



Treatment of Drug-Resistant TB
with New and Repurposed Medications:
A FIELD GUIDE FOR OPTIMAL USE

Third Edition: July 2017
Cover photo courtesy of Justin Ide

The Drug-Resistant TB Scale-Up Treatment Action Team

This handbook was developed and written by DR-TB STAT (<http://drtb-stat.org/>) based on an earlier version prepared by The SWIFT Response Project.

Preferred citation: Treatment of Drug-Resistant TB with New and Re-Purposed Medications: A Field Guide. Cleveland, USA. DR-TB STAT; July 2017.



© 2017, DR-TB STAT

Founded in 2015, DR-TB STAT is a collective made up of practitioners, researchers, survivors, and policy makers who have direct experience using new and repurposed drugs for the treatment of multi-drug resistant tuberculosis (DR-TB). The group was founded in response to a “Call to Action” issued by 88 civil society organizations who were concerned about slow rollout of new drugs for the treatment of MDR-TB. At a meeting held in April 2015, the “Drug-Resistant TB Scale-Up Treatment Action Team” (DR-TB STAT) was officially inaugurated; DR-TB STAT received partial funding support from the Global Drug Resistance Initiative (GDI) as a formal Task Force in July of that year.

The goal of DR-TB STAT is to monitor and support the use of new drugs and regimens for the treatment of MDR-TB. Because it can take years for clinical trials to be completed and their findings incorporated into WHO guidelines, DR-TB STAT utilizes the knowledge and practical experience of front-line providers who have experience using the new agents to help support other practitioners, programs, and patients involved in MDR-TB care.

More information can be found at <http://drtb-stat.org/>

Acknowledgments

The main writing committee for this handbook is: Jennifer Furin, Vivian Cox.

Based on an earlier version prepared by: Jennifer Furin, J. Sean Cavanaugh, Francesca Conradie, Susan van den Hof, Abdul Ghafoor, Lorenzo Guglielmetti, Ekaterina Kurbatova, Liga Kuska, Phuong Nguyen Thi Mai, Michael Rich, and Nicolas Veziris.

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 survived DR-TB. They are the inspiration for this field guide and for all the work we do.

TABLE OF CONTENTS

Introduction	1
Summary Information about New and Repurposed Drugs	3
Diagnosis and Patient Selection	7
Regimen Composition and Design	16
Special Populations	22
Monitoring and Management of Adverse Events	30
Management of Selected Adverse Events	31
Adherence Support	37
Active Drug Safety Monitoring and Management for Providers	39
Ethical Issues and Informed Consent	43
Conclusions	48
Selected References	53

Disclaimer

As between The Drug-Resistant Tuberculosis Scale-Up Treatment Action Team (hereafter referred to as “DR-TB STAT”) and you, DR-TB STAT or its licensors always owns and retains all right, title, and interest in and to the “Treatment of Drug-Resistant TB with New and Re-Purposed Medications: A Field Guide” including all intellectual property rights therein and thereto. You may use and copy the Field Guide, or portions of the Field Guide, provided that you (i) promptly notify DR-TB STAT via email at jenniferfurin@gmail.com of any such use and (ii) reproduce all copyright notices, claims, or reservation of rights appearing on the Field Guide, as delivered to you, on all copies made pursuant to this sentence.

By using the Field Guide, you acknowledge that (i) the Contributors and Authors are not guaranteeing the completeness or accuracy of the information contained in the Field Guide, (ii) the Field Guide does not represent nor comprise all of the data or other information that may be relevant to you, (iii) portions of the Field Guide may be outdated and may have been superseded by subsequent changes in applicable law, regulation, or conditions affecting nonprofit health organizations generally, and (iv) the Contributors and Authors do not have any duty to update the Field Guide or, if updated, to provide further updated versions of the Field Guide.

To the maximum extent permitted under applicable laws, none of the Contributors and Authors are liable, under any circumstance or under any theory of law, tort, contract, strict liability or otherwise, for any direct, indirect, special, incidental, consequential, exemplary or punitive damages, or any other injury and/or damage (actual or perceived), including, without limitation, damages based on errors, omissions, or reliance upon, use, or operation of any ideas, instructions, procedures, products, or methods contained in the material included in this guide.

By using this guide, you acknowledge and agree to the terms of this notice.

I. INTRODUCTION

For the first time in almost 50 years, two new drugs—bedaquiline (BDQ) and delamanid (DLM) — have been developed, licensed, and approved for the treatment of drug-resistant tuberculosis (DR-TB), offering hope to hundreds of thousands of individuals suffering from this airborne disease. In addition to these new drugs, there are several agents developed for the treatment of other infections that have shown great promise in the treatment of DR-TB, including linezolid (LZD) and clofazimine (CFZ). In 2016, the WHO recommended a shorter 9-12 month regimen for selected patients diagnosed with MDR-TB. It is an exciting time to be in the field of DR-TB.

While there are multiple planned and ongoing clinical trials looking at optimization of new and repurposed TB drugs, many of these have just recently started to enroll, and it will likely be 2020 before clinical trials results are available. Patients and programs cannot wait for these trials to begin using these drugs and regimens, both for the health reasons of sick individuals, as well as reducing ongoing transmission of DR-TB and amplification of resistance in the absence of robust regimens.

Against the backdrop of high rates of toxicity and low rates of treatment success, the WHO issued guidance on the use of BDQ and DLM for routine program conditions in June 2013 and October 2014 respectively. In 2016, the WHO issued updated treatment recommendations, including the use of shorter MDR-TB regimens. To supplement these recommendations, the WHO has issued a companion handbook for the treatment of DR-TB; the handbook not only contains information about BDQ and DLM, but also about shorter regimens, LZD, and CFZ, as well as other potentially useful agents (i.e. the carbapenems). These guidelines are comprehensive and evidence-based, but often lack the types of recommendations needed for implementers in the field. For this reason, this field guide was developed as a supplement to existing materials; this guidance is comprehensive and includes a wealth of literature on the new drugs.

This field guide is intended to provide practical information, tools and algorithms to persons working in DR-TB who are using or thinking about using new and repurposed drugs and shorter regimens for their patients and programs. It is an attempt to share best practices from providers who have used BDQ, DLM, LZD and CFZ and shorter regimens. These field-based guidelines will be updated regularly as new evidence becomes available. There are a few differences between the clinical trials, WHO guidelines, and this handbook, which are summarized below:

- In general, this handbook provides additional information for interpreting the WHO recommendations for field providers. Of note, not all recommendations in this handbook follow current WHO recommendations.
- Both BDQ and DLM were tested and licensed as additions to backbone therapy for patients with MDR-TB, and this is how they will be indicated for use in countries where the drugs are registered or being accessed through other mechanisms (i.e. emergency waivers, compassionate use, expanded access).
- The clinical trials only included individuals with pulmonary disease between the ages of 18-65 years, and thus this is the population for whom the drugs are licensed; this does not mean the drugs are not useful or indicated in other populations, only that those populations were not included in the trials. WHO recommends Delamanid down to the age of 6 years old.

- For multiple reasons (including costs and logistics) the WHO guidelines recommend using these drugs in patients with resistance or intolerance to second line drugs (SLDs), especially the quinolones and the injectables.
- The new drugs BDQ and DLM are also recommended for patients who do not qualify for shorter MDR-TB treatment regimens.
- Because of the lack of data in other populations (i.e. HIV co-infected individuals, adolescents, and children when treatment options are limited), the WHO recommends that these drugs be used with caution in these populations. WHO does not currently recommend the use of the new drugs in pregnancy, however the risks and benefits may mean that the new drugs should be used for pregnant women.
- DLM has been tested for pharmacokinetics (PK) and safety in children as young as three years, and studies are ongoing in children aged two years and under. BDQ has been safely used in adolescents aged 12-18 years, and PK and safety in children is formally being assessed. The Sentinel Project on Pediatric Drug-Resistant Tuberculosis (<http://sentinel-project.org/>) provides additional details on the use of the newer agents in children.
- BDQ and DLM are currently being tested in combination together, but there are emerging data on the efficacy and safety of this combination in a select number of patients, suggesting they can be used together in patients with limited options.
- Phase III trials results for DLM are expected in 2018 and recommendations may change based on these results.
- Shorter regimens have been recommended broadly by the WHO for treatment of MDR-TB in persons for whom resistance to any of the components of the regimen are is not documented or unlikely (except for INH).
- A modified shorter regimen could be considered under operational research conditions in settings where the standard shorter regimen cannot be used for reasons of resistance or intolerance to components of the regimen. Modifications that include substituting the injectable agent or replacing PTO with ETO do not require a research framework. National TB Programs should finalize the protocol and ensure there is a due process for informed consent and that close monitoring is provided.
- The results of the phase III randomized controlled trial of the shorter regimen (the STREAM study) are expected in 2018 and recommendations may change based on these results.
- New drugs should be considered additional tools in the fight against DR-TB and parallel systems outside of the routine programmatic management of DR-TB (PMDT) should not be created just for these drugs.

Although this field guide focuses on the use of new and repurposed drugs and shorter regimens, it cannot be emphasized strongly enough that these new and repurposed drugs must be used in the context of overall PMDT. The principles of PMDT will not be reiterated here, but readers are referred to the 2016 WHO PMDT guidelines.

2. SUMMARY INFORMATION ABOUT NEW AND REPURPOSED DRUGS (in alphabetical order)

Bedaquiline

Bedaquiline (BDQ) is a new drug for the treatment of DR-TB that was approved by the U.S. Food and Drug Administration (FDA) in 2012, the European Medicines Agency (EMA) in 2013, and the South African Medicines Control Council (MCC) in 2014. The WHO recommended BDQ for the treatment of MDR-TB in 2013, if it is used under optimal conditions, including careful selection of patients, close patient monitoring, use in a multi-drug regimen that follows WHO principles, a due process of informed consent is followed, and active pharmacovigilance is done. The WHO renewed this recommendation in 2017. The drug has a novel mechanism of action and works by inhibiting mycobacterial ATP synthase. The drug is in a completely novel class, but data has shown it has cross-resistance with clofazimine through a shared efflux pump mechanism.

The efficacy of BDQ has been demonstrated in a phase IIB trial done in multiple sites. In this trial, patients were randomized to receive a multi-drug backbone regimen with either placebo or BDQ. Those who received BDQ had a higher rate of culture conversion and a higher rate of cure at the end of 120 weeks of follow-up. The drug has also been given to more than 10,000 patients as part of programmatic use, with countries reporting rates of six-month culture conversion above 75% when the drug was given as part of an optimized backbone regimen, usually including linezolid and clofazimine. A large observational cohort of almost 2,000 patients from South Africa found that patients who received BDQ as part of treatment for MDR-TB had a significantly lower mortality than those who did not.

In terms of safety, the drug is relatively well tolerated, although when compared with placebo, higher rates of liver function test abnormalities were seen. BDQ has also been associated with moderate QTc prolongation, although no clinical cardiac events have been associated with its use. In the phase IIB trial of BDQ, the mortality rate of patients receiving BDQ was five times higher than that of the group receiving placebo, although none of this was determined to be casually related to the drug. Data from multiple expanded access programs also show the drug to be well tolerated. QTc prolongation was again noted, although there were no clinical cardiac events seen. And, as noted above, mortality data from South Africa show that BDQ is associated with lower mortality rates among persons who received the drug as part of MDR-TB therapy compared with those who did not.

The drug comes in tablets of 100 mg with a shelf life of 3 years. There is a loading dose phase in which the drug must be given at a dose of 400 mg daily for 14 days. After this, the drug is given at a dose of 200 mg three times a week for an additional 22 weeks, although some providers have used this drug for a longer duration in patients with limited treatment options. The half-life of the drug is 5.5 months. When used with efavirenz (EFV), the concentration of BDQ is reduced, and thus it is highly recommended that alternative antiretroviral therapy (ART) agents be used—including nevirapine (NVP) and dolutegravir. One study found that persons receiving both lopinavir/ritonavir and BDQ had higher serum concentrations of BDQ, but the clinical implications of this are unclear. The safety of the drug has not been firmly established in younger children, the elderly, or in pregnant or breastfeeding woman, although the benefits of the drug may outweigh the risks in some circumstances. Case reports and small observational cohort studies done in these populations suggest that there are no additional adverse events observed, but because the cohorts are small, additional monitoring is needed and the patients should be informed of the benefits and risks of receiving the drug.

Clofazimine

Clofazimine (CFZ) is a drug which has been used for the treatment of leprosy for decades and has been used in the treatment of patients with MDR-TB in a variety of program settings. CFZ is a fat-soluble riminophenazine dye. The drug does not yet have a formal indication for the treatment of MDR-TB, but it is a chief component in the shorter 9-12-month regimen which was recommended for use by the WHO in 2016. The drug has a mechanism of action that is not completely understood, and it has been shown to have cross-resistance with BDQ.

Safety and efficacy data in DR-TB comes from observational data and from a recent non-blinded randomized study; the drug is currently being tested in a large Phase III trial as part of a multi-drug regimen (STREAM Trial). In the phase III randomized trial, 105 patients with MDR-TB in China were randomized to receive a multidrug backbone regimen versus a multidrug backbone regimen plus 100 mg of CFZ daily. Those who received CFZ had a higher rate of culture conversion; the treatment success rate was 73.6% versus 53.8% in the group that did not receive CFZ ($p= 0.035$).

The drug has three main classes of side effects: skin, gastrointestinal, and depression. CFZ causes skin pigmentation changes that range from an orange color to a dark black/purple color. These skin changes are reversible over time. CFZ can also cause symptoms of abdominal pain, as the drug accumulates in the wall of the GI tract. Depression can be profound and is one cause of treatment interruption. CFZ has been associated with QTc prolongation.

