Tuberculosis

Section III.

Treatment of Pulmonary Tuberculosis

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Regimens for Treatment of Drug-Susceptible Tuberculosis

All individuals with highly suspected or confirmed tuberculosis should receive initial treatment as soon as appropriate specimens are collected. Treatment should not be delayed while waiting for confirmation by culture and susceptibility results.

Most patients with TB can be treated with a standard 6-month drug regimen. Treatment is divided into 2 phases: the intensive phase and the continuation phase. The intensive phase consists of the first 2 months of treatment, which begins empirically with a standard 4-drug regimen. This is done since susceptibility results are not available at the start of most patients' treatment. Regimens can be adjusted as susceptibility results become available. The continuation phase usually lasts 4 months and consists of fewer drugs. Under certain circumstances, the continuation phase may be extended beyond 4 months.

There are 4 recommended regimens for treating patients with TB caused by drug-susceptible organisms. Although these regimens are broadly applicable, modifications should be made under certain circumstances. Each regimen has an initial phase of 2 months, followed by several options for the continuation phase, which may last either 4 or 7 months.

Current recommendations for treatment of TB in adults who are HIV infected are, with few exceptions, the same as for the rest of the population.

Standard Regimen

The standard regimen should begin with isonazid, rifampin, ethambutol and pyrazinamide unless there are absolute contraindications.

Use Rifamate® (capsules combining isoniazid and rifampin) for patients who are not receiving directly observed therapy (DOT).

- Discontinue ethambutol and pyrazinamide at the end of the intensive phase of treatment unless:
  - Drug susceptibility results show resistance to isoniazid or rifampin.
  - Drug susceptibility results are not available and drug resistance is suspected. This may be either because of a history of TB treatment or because of a high rate of resistance in the community.
- Ethambutol can be discontinued earlier, if drug susceptibility results show susceptibility to isoniazid and rifampin.

If clinical response is not adequate in 2 weeks, consider adding additional drugs to the regimen, since drug resistance may be present.

It is important to make sure that patients being treated for TB receive the appropriate number of doses within the recommended length of treatment (see p. 45, Table III-1).

See p. 208, Appendix I-A for dosages of primary medications used in the treatment of TB.

Length of Treatment

Culture-positive pulmonary disease. The standard 6-month treatment (short-course chemotherapy) for drug-susceptible TB consists of a 2-month intensive phase followed by a 4-month continuation phase. However, clinical trials have shown that selected patients have a higher rate of relapse with a 6-month regimen (see p. 46, Table III-2) and may benefit from longer treatment as noted below. (If the strain is drug-resistant, see p. 86, Table V-1 for guidelines on length of treatment.)

- The 4-month continuation phase of treatment should be used for most patients. However, a 7-month continuation phase should be given to the following 4 groups:
  - Patients who have drug-susceptible pulmonary TB, with **initial** cavitation on chest X-ray (CXR), whose sputum cultures remain positive after the intensive phase (i.e., the first 2 months of treatment).
  - Other patients who are still culture positive at 2 months, regardless of CXR results.

- Patients whose treatment regimen did not include pyrazinamide in the intensive phase, or whose organism was resistant to pyrazinamide.
- Patients being treated with once-weekly isoniazid and rifapentine, whose sputum culture remains positive after the 2-month intensive phase of treatment.

Susceptibility results for first-line drugs are usually available within 2 weeks of culture confirmation. If results are delayed, contact the lab and ask the reason for the delay. If it is related to technical issues, continue all 4 drugs until the lab confirms the results. If the delay is due to a mixed or non-viable culture, make sure that the lab tests another specimen.

For patients who are *Mycobacterium tuberculosis (M. tb)* culture positive without available susceptibilities at the end of the intensive phase, discontinue pyrazinamide and ethambutol unless drug resistance is suspected.

The patient receiving treatment for tuberculosis may have sputa that are smear positive but culture negative. In patients with drug-susceptible organisms, this may occur during initial treatment, when the patient is beginning to culture convert. It may also occur later in treatment, as a result of dead organisms. This can be verified when cultures come back negative.

In the meantime, a clinical decision must be made regarding the management of these patients. If the patient is on a standard regimen, is tolerating TB medications and has clinically improved (e.g., there is resolution of fever and cough, plus weight gain and an improved CXR), it may not be necessary to change treatment.

Culture-negative pulmonary disease. Multiple studies have shown that clinically confirmed or culture-negative pulmonary TB can be treated successfully in only 4 months, as the bacillary load is believed to be decreased in such patients. As a result, for patients whose initial sputum cultures are negative, the intensive phase of treatment should be followed by a 2-month continuation phase of isoniazid and rifampin only, as long as the patient has not received treatment for TB in the past.

- If the patient has received treatment in the past, isoniazid, rifampin, pyrazinamide and ethambutol should be continued for the full 4 months, as drug resistance may be present.

Intermittent Regimens

For most patients with drug-susceptible TB, intermittent therapy (i.e., regimens given 2 or 3 times a week, or even once weekly when rifapentine is used, [see below]) is well documented to be at least as effective as a daily regimen. Intermittent therapy is easier to supervise than daily therapy, helps ensure adherence and should be offered to all eligible patients (see p. 45, Table III-1).

- Intermittent therapy should be given only under a DOT program.
- If adherence to 2 or 3 times a week DOT falls below 80%, the patient should be put on daily DOT until it is established they can be placed on intermittent DOT.
- Recent data show that patients with cavitary pulmonary TB may be at increased risk of relapse if treated with intermittent regimens in the intensive phase. Such patients should be treated with a daily regimen during this time. Intermittent regimens can be given in the continuation phase.
- Three-times-a-week intermittent therapy may be given in the intensive phase with isoniazid, rifampin, pyrazinamide and ethambutol—with all 4 drugs continued throughout the intensive phase. Isoniazid and rifampin can be continued 3 times a week in the continuation phase.
- Rifapentine should be used in specific instances (see p. 47, Figure III-1) after the patient has completed the 2-month intensive phase.
- Patients who are HIV infected, with CD4 counts lower than 100 should only be treated with either daily or 3-times-a-week regimens. The Bureau of Tuberculosis Control (BTBC) recommends daily treatment in the intensive phase.
- Patients with TB that is resistant only to isoniazid or that is resistant to isoniazid and any of the second-line medications (including streptomycin) can be treated with intermittent regimens as indicated on p. 87. However, if resistance only to isoniazid is discovered, the drug should be removed from the regimen.
- Patients with TB resistant to rifampin alone, or to both isoniazid and rifampin, should not be treated with an intermittent treatment regimen.

Table III-1

Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

Regimen	Drugs	Intensive Phase Interval[1] and Doses[2] (minimal duration)	Drugs	Continuation Phase Interval[1] and Doses[2,3] (minimal duration)
1	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days per week for 56 doses (8 wk) **or** 5 days per week for 40 doses (8 wk)[4]	Isoniazid/ Rifampin Isoniazid/ Rifapentine[6]	7 days per week for 126 doses (18 wk) **or** 5 days per week for 90 doses (18 wk)[4] **or** 3 times per week for 54 doses (18 wk) **or** 2 times per week for 36 doses (18 wk)[5] 1 time per week for 18 doses (18 wk)
2	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days per week for 14 doses (2 wk), then 2 times per week for 12 doses (6 wk) **or** 5 days per week for 10 doses (2 wk)[4] then 2 times per week for 12 doses (6 wk)	Isoniazid/ Rifampin Isoniazid/ Rifapentine[6]	2 times per week for 36[5] doses (18 wk) 1 time per week for 18 doses (18 wk)
3	Isoniazid Rifampin Pyrazinamide Ethambutol	3 times per week for 24 doses (8 wk)	Isoniazid/ Rifampin Isoniazid/ Rifapentine[6]	3 times per week for 54 doses (18 wk) 1 time per week for 18 doses (18 wk)
4	Isoniazid Rifampin Ethambutol	7 days per week for 56 doses (8 wk)	Isoniazid/ Rifampin	7 days per week for 217 doses (31 wk) **or** 5 days per week for 155 doses (31 wk)[4] **or** 3 times per week for 93 doses (31 wk) **or** 2 times per week for 62 doses (31 wk)[5]

Adapted from The American Thoracic Society, Center for Disease Control and the Infectious Disease Society of America. Treatment of Tuberculosis. 2003 (see Key Sources for full citation)

[1] For missed dose, extend treatment to make up the doses, unless there has been prolonged treatment interruption.

[2] When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses per week, extensive experience indicates this would be an effective practice.

[3] Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase regimen (31 weeks; either 217 doses daily or 93 doses 3 times per week or 62 doses 2 times per week).

[4] Five-day-a-week administration is always given by DOT.

[5] Not recommended for patients who are HIV infected, with CD4+ cell counts of less than 100 cells/mm^3

[6] Rifapentine should be used only in patients who are HIV negative, older than 12 years of age, not pregnant and have negative sputum smears at the time of completion of 2 months of therapy, and who do not have cavitation on the initial chest radiograph. For patients started on this regimen and found to have a positive 2-month sputum culture, treatment should be extended an extra 3 months.
See p.47, Figure III-1.

Table III-2

Percentage of Culture-Positive Relapse[1] by Continuation Phase Regimen, Radiographic Status and 2-Month Sputum Culture: USPHS Study 22

Continuation Phase					
Isoniazid-Rifampin twice weekly[2]			Isoniazid-Rifapentine once weekly[2]		
Culture positive at 2 months			Culture positive at 2 months		
Cavity	Yes	No	Cavity	Yes	No
Yes	20.8 (48)[3]	4.7 (15)	Yes	22.2 (72)	9.1 (154)
No	5.9 (17)	1.7 (181)	No	11.8 (17)	1.9 (162)

[1] Culture-positive relapse with restriction fragment length polymorphism match to initial isolate

[2] Isoniazid-rifampin twice weekly-isoniazid-rifampin for 18 weeks: isoniazid-rifapentine once weekly-isoniazid-rifapentine for 18 weeks

[3] Denominators in parentheses: number enrolled, completed treatment per protocol and assessed for relapse

Source: Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomized clinical trial. Lancet 2002; 360; 28-34 and additional data (A. Vernon, personal communication).

