THERAPEUTIC DRUG MONITORING PROCESS

1. Verify or request order for collecting serum drug levels

Providers may order drug levels on tuberculosis patients not responding to adequate therapy, or those with risk factors for poor absorption. DSHS will cover the cost of drug levels based on below criteria. Programs may draw drug levels using funds outside of the TB and Hansen’s Disease Branch if requests fall outside this criteria. Note: Only rifamycins and isoniazid peak levels will be covered, unless patient is on second-line medications; consultation from a DSHS-recognized Medical Consultant may be needed.

Criteria* for Considering Therapeutic Drug Monitoring for TB patients

<table>
<thead>
<tr>
<th>Bacteriological Criteria (consider at 8 weeks of therapy)</th>
<th>Medical Criteria (consider at 2-4 weeks of therapy)</th>
<th>Clinical Criteria (consider at 8 weeks of therapy)</th>
<th>Criteria based on TB Diagnosis**</th>
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<tbody>
<tr>
<td>Slow response to adequate therapy at <strong>8 weeks</strong> of treatment, evidenced by the following:</td>
<td>• TB/poorly controlled diabetes comorbidity</td>
<td>• No improvement of TB symptoms (i.e. no weight gain, no reduction in cough, etc.) at 8 weeks.</td>
<td>• Patient Relapse: When signs and symptoms of TB return within two years of a prior episode of disease and there was a good possibility that relapse was due to low drug levels (exclude previous poor adherence, missed doses, or N/V)</td>
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<tr>
<td>• Patient remains AFB sputum smear positive 2+ or greater (unless easily explained)</td>
<td>• Mal-absorption due to chronic or acute co-morbidity</td>
<td>• Worsening CXR anytime during course of adequate therapy</td>
<td>• When second line drugs need monitoring, as per consult recommendations</td>
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<td>And/or</td>
<td>• Chronic or excessive vomiting or diarrhea</td>
<td>• New clinical deterioration, likely related to TB (i.e. new evaluation for TB relapse or concern for drug resistance**)</td>
<td>• TB meningitis</td>
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<tr>
<td>• Sputum smear results not decreasing as expected (4+ to 3+, 2+, etc.)</td>
<td>• HIV infection and CD-4 count &lt;100**</td>
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</tbody>
</table>

* Therapeutic Drug Monitoring should be reserved for patients who are not responding to adequate therapy, and not necessarily for patients who meet some of the stated criteria and are otherwise doing well.

** Consultation recommended by a DSHS recognized Medical Consultant, see list here: [http://www.dhs.texas.gov/idcu/disease/tb/consultants/](http://www.dhs.texas.gov/idcu/disease/tb/consultants/)
2. Contact the DSHS TB and Hansen’s Disease Branch for billing instructions

First-time users may contact the TB and Hansen’s Disease Branch at 512-533-3000 and ask for the TB Program administrative or nursing staff. You will be sent the National Jewish Laboratory Requisition which includes DSHS Billing Information. This may be saved and used again for subsequent draws without contacting the Branch, unless criteria for drawing drug levels falls outside the requirements on page 1.

3. Arrange timing of the blood draw and directly observed therapy (DOT) according to which drug(s) are being tested

Steps to collecting serum drug levels

Perform Directly Observed Therapy (DOT) of TB medications being tested, ensuring that the blood draw can occur at the indicated time after the dose of medication is observed.

Timing of draws per drug can be found on the National Jewish Laboratory requisition*. Time of dose and draw must be written on the form. In general, 2-hour levels are typically collected unless otherwise stated on the requisition (i.e. rifabutin is 3 hrs) or if there is a high likelihood of slow absorption or rapid metabolism; in that instance (when testing for delayed drug absorption), a second sample should be collected 4 hours after the specified “peak”.

* The requisition states the name of the drug and hour duration of when to draw the peak level, i.e. “Rifampin (2h)”. If peak Rifampin levels were being tested, the DOT provider would observe the patient taking their current dose of Rifampin, wait two (2) hours, and draw the blood as specified.
THERAPEUTIC DRUG MONITORING PROCESS

Step 2

Perform phlebotomy and collect 4-6 ml of blood in an 8-10 ml plain Red Top tube. (Also acceptable is an 8-10 ml Green Top tube, but it is not preferred.)

- Preferred volume of serum once blood is centrifuged is at least 2 ml per test for adults, 0.5 ml for pediatrics.
- Document timing of the blood draw on the requisition.
- Use a separate tube for each test. (Consider drawing an extra tube to freeze serum and save if needed.)

Step 3

Centrifuge, and aliquot serum into a labeled polypropylene or similar plastic tube, using one tube per test; or, coordinate processing with a local laboratory.

- Draw blood, allow at least 30 minutes to clot, and then centrifuge. Centrifuging should occur within 2 hours of collection. If blood will be processed in a local laboratory and not by collector, it can be kept on ice while in transport. Coordinate with lab to ensure timely processing.
- A pipette can be used to aliquot separated serum into the polypropylene tube.

Step 4

Ensure separated serum is frozen (or kept refrigerated until freezing) to prepare for shipping.

