



Treatment Action Group



SIDE EFFECTS AND CLINICAL AND LABORATORY-BASED MONITORING OF TREATMENT FOR DRUG-RESISTANT TUBERCULOSIS: WHAT TO EXPECT?

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Drug-resistant tuberculosis (DR-TB) treatment is highly effective, but the medications used in therapy can cause side effects. In order to identify and respond to these quickly, it is important for providers and people undergoing treatment to be aware of symptoms that may be early indicators of side effects. It is also essential for providers to do certain types of examinations and tests to detect side effects as early as possible. Early detection and monitoring is the best way to minimize the risks of treatment side effects and ensure that people can regain their health as quickly as possible.

Some testing should be done prior to treatment starting. This is often called **“baseline” testing**. It establishes what is occurring prior to the treatment being started so that changes during treatment can be better understood. **“Routine monitoring/testing”** refers to tests/evaluations that should be done for everyone during DR-TB treatment, even if they are not reporting any problems. **“Symptom-directed testing”** refers to tests and evaluations done when a person on treatment reports certain problems or concerns. Each of these will be reviewed here. All three categories of monitoring tests should be made available at no extra cost to people on treatment as part of a comprehensive package of care for drug-resistant TB provided by the national TB program.

The specific monitoring tests to be done will depend on the drugs included in the treatment regimen. There are currently five main regimens recommended for treating DR-TB in most people. They share many common medications and thus they share many of the same side effects and monitoring tests and strategies. This resource provides a list of lab tests and clinical examinations that people with drug-resistant TB should expect to receive at treatment initiation, during treatment, and in response to reporting specific side effects or experiences.

All people diagnosed with DR-TB should have the following baseline evaluations done prior to starting treatment:



1. Sputum analysis for smear and drug susceptibility testing (DST). At a minimum, DST should include testing for resistance to rifampicin and the fluoroquinolones. Ideally, it would include resistance testing to all the medications used in the prescribed regimen;



2. A chest radiograph (“chest X-ray”);



3. A physical examination of all systems of the body. This examination should also include an assessment of weight, height, vision, and the functioning of the nerves in the hands and feet;



4. An electrocardiogram (ECG) to check the electrical system of the heart;



5. Blood tests to measure the complete blood count, liver function, kidney function, and levels of potassium;



6. HIV testing;



7. Pregnancy testing; and



8. Screening for mental health issues, challenges to adherence, and need for socioeconomic support.

While on treatment, people with DR-TB should expect to see a clinical provider at least once a month. During the visit, the clinical provider should ask about any TB symptoms (cough, fever, weight loss, night sweats, shortness of breath). The provider should also ask about any new symptoms the person with TB might be having that could indicate side effects. This would include nausea, vomiting, diarrhea, changes in skin color, changes in eye color, vision changes, shortness of breath, chest pain, a racing heart, dizziness, fainting, rashes, joint pain, burning or tingling in the hands or feet, nightmares, sadness, loss of interest in usual activities, difficulty sleeping, worrying, or changes in thinking.

All people with DR-TB should also have the following routine monitoring during treatment (summarized in Table 1 below):



1. Sputum sample for smear and culture (monthly);



2. A physical examination of all systems of the body. This examination should also include an assessment of weight, height, vision, and the functioning of the nerves in the hands and feet;



3. An electrocardiogram (ECG) to check the electrical system of the heart (every 4–8 weeks);



4. Blood tests to monitor the blood counts (monthly while on linezolid) and liver function (monthly while on pretomanid or pyrazinamide);



5. Screening for mental health issues; and



6. Screening to identify and overcome challenges with adherence.

TABLE 1. SCHEDULE OF ROUTINE MONITORING DURING SIX-MONTH REGIMENS

Type of test	Prior to starting	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Sputum collection	X	X	X	X	X	X	X
Chest X-ray	X						
Review of any new symptoms or problems that have developed on treatment		X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X
ECG	X	X		X			
Blood test for monitoring blood counts while on linezolid	X	X	X	X	X	X	X
Blood test for monitoring liver function while on pretomanid* or pyrazinamide	X	X	X	X	X	X	X
HIV test	X						
Pregnancy test	X						
Mental health screening	X	X	X	X	X	X	X
Screening for providing adherence support	X						
Vision testing while on linezolid	X	X	X	X	X	X	X
Peripheral neuropathy testing while on linezolid	X	X	X	X	X	X	X

*While on pretomanid, people with underlying liver disease or alcohol use may need monthly testing of liver function. Other individuals may not need to have liver function tested as frequently while on pretomanid.

