

# Therapeutic drug monitoring in the treatment of tuberculosis

Virginia Department of Health TB Program

## Why is this important?

Poor clinical responses can lead to:

- Prolonged infectiousness
- Acquired drug resistance
- Further burden communities and public health systems due to extended treatment duration



Guidance document can be found [here](#).

# Standard of Care

**Table 1: Groups for routine TDM**

<b>Group</b>	<b>Definition</b>	<b>Drugs to check</b>	<b>Follow-up</b>
<b>1 - Slow response</b> (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.  <b>Follow-up drug levels may be checked.</b>
<b>2 - Diabetes</b> [diagnosis of Type 1 or Type 2 diabetes, and/or a hemoglobin A1c (HbA1c) $\geq$ 6.5]	Ideally, test <b>2 weeks</b> 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).  <b>No follow-up drug levels checked.</b>
<b>3 - HIV positive</b> (regardless of CD4 count or viral load)	Ideally test within <b>1- 2 weeks</b> after a stable regimen begins.	ONLY isoniazid and rifampin/ rifabutin	Dose increases in consultation with TB consultants.  <b>Follow-up drug levels may be checked.</b>

## Slow Response

- Before testing explore the possibilities of:
  - Non-adherence
  - Drug/drug or food/drug interactions
  - Suspicion of drug resistance
- ONLY checking isoniazid and rifampin
- 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 drug levels may be checked

# Diabetes

- Draw a 2 hour level for Isoniazid and rifampin **ONLY**
  - If testing of additional drugs is desired, discuss with a TB Consultant
- Automatic dose adjustments for low levels found on table 2
- Follow-up drug level monitoring is not recommended.

# HIV

- **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**
  - **Rifabutin is often used to replace rifampin in the treatment regimen due to drug/drug interactions with antiretroviral drugs (ARVs)**
  - **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**

## Other Conditions

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 ( <i>Schedule for performing TDM of second line drugs is complex, TB consultants will assist</i> )
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 <i>culture</i> positive after 5 months of TB treatment or sputum smear remains high with no evidence of non-tuberculous mycobacteria. <i>PZA/EMB should not have been discontinued.</i>
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.

# Procedure for requesting TDM

- Obtain approval from Central Office
- 804-864-7906 - Speak with a TB Nurse Consultant
- [RedCap Form](#)
- Approvals consistent with recommendations
- Once approved you will receive the laboratory requisition slip
- **All specimens must be shipped overnight Mon-Thurs ONLY to assure arrival on a weekday**

## TUBERCULOSIS

The mission of the Tuberculosis (TB) Program is to control, prevent, and eventually eliminate TB from the Commonwealth of Virginia. TB aims to detect every case of TB in Virginia, assure that every case is adequately and completely treated, and prevent transmission of TB communities.

VDH TB Central Resource Hub

Report Latent Tuberculosis Infection (LTBI)



# VDH VIRGINIA DEPARTMENT OF HEALTH



Please select your affiliation and what you would like to do from the drop down below. You will then be prompted to click a link to take you to the appropriate form.

Please do not click the check mark at the bottom of this screen.

Please choose your affiliation:

\* must provide value

- Health Department
- Non-Health Department

reset

What would you like to do?

\* must provide value

Request Serum Drug Level (SDL) monitoring

[Click here to request Serum Drug Level \(SDL\) monitoring.](#)

Once you've made your selection, click the link above.

If you have any questions, please call the VDH Central Office TB Team at 804-864-7906, or email [tuberculosis@vdh.virginia.gov](mailto:tuberculosis@vdh.virginia.gov).

Submit

## Serum Drug Level (SDL) Monitoring Request



If you have any questions, please call the VDH Central Office TB Team at 804-864-7906, or email [tuberculosis@vdh.virginia.gov](mailto:tuberculosis@vdh.virginia.gov).

Today's Date	11-06-2023  Today M-D-Y
District	<input type="text"/>
Office in District (if applicable)	<input type="text"/>
Client First Name	<input type="text"/>
Client Last Name	<input type="text"/>
Client Date of Birth	<input type="text"/> Today M-D-Y
Client Current Sex	<input type="text"/>
Nurse Case Manager First Name	<input type="text"/>
Nurse Case Manager Last Name	<input type="text"/>
Nurse Case Manager Phone Number	<input type="text"/>



# Procedure for Collecting

- Daily DOT dose
- Assure timing is no less than 12 hours since prior dose
- Record the exact time and date of administration on the requisition slip
- Using a plain green or plain red top vacuum tube, collect blood at the appropriate times. Avoid gel / serum separator / gold tubes.
- After the blood clots (red top only), centrifuge the samples, harvest the serum into labeled polypropylene (or polyethylene) tubes, and freeze (-70°C is preferable, if available). Use a different tube for each test and time of collection.
  - Green top tubes can be centrifuged right away.
- Label the tubes with the patient's name, date and time of collection, and the drug(s) to be assayed

# Lab Requisition Form

## INFECTIOUS DISEASE PHARMACOKINETICS LABORATORY

1600 SW Archer Rd., P4-30  
Gainesville, FL 32610  
Phone: 352-273-6710 Fax: 352-273-6804  
E-mail: [pelequinlab@cop.ufl.edu](mailto:pelequinlab@cop.ufl.edu)  
Website: <http://idpl.pharmacy.ufl.edu>



Patient Last, First Name, M.I. (Required)		<input type="checkbox"/> Male <input type="checkbox"/> Female	Facility Name & Address (Required)	
Date of Birth:	Patient ID:		TB Program Virginia Department of Health 109 Governor Street Richmond, VA 23219 Attn: Program Consultants	
Referring Physician (Required):		Physician Phone #		
Fax # 804-416-5178	Facility Phone #			
Please note: We do not bill 3 <sup>rd</sup> party payers. The laboratory or office shipping the samples accepts responsibility for payment.				
Bill to / Contact Name:			Authorization Number	
Billing Address:			City	
City			State	Zip
Telephone #			Email address:	

Please submit a separate requisition for each sample collection time. All results are reported within 7 days of receiving specimen.