- Freeze at -70C if possible, but at minimum -20C.
- If an ultralow freezer is unavailable, the serum can be frozen in a regular freezer; do not allow it to go through a defrost cycle.
- Alternately, the tube with decanted serum can be placed on a rack and stored on dry ice (the rack should prevent direct contact between the tube and the ice; the serum will slowly freeze without being shocked by contact with the dry ice).
THERAPEUTIC DRUG MONITORING PROCESS

4. Send/Ship Serums to National Jewish Laboratory

Fully complete the National Jewish Laboratory Requisition. Include:
- Drug dosage, frequency, method of administration, and date and time of last dose prior to draw

Ship samples via **overnight delivery on at least 3 pounds of dry ice.**
- Ship samples to be received Monday through Friday
- Do not ship on Friday or Saturday, or the day prior to a holiday
- Package properly for dry ice handling*, including using a dry-ice specific label, and a return label for box to be shipped back to sender

*Not all couriers will ship dry ice, check before sending. Full shipping guidelines can be found on the National Jewish website: [https://www.nationaljewish.org/for-professionals/diagnostic-testing/adx/diagnostic-testing/shipping-guidelines](https://www.nationaljewish.org/for-professionals/diagnostic-testing/adx/diagnostic-testing/shipping-guidelines)

Ship to:

National Jewish Health
Pharmacokinetics Laboratory
1400 Jackson Street, K425
Denver, CO 80206
STOP
Unacceptable Conditions

• Severe hemolysis
• Thawed samples for greater than 6-24 hours, depending on drug being tested- ensure serum is shipped on at least 3 lbs dry ice
• Incomplete laboratory requisition

5. Respond to results as appropriate

Treating provider will determine if medication dosages will need to be changed based on the results of the serum drug level testing

Request consult if needed
Consultation recommended by a DSHS-Recognized Medical TB Consultant, see list here: http://www.dshs.texas.gov/idcu/disease/tb/consultants/
**Billing Information:** Request from DSHS Tuberculosis and Hansen’s Disease Branch if you do not have the requisition with this information already (see page 2 of process).

**Report Delivery Information:** Local Health Department (LHD) or Public Health Region (PHR) information here. Make sure fax number is correct to ensure results are returned to sender.

**Submitter Specimen #:** Can be any ID that the LHD or PHR uses to identify patient specimen; leave blank if none.

**Submitted By:** place the name of the LHD or PHR contact person (i.e. Nurse Case Manager for the patient). Also include contact # of the submitter.

All other sections must be filled out, including patient information, which drugs are being tested, times of dosing, etc.
Shipping Requirements

Three labels are required on the package to ship serum:

1. Shipping label addressed to National Jewish Health Laboratories
2. Category B Biological Substance label UN3373
3. Dry Ice label UN1845

1. Shipping Label. Address “To”:

National Jewish Health
Pharmacokinetics Laboratory
1400 Jackson Street, K425
Denver, CO 80206

2. Category B – Biological Substances Label UN3373

From FedEx: “Biological Substance, Category B” must appear in 6-mm-high text on the outer package adjacent to a diamond-shaped mark. The UN 3373 marking must be in the form of a square set at an angle of 45 degrees. Each side of the UN 3373 diamond should measure a minimum of 2” (50 mm). The width of the diamond rule line must be a minimum of 2 mm, and the letters and numbers must be at least 6 mm high.”

Contact FedEx for labels, or go to a FedEx location for assistance.

https://www.fedex.com/content/dam/fedex/us-united-states/services/UN3373_fxcom.pdf
3. Dry Ice – Class 9 Miscellaneous Dangerous Goods UN1845

An International Air Transport Association (IATA) Class 9 Miscellaneous label must appear on all dry ice shipments. FedEx Express offers a dry ice label that, when correctly completed, satisfies the IATA marking and labeling requirements, available free of charge at fedex.com or by calling 1.800.GoFedEx 1.800.463.3339

The following permanent markings are required on the outer packaging of all IATA dry ice shipments:

- “Dry Ice”
- “UN 1845”
- Net weight of dry ice in kilograms
- Name and address of the shipper
- Name and address of the recipient

To print labels, follow this link:

https://www.fedex.com/content/dam/fedex/us-united-states/services/Dry_Ice_Label.pdf
**Supplies Needed**

Local and regional TB programs may need to purchase additional supplies for collecting and shipping the serum drug levels. Contact the laboratory at National Jewish Health for questions regarding acceptable supplies at 1-800-550-6227.

- **Plain red or green top tubes**
  These cannot be used from the DSHS state laboratory, as the state lab does not process the test.

- **Pipettes**
  For aliquoting serum from the red/green top tubes into polypropylene tubes.

- **Polypropylene tubes**
  Used for the aliquoted serum that will be frozen and shipped.

- **Dry Ice**
  Must be purchased locally; typically found at local grocery stores and required for shipping.

- **Cold Boxes for Shipping**
  If the FedEx cold box is not adequate size for specimen and the three pounds of dry ice needed for shipping, a vaccine-size cold box is recommended.
Additional Resources

National Jewish Laboratory Requisition:
https://www.nationaljewish.org/NJH/media/ADX/Requisitions/ADx700-Pharmacokinetics_Req_10-2018.pdf

Instructions per drug (type in drug name being tested in Search box):
https://www.nationaljewish.org/for-professionals/diagnostic-testing/adx/search-adx-tests?ref=bottom

Shipping Guidelines from National Jewish:
https://www.nationaljewish.org/for-professionals/diagnostic-testing/adx/diagnostic-testing/shipping-guidelines

Shipping and Labeling Requirements for Category B shipping from FedEx:
https://www.fedex.com/content/dam/fedex/us-united-states/services/UN3373_fxcom.pdf

DSHS-Recognized Tuberculosis Medical Consultants:
http://www.dshs.texas.gov/idcu/disease/tb/consultants/

DSHS TB and Hansen’s Disease Branch Third Thursday’s Brown Bag, “Therapeutic Drug Monitoring”:
https://www.dshs.state.tx.us/idcu/disease/tb/Calendar/