Virginia Department of Health
Recommendations and procedures for the use of therapeutic drug monitoring (TDM)

Background

Slow response to tuberculosis (TB) treatment may be due to several different factors: non-adherence, drug resistance, inadequately prescribed regimens, intolerance to TB medications, and poor absorption often due to comorbidities (1-2). Poor clinical response to TB therapy may lead to prolonged infectiousness or acquired drug resistance and further burden communities and their public health systems due to extended treatment duration. Measurement of serum drug levels (SDL) at the time of estimated peak concentration (C_{max}), termed therapeutic drug monitoring (TDM), has been performed for clients with poor clinical response to TB treatment in Virginia since 2007 (3-4).

Procedure for requesting TDM

- Obtain approval from the central office TB program for TDM prior to scheduling, collecting and shipping of samples to the Infectious Disease Pharmacokinetics Laboratory (IDPL) in Gainesville, Florida. Other laboratories are not eligible for TB program payment. If an alternative laboratory is used, the cost of testing will be the responsibility of the district.
- Obtain approval by calling 804-864-7906 to speak with one of the nurse consultants or by completing the online request form for serum drug level monitoring. Some approvals may require review by a TB program medical consultant.
- 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.*
- When approved, the laboratory requisition slip, including a specimen authorization number, will be sent by encrypted email to the person requesting approval.
- Follow the directions on the requisition slip regarding the specific timing requirements for each drug tested. Most are drawn two hours after the last full dose of medication was taken by directly observed therapy (DOT). IDPL accepts specimens on weekdays only. **All specimens must be shipped overnight Monday through Thursday ONLY to assure arrival on a weekday.**

Procedure for collecting SDL specimens

- The daily medication dose must be directly observed.
- Assure timing between the prior dose and the testing dose is no less than 12 hours.
- Clients should avoid antacids, milk products or vitamin supplements within two hours of taking medications.
- Record the exact time and date of administration on the requisition slip.
- Complete each column under each drug. Accurate results are directly related to this information.
- Four medications can be recorded on one requisition slip if blood is drawn at the same time.
- One filled plain red top 10 ml tube is enough to test two separate drugs when drawn at the same time.
- Please note medications and dosages, including the anti-tuberculosis medications taken within the last 24 hours, in the space provided at the bottom left of the requisition slip. If there are too many medications to list in the space provided, attach a medication list to the requisition slip.
- Results from IDPL are returned to the central office TB program within 7-10 days of specimen shipping and are sent to the district by encrypted email or fax. If multiple drugs are tested, it is common for results to arrive over the course of several different days.
- It is not always possible or necessary to achieve drug levels in the expected range especially with isoniazid.
- In rare circumstances, a level may be higher than expected and a dose reduction may be needed.
- VDH TB consultants are available for interpretation at 804-864-7906.

The dosage recommendations offered in the IDPL report may differ from Virginia recommendations. Prior to using a dose adjustment greater than VDH recommendations consult with a TB consultant at 804-864-7906.

Table 1: Groups for routine TDM

Group	Definition	Drugs to check	Follow-up
1 - Slow response (failure to clinically improve as expected)	Clients with smear positive pulmonary disease and minimal to no clinical improvement by one month of treatment	ONLY isoniazid and rifampin	Dose increases in consultation with TB consultants. **Follow-up drug levels may be checked.**
2 - Diabetes [diagnosis of Type 1 or Type 2 diabetes, and/or a hemoglobin A1c (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 and TDM should not be performed (unless slow response or another reason is identified)	ONLY isoniazid and rifampin	Automatic dose adjustment for low level (See Table 2). **No follow-up drug levels checked.**
3 - HIV positive (regardless of CD4 count or viral load)	Ideally test within **1- 2 weeks** after a stable regimen begins.	ONLY isoniazid and rifampin/ rifabutin	Dose increases in consultation with TB consultants. **Follow-up drug levels may be checked.**

