

Chapter VII: Practical Aspects of Active TB Treatment

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A. Directly Observed Therapy (DOT)

Poor adherence to TB medication regimens is a common problem and leads to inadequate treatment. The consequences of inadequate and incomplete TB treatment are serious:

- Prolonged illness and disability for the patient
- Prolonged infectiousness, with continued TB transmission in the community
- Increased risk of developing drug-resistant TB
- Death.

1. Maintaining a Consistent Definition of DOT and SAT

Directly observed therapy (DOT) is defined as a treatment in which a health care provider or other responsible person observes the patient ingesting each dose of anti-TB medication. The observer should generally be a health care provider, but in some situations, other designated people may be used with CDPHE approval. DOT may be administered to patients in the public health clinic, but can also be given by a clinic staff member or another designated community member at another location. For example, a home health care worker, school nurse, or other designated person can go to the patient's home, place of employment, school, or other mutually agreed-upon place. DOT is the standard method of providing treatment to all persons with active TB. Medication that is delivered to a patient without observing ingestion, is considered a dose of self-administered therapy (SAT) and should be designated as such. The self-administered treatment doses do not count towards completion of DOT, and will result in an extension of the length of treatment. If it is decided to use a combination of DOT and SAT for TB treatment, it would be most consistent with these definitions to indicate the number of weeks of treatment given by DOT and the number given by SAT.

2. Counting Weeks of DOT

The 2003 revised ATS/CDC TB treatment guidelines base the completion of treatment on the number of doses of DOT received rather than the passage of time (e.g., "6 months"). Doses missed due to non-adherence or other treatment interruptions are still given after treatment is resumed. The guidelines then list the number of doses required to reach "completion" for several typical regimens. The problem with applying these "required doses" is that the number of doses is correct only when the regimen is followed exactly as planned and does not account for changes in the number of weeks given by daily doses or a change from twice-weekly dosing to doses given three times or once weekly. One way to accurately account for changes in the planned regimen is to calculate "DOT-weeks" in which a week of DOT is defined as:

DOT schedule	No. of doses per week	DOT weeks per dose
Daily	5 to 7	0.2
Thrice-weekly (3 times)	3	0.33
Twice-weekly (2 times)	2	0.5
Once-weekly (1 time)	1	1.0

3. Additional Strategies for Treatment Success

DOT allows for the immediate detection of non-compliance, barriers to treatment acceptance, and adverse effects of treatment so that actions can be taken to avoid treatment failure. It is not the mode of administration but the recognition and timely application of interventions that are critical to the success of a DOT program. Most patients will adhere to treatment when education, incentives, housing, enhanced social services, addressing psychosocial concerns, and home or field DOT is provided.

Health care providers must recognize that even with DOT, additional strategies and efforts are necessary for treatment success. It is important to use any tool available in order to promote adherence to therapy.

- Learn as much as possible about your patient’s health history, beliefs, and attitudes about TB, sources of social support, and barriers to treatment.
- Work with an interpreter who is of the same cultural background as the patient.
- Look for early warning signs of future adherence problems (e.g., patient feels medicine is no longer needed because he or she is feeling well; difficulty in accessing health care).
- Designate a person to do DOT who does not have a strong emotional tie with the patient. Suitable designees might include a school, employee health or visiting nurse, or other health care provider. On occasion, another designated person may be recruited.
- Provide education to the patient and key individuals in the patient’s social environment.
- Provide the patient with needed health or social services referral.
- Mutually agree on a time and location for DOT (be creative and flexible).
- Be aware of patients who may require techniques to assess for ingestion of medication (e.g., hiding pills in mouth or “cheeking”, vomiting after pills swallowed, pocketing).
- Encourage a social support system that enhances adherence to treatment.
- Use incentives and enablers (bus tokens, grocery store or fast food coupons).

In summary, use all available strategies for maintaining adherence to DOT. If, despite your best efforts, the patient does not adhere to DOT voluntarily, Colorado state statutes allow a public health official to require court-ordered DOT or involuntary isolation for treatment of TB.

 For more information on court-ordered DOT and involuntary isolation, contact CDPHE for resources and see *Chapter XI: Infection Control*.