Rifapentine

Patient Selection

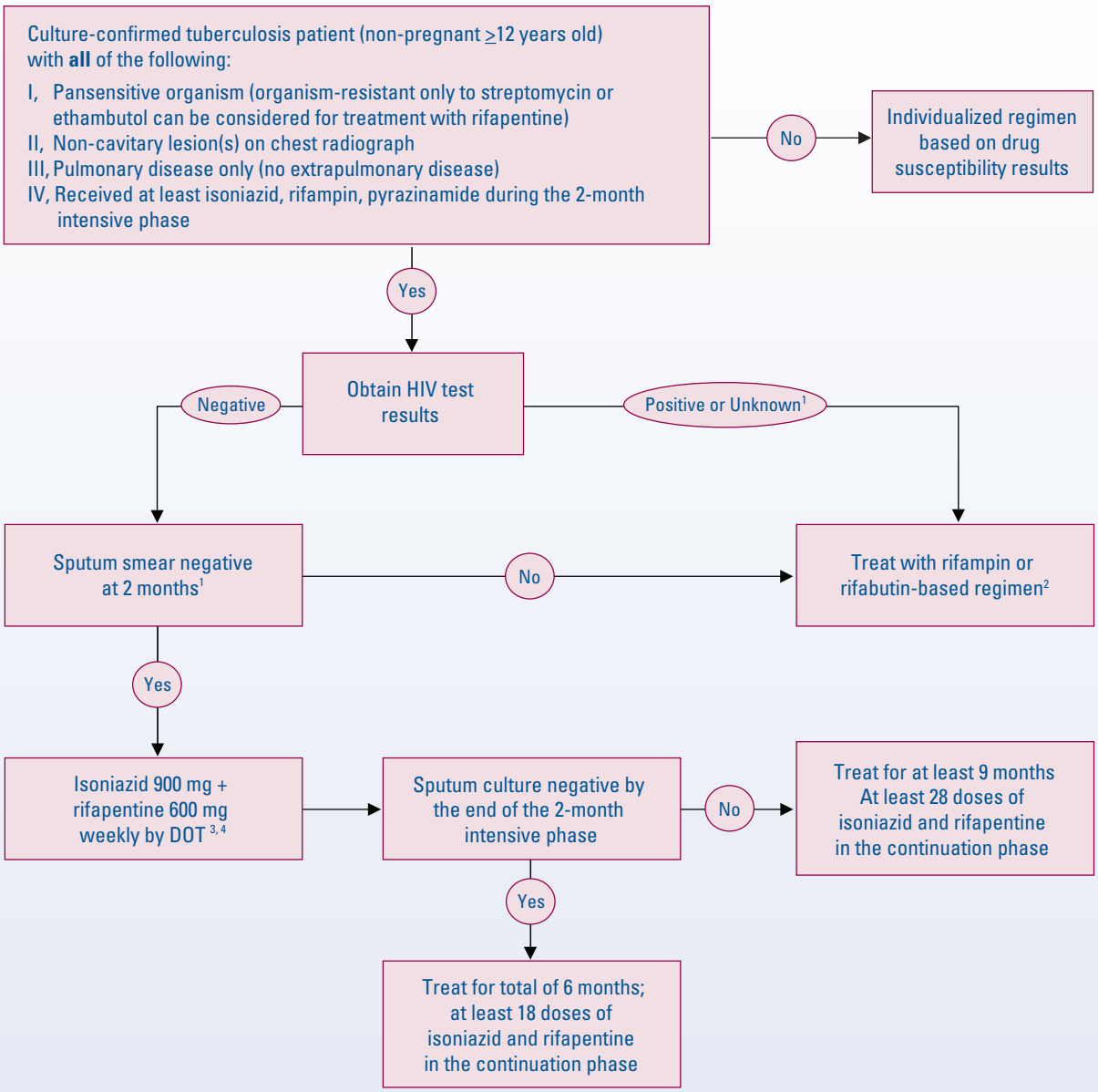
An intermittent regimen that utilizes rifapentine, a long-acting rifamycin, is available. Rifapentine should only be used in carefully selected patients to avoid relapse or development of acquired rifamycin resistance. Potential candidates for rifapentine/isoniazid must be educated about the availability of this option early in their therapy. Patient brochures about this treatment are available. See p. 45, Table III-1 for more information.

- Patients who are HIV-positive should not receive rifapentine, due to risk of developing rifampin resistance. Therefore, a negative HIV test must be documented before initiating this therapy.
- Sputum must be AFB smear negative at the end of the 2-month intensive phase.
- Patients with any form of extrapulmonary TB are not candidates for this regimen; mediastinal and hilar lymphadenopathy accompanying an infiltrate is not considered to be extrapulmonary TB.
- Patients with a cavitary lesion on CXR are at increased risk of relapsing if treated intermittently with rifapentine and isoniazid at currently recommended doses; therefore we recommend these patients not be given this regimen.
- Clinically confirmed cases of pulmonary TB are not candidates for once a week rifapentine plus isoniazid as this regimen has not been studied.
- Patients who are pregnant or younger than 12 years of age should not be offered this regimen.
- Patients must have received isoniazid, rifampin and pyrazinamide with or without ethambutol for the entire intensive phase.

One to 2 weeks prior to the end of the 2-month intensive phase of therapy, sputum samples must be obtained to demonstrate that sputum smears are negative before the rifapentine/isoniazid regimen is initiated. Offering a once weekly regimen to patients also provides an opportunity to reintroduce DOT if a patient is not already on DOT.

Figure III-1

Treating Tuberculosis with Rifapentine



[1] HIV counseling and testing is recommended if unknown

[2] A sputum smear should be performed 1 to 2 weeks prior to the end of the 2-month intensive phase

[3] Intermittent therapy should only be given under DOT

[4] Rifampin or rifabutin should not be given biweekly to HIV-infected patients with CD4 count less than 100 mm^3. Such patients should receive a daily regimen in the intensive phase and either daily or 3 times per week regimen(s) in the continuation phase.

Treatment Length

Treatment length for this regimen is generally 4 months, for a total 6 months of TB treatment. A patient is considered to have completed an adequate regimen if at least 18 doses of rifapentine/isoniazid are taken during the continuation phase of TB treatment. If an appropriate candidate is started on rifapentine/isoniazid and is later found to have positive cultures on sputum obtained at the end of or after the intensive phase of therapy, the total length of therapy should be 9 months, with at least 28 doses of rifapentine/isoniazid in the continuation phase.

Dosing

The recommended dosage of rifapentine is 600 mg weekly, always in combination with isoniazid 900 mg weekly. Rifapentine is available in 150 mg tablets. Dosing rifapentine with food improves absorption of the drug, so the drug should be administered with food, or patients should be encouraged to eat before a dose is given.

If a patient misses a dose, it can be given on another day during the week as long as the subsequent dose is separated from the last dose by at least 72 hours. Patients who are delinquent for 2 consecutive weeks or more should be switched back to a rifampin-based regimen.

Certain patients receiving isoniazid (900 mg) may require supplementation with pyridoxine (vitamin B_6) 25 mg once daily (this can be self-administered). See p. 62, Table III-4 for list of patients eligible for pyridoxine.

Monitoring

Patients should have baseline liver function tests (LFTs) and a complete blood count (CBC) at the beginning of TB therapy. Monthly follow-up blood testing is not necessary if the baseline is normal, unless a patient develops symptoms consistent with adverse drug reactions (see below). Therapeutic levels of rifampin have been known to interfere with assays for vitamin B_{12} and folate. Similar interactions should be considered for rifapentine. Clinical monitoring is the same as for all other Class III patients.

Adverse Reactions

Rifapentine, like other rifamycins, may produce a predominantly orange-red discoloration of body fluids and tissues (skin, teeth, tongue, tears, sputum, saliva, feces, cerebrospinal fluid. Contact lenses may also become permanently stained.

A patient who develops symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice) while taking rifapentine/isoniazid should be instructed to discontinue all medications promptly. The patient should be examined promptly by a physician and have blood drawn for another set of LFTs. (See p. 107.)

If LFTs are normal, drug-induced hepatitis is unlikely. Another cause for the symptoms should be suspected. Depending upon the nature, duration and severity of symptoms, a decision should be made regarding further diagnostic investigation and possible referral.

Use in Pregnant and Breast-Feeding Women

As a precaution, rifapentine should not be used in pregnant women as it has been shown to be teratogenic in rats and rabbits that have been given anywhere from 0.3 to 1.3 times the human dose. There are no adequate data in pregnant women and the effect on the human fetus is unknown. Also, it is not known whether rifapentine is excreted in human milk and therefore should not be used in nursing mothers.

Use in Children

The safety and efficacy of rifapentine in children under the age of 12 has not been established; therefore, rifapentine should not be used in this age group. Children older than 12 years should be prescribed the adult dose of rifapentine and dosed with isoniazid accordingly.

Drug Interactions

Rifapentine is a member of the rifamycin class of drugs and like other rifamycins, it induces the cytochrome p450 system of enzymes, specifically the CY3A4, 2C8 and 2C9 isozymes. Rifapentine increases metabolism and markedly lowers serum concentrations of drugs that are metabolized by these enzymes.

Rifapentine's ability to induce CY3A4 is less than that of rifampin, but greater than that of rifabutin. CY3A4 is important in the metabolism of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifapentine should not be used in persons who are HIV infected, because of the risk of developing rifamycin resistance.

The induction of these enzymes occurs approximately 4 days after the first dose and returns to baseline 14 days after rifapentine is discontinued. The degree of enzyme induction is dose- and frequency-dependent.

Any drug that is known to have an interaction with rifampin should be considered to have similar interactions with rifapentine unless proven otherwise through clinical trials.

See p. 216, Appendix I-F for a list of drugs that interact with rifapentine and the other rifamycins.

Treatment of Co-Existant Tuberculosis and HIV

Given the challenges of managing drug interactions and overlapping toxicities, providers should carefully coordinate treatment of patients with TB and HIV. Close attention should be paid to the possibility of TB treatment failure, antiretroviral treatment failure, paradoxical reactions of TB, unique and synergistic overlapping adverse effects for all drugs used and drug toxicities associated with increased serum concentrations of rifabutin. As new antiretroviral drugs are developed and more information becomes available, recommendations for the use of these drugs with anti-TB medications change.

This section provides updated recommendations for the treatment of TB in patients who are co-infected with TB and HIV. It is based on the BTBC document, *Antiretroviral Drugs and the Treatment of Tuberculosis*, which can be accessed at www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf; it is updated frequently and will have the most recent recommendations.

Antiretroviral Drugs and Rifamycins

Treatment of TB in the setting of HIV infection is complicated by drug-drug interactions between the rifamycin class of antimycobacterial drugs (rifampin, rifabutin and rifapentine) and the PI and NNRTI classes of drugs used to treat HIV infection. Both PIs and NNRTIs are metabolized by hepatic CYP3A, specifically the CYP3A4 isozyme. Rifamycins are inducers of the CYP3A family of enzymes, which includes the CYP3A4 isozyme. Maximal drug levels (represented by C_{max}) or total drug exposure over time (represented by area under the plasma concentration time curve [AUC]) of antiretroviral agents may be reduced when these drugs are co-administered with rifamycins, adversely affecting the ability of the anti-retroviral regimen to adequately suppress the virus, which is the goal of anti-retroviral treatment regimens.

