

# Treatment of Drug-Resistant TB with New and Repurposed Medications: A Supplemental Field Guide for Nurses



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The SWIFT Response Project is a virtual, volunteer community of implementers who can rapidly share best practices, efficiently develop field implementation tools, and come together to problem solve in real-time about the introduction of new drugs. SWIFT stands for Society Working on Implementation to Fight TB and arises from the need to be proactive and bring our best selves forward to respond to the epidemic of drug-resistant TB. The SWIFT Response Project is an independent group with members from multiple agencies and organizations who have a common goal of implementing and supporting the highest quality services for those who suffer from drug-resistant TB.

The objectives of the group are: 1) To form a community of responders to share evidence and resources that can increase access to the best possible care for all persons affected by MDR-TB; 2) To rapidly develop implementation tools to support programs in the introduction of new drugs and technologies; 3) To engage in activities that support our shared vision of a world in which all patients benefit from advances of science and medicine in the treatment of drug-resistant TB, no matter who they are or where they live.

More information can be found at [www.swiftresponseproject.org](http://www.swiftresponseproject.org)

**The *SWIFT* Response Project**

The authors of this handbook are thankful to countless people for the time, expertise and generosity that led to the development of this field guide. We are most mindful of and thankful to the men, women, and children who are living with and have survived DR-TB. They are the inspiration for this field guide and for all the work we do.

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## Introduction

For the first time in almost 50 years there are two new drugs for the treatment of drug-resistant TB (DR-TB): bedaquiline and delamanid. There has also been increased attention given to the safety and efficacy of “re-purposed” drugs that have been widely used to treat other infections but are also showing promise in the treatment of DR-TB, including linezolid and clofazimine. Multiple guidelines, field handbooks, and training materials have been developed but they largely focus program managers and physicians.

The special supplemental guide has been developed for nurses for several reasons. First, nurses are almost always the front-line care providers for patients with DR-TB. They spend the most time with patients, provide the bulk of actual caregiving, and are the people patients tend to turn to first when they have questions or concerns. Because of this, it is essential that nurses be provided with material that maximizes their ability to provide optimal support to patients who are receiving new and re-purposed drugs.

The supplemental field guide will not repeat or rehash concepts and algorithms that exist in the SWIFT Response Project field guide. Rather, it will focus on issues of importance to nurses and the types of care they provide to individuals with DR-TB.

New drugs summary sheets

BEDAQUILINE



		<b>Comments</b>
<b>Drug name(s)</b>	Bedaquiline (BDQ, sirturo, TMC-207)	
<b>Tablet size and description</b>	100mg, white, non-scored	
<b>Dosing</b>	<p>Loading dose: first 14 days of therapy: 400mg daily (four tablets daily).</p> <p>Maintenance dose: 200mg three times a week (2 tablets on Monday, Wednesday, and Friday)</p> <p>Therapy is given for 24 weeks (i.e. 6 months total)</p>	
<b>Administration tips</b>	<p>Patients may tolerate better in the setting of a meal.</p> <p>Caution must be taken to ensure doses are only given three times a week <u>after</u> the first 14 days of therapy</p>	
<b>Main side effects</b>	Nausea, vomiting, changes in the heart rhythm	
<b>Important side effect screening questions</b>	<ol style="list-style-type: none"><li>1) Have you had any dizziness?</li><li>2) Have you had any fainting?</li><li>3) Have you had any chest</li></ol>	If yes to any of the first 3 questions, patient will need further cardiac evaluation (i.e. electrocardiogram,

	<p>pain?</p> <p>4) Have you had any abdominal pain</p>	<p>measurement of potassium).</p> <p>If yes to the 4<sup>th</sup> question, patient will need evaluation for pancreatitis.</p>
<b>Re-dosing with vomiting?</b>	<p>If patient vomits in the first 30 minutes after receiving the medication, then the same dose should be repeated. If the patient vomits after 30 minutes, then do not re-dose.</p>	
<b>Management of missed dose</b>	<p>If a patient misses a dose, continue with the standard dosing schedule and add the missed dose on to the end of therapy. Do NOT make up missed doses on “off” days</p>	<p>Bedaquiline has a very long half-life and stays in the body at high concentrations even if there is a missed dose.</p>
<b>Length of treatment</b>	<p>6 months is recommended, although this could be extended in some cases.</p> <p>Total number of tablets to be taken is 188.</p> <p>Total number of doses to be given is 80</p>	<p>Patient should complete all 188 tablets/80 doses, even if this takes longer than 6 months.</p>



