

Virginia Department of Health Recommendations and Procedures for the use of Therapeutic Drug Monitoring (TDM)

Background

Slow response to TB treatment can be caused by several factors; non adherence, drug resistance, inadequately prescribed regimens, intolerance to TB medications and poor absorption often due to co-morbidities. Poor clinical response to TB therapy may lead to prolonged infectiousness or acquired drug resistance and further burden public health systems by extending treatment duration. Measurement of serum drug levels at the time of estimated peak concentration (C_{max}), termed therapeutic drug monitoring (TDM), has been performed for clients with poor clinical response to tuberculosis (TB) treatment in Virginia since 2007 [3] .

Procedure for requesting Therapeutic Drug Monitoring

- Obtaining approval for TDM must be received prior to scheduling, collecting and shipping of samples to the Infectious Disease Pharmacokinetics Laboratory (IDPL) in Gainesville, Florida. Other laboratories are not included in this program. If a decision to use an alternative lab is made, the cost of testing will be the responsibility of the district.
- Approval is obtained by calling 804-864-7906 and speaking with one of the nurse consultants. Some approvals require the recommendation of one of the TB clinical consultants.
 - Denise Dodge, RN – 804-864-7968
 - Debbie Staley, RN– 804-864-7972
 - Lisa McCoy, MD – 804-864-7920
- Approvals will be consistent with the recommendations outlined in this document. Consultation is recommended for any second dose adjustment and for any client taking second-line medications.
- If approved, the laboratory requisition slip will be faxed to the district with the medications approved and will include a specimen authorization number.
- Follow the directions on the requisition slip regarding the specific timing requirements of testing. Most blood draws will be 2 hours after the last full dose. **Specimens can only be shipped Monday through Thursday so that they arrive on a weekday.** Specimens are not accepted on weekends.

Procedures for Collecting Serum Drug Level

- The daily medication dose is administered to the client by directly-observed therapy. Assure that the dose is not given within 12 hours of the prior dose.
- Consistent with recommendations for treatment with anti-tuberculosis medications, clients should avoid antacids, milk products or vitamin supplements within 2 hours of taking medications.
- The exact time and date of administration is recorded on the lab authorization.
- Complete each column under each drug. The reliability of results is directly related to the accuracy of this information.
- Four drugs can be included on one slip as long as they are drawn at the same time.
- Two tests can be performed using one plain red top 10 ml tube if completely filled and both medications are **drawn at the same time**. (5 mls of blood [2 mls serum] are required *per drug tested*.) For example, if drawing isoniazid and rifampin at 2 hours one large red top tube filled to the top is sufficient.

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- In the space provided at the bottom left of the form please note medications and dosages, including the anti-tuberculosis medications taken within the last 24 hours
- Results are faxed **from IDPL** to the state TB office within 7 – 10 days of **specimen shipping**. **After review** by a nurse consultant **they are faxed to the district**. When more than one drug is tested it is common for results to arrive separately over the course of several days
- It is not always possible or necessary to achieve drug levels in the expected range, especially with INH.
- In rare circumstances a level may be higher than the expected range. For medications such as ethambutol, which carry dose-related adverse drug reactions, a dose reduction may be necessary.
- VDH TB nurse and medical consultants are available for interpretation of drug levels by calling the TB and Newcomer Health (TBNH) office.

Table 1: Groups considered for TDM

Group	Definition	Drugs to check	Follow-up
1 - Slow responder (failure to clinically improve as expected)	Clients with smear positive pulmonary TB for a prolonged period of time without improvement (defined as a steady decrease from 4+ to 2+; 3+ to 1+; 2+/1+ to smear negative)	Isoniazid and Rifampin ONLY:	Dose increases in consultation with DTBNH staff and medical consultants. Follow-up drug levels can be checked.
2 - All diabetics (HbA1c \geq 6.5)	Ideally test 2 weeks after treatment begins. If a recent HbA1c (<3mo) result is not available, perform HbA1c to avoid delaying TDM upon intake. After 8 weeks the window of opportunity is lost so we do not perform TDM (unless slow response or another reason is identified)	Isoniazid and Rifampin ONLY:	Automatic dose adjustment for low level (See Table 2). No follow-up drug levels checked.
3 - All HIV positive (regardless of CD4 count or viral load)	Ideally test within 1- 2 weeks after a stable regimen begins.	Isoniazid and Rifampin/Rifabutin ONLY:	Dose increase in consultation with DTBNH staff. Follow-up drug levels can be checked.
4 - Others	Other scenarios in discussion with TB consultants (e.g., new clinical deterioration, receiving second-line TB medications, sudden relapse, severe illness, other co-morbidities)	Case-by-case	Case-by-case

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SLOW RESPONDERS

- Explore the likelihood of non-adherence to treatment or drug/drug or food/drug interactions before considering TDM. Ensure directly observed therapy is being adhered to. When evidence of non-adherence is found explore solutions to non-adherence before performing TDM. TDM is not to be used as a marker for non-adherence.
- Suspicion of possible drug resistance should be raised when there is a history of prior inadequate treatment or if the country of origin reports high levels of drug resistant TB. (See High MDR-TB Burden Country list)
- When non-adherence and drug resistance is addressed and response remains slow, perform TDM. Low drug levels are often not the sole cause but are viewed as one element in the evaluation of poor clinical response.