Rifamycins are inducers of the CYP3A system, but rifampin is not metabolized by this system. Of the 3 available rifamycins, rifampin is the most potent inducer of CYP3A and rifabutin is the least potent, with rifapentine falling somewhere in between. Rifapentine should not be used for the treatment of TB in individuals who are HIV infected, because it can lead to rifamycin resistance at the current recommended dose in this population.

Rifampin is **not** metabolized by the CYP3A system and rifampin exposure is not affected by coadministration of PIs or NNRTIs; rifampin dosing does not need adjustment.

Rifabutin **is** metabolized by the CYP3A system and exposure is usually increased by co-administration of PIs or NNRTIs. Rifabutin dosing must be adjusted according to the choice of the co-administered antiretrovirals (See pp. 54 and 55, Figure III-2 and Table III-2.) Because the exposure of the active metabolite of rifabutin (25-O-desacetyl rifabutin) is also affected, recommended dosages for rifabutin allow for this. Attention must be paid to the adherence of the HAART regimen, as well as the TB regimen, because rifabutin levels will likely be subtherapeutic if the patient stops taking the antiretrovirals.

Protease Inhibitors

The currently approved PIs* and rifamycins have opposite effects on the CYP3A family of enzymes in the liver, causing drug-drug interactions when PIs are taken with rifamycins:

- PI serum concentrations and overall exposure may decrease to sub-therapeutic levels because rifamycins accelerate the metabolism of PIs by inducing the CYP3A enzymes.
- Rifampin levels are not affected since it is not metabolized by CYP3A.
- Rifabutin exposure may increase to toxic levels because PIs decrease its metabolism.

*Indinavir, nelfinavir, saquinavir, ritonavir, amprenavir, fosamprenavir, atazanavir, tipranavir/ritonavir and darunavir/ritonavir administered together, and lopinavir/ritonavir fixed combination.

Rifampin and Protease Inhibitors

Previous recommendations specifically contraindicated the use of rifampin with any of the PIs. However, data indicate that rifampin can be used for the treatment of active TB in patients whose antiretroviral regimen includes ritonavir (600/mg twice daily) as the only PI [plus 2 or more nucleoside-nucleotide reverse transcriptase inhibitor (NRTIs)], although this regimen may lead to loss of virologic response (ritonavir AUC is reduced 30% when co-administered with rifampin). The manufacturer does not make any recommendations on the use of rifampin with ritonavir; the utility of high doses of ritonavir is limited by its poor tolerability in many patients.

Low dose ritonavir (100 mg bid) has gained utility as a booster for other PIs (the combination drug lopinavir/ritonavir is an example). However, low-dose ritonavir does not seem to ameliorate rifampin-mediated reduction in lopinavir concentration; this likely applies to other PIs as well. The administration of rifampin with indinavir and low-dose ritonavir has lead to subtherapeutic concentrations of indinavir. Rifampin should not be administered with atazanavir/ritonavir 300 mg/100 mg once per day. Even in the presence of a low dose of ritonavir, there is a clinically significant reaction between atazanavir and rifampin. Some experts have advised against using rifampin with antiretroviral regimens containing low-dose ritonavir.

Tipranavir was FDA-approved for use in a ritonavir-boosted combination and is contraindicated with rifampin. Tipranavir is actually a CYP3A inducer, but when administered with ritonavir, as currently approved, the induction effect is negated by the potent inhibitory effect of ritonavir on CYP3A. Tipranavir can be used with rifabutin at reduced dosage (see p. 54, Figure III-2).

Darunavir is also an inhibitor of CYP3A and is approved for use in a ritonavir-boosted combination. Co-administration of darunavir/ritonavir is contraindicated with rifampin.

Data have indicated that rifampin may be co-administered with ritonavir 400 mg twice daily, given with saquinavir 400 mg twice daily; however, more recent data show that 39.3% of normal subjects exposed to rifampin 600 mg once daily taken with ritonavir 100 mg/saquinavir 1000 mg given twice daily (ritonavir-boosted saquinavir) developed significant hepatocellular toxicity during a 28-day study period. Among these subjects, transaminase elevations of greater than 20 times the upper limit of normal values were noted, and one subject was admitted to the hospital with marked transaminase elevations. Based on this, the manufacturer does not recommend co-administration of rifampin with any ritonavir/saquinavir combinations.

Rifabutin and Protease Inhibitors

Rifabutin can be used with regimens containing a single PI (except saquinavir alone) with some dose adjustments (see p. 54, Figure III-2). Rifabutin can also be used in the following FDA-approved combinations:

- Lopinavir/ritonavir
- Fosamprenavir/ritonavir
- Tipranavir/ritonavir
- Darunavir/ritonavir

Rifabutin should not be used with ritonavir alone because of high rates of adverse effects. For any boosted regimen containing ritonavir, the dose of rifabutin should be reduced to 150 mg 3 times per week.

Non-nucleoside Reverse Transcriptase Inhibitors

The NNRTIs—delavirdine, nevirapine and efavirenz—are all metabolized by the hepatic CYP3A. Therefore, NNRTI levels are adversely affected by the rifamycins. The effect of NNRTIs on the CYP3A is less uniform; delavirdine inhibits the CYP3A, whereas nevirapine and efavirenz induce the CYP3A (see p. 54, Table III-2). Delavirdine should not be used with either rifampin or rifabutin because both rifamycins greatly diminish the levels of delavirdine.

Rifampin and Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz. Clinical experience supports the use of efavirenz and rifampin together. Rifampin modestly decreases efavirenz exposure. However, it is safe to use rifampin concomitantly with efavirenz at the 600 mg daily dose, as excellent virologic outcomes have been found in patients on anti-TB treatment with rifampin and efavirenz-based HAART regimens. Some experts recommend the 800 mg dose of efavirenz for patients weighing more than 60 kg.

Nevirapine. Nevirapine exposure is reduced by rifampin. Several small observational studies have shown a favorable clinical response for patients receiving rifampin and nevirapine. Co-administration of nevirapine and rifampin may be particularly useful for pregnant patients in resource-poor countries, since efavirenz cannot be used in pregnancy and use of a PI-based regimen is limited due to general unavailability of rifabutin. If used under these circumstances, close clinical and virologic monitoring is necessary (see p. 53).

Rifabutin and Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz. Efavirenz exposure is not significantly affected by rifabutin, but efavirenz does decrease rifabutin exposure. Therefore, rifabutin dosage must be increased (from the usual dosage of 300 mg to a daily dose of 450-600 mg, or 2 or 3 times weekly at a dose of 600 mg) when it is given with efavirenz. An increased dose of rifabutin given daily should be used with caution, since adverse events—including anterior uveitis and reduced white blood cell count—have been reported. Those reports relate to high-dose rifabutin used in regimens that included a macrolide to treat disseminated *Mycobacterium avium* complex infections. Monthly monitoring with a CBC is recommended.

Nevirapine. Nevirapine exposure is slightly decreased by rifabutin, and nevirapine also slightly decreases rifabutin exposure. Therefore, nevirapine can be used with rifabutin, both at their usual doses.

Using More Than 1 PI and/or 1 NNRTI. Drug-drug interactions between rifamycins and antiretroviral regimens containing 2 PIs, 2 NNRTIs, or both a PI and an NNRTI have not been well studied, with the exception of ritonavir (see above). However, based on knowledge of metabolic pathways, some authors have recommended the use of efavirenz or nevirapine plus a PI (other than ritonavir) with rifabutin at its usual dose of 300 mg daily, or 3 times a week. These recommendations are based on theory and not on hard data. Avoiding antiretroviral regimens that contain more than 1 PI (with the exception of ritonavir-boosted regimens) or a PI and an NNRTI, when given simultaneously with a rifamycin-containing regimen for the treatment of TB, is advisable until more data are available.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) and Other Antiretroviral Agents

NRTIs include:

- Zidovudine
- Lamivudine
- Didanosine
- Zalcitabine
- Stavudine
- Emticitabine
- Tenofovir
- Abacavir

There is a slight decrease in the level of zidovudine, and probably abacavir, when coadministered with rifampin. The clinical significance of this interaction is not clear. The other NRTIs do not interact significantly with rifamycins. Therefore, rifamycins can be included in the anti-TB regimen if a PI- or NNRTI-sparing antiretroviral regimen is chosen. A small clinical trial comparing 4 NRTIs (zidovudine, lamivudine, abacavir and tenofovir) to efavirenz-based HAART regimen, found both to be equally effective. Triple NRTIs regimens have been shown to be less potent than efavirenz-based HAART. These regimens may be alternatives for patients unable to take NNRTIs because of adverse reaction or HIV drug resistance.

The fusion inhibitor T20, also known as enfuvirtide, is not known to be a substrate for the CYP450 enzymes or to have any effect on the levels of these enzymes. It can be used with all of the anti-TB drugs (see p. 55, Table III-3).

Several new HIV drugs have recently become available. They should be used with caution in TB patients. Raltegravir is a recently approved HIV integrase inhibitor drug. Rifampin decreases the trough concentration of this drug by 60%; however, it is recommended to be used at the standard dose with rifampin.

Rifampin substantially reduces levels of the recently approved CCR5-receptor antagonist, maraviroc, and increased dose of the latter is recommended when co-administered with rifampin. There is no clinical experience at present with this combination.

A newer NNRTI, etravirine, is available through an expended access program and is predicted to be substantially decreased in the presence of rifampin. No data is available on these interactions.

Other Anti-Tuberculosis Agents

The other major anti-TB drugs (isoniazid, pyrazinamide, ethambutol, the aminoglycosides [streptomycin, kanamycin and amikacin], capreomycin, para-amino salicylic acid, and the fluoroquinolones) are not primarily metabolized by CYP3A. Therefore, they do not have clinically important interactions with current PIs and NNRTIs. However, ethionamide is primarily metabolized by CYP3A, and its AUC may increase if it is co-administered with PIs or delavirdine; efavirenz and nevirapine may decrease levels of ethionamide. The clinical significance of this interaction is unknown.

Treatment Options

For drug-sensitive TB, several rifamycin-containing anti-TB regimens can be safely administered with effective antiretroviral therapy. Rifampin and rifabutin are the preferred rifamycins for patients who are HIV infected and taking PIs or NNRTIs. (See p. 54, Figure III-2.)