Slow Response

Explore the possibility of non-adherence to treatment, drug/drug or food/drug interactions before considering TDM. Ensure adherence by using DOT. With DOT or video enhanced therapy (VET), evaluate opportunities for 'cheeking', spitting out, dropping, post administration emesis or other methods used to avoid taking medication. When evidence of non-adherence is identified, implement interventions. *TDM is not used as a marker for non-adherence.*

Suspicion of drug resistance: A prior history of TB disease treatment, inadequate TB treatment, and a country of origin with high rates of drug resistant TB should prompt consideration of the possibility of drug resistance. This should be addressed before performing TDM. For reference, use the High Burden Rifampin Resistant/Multi-Drug Resistant TB Country List. When risk of non-adherence and drug resistance is not presumed or identified, perform TDM. Low drug levels are often not the sole cause but are one element in the evaluation of poor clinical response.

Procedure

- Draw a two hour level for isoniazid (INH) and rifampin (RIF) only.
- If testing of additional drugs is desired, discuss with a TB consultant.

Intervention

- Suggested dose adjustments on the IDPL report, for clients who are not responding to standard treatment, should be discussed with a TB consultant or the Global TB Institute.
- Follow-up TDM **may be recommended** for these clients and can be performed as early as 24 hours after a dose adjustment. One week post dose adjustment testing *may* assure a more accurate result. Seek TB consultation to discuss timing of repeat testing.
- If TDM results remain low after repeat testing, consultation to discuss multiple hour testing (for delayed absorption) is required.
- Daily treatment should continue for these clients (2).
- Intermittent therapy approved by the medical provider must be thrice weekly, not twice weekly.

Diabetes

Diabetes increases the risk of treatment failure, relapse, and death among patients with TB. Clients with TB and diabetes tend to have more serious illness, severe symptoms with atypical presentations, prolonged sputum conversion, and reduced plasma concentrations of TB medications, particularly rifamycins (5-6). The goal for TDM in these clients is to make early changes in treatment regimens to reduce the time to sputum conversion and diminish the rate of slow response. Based on favorable findings of a Virginia study, routine early TDM for clients with diabetes has been incorporated into Virginia's case management recommendations leading to a shorter time to sputum culture conversion to negative (7).

Pediatric Clients: Optimal methods for screening and/or diagnosing diabetes in pre-pubescent children may include HbA1c testing although this test is not fully validated in children. Collecting HbA1c specimens at the beginning of treatment for confirmed or presumptive pediatric TB cases shall be limited to children $\geq$ 10 years of age and/or those who have a body mass index (BMI) $\geq$ 85%. A child with a documented HbA1c result within the prior three months does not require a repeat test. HbA1c results $\geq$ 6.5 indicate a need for TDM which should be collected 2-4 weeks after treatment start date (Expert guidance - VDH Pediatric TB Medical Consultant, Dr. Tania Thomas, Associate Professor, Infectious diseases, University of Virginia, 2019).

Calculating the BMI requires the sex, age, weight and height of the child. To calculate BMI use the CDC Pediatric BMI calculator, KidsHealth BMI Calculator or other standardized BMI calculation tool. If manual calculation is preferred, use the formula below. Results of calculations are plotted on a corresponding BMI boy or girl percentile growth chart.

$$\frac{\text{Weight (lbs)}}{\text{Height (in)}^2} \quad X\ 703 = \text{BMI}$$

Procedure

- All confirmed and presumptive TB cases with a diagnosis of Type 1 or Type 2 Diabetes should have TDM performed regardless of HbA1c result.
- All confirmed and presumptive TB cases should have the HbA1c test drawn at the start of treatment unless there is a documented result within the past 3 months. Clients with a result of HbA1c ≥ 6.5 should have TDM performed.

- IMPORTANT: Pyrazinamide (PZA) and ethambutol (EMB) continued until after TDM results are available and evaluated by the treating clinician and/or TB medical consultant.
- A single two hour level for isoniazid and rifampin is recommended as soon as feasible after treatment initiation, ideally at two weeks after treatment starts (Table 1).