CFZ comes in caplets of 50 mg and 100 mg, and the usual dose is 100-200 mg per day. It is used for the entire duration of the treatment course. The drug has a shelf life of 5 years and a half-life of 70 days. It appears to be safe to give with all forms of ART. It has been used in pregnant and breastfeeding women, children, and the elderly.

Delamanid

Delamanid (DLM) is a new drug that was approved for the treatment of DR-TB by the EMA in 2013 and by the Pharmaceutical and Medical Device Agency of Japan in 2014. The drug was recommended for the treatment of DR-TB by the WHO in 2014 if it is used under optimal conditions, including careful selection of patients, close patient monitoring, use in a multi-drug regimen that follows WHO principles, due process for informed consent, and active pharmacovigilance. In 2016, the WHO recommended DLM for use in children ages six years and above. DLM is a nitro-imidazole agent that works by inhibiting mycobacterial cell wall synthesis.

The efficacy of DLM was demonstrated in a multi-site, phase IIB trial in which patients were randomized to receive a multidrug-backbone regimen plus either placebo or DLM. Randomization was maintained for 8 weeks, then patients were offered to continue or receive DLM as part of an observational cohort for 6 months. The 8-week data showed higher rates of culture conversion in patients who received DLM compared with placebo. The continued observational cohort also showed higher rates of culture conversion in patients who received longer courses of DLM, but this part of the trial was not randomized. The phase III trial for DLM has completed enrollment and the results are anticipated in 2018. DLM has been given to about 500 patients under expanded access conditions and routine program conditions.

In terms of safety, the drug is well tolerated, and the main side effect reported was moderate QTc prolongation without clinical cardiac events. Of note, the drug is metabolized

by albumin, and increased rates of adverse events were seen in patients with low albumin.

DLM is given at a dose of 100 mg twice daily for 24 weeks, although a phase III trial of the drug is evaluating a dose of 200 mg once daily. Of note, some providers have used this drug for a longer duration in patients with limited treatment options. The drug comes in tablets of 50 mg and has a shelf life of 5 years; the half-life of the drug is 38 hours. DLM can be given safely with most forms of ART based on short-term studies. DLM has been given to children as young as 3 years and is considered safe in this population. The safety of the drug has not been established in children under the age of 3 years (although PK and safety studies are ongoing), the elderly, or in pregnant or breastfeeding woman, although the benefits of the drug may outweigh the risks in most circumstances.

Linezolid

Linezolid (LZD) is an oxazolidinone antibiotic that was initially approved to treat resistant gram-positive infections, but has been used off-label for the treatment of DR-TB. Multiple observational cohorts have shown that LZD can be effectively used to treat patients with highly-resistant forms of TB, and the drug is being proposed as a key component in multiple clinical trials.

Safety and efficacy data on LZD come from primarily from observational cohorts, although there was one randomized delayed start trial done in patients with XDR-TB. In this study, 41 patients in South Korea with confirmed XDR-TB were randomly assigned to receive a multidrug backbone regimen plus LZD, with the LZD either started immediately or after 2 months. In this study, patients who received LZD earlier had a more rapid rate of culture conversion, and by 4 months after randomization, 79% in the early group had culture converted as opposed to 35% in the delayed group.

The drug has multiple adverse events - especially when given at doses exceeding 600 mg per day - including bone marrow suppression and peripheral neuropathy. Bone marrow suppression is usually manifested as anemia or thrombocytopenia. Adverse events seem to be related to the cumulative trough dose, and there are clinical trials trying to establish the optimal dose of LZD, including every-other-day dosing strategies. For now, the most commonly used dosing strategy is to start with 600 mg daily and decreased the dose to 300 mg should toxicity occur. When possible, LZD should not be used with anti-depressants of most classes, as this can precipitate serotonin syndrome.

The drug is available as a 600 mg tablet with a shelf-life of 3 years. The half-life of linezolid is 5-7 hours. It can be safely given to children as well as to pregnant and breast-feeding women. When used in the elderly, the rates of peripheral neuropathy and bone marrow suppression may be increased. The drug can be given safely with ART. It is used for the entire duration of the treatment course.

Shorter regimen

The shorter MDR-TB regimen was developed based on a series of observational cohorts studies done primarily in Bangladesh. The regimen last 9-12 months and consists of an “intensive phase” of 4-6 months that includes the following seven drugs: isoniazid (high-dose), pyrazinamide, ethambutol, kanamycin, prothionamide, moxifloxacin (high dose) and clofazimine followed by 5 months of PZA, EMB, moxifloacin (high dose) and clofazimine. The duration of the intensive phase is based on smear- and culture-conversion. Initial studies in Bangladesh showed treatment success rates of above 85% and similar results were seen in observational cohorts in Niger and Cameroon. More than 1,000 people in Francophone Africa have received these regimens, as have cohorts of carefully selected

patients in Uzbekistan and Swaziland. This regimen is not recommended in persons with known or suspected resistance to any of its components (except for INH), persons with meningeal or osteoarticular disease, or in pregnant women.

Because the drugs used in the initial four to six months of treatment are similar to those used in the “conventional” MDR-TB regimen, there are still significant adverse events to be managed, including hearing loss which has been reported in 13-44% of persons on the shorter regimen. Cumulative rates of toxicity may be lower given the shorter duration of treatment, and rates of loss-to-follow-up are lower in the observational cohorts treated with shorter regimens. Mortality rates of 10-20% have been reported in some cohorts.

The components of the shorter regimen are available from the GDF. Adverse events are similar to those reported in MDR-TB cohorts, although with the combination of moxifloxacin given at higher doses and clofazimine, there may be an increase in QTc prolongation.

Table 1: summarizes the characteristics of the 4 most commonly used new and repurposed drugs

	BDQ	CFZ	DLM	LZD
Dose	400 mg daily for 2 weeks followed by 200 mg three times a week	100-200 mg daily	100 mg twice daily	600 mg daily (with decrease to 300 mg if side effects); optimal dose still being assessed
Duration	24 weeks, although could be extended in patients with limited options	Entire course of treatment	24 weeks, although could be extended in patients with limited options	Entire course of treatment
Half-life	150 days	70 days	38 hours	5-7 hours
Shelf-life	3 years	5 years	4 years	3 years
Adverse events	QTc prolongation, liver function abnormalities	Skin discoloration, abdominal pain, QTc prolongation	QTc prolongation, worse with low albumin	Neuropathy, marrow toxicity, optic neuritis
Type of evidence	Phase IIB	Randomized, non-placebo controlled trial	Phase IIB	Delayed start randomized trial, mostly observational
Use with ART	Not with EFV, caution with lopinavir/ritonavir	Yes	Yes	Yes
Children	Yes ages 12 years and above	Yes	Yes, ages 3 years and above	Yes
Pregnant/breastfeeding	Safe based on animal data	Yes	Safe based on animal data	Yes

Cross-resistance	CFZ	BDQ	Other nitroimidazoles (i.e. PA-824 [pretomanid])	Other oxazolidinones
	BDQ	CFZ	DLM	LZD
Current costs and accessibility	GDF; per 6-month patient course: 900 USD for low-income countries, 3000 USD for middle income countries 30,000 treatments available for free from USAID/GDF	GDF; 1-3 USD per 100 mg tablet; global stock outs common	GDF; per 6-month patient course: 1700 USD	GDF; 2-3 USD per 600 mg tablet
Other comments	Higher mortality rate seen in patients given BDQ in the registration trial; this was not felt to be drug related and has not been shown to be a problem in the cohort of 8000 persons who have received BDQ under program conditions. Observational study in South Africa found lower rates of mortality in persons with MDR-TB treated with BDQ compared to those who did not receive the drug		Newer agent of choice in children; could be considered to replace the injectable agent in the pediatric population	

3. DIAGNOSIS AND PATIENT SELECTION

Diagnosis

Current WHO guidance recommends the new drugs (BDQ and DLM) be used as part of a combination treatment regimen in settings where there is resistance or intolerance to an aminoglycoside, a fluoroquinolone, or both. DLM has also be recommended in persons who are at high risk of failing treatment. WHO also recommends the drug be used in patients with other types of second-line drug resistance, and notes that BDQ should be given to persons who do not qualify for shorter regimens. While neither LZD nor CFZ have such a detailed indication, they are recommended as group C agents (along with ethionamide and cycloserine) to be used in constructing an MDR-TB regimen. As noted above, CFZ is also a component of the shorter regimen recommended by the WHO in 2016 for selected patients.

In terms of the shorter regimen, it should be offered to persons with newly diagnosed TB as long as they are not pregnant and do not have extrapulmonary TB. Shorter regimens

should not be used in persons with known or suspected resistance to any of the regimen components, with the exception of high-dose INH.

Thus, access to rapid PZA resistance testing and SLDST is a key part of initiating the new and re-purposed drugs and the shorter regimens. SLDST is essential to ensure patients access these therapeutic agents as quickly as possible to avoid resistance amplification, ongoing transmission, and worsening lung parenchymal damage. To date, there are limited reliable tests for PZA resistance, although there may be genetic-based testing emerging in the market in the next several years. Many countries are establishing SLDST in liquid culture, although these results can take some time to be received from the lab and acted upon (lab time alone can be 4-6 weeks). The HAIN SLDST can be used to obtain information more rapidly on resistance to isoniazid (INH), rifampicin (RIF), the injectables, and the fluoroquinolones (FQ); the newer HAIN platform can be performed on sputum samples even if they are smear negative. GeneXpert MTB/RIF (GXP) is also developing an expanded cartridge that can test for resistance to INH, kanamycin (KM), and the FQs; the cartridge is currently undergoing validation and may be in use in 2018. These cartridges will function in the existing GXP machines.

One problem with the rapid tests is that they are good “rule in” tests for resistance but not good “rule out” tests. That is, if the test says there is resistance detected, then resistance is likely there. However, because of the multiple mutations that can cause resistance to the FQs and injectables, if the test says resistance is not detected, it does not mean resistance is not there. Thus, patients who do not have resistance on the molecular tests will still need to undergo culture-based DST to prove resistance is not there.

Additionally, many settings do not have access to rapid tests for the detection of SLD resistance. BDQ and DLM can be used in these settings while awaiting culture-based DST if the patient is high risk for having resistance to an injectable, FQ, or both. This high risk population would include any patient who had received these drugs for 30 days or more, any patient who is a contact for a patient with resistance to these drugs, and any patient coming from a high risk epidemiologic setting. Care should be taken to not add a single drug (DLM or BDQ) to the regimen if culture-based DST returns with resistance to an FQ or injectable. Additional recommendations on this population are in the clinical care section below.

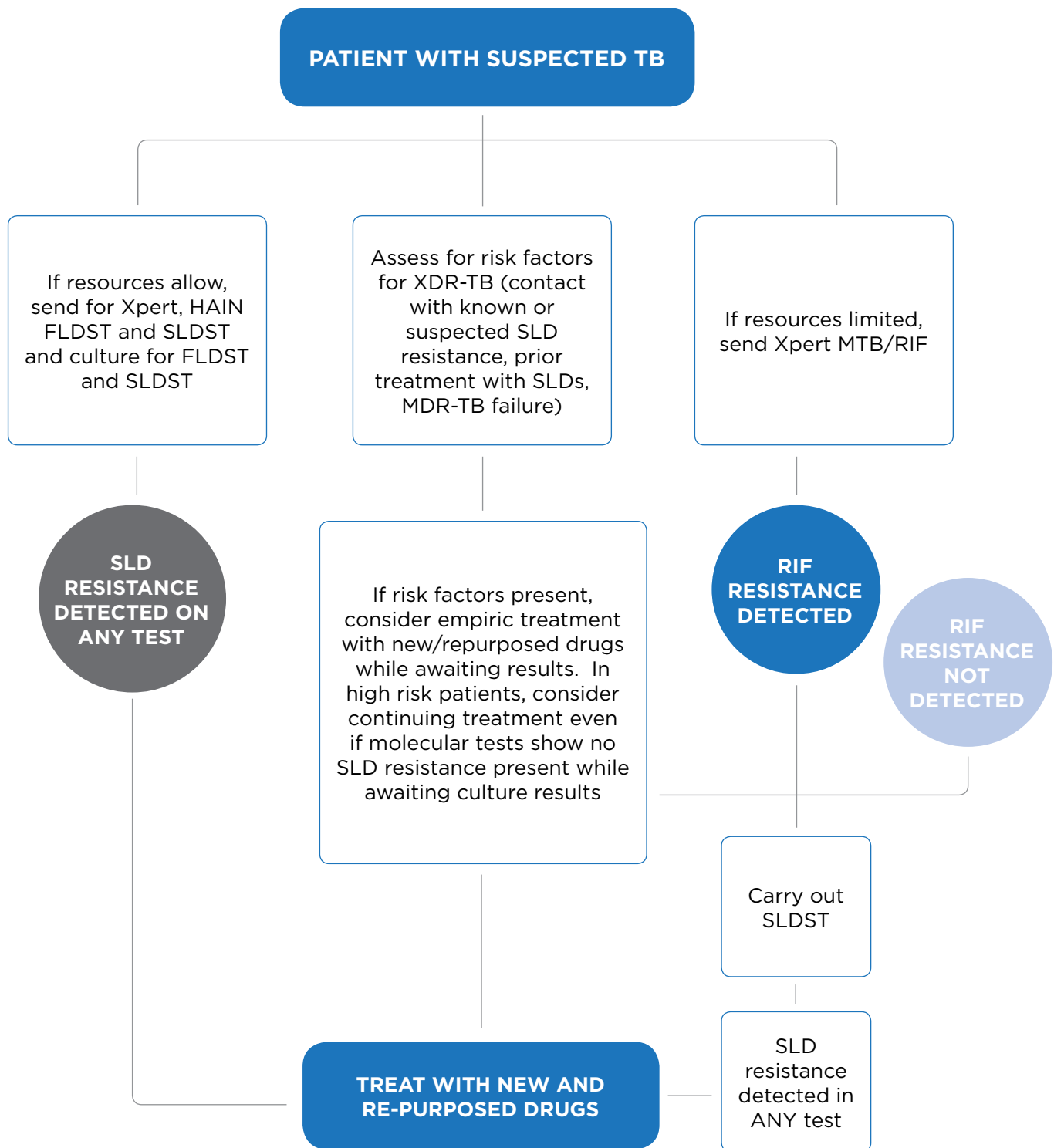
Avoiding Amplification and Misinterpretation of Results

As a key point, patients likely to have resistance to an injectable or FQ or both, including persons who have received these drugs in the past, persons with contacts who are resistant to these drugs, and persons failing MDR-TB treatment, can be started on BDQ or DLM even in the absence of confirmed DST.