If possible, DOT should be clinic-based. DOT outside the clinic should be reserved for patients who:

- are unable to attend clinic for medical or social reasons (transportation/job/school conflicts), or
- have failed more than 3 attempts at clinic-based DOT but are willing to be part of a DOT program outside the clinic.

B. DOT in Other Institutions

1. Schools

Because DOT treatment is difficult to arrange for school-aged children it is very helpful if the school health nurse or other designated school personnel, can administer the child's medication at school. School personnel are required to document the DOT doses and make those records available to the local public health nurse and CDPHE. School personnel should alert the local public health nurse of any possible side effects or other problems with medications and of school holidays or other days when students will not attend school. The local public health nurse will maintain contact with the student over extended holidays such as winter break or summer vacation. School personnel should report adverse side-effects or missed doses to the local public health nurse within the same day or the next working day. And the local public health nurse should make arrangements to have the missed dose given at the clinic or home that same day or at school the next day.

 For more information on school-based DOT and Directly Observed Preventive Treatment (DOPT) contact CDPHE at 303-692-2638.

2. Long-Term Care Facilities

Once a patient is no longer considered infectious, he or she may return to a long-term care residential facility. Nursing staff in that facility may provide TB treatment by DOT. Typically, the TB clinic nurse will fax a copy of the medication orders to the residential facility and the staff there will order and dispense the medications. The public health nurse case manager should arrange with the nursing staff or infection control nurse at the facility to receive copies of the medication sheets on a weekly basis. The facility

nursing staff should be instructed to contact the public health nurse case manager with any questions, concerns, side effects, or missed doses within 1 to 2 days.

 For more information on determining infectiousness, see *Chapter XI: Infection Control*.

3. Dialysis Centers

In general, anti-TB drugs should be given after hemodialysis to avoid any loss of the drugs during hemodialysis, and to facilitate DOT. Patients who are receiving dialysis typically receive their medication at the dialysis center 3 times a week after their treatments. If this is the case, TB medication doses should be provided to the center on a weekly basis.

4. Correctional Facilities

Once a patient is no longer considered infectious, he or she may return to regular housing in a correctional facility. Nursing staff in that facility may provide TB treatment by DOT. The local public health nurse should arrange with the local jail clinic staff to receive copies of the medication sheets on a weekly basis. The clinic staff should be instructed to contact the TB clinic nurse case manager with any questions, concerns, or side effects within 1 to 2 days of the complaint. The CDPHE TB Nurse Consultant will act as the case manager for all active TB cases in the Department of Corrections.

C. Incentives and Enablers

Patient adherence to therapy can be influenced by offering incentives or enablers.

- **Incentives** are small rewards given to patients to encourage them to take their own medicines or to keep their DOT or clinic appointments. For example, patients may be given food, restaurant coupons, clothing, or other items as an incentive.
- **Enablers** are things that help the patient receive treatment, such as bus tokens to get to the clinic.

Incentives and enablers should be chosen according to the patient's needs, and they are frequently offered along with DOT. If incentives and enablers are needed, contact the CDPHE TB Program to determine if funds are available or if you may use your TB contract funds.

D. Drug Administration

1. Route, Timing, and Schedule

The first-line, anti-TB medications should be administered together as a single oral dose rather than in divided doses. A single dose leads to higher, and potentially more effective, peak serum concentrations and also encourages and supports the DOT methodology at the heart of TB treatment and control.

When medication dosing goes from daily to twice-weekly, and if patients complain of an increase in side effects or difficulty taking the large amount of pills, contact the CDPHE TB Program. In some cases, resumption of we daily dosing may be recommended.

Intravenous therapy is indicated for severely ill patients who cannot take oral therapy. Preparations of INH, RIF, the aminoglycosides (preferably amikacin but also streptomycin), capreomycin, and most fluoroquinolones are available for IV administration.

2. Absorption

Food. It is preferable to administer anti-TB drugs on an empty stomach if they are tolerated. Ingestion with food delays or moderately decreases the drugs' absorption. However, given the wide therapeutic margin of the first-line agents, the effects of food are of little clinical significance. Thus, if patients have epigastric distress or nausea with the first-line drugs, dosing with food is recommended. Administration with food is preferable to splitting a dose or changing to a second-line drug.