The importance of rifamycins must be strongly emphasized. Regimens that include rifampin are much shorter (6-9 months vs. 18-24 months) and have faster sputum conversion rates, higher cure rates and lower relapse rates than regimens that do not include rifampin. Higher mortality has also been reported with non-rifamycin regimens in patients who are HIV positive. Regimens that have used only 2 months of rifampin (or rifamycin) have been shown to have much higher relapse rates, particularly for patients who are HIV infected. Rifabutin may be substituted for rifampin (either initially or during the continuation phase of treatment). Rifabutin should be substituted at least 2 weeks before the planned initiation of a PI or an NNRTI to allow for the resolution of the effect of rifampin on CYP3A. Rifabutin can be administered with all the currently approved PIs (except saquinavir alone), as well as efavirenz and nevirapine. The dose and frequency of rifabutin depends on the PI or NNRTI with which it is being co-administered. (See p. 54, Figure III-2; p. 55, Table III-3.) Rifampin exposure is not affected by the co-administration of the PIs or NNRTIs, and rifampin dosing does not need to be adjusted.

The following regimens can be used:

- Two months isoniazid, rifampin, pyrazinamide, ethambutol, then 4 months isoniazid, rifampin
- Two months isoniazid, rifabutin, pyrazinamide, ethambutol, then 4 months isoniazid, rifabutin
- Two months isoniazid, rifampin, pyrazinamide, ethambutol, then 4 months isoniazid, rifabutin
- Nine months isoniazid, pyrazinamide, streptomycin

General Considerations

Most patients who are HIV positive with TB in NYC have CD4 T-lymphocyte counts below 200 cells/mm^3 and are eligible for antiretroviral treatment.

HAART regimens have been shown to be life saving, and many TB patients have advanced AIDS and will benefit from initiation of HAART early in the 2-month intensive phase. (See p. 54, Figure III-2.)

For patients who are not already taking antiretrovirals at the time of TB diagnosis, physicians should consider deferring the initiation of an antiretroviral regimen until after the intensive phase of TB therapy (the first 2 months of treatment for drug-susceptible TB). This allows the clinician to manage the adverse effects associated with TB drugs without having to deal with the complications of antiretroviral drugs, and may minimize the likelihood of immune reconstitution syndrome (IRIS) (see p. 56). Patients may also find the pill burden more tolerable when the antiretroviral drugs are started after some of the anti-TB medications have been discontinued, in the continuation phase. If the patient is unable to tolerate or manage the multiple drugs needed to treat both conditions, it may be necessary to defer HIV treatment until TB treatment is completed.

If a patient is already on a PI- or an NNRTI-containing antiretroviral regimen that is not compatible with rifamycins, consideration should be given to changing the antiretroviral regimen. Currently, treatment interruptions are not recommended for most patients taking antiretroviral therapy—in some patients it may be associated with poorer treatment outcomes. An expert in the management of HIV disease should be consulted.

Alternatively, for patients undergoing therapy with complex combinations of PIs and/or NNRTIs, anti-TB regimens that do not contain rifamycins can be used. Only 1 regimen without a rifamycin—9 months of isoniazid, pyrazinamide and streptomycin—has been shown (in patients who are HIV-seronegative) to have high efficacy in less than 12 months. This regimen is rarely used, however, since the injectable drug has to be administered for the full 9 months.

If an isoniazid-resistant, rifampin-susceptible organism is isolated, it is essential to try to adjust the regimen so that a rifamycin can be used. Otherwise, the patient will need at least 18 to 24 months of treatment with one of the weaker, more toxic regimens used for multidrug-resistant TB.

Women of childbearing age and pregnant women. Treatment of HIV and TB in pregnant women is challenging. Efavirenz is contraindicated both for pregnant women and for women of childbearing potential who are not on adequate contraception. Nevirapine is the only other highly active antiretroviral therapy (HAART) regimen that can be administered with rifampin. However, nevirapine is associated with an increased risk of severe hepatotoxicity in women with CD4 T-lymphocyte counts greater than 250 cells/mm^3 and is a relative contraindication. In such women who are pregnant, HAART regimen is difficult to administer during TB treatment when rifabutin is not available. If nevirapine is used with rifampin, close clinical, hepatic and virologic monitoring is necessary.

Length of Therapy. Recommended treatment regimens and length of therapy are similar for individuals who are HIV infected and those who are not. The length of therapy is not affected by antiretroviral use, and short course therapy is possible if a standard rifamycin-containing regimen is used. The clinical, radiographic and microbiologic responses to therapy are similar irrespective of HIV status. Relapse rates are low. Though several studies have shown that relapse rates are higher in individuals who are HIV infected, others have shown similar relapse rates in both groups. If cultures remain positive after 2 months of rifamycin-based treatment, the therapy should be extended to 9 months.

Intermittent Regimens Containing Rifamycins

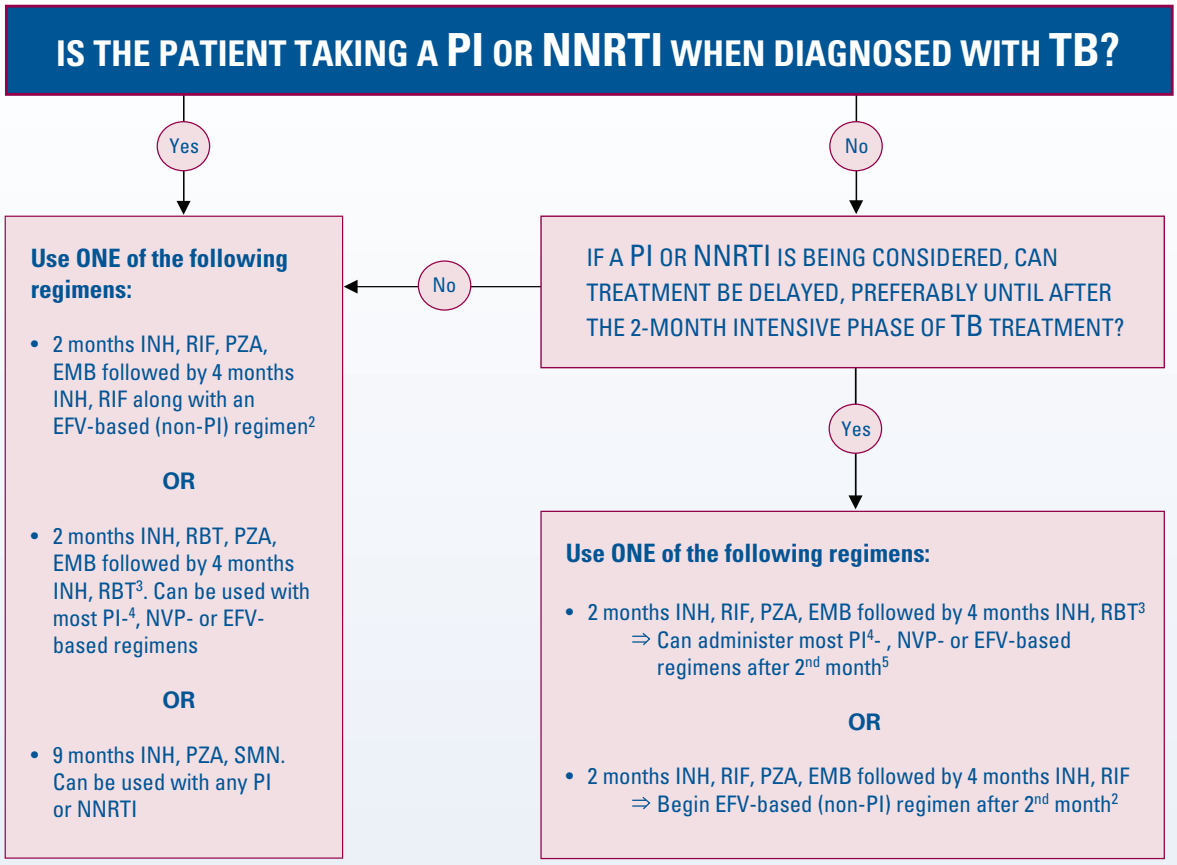
Independent of CD4 counts, all patients with HIV-TB coinfection should be treated with a daily regimen during the intensive phase, regardless of whether they are also receiving antiretroviral drugs. Rifabutin dose may be intermittent, depending on the HAART regimen. (See p. 54, Figure III-2.) During the continuation phase of treatment, the patient's CD4 count is of primary importance in determining frequency of intermittent therapy.

Patients with HIV-associated TB and CD4 cell count of less than 100/mm^3 should receive daily therapy during the intensive phase and daily or 3 times per week therapy during the continuation phase. Regimens should not be given at a frequency of less than 3 times per week in HIV-infected TB patients with CD4 cell counts lower than 100/mm^3. Administering rifabutin-containing regimens twice a week has been associated with the development of acquired rifamycin resistance. The Centers for Disease Control and Prevention (CDC) suspended enrollment of patients into Study 23 (a study designed to evaluate the efficacy of twice-weekly rifabutin-based regimens for treatment of HIV-associated TB), because 7 cases of acquired rifamycin resistance occurred among study patients. All had received a biweekly rifabutin-containing regimen at some point, during the treatment of TB with a drug-susceptible organism. In addition, NYC experience confirms that use of intermittent rifamycin-containing regimens in the intensive phase of treatment is associated with development of acquired rifampin resistance in patients with very low CD4 cell counts. Rifapentine should not be used at all for the treatment of TB in patients who are HIV infected, because of the increased rate of rifamycin resistance that occurs with highly intermittent therapy.

For patients with a CD4 cell count of less than 100/mm^3 receiving lopinavir/ritonavir or any other ritonavir-boosted regimen, TB therapy should be daily during the intensive phase, with the exception of the rifabutin component. Isoniazid, pyrazinamide and ethambutol should be given daily at standard doses. Rifabutin should be given as 150 mg 3 times per week. During the continuation phase of therapy, isoniazid and rifabutin can both be given 3 times per week.