Intervention

- Recommendations for incremental dosage increases (Table 2) are based on the prior Virginia studies.
- **Follow-up drug level monitoring is not recommended**. Previous work in Virginia demonstrated that most clients will improve their levels with a single incremental increase (3).
- A daily or thrice weekly regimen is used in the continuation phase (Table 2). **Do not use biweekly treatment unless recommended by a TB consultant.**
- Dose counting to determine treatment duration is not typically altered by TDM results. Decisions to restart a dose count are individually made based on the unique characteristics of the case and with the assistance of the TB consultants.

Human Immunodeficiency Virus (HIV)

An association exists between HIV disease, slow response to TB treatment, and increased risk for poorer outcomes from inadequate treatment. Drug/drug interactions between TB and HIV treatment are common. Recommendations for case management in Virginia include early TDM of TB medications once a TB regimen has been established (1).

The goal of TDM is to make early changes in treatment regimens that could reduce the time to sputum culture conversion, diminish the rate of slow response, prevent acquired drug resistance, and ultimately improve treatment outcomes.

Procedure

- Perform TDM after adjustments of medications have been finalized in the treatment plan. Rifabutin will often replace rifampin in the treatment regimen due to drug/drug interactions between antiretrovirals and rifamycins, particularly rifampin.
- Rifampin and rifabutin are NOT surrogates for each other and require a different collection schedule. If rifampin TDM was performed it does not take the place of rifabutin TDM.
- A single two hour level for isoniazid and rifampin (or three hour level for rifabutin) should be performed one to two weeks after a stable regimen is established.

Intervention

- Prior to a dose adjustment greater than VDH recommendations, discuss with a TB consultant.
- Daily or thrice weekly regimens are acceptable. **Do not use biweekly regimens in this population unless discussed with a TB consultant.**
- Dose counting to determine treatment duration is not typically altered by TDM results. A decision to restart a dose count is based on the unique characteristics of the client with the assistance of TB consultants.

Table 2: Dose adjustment for clients with diabetes and/or HIV

	Medication Administration	**Normal drug levels**	**Sub-target INH Normal RIF**	**Normal INH Sub-target RIF**	**Sub-target INH Sub-target RIF**
Initiation phase regimen*	5x/week, M-F (may or may not self-administer on weekends)	Continue INH 300mg Continue RIF 600mg	Increase INH to 450mg Continue RIF 600mg	Continue INH 300mg Increase RIF to 900mg	Increase INH to 450mg Increase RIF to 900mg
Continuation phase regimen	5x/week, M-F (may or may not self-administer on weekends)	Continue INH 300mg Continue RIF 600mg	Increase INH to 450mg Continue RIF 600mg	Continue INH 300mg Increase RIF to 900mg	Increase INH to 450mg Increase RIF to 900mg
	3x/week	INH 900mg RIF 600mg	INH 900mg RIF 600mg	INH 900mg RIF 900mg	INH 900mg RIF 900mg

*All initiation phase regimens assume concomitant pyrazinamide and ethambutol, and common adult target doses of isoniazid of 5 mg/kg and rifampin of 10 mg/kg. M-F= Monday through Friday. Sub-target concentrations are any below the expected C2hr range.

Others

Table 3: Other circumstances under which TDM may be recommended

Category	**Medications Tested**	**Frequency**	**Definition**
Drug Resistance	Any TB drugs requested	Within 1-2 weeks of start of treatment with second line drugs	Any resistance: mono, poly or multi drug resistance *(Schedule for performing TDM of second line drugs is complex, TB consultants will assist)*
Reactivation	Any TB drugs requested	At time of concern	Radiographic evidence of old TB, with a history of previous TB treatment, that is now active.
Treatment Failure	INH/RIF	When indicated	Sputum *culture* positive after 5 months of TB treatment or sputum smear remains high with no evidence of non-tuberculous mycobacteria. *PZA/EMB should not have been discontinued.*
Severe Gastrointestinal Comorbidities (8)	INH/RIF	Within 1-2 weeks of start of treatment	E.g., Short gut syndrome, severe Crohn's disease, gastroparesis, celiac disease, cystic fibrosis, other known malabsorption morbidities
Relapse	Any TB drugs requested	Within 1-2 weeks of restarting treatment	Become culture positive or has clinical or radiographic deterioration that is consistent with active TB after successfully completing a full course of treatment and considered cured.
Treatment Default	INH/RIF	When indicated	A client who does not complete a full course of recommended treatment for any reason.