## DELAMANID



		<b>Comments</b>
<b>Drug name(s)</b>	Delamanid (DLM/DEL, deltyba, OPC-07083)	
<b>Tablet size and description</b>	50mg, pink/beige, non-scored	
<b>Dosing</b>	100 mg twice a day (2 tablets twice a day)  Therapy is for 6 months (i.e. 24 weeks total)	
<b>Administration tips</b>	Patients may tolerate better with a meal.  A high-protein diet should be provided	
<b>Main side effects</b>	Nausea, vomiting, inability to sleep, changes in heart rhythm	
<b>Important side effect screening questions</b>	1) Have you had any dizziness? 2) Have you had any fainting? 3) Have you had any chest pain?	If yes to any of the first 3 questions, patient will need further cardiac evaluation (i.e. electrocardiogram, measurement of potassium).
<b>Re-dosing with vomiting?</b>	If patient vomits in the first 30 minutes after receiving the medication, then the same dose should be repeated. If the	

	patient vomits after 30 minutes, then do not re-dose.	
<b>Management of missed dose</b>	If a patient misses a dose, continue with the standard dosing schedule and add the missed dose on to the end of therapy.	
<b>Length of treatment</b>	6 months, although has been given safely to large populations for as long as 8 months.  Total number of tablets is 672. Total number of doses is 336	Patient should complete all 672 tablets/366 doses, even if this takes longer than 6 months.

## LINEZOLID



		Comments
<b>Drug name(s)</b>	Linezolid (LZD, zyvox)	
<b>Tablet size and description</b>	600mg, film coated, non-scored	
<b>Dosing</b>	600mg daily	Dose can be lowered to 300mg daily
<b>Administration tips</b>	Tablet can be difficult to split if patient needs 300mg daily and a pill cutter should be used	Is available in a syrup formulations
<b>Main side effects</b>	Low blood counts (including hemoglobin and platelets), peripheral neuropathy, optic nerve inflammation.	All are reversible with early recognition and lowering of/holding of doses
<b>Important side effect screening questions</b>	<ol style="list-style-type: none"> <li>1) Have you had any dizziness?</li> <li>2) Have you had any nosebleeds or bleeding from your mouth?</li> <li>3) Have you noticed that you are easily getting bruises?</li> <li>4) Have your periods been longer or heavier than usual?</li> <li>5) Do you have any burning or tingling in your hands or feet?</li> <li>6) Have you noticed any changes with your vision?</li> <li>7) Have other people noticed any changes with your vision,</li> </ol>	<p>If yes to any of the first 4 questions, patients will need a blood test to measure their level of hemoglobin and platelets.</p> <p>If yes to question 5, patient will need evaluation for neuropathy.</p> <p>If yes to questions 6 or 7 patient will need evaluation of vision and color perception.</p>

	especially with the way you see colors?	
<b>Re-dosing with vomiting?</b>	If patient vomits in the first 30 minutes after receiving the medication, then the same dose should be repeated. If the patient vomits after 30 minutes, then do not re-dose.	
<b>Management of missed dose</b>	If patient misses a dose, can give a “make-up” dose on Sundays/ “day off”.	
<b>Length of treatment</b>	For the entire length of therapy if tolerated.	

CLOFAZIMINE



		<b>Comments</b>
<b>Drug name(s)</b>	Clofazimine (CFZ, clofa)	
<b>Tablet size and description</b>	100mg, brownish-red, soft, gel caps	
<b>Dosing</b>	100mg daily	
<b>Administration tips</b>	Often better tolerated with food	
<b>Main side effects</b>	Skin discoloration, skin dryness, abdominal pain, nausea, vomiting, changes in the heart rhythm.	Skin discoloration is always reversible but can take months to resolve from the time therapy is stopped. Patients with skin discoloration may feel especially stigmatized and are likely to need additional emotional and social support.
<b>Important side effect screening questions</b>	1) Have you had any abdominal pain? 2) Have you noticed any changes in your appearance/skin? 3) Have other people commented to you about changes in your appearance/skin? 4) Have you had any dizziness? 5) Have you had any fainting? 6) Have you had any chest pain?	If yes to either question 2 or 3, patient will need additional support and counseling around these issues. If yes to any of questions 4, 5 or 6, patient will need further cardiac evaluation (i.e. electrocardiogram, measurement of potassium).