Procedure

- Draw a 2-hour level for isoniazid and rifampin only. Additional medications must be approved by a medical consultant.

Intervention

- Dosing is adjusted according to the guidelines presented in *Table 2*.
- **IMPORTANT: Do not follow the suggested dose adjustment recommended on the SDL report from IDPL.** They may recommend more than the incremental increase recommended in *Table 2*. Prior to implementing more than a single incremental dose adjustment, the case should be discussed with a TB clinical consultant.
- **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** (*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 2 and 6 hour level (for delayed absorption) may be recommended.

DIABETIC PATIENTS

The goal for obtaining serum drug level testing in diabetics is to make early changes in treatment regimens to reduce the time from start of treatment to sputum conversion and diminish the rates of slow response. Based on the favorable findings of the Virginia study, routine early TDM for diabetics undergoing treatment for TB has been incorporated into Virginia's case management recommendations.

Procedure

- All confirmed and presumptive TB cases should have a Hemoglobin A1C drawn at the start of treatment unless there is a documented result within the past 3 months. Clients with a hemoglobin A1C ≥ 6.5 should be considered diabetic and have TDM performed.
- **IMPORTANT:** Do not discontinue PZA and EMB before SDL testing is performed.
- For diabetic patients, a single 2 hour level for isoniazid and rifampin is recommended as soon as feasible after treatment initiation, **ideally at 2 weeks** after treatment start. (*Table 1*)

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Intervention

- If one or both levels are low, dosing should be adjusted according to the guidelines presented in *Table 3*.
- **IMPORTANT: Do not follow the suggested dose adjustment provided on the SDL report from IDPL.** They may recommend more than the incremental increase recommended in *Table 3*. Prior to implementing more than a single incremental dose adjustment the case should be discussed with a TB clinical consultant.
- **No follow-up drug level monitoring is recommended.** The VA study has shown that most clients will improve their levels with a single incremental increase.
- For those found to have low levels, a daily or thrice weekly regimen should be used in the continuation phase (*Table 3*). Do not use biweekly treatment unless recommended by a TB clinical consultant.
- Dose counting for determination of treatment duration is not generally altered by the TDM result. Decisions to restart a dose count will be individually made based on the unique characteristics of the index case with the assistance of the medical consultants.

HIV/AIDS PATIENTS

An association exists between HIV infected TB clients and slow response to TB treatment. The goal for obtaining serum drug level testing in HIV infected clients is to make early changes in treatment regimens that may reduce the time from start of treatment to sputum conversion, diminish the rates of slow response, prevent acquired drug resistance, and improve treatment outcomes.

Treatment regimens for this population often require substituting rifabutin for rifampin due to the many drug-drug related interactions between rifamycins and commonly used antiretrovirals. Scheduling TDM must consider the anticipated adjustments in treatment. Testing absorption of rifampin is not a surrogate for rifabutin and requires a different schedule for testing. If the rifamycin is changed during treatment it may be necessary to repeat SDL testing.

Procedure

- **IMPORTANT:** Do not discontinue PZA and EMB before SDL testing is performed
- A single 2 hour level for isoniazid and rifampin (or a 3 hour level for rifabutin) is recommended **1 - 2 weeks, after a stable regimen** is initiated or as soon as feasible. (*Table 1*).

Intervention

- If one or both levels are low, dosing should be adjusted according to the guidelines presented in *Table 3*.
- **IMPORTANT: Do not follow the suggested dose adjustment provided on the SDL report from IDPL.** They may recommend more than the VDH incremental increase recommended. Prior to implementing more than a single incremental dose adjustment the case should be discussed with a TB medical consultant.
- Thrice weekly regimens may be acceptable with approval from a TB medical consultant. Do not use biweekly regimens in this population.
- Dose counting for determination of treatment duration could be, but may not be, altered by the TDM result. Decisions to restart a dose count will be individually made based on the unique characteristics of the index case with the assistance of the medical consultants.

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OTHERS

	Medications tested	Frequency	Definition
Drug Resistance	Any TB drugs requested	Within 1-2 wks of start of treatment	Any resistance: mono, poly or MDR
Reactivation	Any TB drugs requested	When indicated	Radiographic evidence of old TB, possibly previously treated, that is now active
Treatment Failure	INH/RIF	When indicated	A patient who is sputum smear or sputum culture positive at 5 months or later after the initiation of anti TB treatment.
Severe Gastrointestinal comorbidities	INH/RIF	Within 1-2 wks of start of treatment	Eg. Short gut syndrome, severe Crohn's disease, known malabsorption
Relapse	Any TB drugs requested	Within 1-2 wks of start of treatment	A patient who became culture negative while treated but after completion becomes culture positive again or has clinical or radiographic deterioration that is consistent with active TB
Treatment default	INH/RIF	When indicated	A patient who does not complete a full course of recommended treatment for any reason.
Renal Disease	EMB/PZA	Only when indicated	Reduced renal function could lead to sub-therapeutic or toxic drug concentrations
Drug-Drug interactions	Any TB drugs requested	As advised by consultant	Many drug-drug interactions exist between Rifamycins and antiretrovirals.