Renal Disease (8) (creatinine clearance <30mL/min or, dialysis clients)	PZA/EMB most common, any TB drug requested	When indicated	EMB/PZA is administered 3X weekly after dialysis. Dialysis does not effect INH/RIF. For additional information see: Treatment of Drug-Susceptible Tuberculosis Table 12
Drug/Drug Interactions	Any TB drugs requested	As advised by consultant	Many drug/drug interactions exist between rifamycins and other medications. Drug interaction checks are a TB nurse case manager responsibility.
Alcohol use	INH/RIF/ fluoroquinolones	When indicated	Ongoing alcohol use may alter medications metabolized through the liver or lead to malabsorption

TDM is only one part of the care of patients with TB. However, it is often a valuable tool for determining the best treatment strategy for complex clients. Table 3 provides a list of some characteristics that may warrant TDM but is not exhaustive (8). If there is an indication that TDM would benefit the TB client, discuss with the TB consultants or GTBI.

Procedure

- Other TB medications should continue, unless medically contraindicated, until after TDM confirms adequate peak concentration.
- Initially, a two-hour TDM test for each medication ordered will be performed within one week of the request. Be sure to note the different draw times required for each drug and use a separate requisition slip for different draw times.
- A single authorization number will be assigned for all medications drawn on a given date.
- Each requisition slip can include four separate medications as long as the specimens are collected at the same time and on the same day.

Intervention

- Each unique case will warrant a different recommendation. TB consultants are available to assist in developing an appropriate 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 are dependent upon the unique characteristics of the case and with the assistance of TB consultants.

Table 4: VDH recommended automatic dose adjustments (4)

Medication (expected Cmax range- mcg/ml)	Dose adjustment when below expected peaks
Isoniazid daily (3-5)	Increase daily dose from 300mg to 450mg
Rifampin daily (8-24)	Increase dose from 600mg to 900mg
Pyrazinamide (20-60)	Adjust according to medical consultant recommendation
Ethambutol (2-6)	Adjust according to medical consultant recommendation
Levofloxacin (8-12)	Second line medications will be used when drug resistance is identified or when a TB regimen is failing. Seek medical consultation for appropriate dose adjustments
Cycloserine (20-35)	
Linezolid (12-26)	
P-Amin-Salicylic Acid-PAS (20-60)	

CMax= peak serum concentration. For isoniazid and rifampin 2 hour levels, C2hr, [4, 5]

References

1. Alffenaar JWC, Tiberi S, Verbeeck RK, Heysell SK, Grobusch MP. Therapeutic drug monitoring tuberculosis: practical application for physicians. *Clin Infect Dis.* 2016;64:104-105.

2. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs.* 2014;74(8):839-854. doi:10.1007/s40265-014-0222-8.

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;16:1546-1553.

4. Heysell SK, Moore JL, Staley D, Dodge D, Houpt ER. Early therapeutic drug monitoring for isoniazid and rifampin among diabetics with newly diagnosed tuberculosis in VA, USA. *Tuberc Res Treat.* 2013;2013:129723. doi:10.1155/2013/129723.

5. Yorke E, Atiase Y, Akpalu J, Sarfo-Kantanka O, Boima V, Dey I. The bidirectional relationship between tuberculosis and diabetes. *Tuberc Res Treat.* 2017;2017:1702578. doi:10.1155/2017/1702578.

6. 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;43:848-854.

7. Alkabab Y, Keller S, Dodge D, Houpt E, Staley D, Heysell S. Early interventions for diabetes related tuberculosis associate with hastened sputum microbiological clearance in Virginia, USA. BMC Infect Dis. 2017 Feb 6;17(1):125

8. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis.* 2016;63(7):e147–e195. doi:10.1093/cid/ciw376.