Figure III-2

Treatment Options for Patients Who Have Tuberculosis and Are HIV Infected[1]



Abbreviation Key:
EFV efavirenz
EMB ethambutol
IDV indinavir
INH isoniazid
NFV nelfinavir
NNRTI non-nucleoside reverse transcriptase inhibitor
NVP nevirapine
PI protease inhibitor
PZA pyrazinamide
RBT rifabutin
RIF rifampin
SMN streptomycin

NOTES

1. Patients who are HIV infected, with a CD4+ count of less than 100 cells/mm^3 should receive a daily regimen in the intensive phase and either daily or 3 times per week regimen in the continuation phase.
2. With RIF: EFV daily dosage may need to be increased to 800 mg.
3. RBT dosage and frequency vary depending on the PI or NNRTI being used.
   - With EFV: RBT 450-600 mg daily or 600 mg 2 or 3 times per week. EFV daily dose is unchanged with RBT.
   - With NVP: RBT 300 mg daily or 300 mg 2 or 3 times per week
   - With amprenavir, fosamprenavir, IDV or NFV: RBT 150 mg daily or 300 mg 2 or 3 times per week
   - With amprenavir/ritonavir, atazanavir, atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir, or tipranavir/ritonavir: RBT 150 mg every other day or 3 times per week. Other anti-TB drugs should be given daily in the intensive phase for patients with a CD4+ count <100 cells/mm^3.
4. With RBT the following PI dose changes are recommended:
   - Increase NFV to 1000 mg 3 times per day or use standard 1250 mg 2 times/day.
   - Increase IDV to 1000 mg 3 times per day.
5. There should be a 2-week washout period after the discontinuation of RIF and before starting a PI or NNRTI.

For further details, see "Antiretroviral Drugs and Treatment of Tuberculosis" at: http://www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf

Useful websites:
http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm or www.AIDSinfo.nih.gov

Table III-3

Treatment Adjustments in Patients Who Are HIV Positive and Taking Antiretroviral Agents

Generic Name	Brand Name	OK with rifampin?	OK with rifabutin?*
Protease Inhibitors (PIs)			
Amprenavir	Agenerase®	no	yes
Atazanavir	Reyataz®	no	yes
Darunavir/Ritonavir	Prezista™ & Norvir®	no	yes
Fosamprenavir	Lexiva®	no	yes
Indinavir	Crixivan®	no	yes
Lopinavir/Ritonavir	Kaletra®	no	yes
Nelfinavir	Viracept®	no	yes
Ritonavir	Norvir®	no	yes
Saquinavir	Invirase®, Fortovase®	no	no
Tipranavir/Ritonavir	Aptivus® & Norvir®	no	yes
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Delavirdine	Rescriptor®	no	no
Efavirenz	Sustiva®	yes	yes
Efavirenz/Emtricitabine/Tenofovir combination	Atripla™	yes	yes
Nevirapine	Viramune®	yes**	yes
Other Antiretroviral Drugs			
Abacavir	Ziagen®	yes	yes
Didanosine	Videx®	yes	yes
Emtricitabine	Emtriva®	yes	yes
Enfuvirtide	Fuzeon®	yes	yes
Lamivudine	Epivir®	yes	yes
Stavudine	Zerit®	yes	yes
Tenofovir	Viread®	yes	yes
Zalcitabine	Hivid®	yes	yes
Zidovudine	Retrovir®	yes	yes
Zidovudine + Lamivudine	Combivir®	yes	yes
Abacavir + Zidovudine + Lamivudine	Trizivir®	yes	yes
Emtricitabine + Tenofovir	Truvada®	yes	yes
Abacavir + Lamivudine	Epziom®	yes	yes

Use of brand names is for informational purposes only and does not imply endorsement by the New York City Department of Health and Mental Hygiene

* When antiretrovirals are used with rifabutin, the dosage of the PI, NNRTI and/or rifabutin may need to be adjusted. Please refer to the text and Figure III-2 on preceding page for details on drug dosages.

** Limited circumstances; refer to text.

For further details, see "Antiretroviral Drugs and Treatment of Tuberculosis" at: www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf

Useful websites:
www.cdc.gov/tb/TB_HIV_Drugs/default.htm or www.AIDSinfo.nih.gov

Patients with CD4 count greater than 100 cells/mm^3 at the time of TB diagnosis should be treated with a daily regimen in the intensive phase, and with either 2 or 3 times per week regimens in the continuation phase.

Indinavir, nelfinavir, atazanavir, amprenavir and fosamprenavir can all be administered with daily rifabutin (150 mg/day), as well as with 2 or 3 times per week regimens (during the continuation phase only) at a dose of 300 mg. Efavirenz can be given with rifabutin 450 mg daily or 600 mg 2 or 3 times a week. An increased dose of rifabutin given daily should be used with caution since adverse events, including anterior uveitis and a reduced white blood cell count, have been reported with high-dose rifabutin when it is used in regimens that include a macrolide. Monthly monitoring with a CBC is recommended.

Immune Reconstitution Inflammatory Syndrome

Immune Reconstitution Inflammatory Syndrome (IRIS), also known as paradoxical worsening of TB, is the development of new manifestations of TB or worsening of existing signs and symptoms of TB in patients receiving appropriate medication regimens. IRIS is thought to be an inflammatory response to *M. tb* antigens as the body's immune system recovers while on TB and/or HIV treatment. This theory is strengthened by the observation that patients with HIV-associated TB who are started on antiretroviral regimens seem to be at a particularly increased risk of developing this syndrome.

A number of studies have estimated frequency of IRIS to be 11% to 45%, and find that it occurs more often in patients with lower CD4 counts, extrapulmonary disease, disseminated disease and with a shorter interval from TB diagnosis to HAART administration. Paradoxical reaction occurs within a few weeks of starting HAART, and coincides most closely with viral load decline. Thus the timing of HAART initiation in patients with TB is further complicated by the potential for a paradoxical or IRIS reaction.

Patients may experience substantial morbidity due to IRIS reactions even though the prognosis for survival is favorable. The CDC/ATS/IDSA guidelines suggest delaying HAART initiation until after 4 to 8 weeks of TB therapy. A practical strategy for dually infected patients who were not on HAART prior to TB diagnosis may be to give TB treatment alone until clinical improvement plateaus, or until the end of the intensive phase. This will also minimize overlapping toxicities, reduce pill burden and make both treatments more tolerable.

Paradoxical worsening can manifest in a wide variety of sites, including cervical or mediastinal adenopathy, worsening infiltrates on CXR or enlarging central nervous system (CNS) lesions. Fever may or may not be present.

The course of paradoxical worsening is often unpredictable. It can be brief or prolonged, with multiple recurrences and exacerbations.

The diagnosis of paradoxical reactions remains a diagnosis of exclusion. Diagnosis relies on negative culture of clinical samples; decrease in HIV viral load and lack of other etiologies, such as relapse of TB, poor adherence to treatment, adverse effects of drugs, worsening TB due to drug resistance or other infections.

Treatment of paradoxical reactions is not well established. Mild and moderate reactions can be managed by reassuring the patients or by non-steroidal anti-inflammatory agents. Repeated aspirations for decompression have been used to avoid surgical drainage. Some experts advocate the use of corticosteroids or discontinuation of antiretroviral therapy for severe cases, such as patients who have lymphadenopathy that may compromise respiration and swallowing, or the development of CNS mass lesions. Prednisone at doses ranging from 20 to 50 mg daily, tapered over as little as 2 weeks, has been used. The use of corticosteroids for short periods of time does not seem to adversely affect the outcome of the TB treatment. Data on the use of corticosteroids for the treatment of paradoxical reactions in HIV-associated TB are limited. Their use should therefore be reserved for severe cases.

Regimens for Pregnant Women

In almost all situations, a pregnant woman who has a positive *M. tb* culture (Class III), or who is suspected of having TB (Class V [High]), should be treated without delay. Very rarely, and with the approval of the Bureau Director or Director of Medical Affairs for the BTBC, treatment for suspected TB may be deferred until the end of the first trimester. This may be done if the pregnant woman is very reluctant to take the treatment, and meets all of the following criteria:

- Sputum smear negative for AFB
- HIV-negative
- No risk factors for HIV infection
- No symptoms of TB (i.e., no cough, fever, night sweats, weight loss)
- No cavities on CXR

Treatment regimens for pregnant women differ from standard treatment regimens because streptomycin is contraindicated and pyrazinamide should be avoided. Streptomycin has been shown to have teratogenic effects on the fetus, and the effect of pyrazinamide on the fetus is not known. However, if treatment is started after the first trimester, pyrazinamide should be included in the initial treatment regimen for: women who are HIV positive; women who have behavioral risk factors for HIV infection but decline HIV testing; and women suspected of having multidrug resistant TB (MDRTB, resistant to at least isoniazid and rifampin). Pyrazinamide should be included in the treatment regimen, regardless of the stage of pregnancy, for women who are HIV positive strongly suspected of having TB resistant to isoniazid and rifampin. Note that despite the lack of data on pyrazinamide, the World Health Organization recommends this drug at all stages of pregnancy for all pregnant women.

TB during pregnancy is rarely, if ever, an indication for a therapeutic abortion. One possible exception, however, is multidrug-resistant tuberculosis (MDRTB). See p. 58 for further discussion.

Whether a mother who has disease should be separated from her infant at delivery depends on how infectious she is. Clinicians should assess the mother's infectiousness. (See p. 130.) If the mother is considered infectious, she should be separated from the infant until she becomes noninfectious on treatment, or until the infant starts treatment for latent tuberculosis infection (LTBI).

Standard Regimen for Pregnant Women

Start with a regimen of isoniazid, rifampin, and ethambutol unless there are absolute contraindications. Use Rifamate® (capsules combining isoniazid and rifampin) for patients who are not receiving DOT. See p. 208, Appendix I-A for dosages. (See below for treatment for pregnant women who are HIV-negative, and who are suspected of having MDRTB.)

- Use pyrazinamide from initiation of treatment, regardless of month of gestation, if drug resistance is strongly suspected.
- Also give pyrazinamide if the woman is HIV-infected and TB treatment is started after the first trimester.
- Discontinue ethambutol (and pyrazinamide) at the end of the intensive phase of treatment unless:
  - Drug susceptibility results show resistance to isoniazid or rifampin.
  - Drug susceptibility results are not available and drug resistance is suspected because of a history of prior TB treatment.
- Ethambutol can be discontinued earlier once drug susceptibility results are available and show susceptibility to isoniazid and rifampin.

For pregnant women taking isoniazid, give pyridoxine (Vitamin B_6) 25 mg a day 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 4-drug regimen that includes pyrazinamide, the pyrazinamide can be stopped if the woman is in the first trimester of pregnancy and if the above risk factors are not present. If the first trimester has passed before the pregnancy is discovered, continue all 4 drugs, in order to finish a 2-month intensive phase of treatment. This allows the total duration of treatment to be shortened significantly.

Length of Treatment

Culture-positive pulmonary disease

- If the strain is fully susceptible, treat for a total of 9 months if the patient is treated with isoniazid, rifampin and ethambutol. However, if pyrazinamide was given for the initial 2 months of treatment, (i.e., before the woman was discovered to be pregnant or if the woman was HIV-infected), a total of 6 months of treatment is appropriate. (If the strain is drug resistant, see p. 86, Table V-1 for guidelines on the length of treatment.)

