

Recommendations and procedures for the use of therapeutic drug monitoring in clients with drug-susceptible tuberculosis receiving directly-observed therapy

Background

Slow response to tuberculosis (TB) therapy may lead to prolonged infectiousness or acquired drug resistance, and further burdens public health systems by extending treatment duration. There are many reasons for slow response, but low serum drug levels may be a remediable cause in some clients [1-3]. Measurement of serum drug levels at the time of estimated peak concentration (C_{max}), termed therapeutic drug monitoring (TDM), has been performed in clients with slow response to TB treatment in Virginia since 2007 [3]. Low drug levels are often secondary to poor absorption and therefore TDM is not to be used as a marker of adherence. It is assumed that if a client is to undergo TDM for slow response that adherence is assured through directly-observed therapy and that drug-susceptibility testing is known.

Low drug levels are not causative of poor clinical response in all situations. Therefore, drug level monitoring should be viewed as just one element in the evaluation of those with poor clinical response. A high index of suspicion must be maintained for drug-resistant TB or other co-morbid conditions that may be contributing to delayed response to therapy. Table 1 provides indications for TDM and what medications to check to optimize the use of TDM.

In a recent University of Virginia (UVA)/Virginia Department of Health (VDH) study, diabetes was found to be significantly associated with slow response to TB treatment. A pilot project initiated in 2011 for early TDM (at 2 weeks of anti-TB therapy) in diabetics showed that 76% had a low level to isoniazid, rifampin or both. Furthermore, the majority of diabetics with pulmonary TB that had early TDM also had a favorable time to culture conversion of less <2 months, thus potentially reducing the length of the infectious period. Based on these findings, early TDM for diabetics undergoing treatment for TB has been incorporated into the overall recommendations for serum drug level testing.

Table 1. Indication and timing of therapeutic drug monitoring (TDM) in clients slow-to-respond

Reason for TDM	Drugs to check
1. In any client with known diabetes, either IDDM or NIDDM within 2 weeks of treatment initiation or soon thereafter.	Isoniazid, Rifampin
2. In any client with slow response at 4-6 weeks of treatment suggested by either or both of the following: <ul style="list-style-type: none"> a. For clients with smear positive pulmonary TB, sputum smear (+) not decreasing [adequate decrease is 4+ to 2+; 3+ to 1+; or 2+/1+ to smear negative] b. no improvement in TB symptoms (e.g. no weight gain, no reduction in cough, persistent fever, or worsening of chest x-ray if performed) 	Isoniazid, Rifampin All TB medications*
3. New clinical deterioration and unclear if related to TB (e.g. new evaluation for TB relapse or concern for drug resistance)	Selected second-line TB medication
4. Client receiving selected second line TB medications (e.g. drugs such as cycloserine where there is a narrow therapeutic range and potential for toxicity)^	Isoniazid, Rifampin Isoniazid, Rifampin
5. Consider for client with HIV infection and CD4<100^	
6. Consider shortly after treatment initiation for clients who have relapsed within 2 years of a prior episode of TB disease^	

*Pyrazinamide is very well absorbed. Low pyrazinamide levels may be marker of significant malabsorption or adherence issues (vomiting or tonguing pills after DOT). Both pyrazinamide and ethambutol should be increased only after discussion with a TB consultant. IDDM = insulin dependent diabetes mellitus; NIDDM = non-insulin dependent diabetes mellitus. Diabetic clients should be assessed for oral hypoglycemic or insulin use and this information is collected on TDM request form.

^Only after discussion with a TB consultant.

Methodology of drug level monitoring

Approval for serum level testing must be obtained and received prior to shipment of samples to the laboratory. Other potential causes such as drug resistance and compliance must be addressed before serum drug levels are obtained. Approval for testing can be obtained by calling 804-864-7906 and speaking with one of the nurse consultants. As outlined below, some approvals require the recommendation of one of the VDH TB clinical consultants. Approvals will be consistent with the recommendations outlined in this document. Clinicians may undertake additional testing, but will not be covered by the VDH serum drug level program.

The daily medication dose is administered to the client by directly-observed therapy. The exact time and date of administration is recorded. Notation is made for all medications and dosages, including the anti-tuberculosis medications, taken within the last 24 hours. The client should avoid antacids, milk products or vitamin supplements within 2 hours of taking medications, as would otherwise be advised for anti-tuberculosis medication administration.

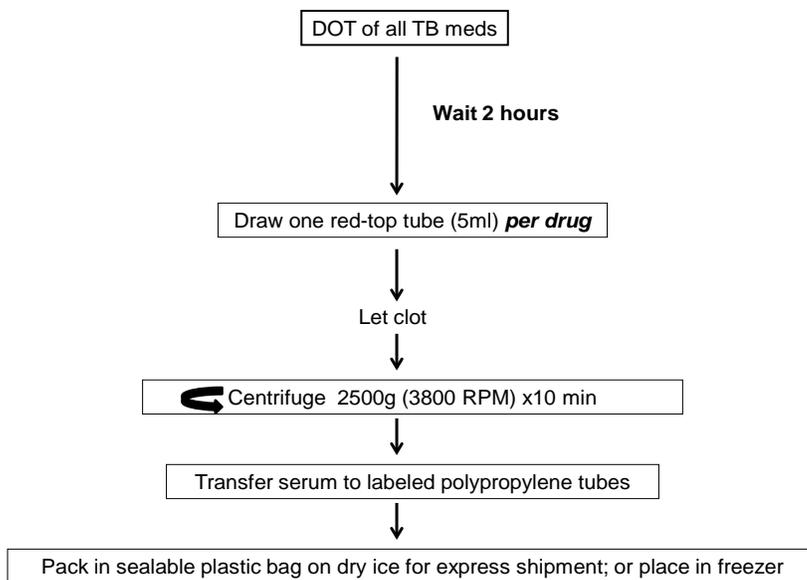
Blood draw for most medications (including those of the first-line regimen; Isoniazid, Rifampin, Ethambutol and Pyrazinamide) can be checked at two hours after administration. Because of practical resource constraints, **initially only a two hour level is currently recommended.** If the two hour level returns near the lower limit of the expected range, a six hour draw can be performed if the client is at

significant risk of delayed absorption (e.g., known diagnosis of gastroparesis). **A six hour level will only be approved following discussion and recommendation by one of the VDH TB clinical consultants.**

