

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

1. 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 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.

When medication dosages are adjusted based on a low drug level, toxicities remain 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. Increases in daily dosing are well tolerated for rifampin, a common medication targeted for dose adjustment.

Table 1. Indication and timing of therapeutic drug monitoring (TDM)

Group	Reason for TDM	Drugs to check	Follow-up
All diabetics	Any client with known diabetes* as soon as feasible after treatment initiation (ideally at 2 weeks after treatment initiation and not more than 4 weeks after treatment start)	Isoniazid and Rifampin ONLY : 2 hours after DOT	Automatic dose adjustment for low level (See Table 2). No follow-up drug levels checked.
Slow responders	In any client with slow response 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 and Rifampin ONLY : 2 hours after DOT	Dose increases in consultation with DDP-TB staff. Follow-up drug levels checked. Goal is to achieve levels in the expected range although this is not always possible, especially with INH.
Others	Other scenarios in discussion with TB consultants (e.g., new clinical deterioration and unclear if related to TB, client receiving selected second-line TB medications, client with HIV infection and CD4<100, client with early relapse)	Case-by-case	Case-by-case

2. Diabetics

In the study of TDM from Virginia, diabetes was found to be significantly associated with slow response to TB treatment. A pilot project initiated in 2011 for routine early TDM (at 2 weeks of anti-TB therapy) in diabetics showed that 76% had a low level to isoniazid, rifampin or both. Dose adjustments were made, and the majority converted to culture negative in less than 2 months. Additionally, the overall number of slow responders in Virginia with requests for TDM decreased. Based on these favorable findings, routine early TDM for diabetics undergoing treatment for TB has been incorporated into the recommendations for serum drug level testing.

The goal for obtaining serum drug level testing in diabetics is to make early changes in treatment regimens to improve sputum conversion and diminish the rates of slow response.

- For diabetics, only a single 2 hour level for isoniazid and rifampin is recommended as soon as feasible after treatment initiation, ideally at **2 weeks** after treatment initiation and not more than 4 weeks after treatment start. Testing after 4 weeks following treatment initiation in the diabetic population should only be performed if there is evidence of slow response (see Table 1).
- If one or both levels are low, dosing should be adjusted according to the guidelines presented in Table 2. If the drug levels are very low, the referral laboratory may recommend more than an incremental increase (e.g. rifampin 600 mg per day to 1200 mg per day), in which case the client should be discussed with a TB clinical consultant prior to implementing more than a single incremental dose adjustment.
- **No follow-up drug level monitoring is recommended as study has shown that most will improve their levels with the single increase.** Also, as many diabetic clients will do well without TDM, this avoids multiple rounds of TDM and dose increases with unclear benefit. **This recommendation to not do follow-up TDM may differ from suggestions provided on the serum drug level lab report from the referral laboratory.**
- For those found to have low levels, a daily or thrice weekly regimen should be used in the continuation phase (see Table 2).
- Dose counting for determination of treatment duration should not be altered by the TDM result.
- Due to the potential to impact sputum conversion and reduce transmission potential, screen all new clients initiating TB treatment with hemoglobin A1C to detect unrecognized diabetes which may impact and prolong TB treatment. Clients without a known history of diabetes and hemoglobin A1C ≥ 6.5 should be considered diabetic and have TDM performed. Diabetic clients should be assessed for oral hypoglycemic or insulin use.

Table 2. Dose adjustment for diabetics with early routine TDM

	Normal drug levels	Sub-target INH, normal RIF	Normal INH, Sub-target RIF	Sub-target INH and Sub-target RIF
Initiation regimen*	Continue INH 300 mg M-F; RIF 600 mg M-F	Finish initiation with INH 450 mg M-F; RIF 600 mg M-F	Finish initiation with INH 300 mg M-F; RIF 900 mg M-F	Finish initiation with INH 450 mg M-F; RIF 900 mg M-F
Continuation regimen	Continue INH and RIF (biweekly acceptable)	INH 900 mg and RIF 600 mg, thrice weekly	INH 900 mg and RIF 900 mg, thrice weekly	INH 900 mg and RIF 900 mg, thrice weekly

*All initiation phase regimens assume concomitant pyrazinamide and ethambutol, and common adult target doses of isoniazid (INH) of 5 mg/kg and rifampin (RIF) of 10 mg/kg. M-F= Monday through Friday, 5 x weekly schedule. Sub-target concentrations are any below the expected C_{2hr} range.