<b>Re-dosing with vomiting?</b>	If patient vomits in the first 30 minutes after receiving the medication, then the same dose should be repeated. If the patient vomits after 30 minutes, then do not re-dose.	
<b>Management of missed dose</b>	If patient misses a dose, can give a “make-up” dose on Sundays/ “day off”	
<b>Length of treatment</b>	For the entire length of therapy if tolerated.	

### Who can get new and re-purposed drugs?

The new and re-purposed drugs are likely to benefit almost any patient with DR-TB. However, because of their cost, and the limited experience in giving them (have been given to fewer than 1000 patients worldwide), most programs choose to give them to patients with more limited options. These patients include:

- Individuals with resistance to fluoroquinolones, injectables or both;
- Individuals who are failing current DR-TB therapy (i.e. still have a positive culture at treatment month 4)
- Individuals who are known contacts of those with resistance to fluoroquinolones, injectables or both;
- Individuals who are known contacts of those who are failing current DR-TB therapy;
- Individuals who develop side effects to the fluoroquinolones or injectables, most notably those who develop early signs of hearing loss, kidney problems, or other possibly permanent problems;
- Individuals who require discontinuation of another drug in their regimen for reasons of resistance or intolerance.

Often, nurses will be the first people to notice that use of a new or re-purposed drug may be indicated, especially in the case of early signs of toxicity. Nurses play a key role in bringing these patients to the attention of treatment teams and should specifically ask treatment teams to consider the use of new or re-purposed drugs in these patients.

## How to talk with patients about new and repurposed drugs

Because this is the first time in decades that DR-TB treatment entails the use of newly approved medications, patients, family members, and the community may have multiple questions about these medications. Furthermore, there are often myths and misperceptions on the parts of patients, family members, and the community as well as other providers about new drugs: nurses can play a key role in addressing these misperceptions as well as answering any questions that may come up about the new drugs. Here are some important briefing points:

- The use of these new drugs is NOT an experiment: these medications have been approved by strict regulatory bodies and are recommended by the World Health Organization for the treatment of patients with DR-TB;
- As a priority, these drugs are being offered to patients who are at high risk of not being cured of their DR-TB because the regular medications will not work or have caused too many side effects;
- So far, the drugs have been given to about 1000 patients around the world, compared with the usual treatment that has been given to about 40,000 patients around the world. For this reason, there may be side effects that we do not yet know about.
- One of the drugs, bedaquiline, was found in one small study to both cure more patients but also to have a higher death rate compared with standard treatment. A majority of patients taking this medication have done very well, and if you are being offered this drug it is because the chance that you will die from DR-TB is higher than the chance you will die from the medicine;
- You should not be charged any money for these new medicines, nor should you be asked to pay for any monitoring tests or treatments that are needed when you are on these medicines;
- You should communicate any worries or questions you have about these new drugs to your nurse and treating team.
- You may be asked to sign a special form saying specifically that you were given information about the new medications. This is to ensure you have been provided with facts about the drugs as well as the opportunity to ask and have answered any questions you have.



## Responding to common patient complaints

Nurses are often the first care providers to notice or hear about any problems or complaints patients may have with the medications they are taking or the treatment they are receiving. Detailed reviews of adverse events management has been well-described in other clinical guides and will not be reviewed here. This section, however, will focus on important issues to be aware of with the side effects of new drugs and suggest management strategies that can be implemented by nurses or requested from physicians if patients complain of the following issues.

### *Nausea/vomiting/diarrhea*

Nausea, vomiting, and diarrhea are common in patients who are being treated for DR-TB and can be caused by a number of medications. Nausea, vomiting, or diarrhea become significant in the setting of new and re-purposed medications because many of these medications can cause a change in the rhythm of the heartbeat. These changes can be worse when there are low levels of potassium and magnesium in the blood, and patients who have nausea, vomiting, or diarrhea are at high risk of having low levels of potassium and magnesium in the blood. All patients who complain of nausea, vomiting, or diarrhea should have a potassium level checked immediately and if the level is low, be given both potassium and magnesium.