Procedure

- Initially, a single SDL for each medication ordered is recommended within one week of the request. Be sure to note the different draw times required for each drug. Lab requisitions will be created to ensure each specimen collection times has separate authorization numbers.

Intervention

- Each circumstance will warrant different recommendations. Medical consultants are available to assist in developing an adequate treatment plan.
- Dose counting to determine treatment completion could be altered by dosage changes as a result of TDM. Decisions to restart a dose count will be individually made based on the unique characteristics of the index case with the assistance of the medical consultants.

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Table 2. Expected peak concentrations for Isoniazid and Rifampin with VDH recommended automatic dose adjustment

Medication (expected C _{max} range)	Dose adjustment when below expected peak
Isoniazid: daily (3-6 µg/ml)	Increase daily dose from 300 mg to 450 mg
Rifampin: (8-24 µg/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]

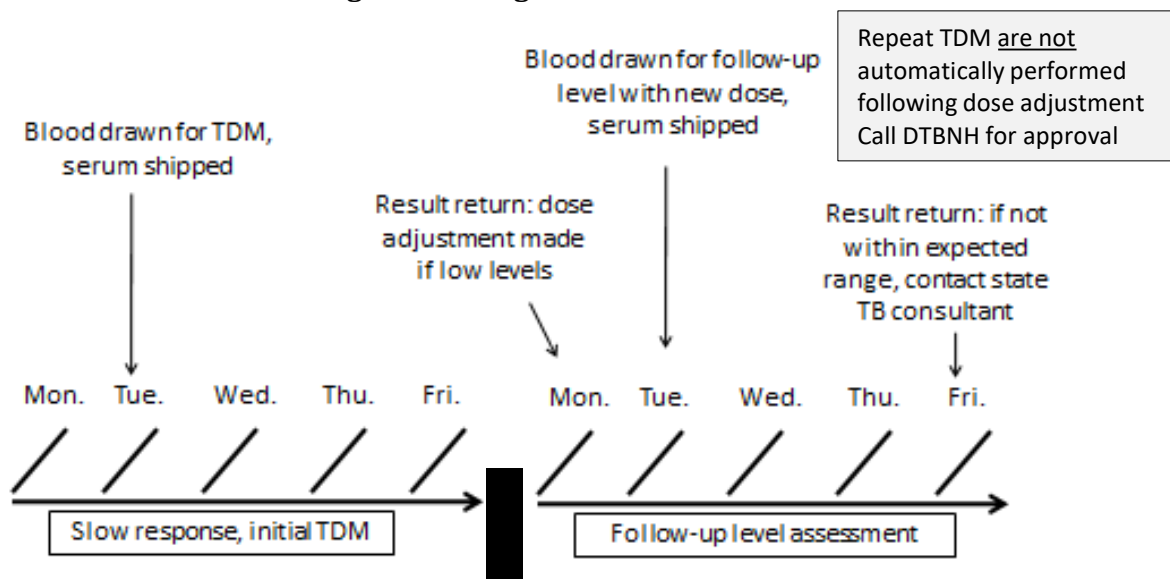
Table 3. Dose adjustment for diabetics and HIV/AIDS infected populations

	Normal drug levels	Sub-target INH Normal RIF	Normal INH Sub-target RIF	Sub-target INH and Sub-target RIF
Initiation Phase regimen*	Continue INH 300 mg and RIF 600 mg M-F	Increase INH 450 mg Continue RIF 600 mg M-F	Continue INH 300 mg Increase RIF 900 mg M-F	Increase INH 450 mg and RIF 900 mg M-F
Continuation Phase regimen	Continue INH and RIF M-F or thrice weekly	INH 900 mg RIF 600 mg M-F or thrice weekly	INH 900 mg RIF 900 mg M-F or thrice weekly	INH 900 mg and RIF 900 mg, M-F or 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.

Figure 1.

Suggested timeline for redrawing Serum Drug Levels



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References

1. Alffenaar JWC, Tiberi S, Verbeeck RK, Heysell SK, Grobusch MP. Therapeutic drug monitoring tuberculosis: practical application for physicians. *Clin Infect Dis* 2016, online ahead of print doi:10.1093/cid/ciw677
2. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. An update. *Drugs* 2014; 74:839-854
3. Heysell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring among slow responders to tuberculosis therapy in a state control program. *Emerg Infect Dis* 2010; 16:1546-53.
4. Nijland HMJ, Ruslami R, Stalenhoef JE, Nelwan EJ, et al. Exposure to rifampin is strongly reduced in patients with tuberculosis and type 2 diabetes. *Clin Infect Dis* 2006; 43:848–54.