People experiencing any symptoms should report them to their clinical providers. When doing so, they should expect to have a thorough examination of the body system associated with the symptoms. **In addition to the physical examination, the following lab tests/evaluations should be done for people experiencing the following symptoms:**



Nausea/vomiting, changes in color of skin or eyes: blood sample for liver function tests.



Rash: full examination of the skin, eyes, mouth.



Chest pain, dizziness, fainting, shortness of breath: ECG to check the electrical system of the heart, blood sample to check potassium level.



Fatigue, shortness of breath, paleness, easy bruising: blood sample for complete blood count.



Burning or numbness/tingling in hands/feet: full neurologic exam, including testing for reflexes and sensation in the hands and feet.



Vision changes: full eye exam, including testing of vision accuracy, color perception, and deep eye exam with ophthalmoscopy (a bright light that can look into the back of the eye).

If the routine monitoring or symptom-directed evaluations indicate any potential side effects, then the clinical provider will make changes to the treatment regimen. This may include decreasing the dose of the drug(s) suspected to be causing the problems, stopping the drug(s) suspected to be causing the problems, or stopping treatment completely. The clinical providers may also recommend new medications that can help with symptoms, many of which should be provided free of charge as part of the DR-TB treatment.

Table 2 summarizes symptoms of common drug-resistant TB treatment side effects, their likely cause, and possible actions that can be taken to address them.

TABLE 2. SYMPTOMS, CAUSES, AND ACTIONS FOR POSSIBLE DR-TB SIDE EFFECTS

Symptoms	Possible causes	DR-TB drugs that may be associated with the symptoms	Possible actions
Nausea/vomiting	Adjustment to medications; Problems with the liver	Pretomanid, pyrazinamide, any TB drug when it is started	Check liver function via blood tests, consider spacing out medications and/or introducing anti-nausea medications. If liver damage is observed, then TB medications may be stopped until the liver recovers.
Changes to skin color/eye color	Hyperpigmentation; Problems with the liver	Clofazimine, pretomanid, pyrazinamide	Check liver function via blood tests. If liver damage is observed, then TB medications may be stopped until the liver recovers. Hyperpigmentation gradually resolves after clofazimine is stopped.
Dizziness, fainting, chest pain	Changes to the electrical system of the heart	Bedaquiline, clofazimine, levofloxacin, moxifloxacin	Check ECG, check levels of potassium via blood tests. If changes to the electrical system of the heart are observed, then TB medications may be stopped.
Changes in vision	Problems with the optic nerve	Linezolid	Examination of the eye, possible referral to eye specialist, discontinuation of linezolid.
Fatigue, paleness, easy bruising	Problems with the cells in the bone marrow that make blood cells	Linezolid	Check blood cell levels via blood tests. If levels are abnormal, linezolid dose may be lowered or linezolid may be stopped.
Burning or numbness/tingling in hands or feet	Problems with the nerves	Linezolid	Physical examination of the nerves in the hands/feet. If abnormal, linezolid dose may be lowered or linezolid may be stopped.
Joint pain/muscle pain	Mild irritation of muscles, tendons, or joints	Levofloxacin, moxifloxacin, pyrazinamide	Physical examination of joints and muscles, use of anti-inflammatory medications.
Nightmares, changes in thinking	Effects of the medications on the brain	Delamanid	Assessment to ensure no risks of harm to self or others, medications to help with sleeping, discontinuation of delamanid.

Monitoring should also continue after treatment is completed. This is done to identify any new symptoms that could indicate a TB relapse or recurrence (for example, new cough, new fever, new weight loss). It is also done to monitor any long-term health issues that may have occurred as a result of having TB. These health issues are sometimes referred to as “post-TB lung disease.” They could include wheezing, shortness of breath, difficulty carrying out daily activities, etc. In some settings, the monitoring done after treatment is completed is provided by a primary care physician or a lung physician who is not involved in treating TB. In all settings, however, clinical providers involved in treating TB should be willing and able to assess people who have been cured and help with additional TB or other testing that might be needed or with other measures to address respiratory or other health challenges that have occurred as a result of a person having TB.



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