Five milliliters of blood (2 mls serum) are required *per drug tested*. The blood should be drawn in a red top tube and labeled with the client's name, date of collection and drugs(s) to be tested. Use one tube per drug to be assayed. After the blood clots, the sample will need to be centrifuged, and harvested into labeled polypropylene (or polyethylene) tubes. The tubes should be frozen at -70°C if available. If a local health department is unable to perform these steps, assistance should be sought from a community partner such as a local hospital or other laboratory. When prepared, the samples should be placed in a sealable plastic bag pack, upright in a Styrofoam box and packed with minimum of 5 lbs. of dry ice. Samples should be shipped by an overnight service that accepts dry ice packages [see Figure 1]. Samples are shipped to:

Infectious Disease Pharmacokinetics Laboratory
UF & Shands
1600 SW Archer Road, P4-30
Gainesville, FL 32610

Figure 1. Obtaining a sample for TDM



Dose adjustment and follow-up testing

Previous data from Virginia suggest that among slow responders, approximately 80% will have a low level of either Isoniazid or Rifampin [3]. Table 2 provides the standard dose adjustments for clients taking Isoniazid and Rifampin.

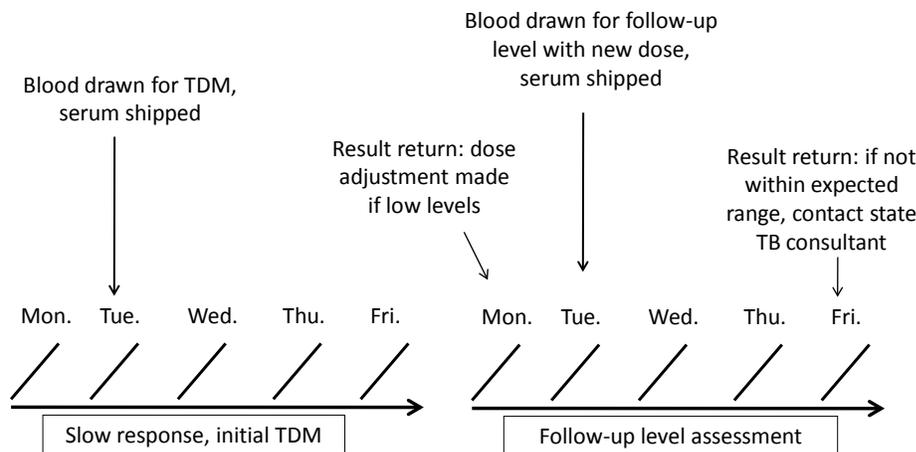
Table 2. Isoniazid and Rifampin expected peak concentrations and usual dose adjustment*

Medication (expected C _{max} range in µg/ml)	Client Serum Result	Dose adjustment
▪ Isoniazid / daily (3-6) / biweekly (9-18)	If client is on daily therapy and serum level is <2	Increase daily dose to 450 mg from 300 mg
	If client is on biweekly therapy and serum level is <7	Increase biweekly dose to 1200 mg from 900 mg
▪ Rifampin (8-24)	If serum level is <6 (for both daily and intermittent therapy)	Increase dose to 900 mg from 600 mg (both daily and intermittent therapy)

C_{max}= peak serum concentration. Referral laboratory will offer dose adjustment recommendations. Pyrazinamide and ethambutol are not routinely increased and should be done only after discussion with TB consultant. *Adapted from refs [4,5].

Follow-up levels can be checked 24 hours after a dose adjustment is made. The first follow-up level will be at the two hour mark. If this level is also low, discussion with a TB clinical consultant is recommended [see Figure 2]. Depending on the clinical scenario, further dose increases or holding at the current dose may be recommended. It is not always possible or necessary to achieve drug levels in the expected range. In rare circumstances a level may be higher than the expected range, and for medications such as Ethambutol which carry dose-related adverse drug reactions, a dose reduction may be necessary. The referral laboratory will make suggestions for dose adjustment, yet these recommendations must be considered in the context of the client’s clinical status and original indication for drug-level monitoring. State TB consultants are available for interpretation of drug levels and consultation is recommended for any second dose adjustment and in any client taking second-line medications.

Figure 2. Suggested timeline for TDM. Follow-up levels only performed if a dose adjustment is made for initial low levels.



Actual timeline may vary depending on receipt of initial results

Overall toxicities related to dose adjustment of a low level are rare. In the study of TDM from Virginia [3] where Rifampin, Isoniazid and Ethambutol doses were increased when below the expected range, no adverse drug reactions were reported. For the most common medication to be adjusted, Rifampin, increases in daily doses are very well tolerated. However, twice or thrice weekly doses that are increased can be associated with flu-like symptoms from anti-rifampicin antibody accumulation that is more likely to occur with the intermittent dosing schedule [6].

References

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