INH elixir. The commercial preparation of INH elixir uses sorbitol for flavor. Sorbitol can cause diarrhea, limiting the acceptability of the commercial INH elixir. This preparation is not available through the CDPHE TB Program's Apothecary. Alternatively, INH tablets can be crushed and administered with food. Absorption issues have not been formally evaluated but this method has been used successfully by many providers.

Antacids have minimal effects on the absorption of the first-line anti-TB drugs. With the exception of fluoroquinolones, there is little information regarding the effect of food and antacids on the second-line drugs.

However, antacids and other medications containing divalent cations markedly decrease the absorption of the fluoroquinolones, an interaction that has been associated with failure of antibiotic therapy. It is critical that any fluoroquinolone not be administered within 2 hours of a dose of antacids, the chewable tablet form of didanosine, sucralfate, iron, magnesium, calcium, zinc, or vitamin or dietary supplements (e.g., Ensure, Sustical) containing significant amounts of these cations.

3. Giving Medication to Patients Unable to Swallow Pills

If a young child or an adult cannot swallow pills or capsules; crush pills between two spoons or in a pill crusher, or empty the capsule into a small bowl and mix the crushed pills or capsule contents with a small amount of non-sugary liquid or food. INH is not stable in sugary liquids or foods so these substances are not recommended.

Medications should be crushed immediately before administration and mixed with the smallest amount of food or liquid possible.

Infants (less than 1 year of age): Measure liquid medications and give to the infant using a dropper or a syringe without a needle. Liquids can also be administered using just the nipple of a baby's bottle. Medication can also be mixed in less than 1 ounce of another liquid and administered in a baby's bottle. Make sure the entire content of the bottle is swallowed.

Avoid mixing complex proteins such as dairy products and peanut butter as they may interfere with absorption of medicine. Check with a pharmacist before using other liquids or foods.

Teaching older children or adults to swallow pills or capsules: Tablets tend to SINK, so tilt head UP to swallow. **Capsules** tend to FLOAT, so tilt head DOWN to swallow.

E. Fixed-Dose Combination Preparations

There are two fixed-dose combination preparations currently available for use in the United States to be used when DOT is not possible. These include a combination of:

- Rifamate - INH and RIF
- Rifater - INH, RIF, and PZA.

A 4-drug combination of INH, RIF, EMB, and PZA is available in some countries, but not in the United States.

Care should be taken when using fixed-dose combination preparations because of the similarity in trade names of the various medications.

- Rifampin (rifadin)
- Rifamate (INH & RIF)
- Rifater (INH, RIF, PZA)
- Rifapentine (long-acting rifampin)
- Rifabutin (substitute for rifampin when drug interactions are a problem)

These fixed-dose combinations have been formulated for use in daily therapy, although some programs use rifamate plus extra INH tablets for twice-weekly treatment.

1. Rifamate

Two tablets of Rifamate provide conventional daily doses of both INH (300 mg) and RIF (600 mg).

2. Rifater

The Rifater tablet that is available in the United States contains INH (50 mg), rifampin (120 mg), and PZA (300 mg). Six tablets of Rifater would provide INH (300 mg), rifampin (720 mg), and PZA (1800 mg). The rifampin dose is higher than is used typically in the United States because the rifampin is less bioavailable in this form. It should be noted that the dose of PZA in Rifater is such that additional PZA tablets will be required to provide an adequate dose for persons weighing more than 90 kg.

F. Management of Mild Side Effects

As is true with all medications, combination chemotherapy for tuberculosis is associated with a predictable incidence of adverse effects, some mild, some serious. Mild adverse effects can generally be managed with symptomatic therapy, whereas with more severe effects, the drug or drugs must be discontinued. Although it is important to be attuned to the potential for adverse effects, it is equally important that first-line drugs not be stopped without adequate justification. Please contact the CDPHE TB Program as soon as possible if the patient is experiencing any side effects.