- If the patient is *M. tb* culture positive without available susceptibilities and if drug resistance is not suspected, the patient should be treated with isoniazid, rifampin and ethambutol (and pyrazinamide) during the intensive phase, and then isoniazid and rifampin during the continuation phase.
    - If drug resistance is suspected, the 3-drug regimen of isoniazid, rifampin and ethambutol should be continued for 9 months. The 4-drug regimen that adds pyrazinamide can be given for 6 months.
- If cultures have not converted by 4 months, assess the patient for adherence to treatment, absorption of anti-TB medication(s) and drug resistance. (See p. 84 and p. 214, Appendix I-E.)

Culture-negative pulmonary disease
For patients whose initial sputum cultures are negative and who received only isoniazid, rifampin and ethambutol, the intensive phase of treatment should be followed by:

- A 7-month continuation phase of isoniazid and rifampin only, if the patient has not received treatment for TB in the past, and if drug resistance is not suspected.
- If the patient has received treatment in the past, continue isoniazid, rifampin and ethambutol for the full 9 months, as drug resistance may be present.

If pyrazinamide was used in the intensive phase, than the duration and drug regimen is the following:

- The intensive phase of treatment should be followed by a 2 month continuation phase of isoniazid and rifampin only, if the patient has not received treatment for TB in the past and drug resistance is not suspected.
- If the patient has received treatment in the past, isoniazid, rifampin, pyrazinamide and ethambutol should be continued for an additional 2 months, to complete a 4-month regimen.

Regimen for Pregnant Women Suspected or Known to Have Tuberculosis Resistant to Isoniazid and Rifampin (MDRTB)

Unlike the treatment of drug-susceptible TB, it is not possible to develop standardized protocols for the treatment of known or suspected drug-resistant TB. Physicians treating pregnant women suspected or known to have drug-resistant TB should follow the treatment principles in Section V. As with all drug-resistant TB cases, expert consultation should be sought.

Most of the medications used to treat MDRTB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy. (See p. 211, Appendix I-C.) These include streptomycin, kanamycin, amikacin, capreomycin and fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin), cycloserine, ethionamide and, rarely, clofazimine. Therefore, pregnant women with culture-proven MDRTB should be offered abortion counseling.

In the case that a woman continues the pregnancy, physicians should treat for MDRTB despite the potential toxicities. The risk of TB to the fetus outweighs the risk of toxicities from anti-TB medications. The physician should document all discussion with the patient in the chart.

Anti-Tuberculosis Medications in Breast-feeding Women

The small concentrations of anti-TB drugs in breast milk are not toxic to the nursing newborn (see p. 211, Appendix I-C). Therefore, breast-feeding should not be discouraged for a woman who is HIV negative and who is planning to take, or who is taking, isoniazid or other anti-TB medications. Furthermore, the low concentration of anti-TB medications in breast milk should not be considered effective treatment for disease—or for treatment for LTBI in a nursing infant. Women who are HIV-positive should not breast-feed because of the risk of HIV transmission to the infant.

Regimens for Children

In addition to the standard evaluation listed on p. 26, the following areas of evaluation and presentation of TB merit special attention in children.

Children who can be evaluated for visual acuity or color vision should be managed under the protocol for adults. (See p. 43.) If children cannot identify letters on an eye chart, they may be able to discriminate colors, and this can be used for monitoring for potential ethambutol toxicity. Children who cannot be evaluated for visual acuity or color vision should not be treated with ethambutol unless the child is known or likely to have drug-resistant TB or HIV infection, or immunosuppression from other clinical conditions.

When ethambutol is used as part of the initial regimen, the dosage is 20 mg/kg body weight. The recommended daily dose of ethambutol is higher in children than in adults (15 mg/kg), because the pharmacokinetics are different (peak serum ethambutol concentrations are lower in children than in adults receiving the same mg/kg dose).

Although ethambutol was frequently omitted from treatment regimens for children in the past, due in part to concerns about the difficulty of monitoring for toxicity (particularly optic neuritis, in young children), a literature review indicates that it is safe in children at a dose of 20 mg/kg (range 15– 25 mg/kg) daily. Streptomycin should be avoided when possible in children, both because the injections are painful and irreversible auditory nerve damage may occur. The use of streptomycin in children is mainly reserved for the first 2 months of treatment for TB meningitis.

Similar to adults with TB, children with confirmed or suspected TB should be given DOT. If DOT is not given, the reason for this must be clearly documented in the medical record. After the intensive phase of daily therapy, children receiving DOT should be switched to an intermittent regimen. Some physicians may prefer to use 3 times a week dosing, as some children may not completely ingest all doses. (See p. 45, Table III-1.) In some situations, however, the physician may prefer daily therapy for adherence reasons. If intermittent therapy is not used, the physician must clearly document the reasons in the medical record.

If cultures have not converted by 4 months, assess the child for adherence to treatment, absorption of anti-TB medication(s) and drug resistance (see p. 84 and p. 214, Appendix I-E.)

Standard Regimen

Start with a regimen of isoniazid, rifampin and pyrazinamide for at least 2 months.

- Use ethambutol at 20 mg/kg if the child's vision can be tested.
- Use ethambutol, regardless of ability to test vision, for children who are:
  - HIV-positive
  - At risk for HIV infection, and whose parent or guardian declines HIV testing
  - Immunosuppressed from other conditions

However, if the exclusive source patient is known to have TB susceptible to isoniazid and rifampin, ethambutol may be omitted from the initial regimen.

Discontinue pyrazinamide (and ethambutol) at the end of the intensive phase of treatment unless:

- Drug susceptibility results of the child's or source case's isolate show resistance to isoniazid or rifampin.
- Drug susceptibility results are not available, and drug resistance is suspected because of a history of prior TB treatment.
- Ethambutol can be discontinued earlier, once drug susceptibility results are available and show susceptibility to isoniazid and rifampin.

See p. 208, Appendix I-A for dosages of primary medications used in the treatment of TB. For younger children, isoniazid or pyrazinamide tablets can be divided, crushed or added to food or liquids such as fruit, juice or gelatin. Also, rifampin may be emptied from the capsule and added to food or liquids just before ingestion. Liquid formulations are available through the BTBC pharmacy.

If the exclusive-source patient is known or strongly suspected to have *M. tb* resistant to isoniazid and/or rifampin, use ethambutol along with other appropriate medications. (See p. 83 and p. 86, Table V-1.)

Length of Treatment Regardless of Culture Results

The standard 6-month treatment (short-course chemotherapy) for drug-susceptible TB in children should consist of a 2-month intensive phase, followed by a 4-month continuation phase. (If the strain is drug-resistant, see p. 86, Table V-1 for guidelines on length of treatment.)

- The 4-month continuation phase of treatment should be used in the large majority of children. However, a 7-month continuation phase should be given to 4 groups:
  - Children with drug-susceptible pulmonary TB with initial cavitation on CXR, whose sputum culture remains positive after the intensive phase (i.e., the first 2 months of treatment).
  - Children who are still culture positive at 2 months, regardless of CXR results.
  - Children whose treatment regimen did not include pyrazinamide in the intensive phase, or whose organism was resistant to pyrazinamide.
  - Children over 12 years of age who are being treated with once-weekly isoniazid and rifapentine, and whose sputum culture remains positive after the 2-month intensive phase of treatment.

If the child is *M. tb* culture positive without available susceptibilities, and drug resistance is not suspected, the patient should be treated with isoniazid, rifampin, pyrazinamide (and ethambutol) during the intensive phase, and then isoniazid and rifampin during the 4-month continuation phase.

For children whose initial sputum cultures are negative, the intensive phase of treatment should be followed by a 4-month continuation phase of isoniazid and rifampin only (if the patient has not received treatment for TB in the past).

- If the patient has received treatment in the past, isoniazid, rifampin, pyrazinamide (and ethambutol) should be continued for the full 6 months, as drug resistance may be present.

For children who have positive gastric aspirates and a favorable clinical response, repeat gastric aspirates to document culture conversion is not recommended.

If the child has hilar adenopathy or extrapulmonary disease, treatment should be for 6 months with the same regimen as for pulmonary TB. However, if meningeal or miliary TB is present, treatment should be extended to 9-12 months, depending on the location of disease. (See p. 74.)

Adverse Events in Children

Adverse events caused by anti-TB drugs are much less common in children than in adults. The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampin or pyrazinamide. There are some data suggesting that doses of isoniazid greater than 15 to 20 mg/kg may be associated with a greater risk of hepatotoxicity. Serum liver enzyme levels should not be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (less than 5 times the normal values) is not an indication to stop treatment. However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs. Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver function has normalized. An expert experienced in managing drug-induced hepatotoxicity should be involved in the further management of such cases. If treatment for TB needs to be continued for severe forms of TB, nonhepatotoxic anti-TB drugs should be introduced (e.g., ethambutol, an aminoglycoside and a fluoroquinolone).

Regimens for Patients with Chronic Renal Failure

In most patients with chronic renal failure, the regimens for TB treatment must be adjusted. Most experts advise lengthening the interval between conventional doses as the safest method to accomplish adequate but safe serum levels. (see p. 211, Appendix I-C). Three times per week regimens are convenient and should be used. Isoniazid, rifampin, ethionamide and para-aminosalicylic acid (PAS) can be used in conventional doses in patients with chronic renal failure. These medications should be given after hemodialysis.

PAS in its traditional formulations may worsen renal acidosis and provide an excessive sodium load, and should be avoided. However, current formulations of PAS that do not use the sodium salt, (e.g., Paser®), can be used without the hazard of sodium retention.

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, our recommendation at this time is to dose the patient as per hemodialysis dosing.

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

Aminoglycosides and capreomycin can be used in conventional or 750 mg doses, but only 2 or 3 times per week. The dose should be administered immediately after hemodialysis in patients who are receiving maintenance hemodialysis. Levels of amikacin, if used, may be helpful in guiding therapy.

Pyrazinamide can be used at the usual daily dose in patients with mild to moderate renal insufficiency. In patients with severe renal failure, however, a 3 times a week dose of 30 mg/kg (range 25-35 mg/kg) is recommended. The medication should be given immediately after hemodialysis.

Ethambutol and cycloserine are excreted primarily by the kidney, and excessive and toxic blood levels can occur in patients with chronic renal insufficiency. Both medications should be avoided if possible. If ethambutol is essential to the regimen in patients with MDRTB, a conventional 15 mg/kg dose may be given every 2 or 3 days, but visual acuity and color vision must be very closely monitored and blood levels must be monitored. Cycloserine should be given at a dose of 250 mg/day or 500 mg 3 times a week. Drug levels should be monitored. Doses of both drugs should be given immediately after hemodialysis.