### *Abdominal pain*

Abdominal pain may be common for a variety of reasons in patients with DR-TB who are undergoing treatment. However some forms of abdominal pain may indicate pancreatitis, a known side effect of some of the new and re-purposed drugs. Patients with abdominal pain that is severe or associated with nausea or vomiting should be evaluated for pancreatitis either by a physical exam, checking the blood lipase (which will be elevated in pancreatitis), or obtaining an ultrasound or CT scan of the abdomen.

### *Dizziness*

Patients on treatment for DR-TB may develop dizziness for a number of reasons. Dizziness, however, can be an early sign of problems with the rhythm of the heartbeat. If a patient complains of dizziness, careful attention should be given to obtain more details, including how often the dizziness occurs, when it occurs, how long it lasts, and if it is ever associated with fainting. All patients complaining of dizziness should have an electrocardiogram or screening assessment of the heart rhythm.

### *Chest pain*

Patients on treatment for DR-TB may develop chest pain for a number of reasons. Chest pain, however, can be an early sign of problems with the rhythm of the heartbeat. If a patient complains of chest pain, careful attention should be given to obtain more details, including how often the pain occurs, when it occurs, how long it lasts, and if it is ever associated with other

symptoms including fainting, shortness of breath, sweating, or arm pain. All patients complaining of chest pain should have an electrocardiogram or screening assessment of the heart rhythm.

### *Hearing issues*

None of the new or re-purposed drugs are associated with hearing problems. However, they can be given to patients who have early signs of hearing problems from the injection and prevent permanent hearing loss. Nurses should ask all patients about any buzzing or ringing in the ears as well as any problems the patient or his/her social network may have noted. If these are reported to any extent, the nurse should refer the patient/case to the clinical management team for consideration of new or re-purposed drugs.

### *Burning, tingling, or pain in the feet or hands*

Patients on DR-TB treatment may describe a number of different tactile feelings or sensations, but burning, tingling, or pain in the hands or feet is an early sign of permanent nerve damage. Linezolid has been known to cause this problem in about 30% of patients who take the drug, and if not detected and acted upon early, the damage can become permanent. All patients complaining of any of these issues should have a clinical evaluation for neuropathy and nurses should ask the treatment team if the dose of linezolid can be lowered.

### *Problems with vision*

Patients with DR-TB may complain of problems with their vision, and many of these are chronic or related to aging eyes. If patients complain of vision changes, however, this could be due to damage to the eye, most commonly caused by linezolid. One important indicator of damage to the eye is the inability of the patient to tell the difference between the colors red and green. Patients may not notice this themselves, and it is recommended that all patients on linezolid be asked to describe the colors of different objects. If the patient is unable to discriminate the colors red and green, a formal assessment of the nerves in the eyes should be done.

### *Problems with bruising or bleeding*

Patients with DR-TB may report problems with nose bleeding, gum bleeding, or heavy menstrual periods. They may also not bruise more readily. These indicate problems with the blood counts which are a known side effect of linezolid. All patients on linezolid should be asked about any of these symptoms at each visit. If they report any of these, they should have a complete blood count assessed to check the hemoglobin and the platelets. Patients who report bruising should also have a formal safety assessment and be asked if anyone is hurting them, with appropriate social support and follow-up provided.

## Nurses and Cardiac Monitoring

Many of the new and re-purposed medications can cause a change in the rhythm of the heart beat, and such changes may increase the patient's chances of developing a cardiac complication, including sudden death. For this reason, routine cardiac screening is recommended for all patients on bedaquiline, delamanid, or clofazimine prior to starting therapy and at weeks 2, 4, 8, 12, and 24. The cardiac screening is done to specifically assess the QTc interval. The following are important considerations in cardiac screening and monitoring, most of which will be done by nurses

- Screening can be done using simple, handheld devices in most cases, and nurses have a broad experience using these devices in many DR-TB treatment programs. Details on these devices and the training needs can be obtained by writing to the SWIFT Response Project ([jenniferfurin@gmail.com](mailto:jenniferfurin@gmail.com)).
- Another option for screening is the use of a full 12-lead electrocardiogram (ECG). Usually nurses are given the responsibility of obtaining the ECG and details on how to do this can be obtained by writing to the SWIFT Response Project ([jenniferfurin@gmail.com](mailto:jenniferfurin@gmail.com)).
- Patients who have ECG changes may require hospitalization for monitoring and management. If this is the case, the nurses caring for the patient will need to have access to an automated defibrillator and know how to use it.