 For more information, see the sections on “*Adverse effects*” listed under each medication in *Chapter IV: Anti-tuberculosis Drugs in Current Use*.

1. Gastrointestinal Upset

Gastrointestinal reactions, such as nausea, vomiting, poor appetite, and abdominal pain are common, particularly in the first few weeks of therapy. Many of the anti-TB drugs can cause gastrointestinal upset. In the presence of gastrointestinal symptoms, serum ALT and bilirubin should be measured and CDPHE notified. If the ALT level is less than 3 times the upper limit of normal, the symptoms are less likely to be due to hepatic toxicity but the levels should be monitored closely. However, if the ALT level is 3 or more times the upper limit of normal, the symptoms should be assumed to represent hepatic toxicity, and the patient should be evaluated as described below.

The initial approach to gastrointestinal intolerance, not associated with hepatic toxicity, is to change the hour of drug administration or administer the drugs with food. If patients are taking daily DOT, the timing of the drug administration should be altered, preferably to be closer to mealtime. Alternatively, food can be taken at the time of DOT administration. Patients taking self-administered therapy can take the medications at bedtime. If gastrointestinal intolerance persists, it may be best for all medications to be taken with meals.

If the patient is receiving a fluoroquinolone, antacids and other over-the-counter, acid-reducing medications may be used as long as they are taken 2 hours prior to or 2 hours after the TB medication dose.

Further medical evaluation and or prescription medications (e.g., anti-emetics) may be necessary.

2. Rash

Different anti-TB drugs can cause different types of rashes. The management depends on the severity.

a. Minor rash and itching

Minor rash and itching affecting a limited area such as the transient rash or flushing which may occur shortly after PZA or INH dosing may be managed symptomatically. Antihistamines (Benadryl) should be given for symptomatic relief, but all anti-TB medication can be continued. Checking an ALT should be done if other symptoms such as fever, malaise, or anorexia are also present, and should also be considered with more extensive rash as described below.

b. Petechial rash

Petechial rash may suggest thrombocytopenia in patients taking rifampin. The patient's platelet count should be checked and if it is low rifampin hypersensitivity should be presumed to be the cause and urgent medical consultation obtained. Rifampin should be stopped and the platelet count monitored until it returns to baseline. Once stopped, rifampin should not be restarted.

c. Generalized erythematous rash

If there is a generalized erythematous rash, especially if it is associated with fever and or mucous membrane involvement, all drugs should be stopped immediately and CDPHE contacted. Typically, if the patient has severe tuberculosis, 3 new drugs should be started. When the rash is substantially improved, the medications can be restarted one by one, at intervals of 2-3 days with close medical follow-up. Rifampin should be started first because it is the least likely to cause rash and it is the most important agent, followed by EMB, and then INH. If the rash recurs the last drug added should be stopped. If no rash appears after the first 3 drugs have been restarted, the PZA should not be restarted unless the rash was relatively mild and the fourth drug is considered essential for therapy.

3. Drug Fever

Recurrence of fever in a patient who has been receiving therapy for several weeks should suggest drug fever, especially if the patient is showing microbiological and chest x-ray improvement. It should be noted that fever from tuberculosis may persist for as long as

2 months after therapy is initiated. Fever may also be a manifestation of a paradoxical reaction, especially in patients with HIV infection. The clinical hallmark of drug fever is the patient looks and feels well despite having a high fever (often greater than 39° C /101° F). There is no specific pattern to the fever and eosinophilia may or may not be present.

The first step in management of a possible drug fever is to ensure there is no super-infection or worsening of tuberculosis. If these potential causes are excluded, all drugs may need to be stopped. Patients with severe tuberculosis may need to be given 2 to 3 new drugs while symptoms are being evaluated. Once the fever resolves, follow the same protocol for restarting drugs in the presence of a rash.

4. Hepatitis

Drug-induced hepatitis is the most serious common adverse effect of anti-TB medications. Three of the first-line anti-tuberculosis drugs, INH, rifampin, and PZA, can cause drug-induced liver injury.