3. Slow responders

For those in whom slow response to treatment is suspected and other causes such as drug resistance has been ruled out, two hour TDM should be collected for isoniazid and rifampin.

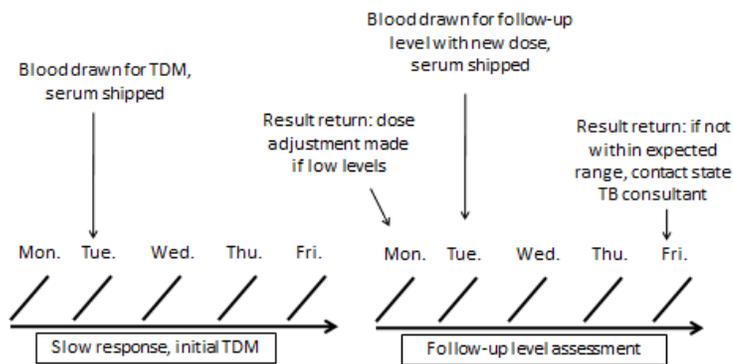
- Initially, only a single 2 hour level for isoniazid and rifampin is recommended.
- If one or both levels are low, dosing should be adjusted according to the guidelines presented in Table 3. If the drug levels are very low, the referral laboratory may recommend more than an incremental increase (e.g. rifampin 600 mg per day to 1200 mg per day), in which case the case should be discussed with a TB clinical consultant prior to implementing more than a single incremental dose adjustment.
- Follow-up drug level monitoring is recommended after dose adjustment for those tested for slow response.
- Follow-up levels can be checked 24 hours after a dose adjustment is made** (see Figure 1). The first follow-up level will be at the two hour mark. If this follow-up level remains low, discussion with a TB clinical consultant is recommended and a 6 hour level (for delayed absorption) 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.
- 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.

Table 3. Isoniazid and Rifampin expected peak concentrations and VDH Recommended Automatic Dose Adjustment

Medication (expected C_{max} range)	Dose adjustment when below expected peak
▪ Isoniazid - daily (3-6 $\mu\text{g/ml}$) biweekly (9-18 $\mu\text{g/ml}$)	Increase daily dose from 300 mg to 450 mg Increase biweekly dose from 900 mg to 1200 mg
▪ Rifampin - (8-24 $\mu\text{g/ml}$)	Increase dose from 600 mg to 900 mg (both daily and intermittent therapy)

C_{max} = peak serum concentration. For isoniazid and rifampin 2 hour levels, C_{2hr} , estimate the C_{max} [4,5].

Figure 1. Suggested timeline for TDM. Follow-up levels only performed in slow responders if a dose adjustment is made for initial low levels.



4. General methodology of drug level monitoring

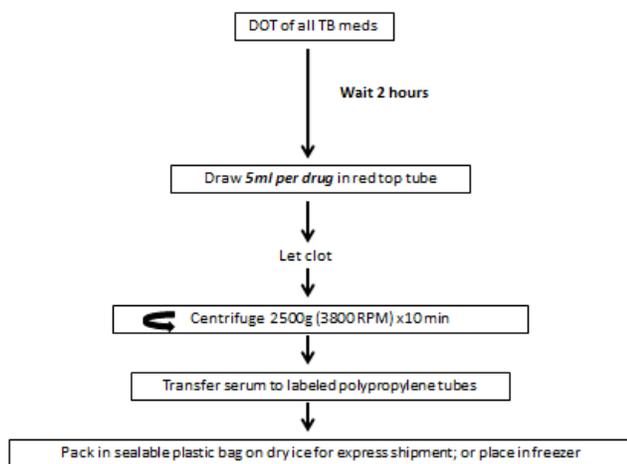
Approval for serum level testing must be obtained and received prior to shipment of samples to the laboratory. Other potential causes such as drug resistance and compliance must be addressed before serum drug levels are obtained. Approval for testing can be obtained by calling 804-864-7906 and speaking with one of the nurse consultants. As outlined above, 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 the cost 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.

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 2]. Samples are shipped to:

Infectious Disease Pharmacokinetics Laboratory
UFHealth
1600 SW Archer Road, P4-30
Gainesville, FL 32610

Figure 2. Obtaining a sample for TDM



References

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