Fluoroquinolones undergo some degree of renal clearance that varies from drug to drug. Levofloxacin at 750-1000 mg 3 times a week is adequate for treatment of TB in patients with end-stage renal disease. Moxifloxacin may be the preferred agent for patients with renal failure, as it is mostly cleared by the liver.

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 (isoniazid, rifampin, pyrazinamide and ethionamide). However, closer monitoring of the patient's liver function, and signs and symptoms of toxicity, should be done. Monthly, and in some cases biweekly, LFTs should be done when a patient with chronic liver disease is receiving these drugs.

The administration of rifampin with isoniazid can increase the possibility of isoniazid toxicity. If it is necessary to exclude one of these agents from the regimen, isoniazid should be considered first. In this situation, the patient may be treated with ethambutol, rifampin and pyrazinamide for 6 to 9 months. (See p. 86, Table V-1 and p. 87.) If rifampin must be excluded, the duration of treatment should be prolonged to 18-24 months (see p. 86, Table V-1 and p. 87). Depending on the severity of the hepatitis, a trial of rifabutin should be considered. If pyrazinamide is not used, isoniazid and the rifamycin should be given for at least 9 months for drug-susceptible tuberculosis.

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, Hepatitis B surface antigen–seropositive individuals with elevated alanine transaminase (ALT) should have hepatitis B e-antigen (HBeAg) testing. If positive, rifampin may be preferred over isoniazid. A gastroenterologist or infectious disease specialist should be consulted regarding further testing and possible pretreatment in individuals with an ALT at least 2 times the upper limits of normal, and who are HBeAg seropositive. In HBeAg-seropositive individuals, clinical and ALT monitoring should occur every 2 to 4 weeks. For patients with chronic hepatitis C, a hepatitis C viral RNA load should be obtained. If it is elevated, the patient should be referred for potential treatment. In these patients, elevated LFTs may be indicative of their underlying liver disease and may not be drug induced.

Table III-4

The Use of Pyridoxine in Tuberculosis Treatment

Drug	Dosage of Pyridoxine	Indicators
Isoniazid	25 mg daily (may be self-administered if patient is on intermittent DOT) 50 mg twice weekly, if isoniazid given at 900 mg twice weekly If patient develops peripheral neuropathy, discontinue isoniazid and continue pyridoxine (25 mg daily) until symptoms abate.	Indicated for children on meat- and milk-deficient diets and for breast-feeding infants on isoniazid Also advised for patients with: • HIV infection • Malnourishment (more than 10% below ideal body weight or any wasting disease) • Diabetes • Cancer • Chronic renal disease • Pregnancy • Alcoholism • Pre-existing peripheral neuropathy • Chronic liver disease • Other immunosuppressive conditions
Cycloserine	50 mg for each 250 mg of cycloserine to a maximum of 200 mg pyridoxine daily*	Required for all patients taking cycloserine

* If an individual is taking 500 mg of cycloserine at the first dose and 250 mg at the second dose, for simplicity, 100 mg of pyridoxine can be given with each dose of cycloserine, or the entire pyridoxine dose can be given with one of the cycloserine doses.

A recent study found that only excessive alcohol consumption and a high baseline ALT concentration were independently associated with isoniazid hepatotoxicity. The presence of HCV antibody was associated with hepatotoxicity only on univariate analysis in this study.

In patients with acute liver failure, a regimen of nonhepatotoxic drugs—such as an aminoglycoside or capreomycin, ethambutol, cycloserine and a fluoroquinolone—should be used until the liver function improves (see p. 109, Figure VI-2). Levofloxacin is the preferred fluoroquinolone to use in patients with hepatic insufficiency. Moxifloxacin 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 isoniazid or rifampin. The duration of therapy depends on whether it is possible eventually to add isoniazid and rifampin to the regimen, and on the final regimen that is tolerated.

The Use of Pyridoxine (Vitamin B_6) in Tuberculosis Treatment

Pyridoxine is often used in conjunction with certain anti-TB medications to prevent side effects in the central and peripheral nervous system (see Table III-4 above.)

Anti-Tuberculosis Drugs and Meals

Rifampin and isoniazid should be taken on an empty stomach whenever possible, as food has been shown to decrease absorption significantly. Absorption of rifapentine is improved when taken with meals. Rifabutin, pyrazinamide and ethambutol can be taken with food. Isoniazid should not be dissolved in, or ingested with, beverages high in glucose or lactose. Isoniazid, ethambutol and fluoroquinolones should not be given with magnesium or calcium-containing antacids, or with medications containing cations, as they may interfere with absorption of these drugs.

Directly Observed Therapy

Directly observed therapy (DOT), the standard of care in TB treatment, is the best way to ensure that patients complete an adequate course of treatment for TB. DOT means that a health care worker, or another responsible individual, directly observes and supervises every dose of anti-TB medication taken by the patient. DOT regimens may be daily, 2 or 3 times a week. Once-a-week DOT is acceptable only when rifapentine is used.

For patients on daily DOT, a 5-days-a-week treatment regimen is acceptable if the patient has drug-susceptible TB, and a standard first-line drug regimen is tolerated. This allows the full treatment to be directly observed. No self-administered doses have to be given to the patient for the weekends and holidays. The necessary number of doses for the duration of the daily treatment should be adjusted accordingly. This should not be attempted for patients on self-administered treatment.

Most patients will adhere to treatment when education, incentives, housing, enhanced social services and home or field DOT are provided. If these less-restrictive measures are likely to fail, or have already failed, the New York City Health Code empowers the Commissioner of Health to issue patients any order deemed necessary to protect the public health (e.g., orders for DOT, isolation or long-term detention). For information on the criteria for a Commissioner's Order, see p. 145.

All HIV-infected patients taking anti-TB treatment should be given DOT. When TB treatment is complicated by drug-drug interactions between drugs used for TB and those used for HIV infection, the need to ensure that patients adhere to their regimens becomes even more paramount. Poor adherence among these patients would be doubly dangerous and catastrophic in that it would create both TB and HIV drug resistance.

In addition to the BTBC, several New York State-sponsored sites provide DOT to TB patients in NYC. DOT can be done either in the clinic or in the field. Arrangements are made to accommodate the patients' schedules. All patient services provided by BTBC are free of charge to the patient.

Non-BTBC physicians who have patients with active TB have 2 treatment options:

1. **Refer the patient to a BTBC Chest Center.** The Health Department will act as the patient's TB care provider. The referring physician remains the primary care provider and receives TB care updates.

2. **Act as the patient's TB care provider.** The physician manages the patient's TB care and treatment. In both cases, all patients can be enrolled in DOT and receive free TB medications. The patient will receive medications through the DOH's Gratis Meds program, where BTBC supplies medications directly to the provider.

The BTBC is required by the CDC to case manage the patient's TB treatment in conjunction with the patient's primary TB provider.

To refer a patient, call the TB Provider Hotline at 212-788-4162.

Protocol for Providing Directly Observed Therapy

- All TB Class III and Class V (High) patients should be given DOT—it is mandatory if intermittent therapy is used. When a patient is not started on DOT, the compelling reason(s) must be clearly documented in the medical record.

- All doses (except those given on weekends and holidays) should be observed; it is not advisable to administer some doses by DOT and allow some to be self-administered.

- TB Class V (Low) patients (patients expected to evolve as TB Class IV) should be treated with an appropriate self-administered regimen. These patients should be monitored by a nurse if they are taking isoniazid alone, or by a physician if they are taking multiple anti-TB medications. If the classification is changed to Class III or Class V (High), DOT should be used.

- DOT should be clinic-based if possible. DOT outside a BTBC chest center should be reserved for patients who (1) are unable to attend the chest center for medical or social reasons; or (2) have failed more than 3 attempts at clinic-based DOT, but are willing to be part of a DOT program outside the chest center.

- A contract should be signed by the patient, the chest center manager or DOT provider (registered nurse or public health advisor)

and the physician who is ordering DOT. There are 2 separate contracts, 1 for field patients and 1 for clinic patients. These are included as Appendix III-C on p. 240 and Appendix III-D on p. 242.

- Patients being cared for by a physician not affiliated with the BTBC may also receive DOT at a BTBC chest center. In this situation, the Physician-in-Charge must review the patient's medical regimen. It is the responsibility of the non-DOH provider to medically follow the patient and order the patient's medication on a monthly basis and provide this information to the chest center.

Priority of Patients for Directly Observed Therapy

In some situations, individuals with suspected or confirmed TB must be assigned priority for DOT. The order of priority for DOT is as follows:

- Drug-resistant TB
- Smear-positive pulmonary TB
- Patients who are HIV positive
- Present or past non-adherence with TB medications
- History of prior treatment of TB
- Disease relapse
- Too ill to self-manage
- History of substance abuse
- Children requiring therapy whose parents are in any of the above categories
- Children and adolescents
- Homeless/shelter residents or unstably housed individuals
- History of being in a correctional facility
- Major psychiatric or memory/cognitive disorder
- Denial of TB diagnosis
- Poor adherence during initial medical management
- Slow sputum conversion or slow clinical improvement
- Clinical deterioration while on TB therapy
- Adverse reaction to TB medication
- At patient's request

Determination of Treatment Completion

It can be difficult to determine when a patient has completed treatment, since not all patients take 100% of prescribed doses, even when on DOT. The 2003 ATS/CDC/IDSA tuberculosis treatment guidelines recommend that treatment should be considered complete after 100% of the prescribed regimen has been taken. Treatment should be lengthened if all prescribed doses have not been taken within the original time frame, although there is limited data to support this recommendation. (See p. 45, Table III-1.)

Most short-course TB chemotherapy trials have considered completion of 80% of the doses prescribed to be adequate. This has been the BTBC guideline for a long time. Though there is little data to show that 100% completion of most short-course chemotherapy regimens is required, some individuals may benefit.

In selected individuals who have not been fully adherent to their treatment, the duration should be extended, to ensure that 100% of the originally recommended doses are given to individuals:

- With cavitary or extensive disease
- With HIV infection
- Who are still culture positive at 2 months after start of treatment
- Who did not receive 2 months of pyrazinamide in the intensive phase

For example, for a patient in the preceding categories who has only taken 80% of the doses in their 6-month regimen, treatment should be extended an additional few weeks to ensure 100% of doses are taken.

For other patients, an attempt should be made to ensure that the full regimen is taken whenever possible. However, if a patient disappears after receiving 6 months of treatment with 80% compliance, and the patient cannot be located, the patient may be considered as having completed treatment.