It is also important to consider the possibility of resistance amplification that can occur if a patient is placed on inadequate (i.e. less than 3 effective drugs or the use of less potent drugs) therapy while awaiting the results of DST. In patients in whom amplification may have occurred (i.e. 2-4 weeks of treatment while waiting for results), additional new or repurposed agents may need to be added to the final treatment regimen.

Care should be taken when interpreting DST results that take weeks to months to obtain from the time the sample was sent. If the patients received therapy in the meantime, result interpretation must consider possible development of additional resistance.

Figure 1: Sample algorithm to follow when attempting to diagnose SLD resistance



Case Example 1: Diagnosis

MR is a 36-year-old man whose brother died while on treatment for MDR-TB. His brother's regimen consisted of Km-Lfx-Eto-Cs-Z. MR is so busy caring for his brother in their one-room shack that he does not know his health is declining until he begins coughing blood in the night. He presents to the health center with cough productive of bloody sputum and a 7-kg weight loss.

He is seen by a clinician there and TB is suspected. He undergoes GeneXpert testing and the next day his sputum results show that there is TB and RIF resistance is detected. His providers decide to start him on the standard retreatment regimen, even though his brother died while on treatment for DR-TB. His sputum is sent for routine culture and DST to the SLDs. Four weeks later the sputum comes back with resistance to INH, RIF, EMB, and streptomycin. He continues to cough and lose weight and presents to the hospital with massive hemoptysis.

While there another sputum sample is obtained and sent for SLDST as his physician notes his lack of improvement coupled with his contact history. Results show he is resistant to Km, Lfx, and Eto. He continues to decline during this period and dies the day his physicians decide to start treatment for XDR-TB.

Patient selection

The new and re-purposed drugs for treating DR-TB should be considered for use in all patients with MDR-TB, as this is how they were assessed in clinical trials. Because many countries cannot receive donated BDQ and thus cannot afford these drugs for all patients, the drugs are usually used in patients who have intolerance or resistance to the injectables, the fluoroquinolones, or both. It is important to mention, however, that reserving these drugs for only the most resistant cases or critically ill patients will not likely lead to positive results.

Because the formal studies of BDQ and DLM only included individuals with pulmonary disease between the ages of 18-65 years, this is the population for whom the drugs are licensed and recommended. However, they can be used in other populations if the likely benefits outweigh the risks. Of note, the PK and safety of DLM has been assessed in children as young as 3 years of age and is currently being assessed in children ages 2 and under.

LZD and CFZ can be used in all patients. The shorter regimen is also broadly recommended although pregnant women and patients with extrapulmonary TB should not receive this treatment. In terms of BDQ and DLM, there are some absolute contraindications for use of the drug (the drug should not be used in these patients), some relative contraindications to these drugs in which they should be used with caution, and some populations in which increased monitoring is required. These are reviewed in the box below.

- **ABSOLUTE CONTRAINDICATIONS:** patient refuses to consent; patient has an allergy to either medication; or patient has a history of certain cardiac complications, including a QTcF>500ms, a history of Torsades de pointes, a history of ventricular arrhythmias, or a history of known severe cardiac disease (there is no standard definition of severe cardiac disease, thus patients with known cardiac disease should be discussed with an expert prior to starting new drugs)
- The drugs should be **USED WITH CAUTION** in persons under the age of 18 for BDQ and under the age of 3 years for DLM; persons who are over the age of 65; patients who are pregnant (although DLM has been shown to be safe in animal studies) or nursing; patients with renal and hepatic impairment; and with certain antiretroviral medications (EFV, lopinavir/ritonavir)
- Prior to initiating either drug, ensure electrolytes are normal and liver function tests are less than three times the upper limits of normal
- Prior to initiating DLM, ensure that the albumin is 2.8 g/dL or higher or that protein supplementation is being given
- Minimize the use of other QTc prolonging agents as much as possible when using either BDQ or DLM

Even though specific guidance has not been issued on the use LZD in these settings, the drug can be toxic to the bone marrow and should be avoided in patients with a platelet count below 75,000/mm³ or a hemoglobin of less than 8g/dL.

Other second-line drug resistance and the use of new and re-purposed drugs

Because the injectables and fluoroquinolones are felt to be the most effective of the second-line drugs, resistance or intolerance to either of these is felt to be enough to consider use of the new drugs in combination with others to achieve better outcomes. The WHO also recommends using new and re-purposed drugs if there is susceptibility to injectables and fluoroquinolones but resistance to ‘two or more’ other SLDs (i.e. ethionamide, cycloserine). There is unclear evidence for this recommendation, and programs may want to consider using the new or re-purposed agents if there is resistance or intolerance to any SLD, depending on the outcomes in their program as well as the clinical status of each patient. Of note, the WHO recently recommended BDQ for patients who do not qualify for the shorter regimen.

Maintenance of patients on traditional SLDs is potentially influenced by the much lower cost of these drugs compared with the new and re-purposed agents, although the cost of a patient being lost to follow up and continuing to transmit in the community is also very high. In addition, the SLDST results for ethionamide, cycloserine, and PAS are somewhat unreliable. In a setting of poor outcomes or widespread use of SLDs, programs could consider using new and re-purposed drugs to improve outcomes of individuals with other forms of SLD resistance, even if it is only to a single agent. The original 2014 WHO guidance on DLM specifically supports this, in that they recommend DLM be used in patients with a risk of poor treatment outcomes.

Optimizing the use of new and re-purposed drugs

A key point is that saving the new drugs BDQ and DLM for only “the most resistant” patients or the “most desperate cases” will result in poor outcomes and is likely NOT the best way to maximize the benefits of these drugs.

Figure 2 shows an algorithm on careful patient selection.

Case Example 2: Patient Selection

RP is a 66-year-old man with HIV who is diagnosed with RIF-resistant TB after presenting with productive cough and back pain for 2 months. As per national protocol, his sputum is sent for testing to SLDs and lineprobe assay (LPA) for resistance to Km and Lfx. He is started on a regimen of Km-Lfx-Z-Cs-PAS-Eto and 5 days later his SLDST results from LPA show resistance to Lfx.

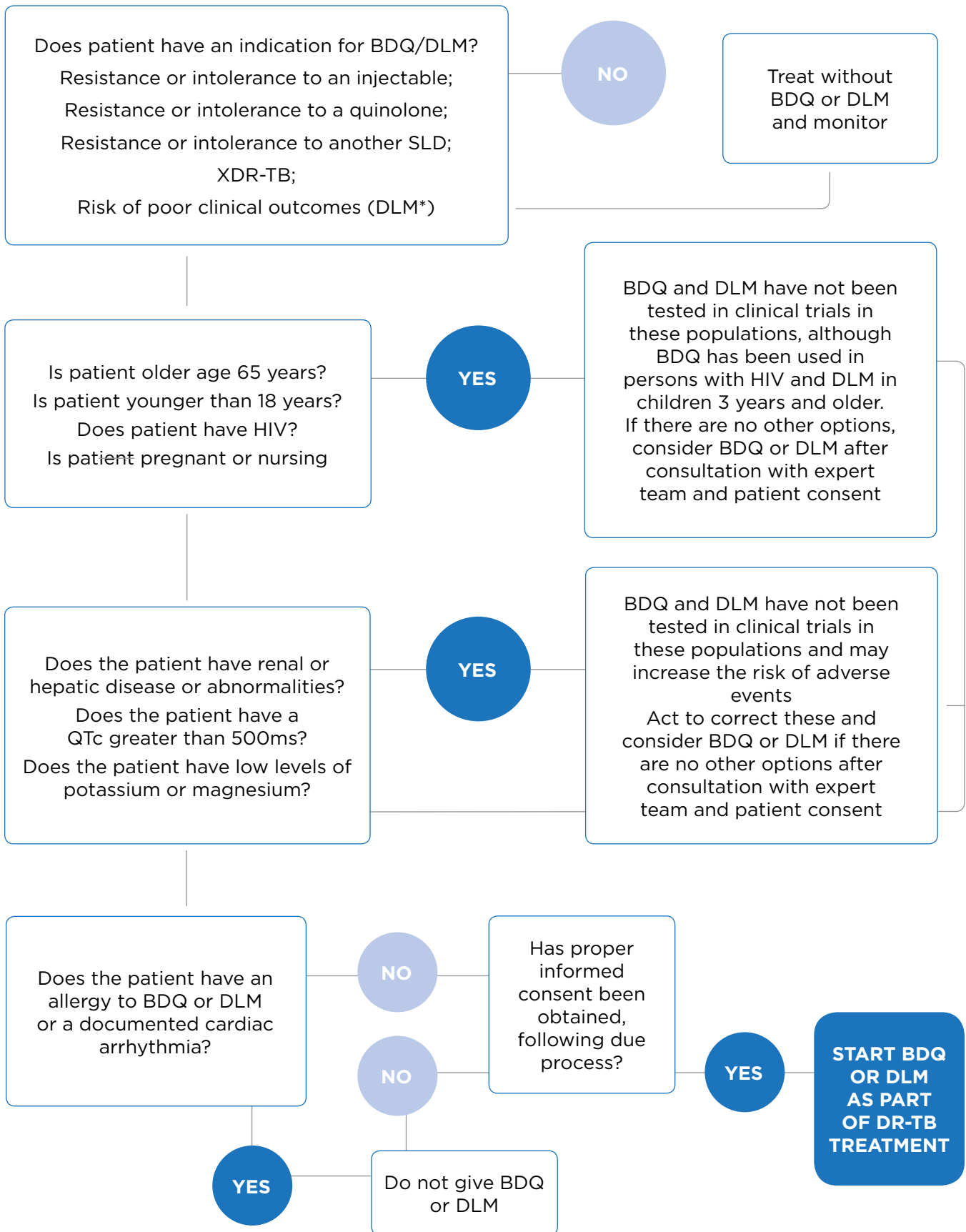
He is presented for BDQ consideration but because he is 65, he is deemed to be ineligible to receive the drug. Instead, his regimen is changed to include Cm-Mfx-Z-Cs-PAS-Eto-high dose INH-Amoxicillin/CLV. LZD is considered but not administered because of his “advanced age.” He continues to deteriorate and leaves therapy to go home “and die in my house.” His 30-year-old son is worried but agrees to care for him at home. As part of the home assessment, the son undergoes routine contact screening, and is found to have findings consistent with TB. His GeneXpert is positive and shows RIF resistance. Given his contact history, he is started on a regimen containing BDQ-Cm-Lfx-Z-Cs-Eto-LZD. He begins to improve and is able to bury his father when the father dies at home 3 months later. The son is ultimately cured of his presumed XDR-TB.

Routine baseline and follow-up testing

In addition to the microbiological tests recommended above, several other laboratory tests for patients initiating new and re-purposed agents may be necessary to ensure the drugs are used in an optimal way. In addition to the standard PMDT testing panel, the following evaluations are also recommended:

1. A baseline 12-lead ECG to assess for arrhythmias, calculate QTc interval, and have a comparison prior to starting treatment should the patient develop problems in the future;
2. A baseline lipase has been recommended for patients starting BDQ, but it is unclear how useful this test will be in the absence of symptoms. In settings with access to routine lipase, all patients could undergo this baseline test. However, it may be necessary to check this only in patients with signs and symptoms of pancreatitis (i.e. nausea, vomiting, severe abdominal pain);

Figure 2: Implementation Tool: Careful Patient Selection



3. DLM is metabolized by albumin, and higher rates of adverse events, most notably QTc prolongation, have been seen in patients with low albumin (i.e. <2.8gm/dL). A baseline albumin is therefore recommended for patients who need DLM, and aggressive nutritional support given to those whose albumin levels 3.0 and below;
4. Low potassium, low magnesium, and low calcium have all been associated with a risk of fatal arrhythmias in patients with QTc prolongation. Thus, it is recommended these tests be evaluated and electrolytes supplemented as needed. If testing for magnesium or calcium is not available, checking just the potassium is reasonable, and if low, supplementation of all three agents should be pursued;
5. Patients being considered for LZD should have a baseline complete blood count assessed.

See Table 4 for a summary of recommended testing at baseline and follow up for patients started on new and re-purposed drugs.