REQUIRED	Drug 1	Drug 2	Drug 3	Drug 4
Drug name to be Assayed	INH 2hr	RIFH 2hr		
Drug Dose (mg) (Specify: PO, IV, IM)				
# Doses per week				
Date of last dose				
Time of last dose (For IV: Start/End)				
Date blood drawn				
Time blood drawn				

### Test Catalog (Recommended Drawn Times)

The number of hours after the dose to collect concentrations are shown in parentheses after each drug name below. To test for delayed drug absorption, a second sample should be collected 4 hours after the "peak". Trough concentrations (prior to next dose) are recommended for some drugs: Rifampentine, beta-lactams, anti-HIV, anti-fungal drugs.

Drug Code	Drug Name (Trough & 2 H)	INH	Isoniazid (1-2 H & 6 H)	PZAH	Pyrazinamide (2 H & 6 H)	Intravenous Drugs (intravenous doses)	
AZL	Azithromycin (2-3 H & 6-7 H)	ISA	Isoniazid (1-2 H & 6 H)	RBN	Rifabutin (3 H & 7 H)	(30-60 min. post infusion & trough)	
BDQ	Bedaquiline (trough, 2 & 5-6 H)	ITRL	Itraconazole (trough&2-3H)	RIFH	Rifampin (2 H & 6 H)	PIPE	Piperacillin
BC	Bictegravir (trough & 2 H)	LDV	Ledipasvir (trough& 4 H)	RPNT	Rifapentine (trough & 5-6H)	AMOX	Amoxicillin
CIPH	Ciprofloxacin (2 H & 6 H)	LFLHL	Levofloxacin (2 H & 6 H)	RILP	Rilpivirine (trough & 4-5H)	AMPI	Ampicillin
CLART	Clarithromycin (2-3 H & 6-7 H)	LNZL	Linezolid (trough, 2 & 5-6 H)	SOF	Sofosbuvir (trough& 1 H)	AZTRE	Aztreonam
CFH	Clofazimine (2-3 H & 6-7 H)	LOPV	Lopinavir (trough & 4-6H)	VORE	Voriconazole (trough& 2 H)	CEFAZ	Cefazolin
CSH	Cycloserine (2-3 H & 6-7 H)	MINO	Minocycline (2 H & 6 H)			CFE	Cefepime
DARU	Darunavir (trough & 2-4 H)	MXFL	Moxifloxacin (2 H & 6 H)			CEFT	Ceftriaxone
DTG	Dolutegravir (trough & 2 H)	OMADA	Omadacycline (2-3 H & 6-7 H)			IMP	Imipenem
DOXY	Doxycycline (2-3 H & 6-7 H)	PASH	p-Aminosalicylic acid (6 H)			MERO	Meropenem
EFVL	Efavirenz (trough & 5 H)	PMD	Pretomanid (trough, 2 & 5-6 H)	CTL	Ceftazidime	NAFC	Nafcillin
EMBH	Ethambutol (2-3 H & 6-7 H)	POSA	Posaconazole (trough& 3H)	DAPTO	Daptomycin	OXA	Oxacillin
ETAH	Ethionamide (2 H & 6 H)						

**Sample preparation and shipment:** Collect in a plain red top, 5 ml tube. Allow the sample to clot and separate serum from cells by centrifugation and aliquot into a labeled polypropylene or similar plastic tube. Use a separate tube for each test ordered. **Freeze 1 ml per test.** Allow room for expansion of sample inside tube. Freeze at -70°C if possible (otherwise -20°C). Ship for overnight delivery on **2-5 lbs. dry ice. SHIP SAMPLES TO BE RECEIVED MONDAY THROUGH FRIDAY. DO NOT SHIP ON FRIDAY OR SATURDAY.**

For UFL Use Only  
Date Received: \_\_\_\_\_  
Time Received: \_\_\_\_\_  
Condition: (circle one)  
Frozen    Partially Frozen    Thawed

(Revised 8/23)

# Procedure for Shipping

- Place samples in a zip-lock plastic bag and pack upright in a Styrofoam box (about 10 cubic inches in size) with at least 5 lbs. of dry ice
- Include the Requisition Form in a plastic bag and tape to the outside lid of the box
- Ship samples via overnight delivery to arrive Monday through Friday.

The University of Florida Infectious Disease Pharmokinetics Laboratory does not accept deliveries on Saturday or Sunday. Shipping Monday – Wednesday is recommended. Please ensure the delivery courier chosen accepts dry ice packages.

## Now What?

- 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
- In rare circumstances, a level may be higher than expected and a dose reduction may be needed
- It is not always possible or necessary to achieve drug levels in the expected range, especially with isoniazid
- VDH TB consultants are available for interpretation at 804-864-7906

# Dose Adjustments

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

	<b>Medication Administration</b>	<b>Normal drug levels</b>	<b>Sub-target INH Normal RIF</b>	<b>Normal INH Sub-target RIF</b>	<b>Sub-target INH Sub-target RIF</b>
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.

## Things to note:

- Dose counting to determine treatment duration is not typically altered by TDM results, but COULD be
- Do NOT use biweekly regimens unless discussed with a TB Consultant
- Prior to dose adjustments greater than VDH recommendations, discuss with TB Consultant
- Other TB medications should continue, unless medically contraindicated, until after TDM confirms adequate peak concentration

# Questions?

Recommendations and procedures for the use of TDM can be found [Here](#)



# References:

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