Interrupted or Incomplete Treatment

General Principles

When a patient has had interrupted or incomplete treatment, the physician must decide the appropriate duration of a new regimen. Reinstitution of treatment requires a continuation of the regimen originally prescribed (for as long as needed to complete the doses of the original regimen), or a complete renewal of the prescribed treatment. (See p. 66, Figure III-3.)

This decision should be based on an estimate of the load of viable tubercle bacilli remaining in the lungs when treatment is restarted. Continuous treatment is more crucial in the initial, intensive phase of the regimen (e.g., during the first 2 months) because the number of organisms is highest in the beginning of treatment. In the continuation phase (e.g., after 2 months) of TB treatment, there are fewer persisting organisms to kill. Therefore, the possibility is small that a large number of organisms are present after a short lapse in treatment in the continuation phase.

In patients who are HIV-positive or otherwise immunosuppressed, the mycobacterial load can rebound rapidly, even with a short lapse in treatment during the continuation phase. In such patients, consideration should be given to renew treatment, even if the lapse is as short as 1-2 months.

The decision regarding completion of treatment should be based both on the total number of medication doses administered, and on the duration of therapy. If more than 80% of the prescribed doses were taken before a lapse in treatment, the regimen may not need to be renewed. The duration of the regimen should be based on the extent of disease revealed by initial CXR, evaluation of nonpulmonary sites involved, and AFB culture studies at 2 months.

Renewal of Tuberculosis Treatment

The following factors suggest a large mycobacterial load in the patient, and may require that the patient completely renew the anti-TB regimen (i.e., the previous doses should be disregarded):

- In patients who have had a lapse of 14 days or longer within the intensive phase (i.e., first 2 months) of treatment, the regimen should be completely renewed.
- In patients with a lapse in treatment 3 months or longer, the treatment regimen should be completely renewed. If the patient is HIV positive, treatment renewal should be considered even if the lapse is less than 3 months.

Continuation of Lapsed Treatment

If a lapse in treatment occurs, and a decision is made to continue the regimen, the anti-TB regimen should last as long as needed to complete the doses of the treatment originally prescribed. The decision regarding completion of treatment should be based both on the total number of medication doses administered and on the duration of therapy. For example, a prescribed regimen of 6 months of daily multidrug treatment should include at least 182 doses; a prescribed regimen of 2 months of daily multidrug treatment (56 doses) with 4 months of 2 times per week doses (36 doses) should include at least 92 doses.

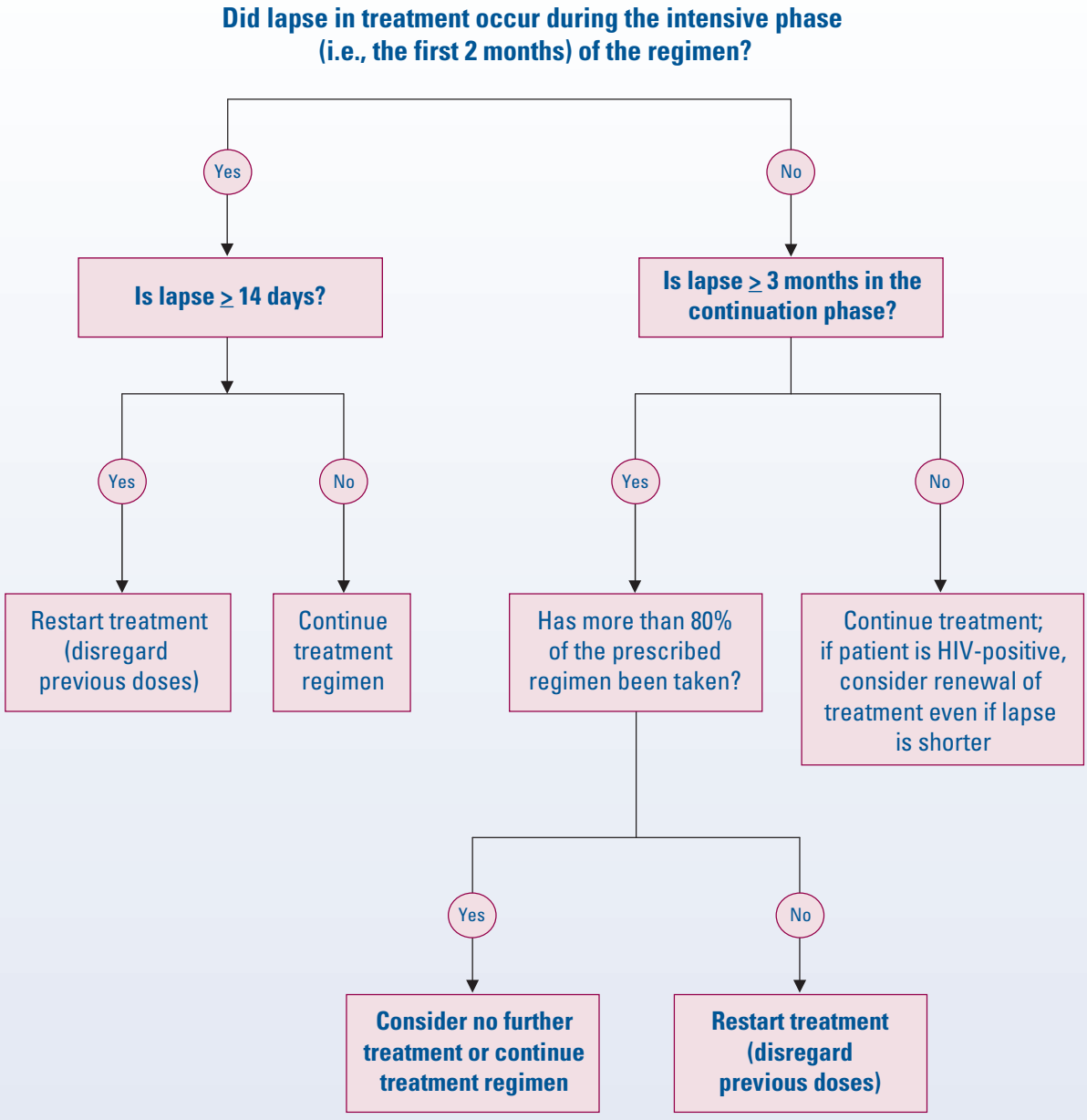
Protocols for Reinstituting Treatment

Clinical evaluation and CXR should be done. Sputum samples should also be examined for *M. tb* prior to reinstitution of treatment. If sputum is culture positive at the time of reinstitution, physicians should renew treatment (i.e., the previous doses should be disregarded), regardless of other factors. In addition, drug susceptibility testing should be repeated at this time, even if the pretreatment isolates were pansusceptible.

- If the patient is not currently receiving DOT, it should be instituted. Every attempt should be made to ensure that the patient completes a continuous course of TB treatment.
- If a patient fails to adhere to DOT, a Commissioner's Order for DOT (D3) should be requested.

Figure III-3

Reinstitution of Interrupted or Incomplete Anti-Tuberculosis Treatment*



* Re-evaluate the patient with appropriate clinical and laboratory tests. If sputum cultures are positive at the time of reinstitution of therapy, physicians should renew the treatment regimen (i.e., the previous doses should be disregarded), regardless of other factors.

Treatment Failure

Treatment failure is defined as a positive *M. tb* culture any time after 4 months of appropriate TB treatment in a patient with pansensitive TB. Treatment failure should be suspected in patients whose cultures are pending, and who have clinical deterioration or worsening of the CXR due to TB.

- If sputum smears or cultures are positive after 4 months of appropriate treatment, 3 new consecutive daily sputum samples should be sent for smear, culture and susceptibility testing. For extrapulmonary TB patients, renewed attempts should be made to obtain appropriate specimens for smear, culture and susceptibility testing.
- Never add a single drug to a failing regimen, as it promotes further drug resistance.
- The most recent positive *M. tb* culture, if 1 is available, should be tested for susceptibility.
- Patients who are clinically stable may be maintained on the current anti-TB regimen ("holding regimen"), until susceptibility results are available to guide the choice of medications.
- Patients who are clinically deteriorating should be given at least 2-3 new anti-TB medications, to which the strain is likely to be susceptible. When susceptibility results are available, the regimen should be modified accordingly.
- DOT should be instituted if the patient is not currently receiving it.
- If a patient fails to adhere to DOT, a Commissioner's Order for DOT (D3) should be requested.

Treatment of Coexistent Tuberculosis and Disseminated Mycobacterium Avium-Intracellulare

Severely immunosuppressed individuals can develop TB and disseminated *Mycobacterium avium-intracellulare* (MAI) infection concurrently, and must be treated for both conditions. Also, AIDS patients with TB are candidates for preventative therapy against disseminated MAI infection, when their CD4 counts fall below 50 cells/mm^3. Daily clarithromycin and once weekly azithromycin are currently the first-line agents for preventing MAI infection; however rifabutin can also be used. MAI prophylaxis can be discontinued in patients whose CD4 counts rise to above 100 cells/mm^3 on HAART and remain at that level for 6 months to a year. Drugs currently recommended to treat disseminated MAI are clarithromycin and ethambutol, with the possible addition of rifabutin in patients with high mycobacterial loads or in the absence of effective HAART. If rifabutin cannot be used due to drug interactions, fluoroquinolones or parenteral amikacin have been used, despite a lack of documentation of efficacy in clinical trials.

General recommendations are that the patient with disseminated MAI should receive at least 12 months of therapy for MAI, and should maintain 6 months of immune reconstitution (CD4 T cell count greater than 100 mm^3 on HAART). Then, MAI treatment can safely be discontinued, but patients should be followed for continued viral load suppression and maintenance of CD4 counts. Lifelong treatment is necessary for disseminated MAI in patients who are HIV infected and patients who are not on HAART, and who do not recover CD4 cell counts above 100 mm^3.

When treating concomitant MAI and TB, rifabutin should not be used at the same time as rifampin, due to the added potential for toxicity. Whenever possible, another agent, such as clarithromycin or azithromycin, should be used instead of rifabutin. If another agent is used, rifampin can be continued in the anti-TB regimen. If another agent cannot be used, and rifabutin is required for MAI treatment or prophylaxis, rifampin should be replaced by rifabutin in the anti-TB regimen.

In general, patients with coexistent MAI and TB can be treated at a BTBC chest center for both diseases, until TB treatment is complete. At such time, the patient should be referred to another provider to continue treatment for MAI.

Patients without HIV infection and TB who have MAI should not be treated at a BTBC chest center. If the patient has a positive test for TB infection and an abnormal CXR, sputum smears should be done to access the activity of the disease. In this case, the patient may receive treatment for TB as a suspect until negative cultures are confirmed. The patient should then finish treatment for LTBI or old TB, if indicated. The patient should be referred to an appropriate provider for the MAI treatment.

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