- Mild toxicity - ALT is less than 5 times the upper limit of normal
- Moderate toxicity - ALT level 5-10 times normal
- Severe toxicity -ALT level greater than 10 times normal (i.e., greater than 500 IU)

In addition to ALT elevation, occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with rifampin hepatotoxicity.

An asymptomatic increase in ALT concentration occurs in nearly 20% of patients treated with the standard 4-drug regimen. In the absence of symptoms, therapy should not be altered because of mild asymptomatic elevations of ALT, but the frequency of clinical and laboratory monitoring should be increased. In most patients, asymptomatic elevations resolve spontaneously.

If ALT levels are more than 5 times the upper limit of normal (with or without symptoms) or more than 3 times normal with symptoms, hepatotoxic drugs should be stopped immediately and the patient evaluated carefully.

A significant increase in bilirubin or alkaline phosphatase is cause for a prompt evaluation. Serologic testing for hepatitis A, B, and C should be performed and the patient questioned carefully regarding symptoms that suggest biliary tract disease and exposures to other potential hepatotoxins, particularly alcohol and hepatotoxic medications. Drug-induced hepatitis is usually a diagnosis of exclusion, but in view of the frequency with which other possible causes are present in any given patient, determining the cause may be difficult.

Restarting anti-TB medications is slower for hepatitis than for rash or drug fever. If hepatotoxicity occurs early in treatment when the patient is ill or infectious, it is better to give 3 non-hepatotoxic drugs (EMB, SM/amikacin, or a fluoroquinolone) until the specific cause can be determined and an appropriate longer-term regimen begun. When hepatic dysfunction occurs later in the course, or the TB disease is mild and non-infectious, treatment can be stopped without using non-hepatotoxic drugs in the interim. The suspect anti-TB medications should be restarted one at a time after the ALT returns to less than 2 times the upper limit of normal. Because RIF is less likely to cause hepatotoxicity, it should be restarted first along with EMB, followed by INH 1 week later. PZA can be restarted 1 week after the INH if the liver injury was not severe. If symptoms recur or ALT increases, the last drug added should be stopped. If RIF and INH are tolerated, and hepatitis was severe, PZA should be assumed responsible and usually should be discontinued. In selected situations, the treating physician may recommend reintroducing PZA as well. Therapy may need to be 9 months depending on the number of doses of PZA that were taken and the severity of the disease. Close monitoring, with repeat measurements of serum ALT and bilirubin and symptom review, is essential.

References

- Centers for Disease Control and Prevention. Treatment of tuberculosis. *MMWR*.2003; 52 (No.RR-11).
- Colorado Department of Public Health and Environment, TB Program. *Tuberculosis Manual*. <http://www.cdphe.state.co.us/dc/TB/tbhome.html>.
- Colorado Revised Statutes, Title 25 Health, Article 4 Disease Control, Part 5 Tuberculosis.
- Colorado State Board of Health Rules and Regulations Pertaining to Epidemic and Communicable Disease Control Amended November 16, 2005, effective January 30, 2006 (Regulation 1 – Reportable Diseases)
<http://www.cdphe.state.co.us/op/regs/diseasecontrol/100901epidemiccommunicablediseasescontrol.pdf>
- Denver Metro Tuberculosis Clinic. Department of Public Health and Preventive Medicine. *Tuberculosis Clinic Protocol Manual*. 1991.
- Lancaster, E. *How to Get TB Medicine in the Child and Not on You!* [brochure]. San Diego County:1995.
- New York City Department of Health. *Clinical policies and protocols, New York City Bureau of Tuberculosis Control*. 3rd ed. June 1999.
<http://www.ci.nyc.ny.us/html/doh/html/tb/tb.shtml>.
- Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, Peloquin CA, Gordin FM, Nunes D, Strader DB, Bernardo J, Venkataramanan R, and Sterling TR. An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. *American Journal of Respiratory and Critical Care Medicine*. 2006 Oct 15; 174 (8):935-52.
- Virginia Department of Health. Tips on administering medication to children & adults unable to swallow pills. *AcidFast Blast*. January 2005;4(1).
<http://www.vdh.virginia.gov/epidemiology/DiseasePrevention/Programs/Tuberculosis/blast/January2005.htm>. Accessed October 22, 2007.