Location of care

Because the new and re-purposed drugs have only been given to a limited number of patients, many experts and programs feel more comfortable hospitalizing patients for a certain period. Much of this concern centers around the possible ECG abnormalities that have been associated with the new drugs and some of the re-purposed drugs (i.e. CFZ). It is important to note, however, that BDQ, DLM, and CFZ—all of which have been associated with QTc prolongation—take several weeks to reach their steady-state concentrations, and thus the QTc prolongation risk may not be apparent soon after starting QTc prolonging drugs alone or in combination. If hospitalization is to occur for reasons for cardiac safety, there should be access to a defibrillator (a simple automated one would suffice) should a fatal arrhythmia develop. Details about QTc management are discussed in the section in adverse event management.

If there is sufficient adherence support, patients can be treated with new and re-purposed drugs in a primary care setting, provided they can access appropriate care after hours if needed. Hospitalization of patients receiving new and re-purposed drugs may contribute to nosocomial transmission and may be associated with higher costs and increased stigmatization for patients and programs. For these reasons, unless there is a clear medical need for hospitalization, patients receiving BDQ, DLM, LZD, or CFZ can be started on treatment in the outpatient setting, provided there is close monitoring and follow up. This is in keeping with the important PMDT achievements in decentralized care over the past decade, and strengthens the capacity of clinicians and support staff to manage DR-TB in an outpatient setting.

The shorter regimen can be initiated in either the inpatient or outpatient setting, depending on the clinical status of the patient.

Box 3: Clinical review committees

Most countries and programs have existing clinical review committees or expert panels who meet to discuss difficult cases and to offer one another support. Some of these meetings may take place in person, but many meet via email or conference calls to be able to provide relevant feedback in a timely fashion. Such groups could discuss the cases in which the new drugs and re-purposed drugs are being considered to ensure there is consensus on the management of patients. Given the airborne nature of the epidemic and the need to rapidly respond to patients, these committees should have an expedited mechanism for clinical decision making.

In reviewing patients who may need new or re-purposed drugs, clinical review committees can also play other key roles, including:

- Making recommendations in complicated situations (i.e. children, pregnant and breastfeeding women, HIV co-infection);
- Linking with international communities for support and discussion (i.e. European Respiratory Society (ERS)/ WHO Consilium, Sentinel Project);
- Supporting decisions to use the new drugs outside of current recommendations, but where the benefits of the new drug outweigh the risks (i.e. use of BDQ and DLM in combination);
- Supporting discussions about management of adverse events or regimen modifications based on updated results or clinical progress.
- All clinical review committees should have standard assessment forms and communicate the results of their discussion effectively and efficiently to the requesting providers, with detailed information provided on the decisions that were made.

Case Example 3: Screening

PR is a 32-year-old woman who is diagnosed with primary XDR-TB 8 weeks after presenting to her health center complaining of cough, fever, and night sweats. She had migrated to a high-burden DR-TB country for work. Her physician sent her sputum for GeneXpert as well as for first- and second-line DST. The decision is made to place her on a DLM containing regimen, but her baseline albumin is 2.3 gm/dL and her QTc interval is slightly prolonged at 490msec.

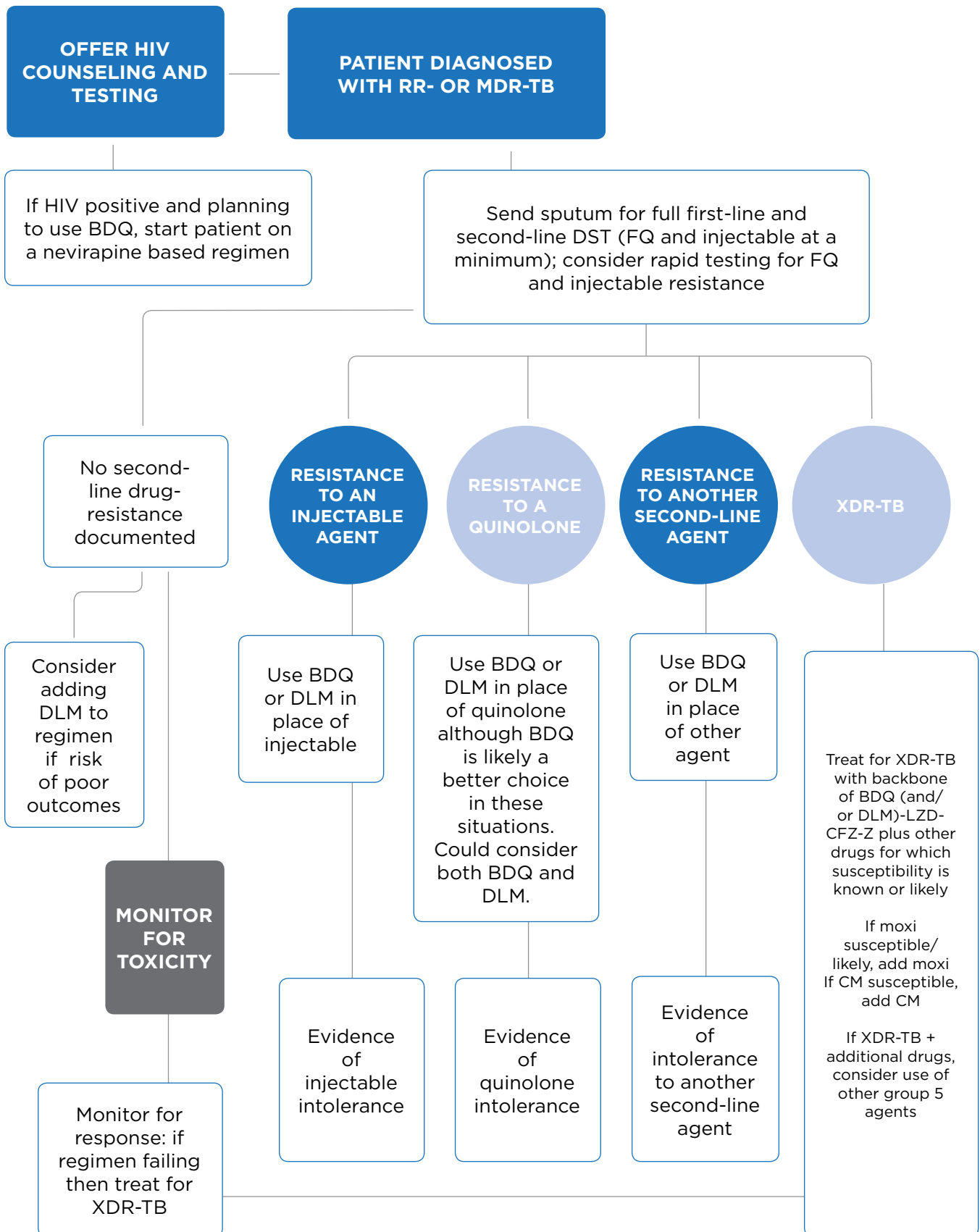
Her physician starts her on aggressive protein and calorie supplementation and finds out that she just completed malaria treatment. The ECG is repeated in 2 weeks and the QTc has normalized. The patient has also gained 1.5 kg. She is started on a DLM-containing regimen and does very well, ultimately being cured of her XDR-TB.

4. REGIMEN COMPOSITION AND DESIGN

In general, the use of new and re-purposed agents follows similar principles to the design of regimens for general DR-TB treatment. In patients with RR-TB or MDR-TB, a regimen with at least 5 effective TB medicines gearing the intensive phase is recommended, including PZA and 4 core second line TB medicines. Principles of regimen design are summarized in the algorithm in Figure 3 and in the summary below:

- Never add BDQ, DLM, LZD, or CFZ as a single drug to a failing regimen
- If patient is culture negative, and the new drugs are being SUBSTITUTED for toxicity reasons, a single drug substitution can be made
- If the patient is failing a current MDR-TB regimen, at least 3-4 new drugs need to be added, including BDQ and/or DLM
- There are limited data on the use of BDQ and DLM given in combination, and larger studies of this combination have only recently started. However, data from case reports and smaller cohorts suggest there is no increased risk of QTc prolongation or cardiac complications when the two newer agents are used together. Currently, there are more than 150 patients with limited treatment options who are receiving or have received both BDQ and DLM at the same time. If these two drugs are to be considered in combination use for patients with extreme resistance, the case should be reviewed by the clinical expert committee prior to initiating treatment and patients should have twice monthly ECGs for the first 3 months they are on the combination;
- Use with caution with other drugs that can prolong the QTc interval (i.e. moxifloxacin, clofazimine)
- The backbone regimen usually consists of a new drug (BDQ, DLM, or both), linezolid, CFZ, and PZA
- Other possible agents could include imipenem with amoxicillin/clavulanate (which requires placement of medi-port) or any other SLD to which susceptibility is likely
- The use of moxifloxacin is controversial as it prolongs the QTc interval; it should be considered if there is evidence for susceptibility or if susceptibility is likely. Of note, expert opinion on the inclusion of moxifloxacin in regimens containing BDQ or DLM and a third QTc prolonging drug (i.e. CFZ) vary widely. Some experts favor using levofloxacin if there are two other QTc prolonging drugs; others believe moxifloxacin is potent enough to justify the risk and the inclusion of a FQ in treatment is associated with better outcomes (although this may not reflect actual therapeutic benefit of the drug). It is recommended that the decision over which FQ to use and for how long be decided on a case-by-case basis with input from the clinical review committee

Figure 3: Implementation Algorithm: Using Bedaquiline or Delamanid in WHO-Recommended Regimen



Box 4: New drugs and the shorter regimen

The nine to 12 month (“Bangladesh” or “shorter”) regimen has now been recommended by the WHO for the treatment of MDR-TB. This regimen contains CFZ, but a programmatic approach introducing this regimen and the new drugs/ LZD is necessary, as the WHO recommends that new drugs be used in persons who do not qualify for the shorter regimens. These two strategies must be complementary, as the shorter regimen is likely to be of limited utility in patients with resistance to the FQ or injectable. In some settings, all patients with RR-TB undergo rapid screening for FQ and KM resistance (HAIN Lineprobe Assay); those with no resistance receive the shorter regimen and those with resistance to either or both receive either BDQ or DLM. Furthermore, in persons who are failed by the shorter regimens or who relapse after being treated with shorter regimens, there will be the need to utilize BDQ, DLM, and LZD in their treatment. Finally, drug substitution with either DLM or BDQ could be considered in the shorter regimen if intolerance should develop. This should be considered on a case-by-case basis, and of note this is not current WHO recommendation. Thus, countries should not plan for using EITHER newer drugs or shorter regimens, but need to plan for BOTH.

Length of regimen

Both DLM and BDQ were tested in six month trials and are recommended for the first six months of therapy only. Since then, cohorts of patients treated with BDQ for up to two years have been reported, with no increases seen in adverse events among persons receiving prolonged courses compared with those who received only six months of treatment.

However, in the phase IIB non-randomized part of the DLM trial, DLM was given in research conditions for up to eight months. In this study, six months was chosen for ease of endpoint analysis. Additionally, several patients receiving BDQ under compassionate use have received more than six months of treatment. Thus in patients with resistance or intolerance to multiple second-line drugs, BDQ or DLM could likely be extended beyond six months of treatment, but this decision should be made on a case-by-case basis. Both the STREAM 2 and NIX clinical trials, which have been approved for study by stringent ethics committees, allow for the use of BDQ for nine months.

Bedaquiline or delamanid?

Since BDQ and DLM are both now available from the Global Drug Facility (GDF), providers will find themselves having to decide which agent to use. Complicating this matter is that there have been no head-to-head comparisons of the two drugs. The clinical trial designs and results show a higher quality of evidence supporting the efficacy of BDQ; in terms of safety, however, DLM is felt to be safer as it was not associated with a higher mortality (although the study design after eight weeks of administration was not randomized).

In places where there is access to both, the following criteria for choosing BDQ or DLM could be used:

1. Bedaquiline has been more widely used than delamanid in treatment programs—with more than 8,000 persons started on bedaquiline treatment as of April 1, 2017 compared with just over 600 started on delamanid. For this reason, until phase III results are available, for patients for whom an effective, tolerable regimen can be constructed with only one newer drug, bedaquiline is the appropriate choice, except in the specific clinical situations below that favor delamanid.
2. Delamanid is the preferred novel agent:
 - for children under the age of 12 years;
 - for pregnant women. Although both drugs are presumed to be safe during pregnancy based on animal data, the long half-life of bedaquiline could mean that the newborn child will have bedaquiline in his or her system after birth;
 - in persons with liver toxicity and those who are using alcohol, as defined in national protocols;
 - for persons on efavirenz-based antiretroviral therapy if the efavirenz cannot be changed;
 - for people on opioid substitution therapy and may be preferred in persons on treatment for hepatitis C due to fewer drug-drug interactions (although have not been formal studies of either bedaquiline or delamanid for persons receiving treatment for hepatitis C);
 - for persons who are at high risk of treatment failure and need an additional agent added to their standard MDR-TB treatment, as per the 2014 WHO recommendations.