## Nurses and emotional/adherence

Patients with DR-TB are often incredibly frightened. They have usually just been told that they have a potentially fatal disease, are usually sent away from their home to receive care, and are often treated badly by friends and family members who fear catching this disease. This can be overwhelming. At the same time, these individuals are often asked to process a large amount of complicated information and to sign multiple forms saying they agree to treatment. Many of the details can be lost under such duress, and patients will require important information to be repeated many times in a compassionate and supportive way. Patients who understand their treatment and who are treated with dignity and respect are more likely to successfully complete treatment, a crucial element in curing people with DR-TB. Although this is the responsibility of the entire treatment team, nurses are usually the front-line workers in this regard as well. The following points should be considered when providing adherence counseling for patients on new drugs:

- Patients offered new drugs usually have more severe forms of DR-TB or have experienced side effects in their standard treatment. These patients are at high risk for non-adherence because they may perceive their situation as “hopeless” or they may feel that treatment is worse than the disease. For this reason, additional time and support may be required for individuals on new medications.
- Every interaction with a patient is an opportunity to enhance the therapeutic bond and to provide patients with additional information on the medicines they are receiving and their disease. This is especially true of hospitalized patients—who are often bored, lonely, and feeling powerless—as well as patients waiting to receive directly observed therapy. Nurses can use these times for creative presentations that can make adherence counseling fun.
- Patients may be more likely to listen to other individuals who have been through a similar experience, and nurses should call upon patients who have been treated with new drugs to help support other individuals.
- Patients may have questions about resuming normal life, interacting with family members, DR-TB and “safe sex” (including hugging or kissing) and these questions should be solicited.
- Family members may have similar questions and should be included in counseling and support sessions as well. Family should be encouraged to provide a loving and supportive environment for the DR-TB patients, and they are best able to do this when provided with facts that can dispel fear-based myths and the propagation of stigma.
- Patients should be screened for other life issues that may affect adherence including deaths of loved ones, important holidays or celebrations, substance use, or depression and additional support provided around these significant events.

### Nutritional and social support with new and re-purposed drugs

It is a well-documented fact that most patients with DR-TB face a number of other challenges in their lives, including poverty, lack of access to food, and poor housing. Often, the person with DR-TB contributes significantly to the functioning of the household, and the loss of this person while undergoing treatment is a calamity for the family. Nurses may be the only care providers to ask about or be aware of the true burden of suffering endured by persons with DR-TB, and may be the first to recognize the need for a variety of social support mechanisms. This is true of all DR-TB patients but the use of new or re-purposed drugs may place additional burdens on individuals and families that need to be mitigated if treatment success is to be achieved. These include:

- Nutritional challenges: most of the new and re-purposed drugs are better tolerated when given with a meal. Delamanid in particular is absorbed better and causes fewer adverse events when the patient has adequate protein intake. To address this, patients are often scolded to “eat more” or “eat more protein” but unable to do this given severe financial constraints. For this reason, nutritional support should be given to all DR-TB patients. This can be done in a variety of ways and should involve other agencies or groups, including churches, mosques, food donations, or “communal kitchens.” Patients can also be given practical advice about common foodstuffs that contain protein, such as eggs, pulses/lentils, or nuts.
- Community-based care should be offered to patients taking new and re-purposed medications, as there is no need to hospitalize a majority of these individuals. Patients should be encouraged to return to normal activities as soon as they are smear-negative, and medications should be provided in a way that allows the patient to take his or her medication and resume the activities that are meaningful to him or her.
- A home visit should be made to all households of individuals started on new or re-purposed drugs to assess any home needs or challenges being faced. Activities should be undertaken to address these needs, and this can be done in collaboration with other community groups.
- Patients on new or re-purposed drugs may be required to have more frequent visits at health centers or may be required to undergo specialized testing or even hospitalization. All of this should be offered free of charge, and nurses should ask patients at each encounter how much they have spent in the last month on care related to TB.

