcified spherical lesion, a “segmental” shadow consistent with bronchial obstruction, or enlarged hilar or mediastinal nodes of unknown cause.

In such circumstances, patients who have no clear-cut response to anti-TB therapy should be referred to a general chest center for additional diagnostic evaluation. However, patients who refuse additional investigation should be scheduled for re-evaluation with a CXR at 3- to 4-month intervals for 12 months. If the lesion appears to progress, vigorous efforts should be made to refer the patient to a general chest clinic for additional diagnostic evaluation.

Special Considerations for Patients Who Are HIV Positive

Whenever possible, every patient with TB who is HIV-positive, and who has been treated in a BTBC chest center should be followed concurrently by an appropriate HIV care center; patients who are not attending an HIV care center should be urged to register at one as soon as possible.

After completing TB treatment, patients who are HIV positive should not be routinely followed by the BTBC chest center, unless they belong to one of the above categories 1-5; their care should be provided by an appropriate HIV care center. The basis for this policy is the fact that the occurrence of a respiratory illness in the future is more likely due to disease other than TB. Moreover, BTBC chest centers have limited access to techniques that are generally required for diagnosis in such cases.

When anti-TB treatment is completed, patients who are HIV positive should receive a letter summarizing their treatment in the chest center, to be given to the responsible physician in the HIV care center. The letter should recommend that sputum specimens be obtained for smears and cultures if the patient develops symptoms or signs suggestive of TB, even if the CXR is negative. It should also suggest referral back to the chest center for treatment if evidence of recurrent TB is found.

Patients who are HIV positive and who refuse enrollment in an HIV care center should also receive a summary letter, and they should be advised to report to a general medical clinic or emergency room if they develop symptoms of a recurrent respiratory illness.

Though relapse rates are quite low in HIV-infected persons with drug susceptible TB, most relapses have been associated with development of rifampin resistance. If a HIV-infected person with a history of TB treatment is suspected of having relapse of TB, the person should be assumed to have rifampin resistance, and the treatment regimen should include adequate drugs to appropriately treat rifampin-resistant TB until final susceptibilities become available.

The Use of Isoniazid after Completion of Tuberculosis Treatment

The policy of the BTBC is not to administer anti-TB drugs as prophylaxis after completion of TB treatment. This policy includes patients who are HIV positive. Some patients, however, may need retreatment if there has been new TB exposure (see p. 163 and p. 193).

Key Sources

Breen RA, Smith CJ, Bettinson H, et. al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*. 2004 Aug;59:704-707.

Girling DJ. Adverse effects of antituberculosis drugs. *Drugs*. 1982;23:56-74.

Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle*. 1978;59(1):13-32.

Binda G, Domenichini E, Gottardi A et al. Rifampicin: a review. *Drugs*. 1971;1:354-398.

Saukkonen JJ, Cohn DL, Jasmer RM, et. al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174:935-952.