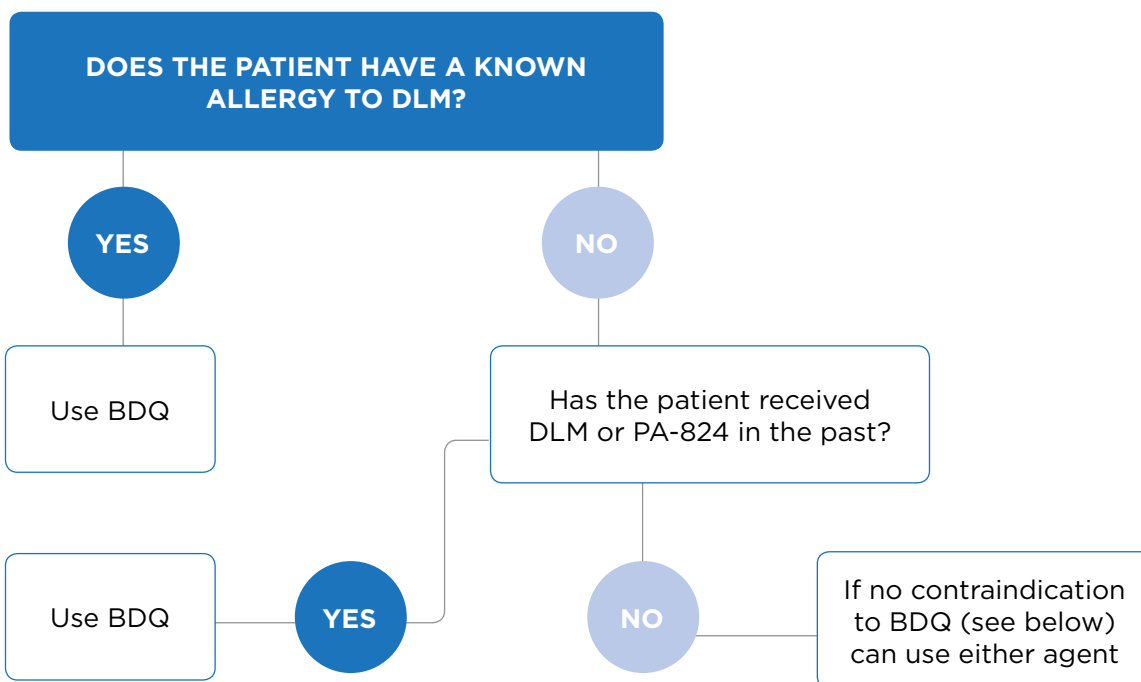
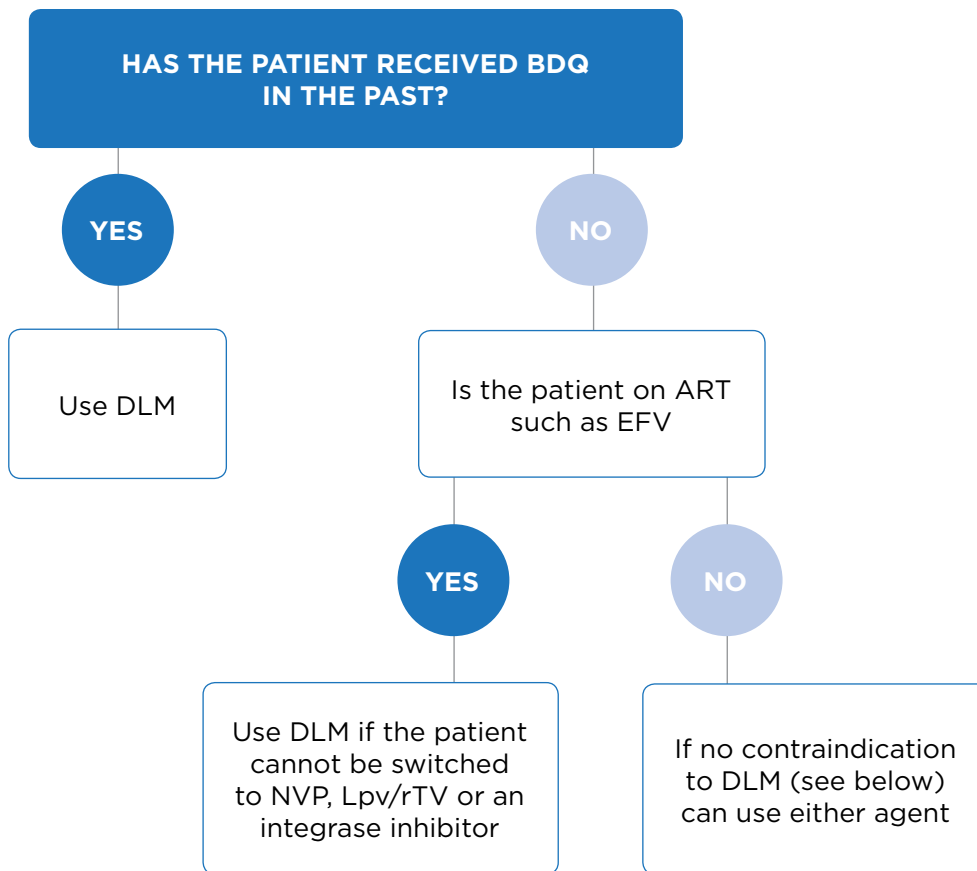
Finally, emerging safety data suggest that a combination of bedaquiline and delamanid could be used as part of multi-drug backbone therapy for persons with limited treatment options. Combination bedaquiline and delamanid should be considered in:

- persons with drug-resistant tuberculosis in whom a four-drug regimen plus PZA cannot be constructed with only one novel agent;
- persons who received the WHO-recommended shorter regimen but did not have a successful treatment outcome;
- persons with prior exposure to clofazimine;
- persons with prior exposure to linezolid;
- persons treated for MDR-TB using conventional regimens who did not have a successful treatment outcome.

See Figure 4 for a simplified flow chart for choosing one drug over the other in settings where both are available.

The WHO recommendation to use DLM in patients who are “at high risk of poor clinical outcomes” is intended to follow more closely the way both new drugs were tested in clinical trials (i.e. added on to standard multi-drug therapy as opposed to being used only patients with higher degrees of drug resistance or intolerance). In addition, some experts feel that DLM is safer than BDQ. There are no more specific guidelines available on this recommendation, and decisions will need to be made at country level.

Figure 4: Bedaquiline or Delamanid: Making A Choice if Both are Available
 (also refer to annex 4.5 in the WHO Companion Handbook)



Recommended Backbone XDR-TB Regimen

Patients with XDR-TB will likely benefit greatly from the use of new and repurposed agents. In such cases, each regimen will need to be individualized to ensure the highest likelihood of success. In most cases, the regimen will be based on the following backbone:

BDQ (and/or DLM)-LZD-CFZ-PZA

PZA is included in this regimen because there may be some synergy when the drug is used with BDQ, even in the setting of phenotypic resistance.

Some experts would suggest that a backbone regimen of BDQ plus DLM-LZD-CFZ-PZA be given to all XDR-TB patients, provided the patient can be closely monitored with twice monthly ECGs for the first 12 weeks of therapy.

Other drugs can be added based on the patient's history and DST results. In general, if there is evidence of susceptibility, an injectable agent should be used. A quinolone should be considered for use but care must be taken in selection of the specific quinolone. While there are data to support superior efficacy of moxifloxacin over levofloxacin for resistant strains of TB, moxifloxacin has been shown to both prolong the QTc interval and cause Torsades de pointes. Ongoing trials may provide additional evidence to support decision making in this setting, but many programs opt to use high-dose levofloxacin under these conditions.

Drugs with limited evidence for their efficacy may need to be selected, most notably the carbapenems. This class of agents has been used in combination regimens with some success in Armenia and is an option if there are no other drugs. There are logistical challenges in the administration of the carbapenems, as they must be given intravenously (IV); must be given with amoxicillin-clavulanic acid as they cannot kill *M. tuberculosis* without clavulanate; and they usually require the placement of a central IV line since they must be given long term. In patients with limited options, however, these agents have been used successfully in program settings and should be considered in the treatment of XDR-TB.

Case Example 4: Regimen Design 1

TM is a 21-year-old woman who is failing current therapy for MDR-TB. She has a history of previous treatment but became lost to follow-up when her sister died and she had to move to take care of her sister's children. She continued to cough and lose weight and eventually presented to a regional health center. There, an GeneXpert was positive and RIF resistance was detected. She was started on treatment with Km-Lfx-Z-PAS-Eto, and despite good adherence she continued to be smear and culture positive after five months of treatment, with signs and symptoms of clinical deterioration.

Sputum was taken for full DST to the first- and second-line drugs, but the culture becomes contaminated and another sample is sent with the same problem occurring. Her physicians are watching her physically decline and after six months of MDR-TB treatment, they decide to start her on an empiric XDR-TB regimen. After normal baseline testing she is given BDQ-LZD-CFZ-Lfx-Cs-PZA. No DST is ever reported back.

She does well on this regimen and is eventually cured of her presumed XDR-TB. When her three-year old nephew falls ill, he is also treated for XDR-TB but given DLM instead of BDQ because of his age.

Case Example 5: Regimen Design 2

PJ is a 43-year-old man who works as a school teacher and is on treatment for MDR-TB with a regimen consisting of Km-Ofx-Z-Cs-Eto. At the third month of therapy, he is smear- and culture-negative but notices buzzing in his ears. He describes the symptoms to his physician who switches his Km to Cm, but the buzzing gets worse and he begins to have trouble hearing. His physician decides to discontinue the injectable and instead substitute it with BDQ, given the severity of the hearing loss. The patient does well but has lost so much of his hearing that he can no longer work as a teacher and loses his home. His physician is happy the man is cured of his DR-TB but wishes he had stopped the Km and started BDQ sooner, as this could have had a major impact on the patient's life.

5. SPECIAL POPULATIONS

Children

In general, children have not been included in the clinical trials of DLM and BDQ that were used to register the drug, thus there is limited information about the long term safety and PK of these new drugs in children—although data are currently being collected and analyzed. LZD and CFZ have been used in children, but there are currently no formal studies on their PK and safety; LZD PK studies are currently being carried out at the Desmond Tutu TB Center in Cape Town, South Africa.

Children, however, are often desperately in need of these drugs, especially in settings where rates of primary transmission of resistant strains are high. Thus, programs must weigh the risk of using these medications in children or letting them die of untreated or poorly treated DR-TB or lose their hearing to the injectable agents—which is devastating for subsequent cognitive and social development.

Of note, some providers recommend that DLM should be given to all children with MDR-TB. If intolerance develops to another medication (especially the injectable), then the offending drug can be discontinued in a timely fashion without compromising the regimen’s efficacy. Some providers feel that it would be reasonable to offer DLM instead of the injectable agent, given the pain the routine injection causes for the children and the severe consequences should a child lose his or her hearing.

DLM is being tested for PK and safety in children and has been given for compassionate use in children as young as three years. For this reason is preferable to BDQ, although BDQ has also been given safely to children ages 12 years and above and could be used in this population. There are pediatric formulations of both BDQ and DLM being developed. Recommendations for pediatric dosing are below, although these have not been confirmed with intensive PK studies for BDQ or for children under three years of age for DLM.

Table 2: Pediatric doses of new and re-purposed drugs

Drug	Recommended Dose	Comment
DLM	>35kg: 100 mg twice daily 20-34 kg: 50 mg twice daily Below 20kg: 3-4 mg/kg divided into 2 doses each day	Currently being assessed in children ages three and under. Dosing recommendations for the <20 kg group are based on current dosing recommendations in the higher weight group
BDQ	Children aged 12 years and above should receive the full dose of BDQ For children under 12 years of age 6mg/kg loading dose daily for 2 weeks followed by 3mg/kg thrice weekly	This is based on current dosing with an adult weight of 65 kg estimated
LZD	10mg/kg/daily or twice daily	Available as a suspension
CFZ	1 mg/kg daily	Comes as capsule or gel cap of 50 or 100mg; consider compounding. Gel caps cannot be split, but could be given every other day if need be with the dose averaged

Of note, the shorter regimen is recommended for children who themselves meet or have a contact who meets criteria for use of the therapeutic strategy.

Case Example 6: Children

MB is a 5-year-old child whose mother died of TB while on treatment for MDR-TB. The mother's full DST results—available only after her death—showed she had XDR-TB, with additional resistance to Eto, Mfx, and all the injectable agents. The child weighs 13 kg.

A post-exposure visit to the house is made by a nurse who took care of his mother, and she notes that MB has swollen lymph nodes in the neck and has fallen precipitously off his growth curve. He is also coughing. A lymph node aspiration is done and sent for culture and an induced sputum sent for GeneXpert which comes back as “saliva.”

The decision is made to start MB on empiric XDR-TB treatment when he becomes short of breath and oxygen dependent. His physician constructs a regimen based on the resistance pattern of his mother, which includes Cs-PAS-LZD-Z-Cfz. Given the severity of the child's illness and the concern about resistance to both PZA and Cs, the physician wants to add one of the new drugs to the regimen. He can access DLM and starts it at a dose of 25 mg twice daily. MB rapidly improves and is cured of his TB, although he has residual peripheral neuropathy from the LZD.

Adolescents

Adolescents (those ages 13 years and above for this handbook) have not been included in clinical trials, usually because obtaining consent can be problematic and many groups do not wish to invest the extra time needed to get approval to include adolescents in their trials. DLM can be used in adolescents. BDQ can also be used safely in this population as well, and many countries give the drug to children as young as 12 years of age. Of note, adolescents may need additional adherence support and are at high risk of “falling through the cracks” at each step of the DR-TB cascade.

Case Example 7: Adolescents

ZD is a 16-year-old girl who lives with her 3 sisters ages 22, 20 and 19. Their parents both died of XDR-TB, and all four girls have signs and symptoms of TB. ZD's GeneXpert result shows resistance to RIF, and all four girls have sputum sent for SLDST. Their physicians fear the worst and start all four girls on an XDR-TB regimen consisting of LZD-Cfz-Z-PAS-Cs-Eto. ZD's older sisters all get started on BDQ as well, but the drug is not given to her as she is “not yet 18.” Despite multiple attempts, the program refuses to give her BDQ because of her age. After four months on therapy, and while watching her sisters all get better, ZD dies of complications for XDR-TB.

Elderly

Persons over the age of 65 years were left out of the clinical trials and many compassionate use programs, but DLM and BDQ could be used in this population provided there is no active congestive heart failure or severe coronary artery disease. LZD has been used in this population, although rates of adverse events are likely to be higher, especially bone marrow toxicity.

HIV

In some regions of the world, a clear majority of persons with DR-TB also have HIV, and most phase III trials go to great lengths to include populations of patients with HIV. However, the number of HIV-infected patients included in the BDQ and DLM registration trials was limited, and for this reason, both drugs are recommended to be used “with caution” in persons with HIV. In fact, given the higher rates of morbidity and mortality seen in persons co-infected with DR-TB and HIV, it is imperative that the new and repurposed drugs be used in this population. The expanded access program for BDQ has allowed for a significant number of patients with HIV on ART to be given this drug and it has been shown to be safe and effective.

The real concern over the use of the new and re-purposed drugs is the selection of ART. Care must be taken to avoid drug-drug interactions that could lower the doses of the TB drugs or ART. Care must also be taken, whenever possible, to avoid overlapping toxicity.

The following principles should be followed when selecting new and repurposed TB drugs and ART:

- DLM can be used with most ART regimens, including efavirenz, lopinavir/ritonavir, and raltegravir (or dolutegravir);
- EFV can decrease levels of BDQ and should not be used unless there are no other options. If used, the BDQ dose should be doubled so that 800 mg daily is given for the first 14 days followed by 400 mg three times a week;
- BDQ should be used with caution with PI-containing regimens;
- BDQ can be used with dolutegravir;
- Patients on BDQ will need to be on NVP while on BDQ. Once BDQ has been stopped, EFV can be restarted without a “washout period” (i.e. waiting for BDQ to clear the system), since it is EFV that lowers BDQ concentrations and not vice-versa;
- Neither LZD nor CFZ appear to have any drug-drug interactions with ART.

Table 3: Possible overlapping toxicities with the new and repurposed TB drugs and ART

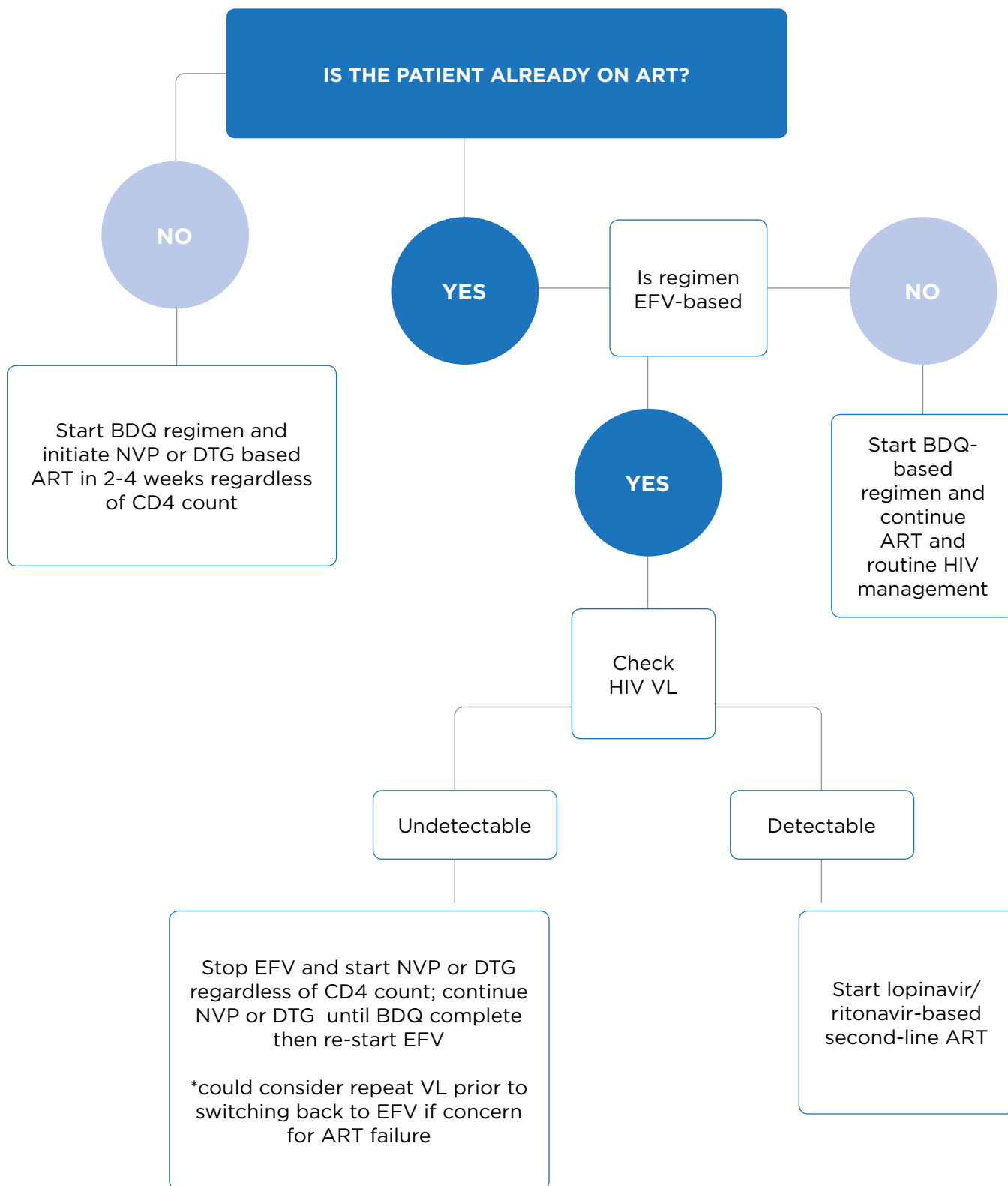
	Bone marrow toxicity	Peripheral neuropathy	QTc prolongation	Hepatotoxicity	GI issues (nausea, vomiting, pancreatitis)
BDQ			X	X	X
CFZ			X	X	X
DLM			X	X	
LZD	X	X		X	
NVP				X	X
EFV			X	X	X
Lopinavir/ritonavir			X	X	X
TDF					
AZT	X		X	X	
3TC				X	
D4T		X		X	X

If BDQ is being used, the patient will need to be on NVP, dolutegravir or lopinavir/ritonavir-based ART. If the patient is not yet on ART, then a NVP-based or dolutegravir-based regimen should be started, regardless of CD4 count. If the patient is already on ART and it is NVP, dolutegravir or lopinavir/ritonavir-based no changes are needed. If the patient is on EFV, then a viral load should be assessed. If the VL is undetectable, then the patient can be switched from EFV to NVP while he or she is on BDQ and then put back on EFV as soon as BDQ is complete. If the VL is detectable, the patient should be switched from EFV to lopinavir/ritonavir and continued on this regimen.

An algorithm for the management of patients with HIV is provided below.

Of note, although the shorter regimen has not been widely used in persons living with HIV, the regimen could be considered provided there is close monitoring for relapse.

Figure 5: Management of HIV Co-Infected Patients



Case Example 8: HIV

PR is a 23-year-old man with HIV, last CD4 count of 72, who has been on ART for one month with TDF-3TC-EFV. He does well initially but within three weeks of starting ART he develops signs and symptoms of active TB. A rapid test shows resistance to INH and RIF and he is started on an MDR-TB regimen with Km-Lfx-Eto-Cs-Z. He starts this regimen and has some minimal relief of symptoms, but his sample sent for SLDST comes back with resistance to Km.

He is started on a new regimen on BDQ-Cm-Mfx-LZD-Cs-PAS-Z-Eto. Moxifloxacin is included on the chance that FQ resistance was not detected but may still be present in phenotypic testing. There is no DLM available in the country. Consideration is given to CFZ but his physicians do not want to have him on three drugs that could prolong the QTc interval. His EFV is changed to NVP given the drug-drug interactions with EFV and BDQ and the fact that his CD4 count was low.

He does well on this regimen, and after completing 24 weeks of BDQ, his NVP is switched back to EFV. He is cured of his XDR-TB and his HIV remains well controlled, with an increase in his CD4 to 398.

Pregnancy and breastfeeding

There are no data on the safety of the new drugs on developing fetus or on breastfed children. Animal studies with BDQ showed no signs of reproductive toxicity. DLM studies in animals have shown no signs of reproductive toxicity and DLM is allowed in pregnant women in the compassionate use/expanded access protocols. LZD can be used safely in pregnancy and breastfeeding. Because CFZ accumulates in the lipids, it will be passed on during breastfeeding. When a woman who is pregnant or breastfeeding needs new drugs, programs must weigh the risks and benefits of using the drugs versus the risks of untreated or under-treated DR-TB in the woman. Clinical expert committees can help make decisions in this population.

As with all PMDT, birth control should be offered to women free of charge as part of routine DR-TB management. There are very limited data on the interactions with different forms of contraceptives and the new drugs. If a woman is on a BDQ containing regimen, and becomes pregnant, the long half-life of this drug should be considered when trying to decide whether to continue therapy. In many cases, the woman may already be past her first trimester of pregnancy and even if the drug is stopped, it will persist in the serum for up to six months.

The shorter regimen is not recommended for use in pregnant women.

Case Example 9: Pregnancy

LK is a 30-year-old woman who is diagnosed with XDR-TB and started on a regimen of LZD-CFZ-BDQ-Eto-PAS-Cs-Z. She has extensive lung damage but begins to feel better on treatment. She routinely receives injections for family planning, but on her last three visits to her health center, they have had no birth control available.

Her menstrual cycles have been quite irregular since her diagnosis of TB, and she is not worried when she misses 3 cycles in a row. When she notes weight gain in the abdomen and breast swelling and tenderness, she presents to the health center where she is found to be pregnant.

She is immediately sent to the MDR-TB hospital where the pregnancy is confirmed. Her physicians are worried given the lack of safety data on BDQ in pregnancy. They discuss the case at length with the patient and her mother and review the risks of continuing BDQ versus the risks of stopping the drug in a case like hers with high-level resistance and massive lung destruction.

After explaining that the fetus will continue to be exposed to BDQ given its long half-life, even if the drug is stopped today, the patient and her mother decide to continue with BDQ for the full 24 weeks. The pregnancy is reported to the National TB Program as part of BDQ monitoring. Four months later, LK gives birth to a small, but healthy baby girl. She herself has improved and is able to sleep with and breastfeed the baby.

Extrapulmonary TB

Patients with primary extrapulmonary DR-TB were not included in the registration trials largely because it is difficult to define outcomes in this population if routine culture specimens cannot be obtained. There is no reason to believe the new and repurposed medications cannot be used in this population. The shorter regimen can be used for EP DR-TB except in cases of meningitis or osteoarticular disease, since longer courses of therapy may be indicated in persons with these forms of EPTB.

Hepatitis B and C

In some regions of the world, there are significant rates of hepatitis B and C in patients who have DR-TB. There are no data on the safety or efficacy of BDQ or DLM in this population of patients. LZD and CFZ have been used, but there can be overlapping toxicity with some of the drugs used to treat hepatitis. The new protease inhibitors for treating hepatitis C have never been used with BDQ and DLM, thus there is no information on drug-drug interactions. If patients with hepatitis B or C meet the criteria for using one of the new drugs, care should be taken to ensure there is no acute liver problem and that the transaminases are less than three times the upper limit of normal and the bilirubin less than 1.5 times the upper limit of normal when starting the drug. More frequent monitoring of liver function tests may also be needed. Clinicians will need to weigh the risks of untreated or poorly treated drug-resistant TB versus the risk of hepatotoxicity when deciding to use BDQ or DLM.

Substance users

Many patients with DR-TB suffer from alcohol and substance use. Such individuals were not included in the clinical trials of new and re-purposed agents, thus there is limited use on their safety. While all attempts should be made to offer persons with alcohol or substance abuse effective substance abuse treatment, the use of the new and re-purposed drugs can be introduced in people using alcohol and other substances. These drugs should be used with caution in patients with active liver damage, and all substance users should undergo testing for hepatitis B and C in regions of the world where these diseases are common. There may also be a higher risk for QTc prolongation among persons actively consuming alcohol, and more frequent electrolyte and QTc monitoring should be considered. Substance abusers also need harm reduction and additional adherence support.

6. MONITORING AND MANAGEMENT OF ADVERSE EVENTS

Routine DR-TB monitoring should follow the standard PMDT monitoring recommendations. In addition, the following should be done for patients on new and repurposed drugs:

- Monthly visits during first 6 months of therapy;
- QTc monitoring (either 12 lead or handheld) monitoring monthly for persons while on BDQ, DLM, and CFZ; if therapy is extended beyond 24 weeks, routine QTc monitoring should be done every quarter while the drug is being given; if BDQ and DLM are given together, ECGs should be done every two weeks for the first 12 weeks of therapy;
- Monthly liver function tests for both BDQ and DLM for the first six months (although this could be done quarterly if the first month results are within normal limits) then monthly thereafter;
- Monthly complete blood count (CBC) and visual acuity if on linezolid;

Symptom directed monitoring should be done for patients throughout the course of therapy, including:

- At each visit, ask the patient if they have had any syncope or palpitations and if so, an ECG should be done;
- Patients with persistent nausea, vomiting, and/or abdominal pain should have a lipase checked if on BDQ.

Routine tests in addition to standard PMDT assessments are summarized in Table 4 below.

Table 4: Recommended monitoring tests for patients on new and re-purposed drugs

Laboratory Evaluation	Baseline	Week 2	Monthly for first 6 months	Quarterly for remainder of therapy	Symptom directed
Liver function tests	X		X#	X	Nausea, vomiting, jaundice, abdominal pain
Lipase					Nausea, vomiting, jaundice, abdominal pain
Potassium	X		X	X	QTc prolongation, cramps, palpitation
Magnesium	X*				QTc prolongation, cramps, palpitation
Albumin	X+				
CBC	X	X	X	X	Fatigue, nose bleeds, gum bleeds, easy bruising
Visual acuity	X		X	X	Changes in vision, problems with color perception
12-lead ECG (for follow up, digital measures of QTc can be done instead of full 12-lead ECG)	X		X	X	Dizziness, syncope, palpitations

#could be done quarterly if first month is within normal limits

*if available

+ if needs DLM

7. MANAGEMENT OF SELECTED ADVERSE EVENTS

Whenever a drug is discontinued, doses are changed, or a patient is hospitalized due to the development of an adverse event, these changes should be recorded and reported as part of the PMDT program’s active TB drug-safety monitoring and management (aDSM).

QTc prolongation

QTc prolongation is being mentioned more and more as an adverse event, in part due to the focus on QTc prolongation by regulators and researchers. It is important to know that QTc prolongation in and of itself is NOT an adverse event. Rather, the focus on QTc prolongation is important since it is a RISK FACTOR for developing Torsades de pointes (TdP), a fatal cardiac arrhythmia. There are thousands of drugs that prolong the QTc interval, but many of them are not associated with TdP nor any clinical cardiac events. Of note, the QTc prolongation with BDQ and DLM was not associated with any clinical cardiac complications.

In addition to medications, other risk factors for TdP include gender, advanced age, low heart rate, electrolyte abnormalities, congestive heart failure, and a genetic predisposition to developing arrhythmias. Programs, providers, and patients must weigh the risk of QTc prolongation and possible cardiac events with the risks of under-treated DR-TB and the risks of the other SLDs.

Patients with QTc prolongation often have vague or no symptoms. They may present with palpitations or a rapid heart rate, dizziness, or syncope. Any patient with these symptoms should undergo QTc evaluation and if prolongation is present, hospitalization should be considered. In addition, routine QTc monitoring should be done at the schedule listed above.

Calculation of QTc interval

The QT interval is measured in milliseconds and is defined as the period from the beginning of the Q wave until completion of the T wave. See figure XX for a graphic representation of the QT interval. Because the QT interval depends on the heart rate, the timing must be corrected (hence QTc), and there are several formulas for doing so, each of which has its own limitations. The most commonly used correction formula is the Fridericia formula. There are ECG machines that can automatically correct the QTc interval and provide a reading, although these machines tend to overcall the duration and thus should be calculated manually if QTc prolongation is noted. There are multiple sites online that can correct the QT interval if the RR interval (i.e. heart rate) and the QT intervals are entered (http://lifeinthefastlane.com/ecg-library/basics/qt_interval/). If such resources cannot be accessed, the interval can be calculated manually by taking the measured QT interval and dividing it by the cube root of the calculated RR interval (QT interval/ $\sqrt[3]{RR}$ interval).

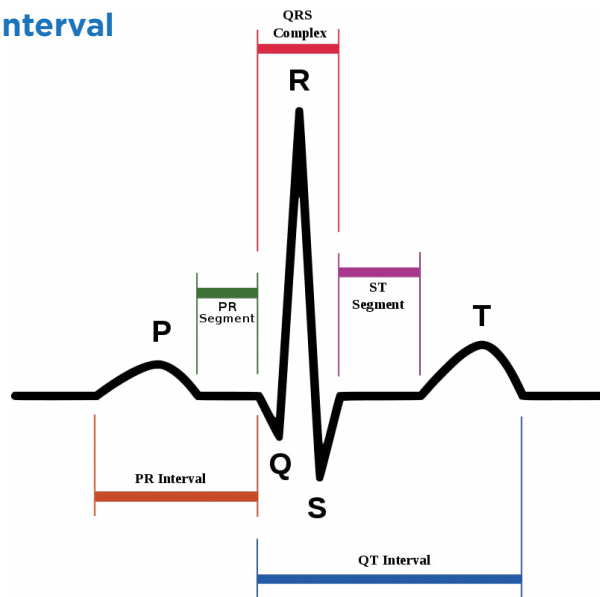
Box 5: Definition of prolonged QTc interval

Definitions vary depending on gender. In general, a QTc interval greater than 450 msec in men and 470msec in women is considered prolonged. In both genders, a QTc interval of 500msec or higher is considered an indication for immediate action. Of note, QTc intervals have diurnal variation, and when possible, should be assessed at the same time of day. Some practitioners have also suggested it is the magnitude of change in the QTc interval from baseline and not the absolute QTc interval that may put patients at an increased risk for Torsades de pointes. Some research protocols note that a change from baseline of 30-60msec may be clinically significant, although the precise nature of this risk has not been delineated. Calculation QTc changes from baseline may also be more complicated if different monitoring methods are used.

HANDHELD DEVICES FOR SCREENING

There are multiple handheld devices that can be placed on the chest and used to obtain the heart rate and the QT interval. These handheld devices may be especially useful in settings where access to 12-lead ECGs are limited. They can be used by nurses or trained health workers for screening, as they tend to overcall the QTc interval. If an elevated QTc interval is noted, then a 12-lead ECG can be done. Such devices have been used in the implementation of the shorter regimen in Niger. Some models of these are shown in Figure 6 along with an explanation of the phases of the waveform.

Figure 6: QT Interval



Sample of handheld ECG unit (for more information, see <http://www.ndsu.edu/pubweb/~grier/Comparison-handheld-ECG-EKG.html>)

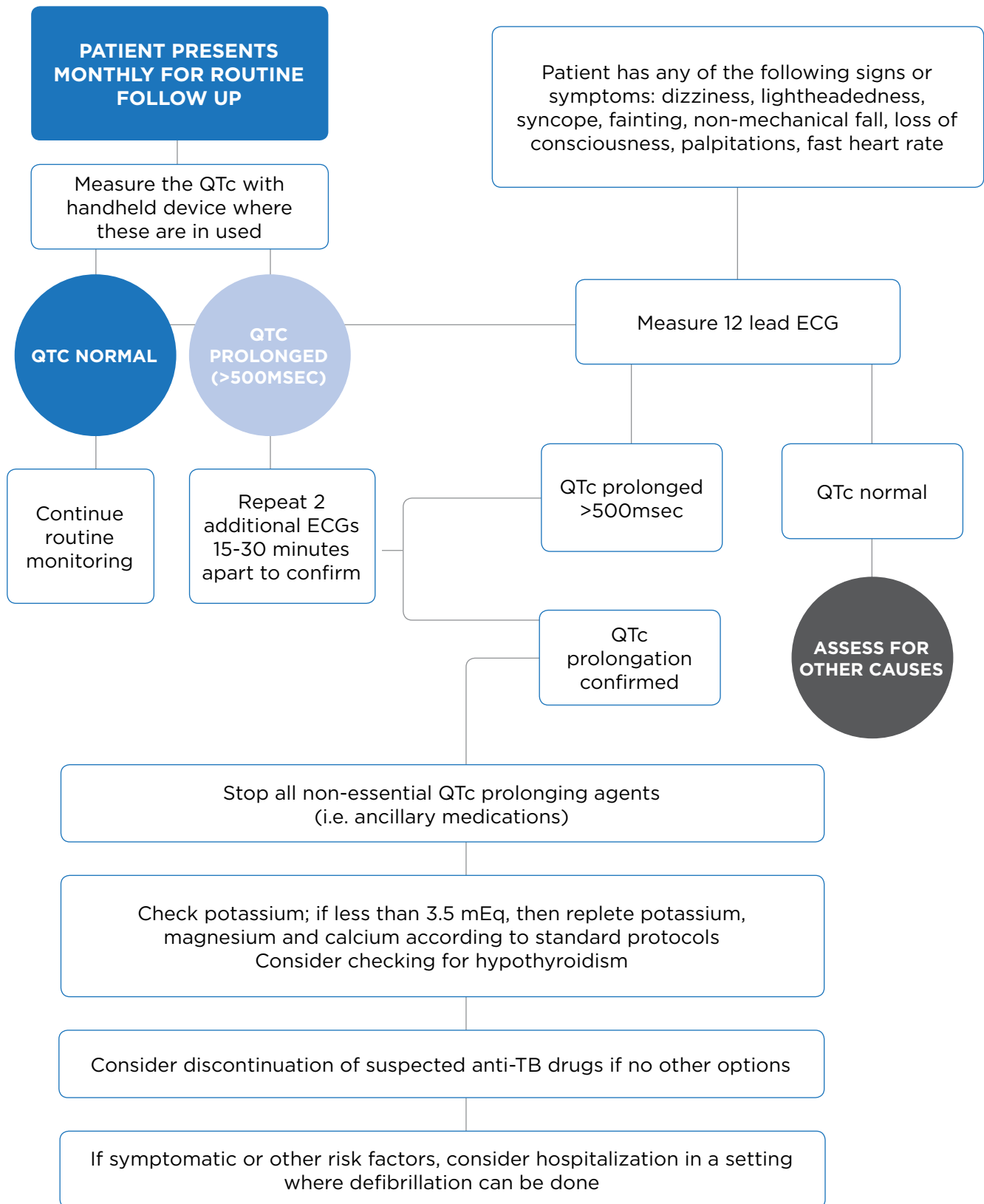
CLINICAL MANAGEMENT

The clinical management of QTc prolongation must consider many factors. Chief among these is that QTc prolongation is only one risk factor for developing TdP, and no confirmed clinical cardiac complications have been reported with BDQ, DLM, or CFZ in clinical trials or expanded access studies reported to date. Thus, the decision to stop a potentially life-saving drug in the setting of QTc prolongation must be weighed alongside the risk of other adverse events and untreated or undertreated DR-TB. The algorithm in Figure 7 presents possible management options when there is QTc prolongation noted. In general, the following points should be considered when QTc prolongation is seen:

- If the QTc prolongation was detected using a handheld device, a full 12-lead ECG should be done;
- Repeat the ECG two additional times within 15-30 minutes of one another to confirm the QTc prolongation; consider discussing with a cardiologist either in local setting or via international consult;
- Assess for symptoms, including dizziness/syncope, palpitations, chest pain, fainting, falling, or fast heart rate, and if symptoms are present take urgent action;
- Discontinue all unnecessary QTc prolonging drugs (i.e. ancillary drugs);
- Check and replete electrolytes (i.e. potassium, magnesium, calcium);
- Consider assessment for hypothyroidism, as this has been associated with the development of torsades de pointes;
- If no other options exist, discontinue BDQ, DLM, or CFZ, keeping in mind the long half-life of BDQ and CFZ;
- If symptomatic, consider admission to a facility where defibrillation is available.

If a patient develops QTc prolongation that is felt to be due to BDQ, then once BDQ is stopped and the QTc is less than 500msec, DLM could be started with ECGs every 2 weeks until the BDQ washout period (three months) is complete.

Figure 7: Management Approach to Patients on QTc Prolonging Anti-Tuberculosis Drugs



Case Example 10: Management of QTc Prolongation

SS is a 42-year-old male currently on treatment for FQ-resistant TB with a regimen of Km-DLM-Eto-Z-Cs-LZD. He has had persistent problems with nausea and vomiting and has been given ondansetron. He had one episode of transient psychosis after one month on therapy and was started on haloperidol at that time.

SS presents for his 12-week appointment and his screening ECG shows a prolonged QTc interval of 510msec. He denies syncopal symptoms and palpitations but he does report he has “been a little dizzy lately” and attributes this to the hot weather.

A repeat ECG is done 30 minutes later and confirms QTc prolongation with a corrected interval of 512 msec. A screening potassium now is low at 3.1mEq. A review of his medications is done, and he is still on both Haldol and ondansetron. He is admitted to the MDR-TB hospital, which is newly equipped with an automated defibrillator. He is given potassium, magnesium, and calcium, and has both his Haldol and ondansetron held. He has a daily ECG to assess for QTc prolongation, and the daily measurements show his QTc hovering between 470 and 480msec. He becomes psychotic, and his Cs is stopped with great improvement. He is continued on DLM given the improvement in his QTc interval and the discontinuation of the Cs reducing the effectiveness of his regimen. His QTc returns to 460msec and CFZ is added to strengthen his regimen. He continues of potassium and magnesium for an additional month.

Anemia

Patients with anemia can often present with vague symptoms, but chief among them are fatigue, dyspnea, and pallor. On exam, these individuals may have pale conjunctiva and a rapid heart rate. Patients on LZD should have a CBC checked monthly to monitor for anemia.

Patients with DR-TB often have multiple comorbidities and reasons to develop anemia, including HIV and other opportunistic infections. When a medication is suspected, LZD and zidovudine (AZT) are the most likely casually related. LZD and AZT should be avoided in persons with a hemoglobin of less than 8g/dL unless there are no other alternatives. Patients with baseline anemia may need iron therapy prior to starting LZD. However, many patients have anemia of chronic disease and will improve when on adequate therapy. In persons with baseline anemia (i.e. hemoglobin of < 8gm/dL) the use of both AZT and LZD should be avoided.

If a person develops a hemoglobin of < 8gm/dL while on therapy, ART should be changed if the person is on AZT. Other causes of anemia should be assessed, and if no other causes found, then LZD should be discontinued until the hemoglobin is above 8gm/dL again. At this point, LZD could be restarted at a lower dose (i.e 300mg/day).

If the patient develops a hemoglobin of <8gm/dL with symptoms of respiratory insufficiency, then transfusion should be considered. If erythropoietin is available, this should also be considered. Otherwise, transfusions should be considered for patients with a hemoglobin of 7gm/dL or less, depending on access to and safety of the blood supply.

Thrombocytopenia

Patients with thrombocytopenia can present with a variety of complaints, including nose bleeds, bleeding gums, easy bruising, and rashes. On example these patients often have petechiae. Patients with DR-TB often have multiple comorbidities, including HIV and other opportunistic infections, that could cause low platelets. When a medication is suspected, the likely cause of thrombocytopenia is LZD. Patients on LZD should have a CBC checked monthly to assess for thrombocytopenia.

Patients who have a platelet count of 50,000/mm³ should have their LZD held while investigating other causes. If no other cause can be identified, then LZD should only be restarted at a lower dose (i.e. 300mg/day) once the platelet count has normalized. In patients with a platelet count of <10,000 mm³ or in whom severe bleeding is occurring, platelet transfusion should be considered.

Case Example 11: Thrombocytopenia

FT is a 32-year-old woman who is being treated for Km-resistant TB with a regimen of Lfx-Cs-PAS-Eto-Z-LZD. Neither BDQ nor DLM are available in her country yet. She also has HIV and is on a regimen on AZT-3TC-NVP, also due to shortages of other medications in her country.

She initially does well but then after two months on DR-TB treatment, she notices her mouth won't stop bleeding after she brushes her teeth. She has had two bloody noses as well. She presents to her health center and her physician checks her CBC, which shows a platelet count of 60,000/mm³. She has no other signs or symptoms. Her physician stops her AZT and starts TDF, but FT continues to have copious bloody noses and returns to her health center when she cannot stop the bleeding. A repeat platelet count is 40,000/mm³. Her physician stops her LZD and the platelets begin to rise with abatement of her symptoms. Her smears and cultures remain negative, so she is given CFZ in place of LZD.

Optic neuritis

Patients with optic neuritis can present with several symptoms, including decreased visual acuity and changes in color perception. Often, however, they have no complaints at all, and routine visual acuity monitoring should be done. If a change from baseline is noted, formal red/green color testing should be done as well as a fundoscopic exam of the optic nerves bilaterally. Ethambutol can also cause optic neuritis; if the patient is on ethambutol, the drug should be stopped when a patient has visual complaints along with changes in color perception and/or evidence of edema of the optic nerve. LZD should be lowered to a dose of 300mg and if problems persist, LZD should be discontinued.

Nausea/Vomiting/Abdominal Pain

These gastrointestinal symptoms are common in patients on DR-TB, and excellent management protocols are available in other field guides. Drugs commonly associated with nausea and vomiting include ethionamide and PAS. In patients on BDQ and/or CFZ, there are additional causes of nausea, vomiting, or abdominal pain that should be considered. If the abdominal pain is severe or the nausea and vomiting protracted, then pancreatitis should be ruled out. Lipase should be evaluated, and if found to be abnormal, potential

causes of elevated lipase should be considered including ART (i.e. D4T), HIV, or alcohol use. If no other underlying cause can be identified, BDQ should be discontinued. If the patient does not have pancreatitis, then acute abdomen should be considered, with CFZ being the most likely agent. Both these drugs accumulate in the adipose tissue, thus even with discontinuation adverse events may take time to resolve.

Patients on new drugs and CFZ who have nausea, vomiting, or diarrhea should have their potassium checked frequently, as they are at risk of developing hypokalemia and fatal arrhythmias in the setting of BDQ, DLM, or CFZ use.

Malnutrition

Patients with DR-TB and malnutrition are at high risk for poor outcomes, thus aggressive nutritional support for all DR-TB patients is recommended as part of routine care. Patients on DLM are at higher risk for drug-related adverse events if they are malnourished, especially if their serum albumin is below 2.8 gm/dL. In patients with albumin levels near this value, aggressive protein and calorie supplementation are recommended.

Neuropathy

Patients with neuropathy often present with burning, tingling or numbing pain in their feet and hands. Neuropathy can become so severe that it limits mobility and greatly decreases quality of life. Patients with DR-TB are at high risk for developing peripheral neuropathy for a variety of reasons, including TB, HIV, alcohol use, or other medications. Excellent protocols for the management of peripheral neuropathy are included in other field guides and guidelines. Patients on LZD are at high risk of developing neuropathy, and in a patient with signs and symptoms of neuropathy, the LZD dose should be lowered to 300mg/day while other causes are being investigated. This should be done early in therapy, as there is some potential for the neuropathy to be reversible if detected early.

8. ADHERENCE SUPPORT

Patients with DR-TB in need of new and repurposed drugs must have sufficient support so that they are able to adhere to therapy and achieve the best possible outcomes. Some of these patients will have had previous treatment for DR-TB and either lost their faith in the ability of medications to cure them or suffered adverse events that have affected their lives in negative ways. Standardized, routine counseling by appropriately trained staff is needed throughout the DR-TB patient's treatment journey (see section below on patient information).

In addition, many patients with DR-TB suffer from a lack of food, housing, and funds for basic needs including transport. Without these necessities, they will be much less likely to achieve a favorable treatment outcome. Although provision of these types of support may be logistically challenging, they are usually much simpler and less expensive than trying to manage patients with high-level drug resistance who are lost to follow up. Furthermore, higher rates of adverse events are seen in patients with low albumin on new drugs, and nutritional support will likely improve efficacy of the new drugs as they are better absorbed with food.

The new and re-purposed medications may also help improve adherence in patients who develop adverse events on standard DR-TB treatment. If identified early, the new or re-purposed drugs could be substituted for the offending agents, offering patients tangible relief from side effects that is often not possible with current management strategies.

Community-based care delivered at health centers close to where the patient lives is an essential strategy for ensuring treatment success and reducing nosocomial transmission. Hospitalization may be necessary for management of adverse events or for critically ill patients, but routine hospitalization with the new and re-purposed drugs should be avoided. Contrary to commonly held beliefs that hospitalization results in better adherence, patients who are hospitalized may be at higher risk for being lost to follow up since they often have pressing issues to attend to at home and lose their social support while in hospital. Furthermore, community-based care offers an ideal way to decrease stigmatization and allows persons with DR-TB to be naturally integrated back into daily life after a diagnosis of DR-TB.

Case Example 12: Adherence Support

HG is a 53-year-old male on treatment for MDR-TB. He is started on therapy in the hospital because of program norms, and he becomes agitated during the first six weeks of therapy. He wants to know when he can leave, or even just “go home for a little to take care of some things,” but he is told he cannot go home until he is done with his injections as there is no support system for him there. He begins to lose his hearing, continues to have positive smears and cultures, and leaves the hospital after four months.

A team of community nurses find him after a sputum sample he submitted on admission shows he has XDR-TB with additional resistance to Eto. He is home and tells them he had to come back to the house to pay some bills and collect some money that was owed to him. He says he wanted to come back to the hospital but was too afraid; he also felt he needed to find some work or he would lose his house.

The nurses explain to him that he has XDR-TB and that he needs to come back to the hospital to get started on “new drugs.” He agrees but only if he can return to his house in two weeks to meet his son who is coming from a neighboring country with some money he owes his father. He says he must be home to get the money, as the son will run away if he finds out his father is sick.

The patient returns to the hospital with the nurses, only to be told he cannot be started on the new drugs because he “is non-compliant” and won’t agree to the hospitalization. He returns home dejected but does not know what else to do.

Fortunately, the TB Program is piloting a community-based intervention and they select him to be one of the households to benefit from decentralized care. A nurse and doctor come to see him and start him on treatment with BDQ-LZD-CFZ-PAS-Cs-PZA. He is treated for two weeks in the community but is briefly hospitalized with severe anemia and shortness of breath. His LZD dose is lowered from 600mg to 300mg and he continues to do well on treatment. Eventually, with the help of the nurse and his treatment supporter, he can disclose his health situation to his son.

The son tells him he is also being treated for TB and they begin to provide emotional support to one another. Since the son is no longer working, a food package is provided to the family, and eventually the patient finds work as a night watchman at the nearby clinic.

9. ACTIVE DRUG SAFETY MONITORING AND MANAGEMENT FOR PROVIDERS

Active drug safety monitoring and management (aDSM) is recommended for all persons on new and repurposed drugs and shorter regimens. Because BDQ and DLM have not been used extensively, nor have the shorter regimens, aDSM is recommended by WHO. With aDSM activities are focused on actively collecting and monitoring data on adverse events that are serious, severe, or result in a change of medical therapy. Data are also collected on adverse events of interest, regardless of their severity, such as QTc prolongation, neuropathy, optic neuritis, etc.

Given the poor treatment success rates seen with current DR-TB therapy and the high rates of toxicity that are also noted, a rare adverse event detected may be unlikely to cause cessation of use of the new drugs. However, it is important for patients and providers to be aware of all adverse events associated with medications. Programs using new and repurposed drugs and shorter regimens need to collect routine data on the safety of such drugs and analyze that data on an ongoing basis. This can be done either by the NPT or by a pharmacovigilance center. Most countries will not be able to establish sufficiently large cohorts of patients within their own programs to be able to detect all rare but serious and severe events. For this reason, the WHO has established an international database to which countries can report information on adverse events. This databased can be found at http://www.who.int/tdr/research/tb_hiv/adsm/en/.

What happens in aDSM?

- aDSM very much follows practices that are part of good clinical care for persons with DR-TB, including frequent and routine monitoring, assessment of symptoms, and actions taken to respond to any symptoms or abnormalities detected;
- For aDSM with the new drugs and regimens, the patient is seen by medical staff on a routine basis (at least monthly for 6 months then at least quarterly) or when a problem occurs
- Symptom screening and routine labs are done and noted in the medical file or electronic medical record

If symptoms are present or lab abnormalities seen, clinical staff then decide on SERIOUSNESS and SEVERITY of the event, attribute likely CAUSALITY, and make an ACTION PLAN, all of which are recorded in the medical record, as well as the final outcome of the symptoms/abnormalities

All adverse events that are SERIOUS should also be reported. Of note serious adverse events differ from severity rating and this category describes events that have health consequences for patients. Serious events include death, life-threatening conditions, congenital abnormalities,, hospitalization to manage the adverse event, and long-term disability. In addition, if TB drugs are discontinued or doses changed, these changes should be recorded and reported as part of active aDSM..

Severity is generally assessed using standard definitions or data dictionaries, with a “grade number” given. Grade 1 events are usually mild and asymptomatic while Grade 4 events are usually life-threatening. Each country should use grading scales that are available in their settings, although for use of comparison, standard grading scales should be considered. Most standard grading scales are used for clinical research studies and may be too detailed for program use, but could be adapted for routine clinical care. Examples of these include

the US National Institutes Division of AIDS Criteria and the Common Terminology Criteria for Adverse Events published by the US Department of Health and Human Services. The use of such scales can help to standardize data collected across sites, but it can also be cumbersome for the provider to use such scales in clinical practice. In general, care providers can make clinical notes in the chart about severity of a complaint by looking at how the patient's activities are affected and what management plans were put in place to deal with the patient complaints.

- If the complaint does not affect the patient's activities and the plan is continued observation, this event is probably mild (grade 1).
- If the complaint has some effects on the patient's activities and a medication is started to help manage the complaint, then it is probably moderate (grade 2).
- If the complaint has a significant effect on the patient's activities and there is consideration of a significant medical intervention OR if doses of TB medications are changed or discontinued, then the complaint is probably severe (grade 3).
- If the patient must be hospitalized or hospitalization is extended to deal with the complaint then the adverse event is probably life-threatening (grade 4).

Causality is initially assessed by a health care provider as the possibility that a specific drug in the regimen could be causing the problems. For example, if a patient develops skin pigmentation, the likely cause is CFZ. Causality can be difficult to assess in multi-drug regimens, especially if looking for a "rare" adverse event. Nevertheless, providers should note in the medical record which drug or drugs are likely to be causing the abnormality. In general, while providers may not be accustomed to a "formal causality assessment", most clinical management strategies are based on deciding which drug is likely to be leading to the problems the patient is experiencing and acting based on this assumption. Noting the rationale in the medical chart for clinical decision making around patient complaints is sufficient for the initial causality assessment.

Finally, a plan of action should be clearly laid out with interventions and the outcome of the adverse event carefully recorded. The plan of action could include adding new drugs to help manage adverse events, lowering the dose of existing drugs, or ultimately discontinuing a drug. Of note, patients who become pregnant while on new drugs for the treatment of DR-TB should also have that event noted with a detailed action plan, including monitoring of the mother and fetus.

Noting these phenomena in the medical record can often be facilitated using standard forms. Care should be taken not to overburden care providers with excessive forms and whenever possible, PV sections should be added into standard DR-TB treatment forms or records. Electronic records would be ideal for capturing and tabulating data, and are being used increasingly in DR-TB treatment programs. Please note that in most countries with a national PV center, serious adverse events should be noted and reported within 24 or 48 hours.

Clinical team responsibilities for aDSM

- In general, the role of the clinical team in aDSM is to provide excellent clinical care for patients with adverse events and to record their activities in the medical chart in a way that can later be assessed by others on a cohort level.
- Management of individual patients so that optimal interventions can be implemented to ensure the patient has the best possible outcome.

- aDSM should place a minimal burden on physicians and nurses, as good patient care includes the monitoring and documenting of adverse events.
- aDSM may require additional details in the chart/medical record about severity, causality and plan of action
- If this information is well documented in the chart, then aDSM will be straightforward.
- Physicians should be expected to report serious adverse events to the central sDSM team within 24-48 hours using a standard AE reporting form. The content and structure of this form will vary by country.

Centrally designated team responsibilities for active PV

Centrally designated team responsibilities for aDSM

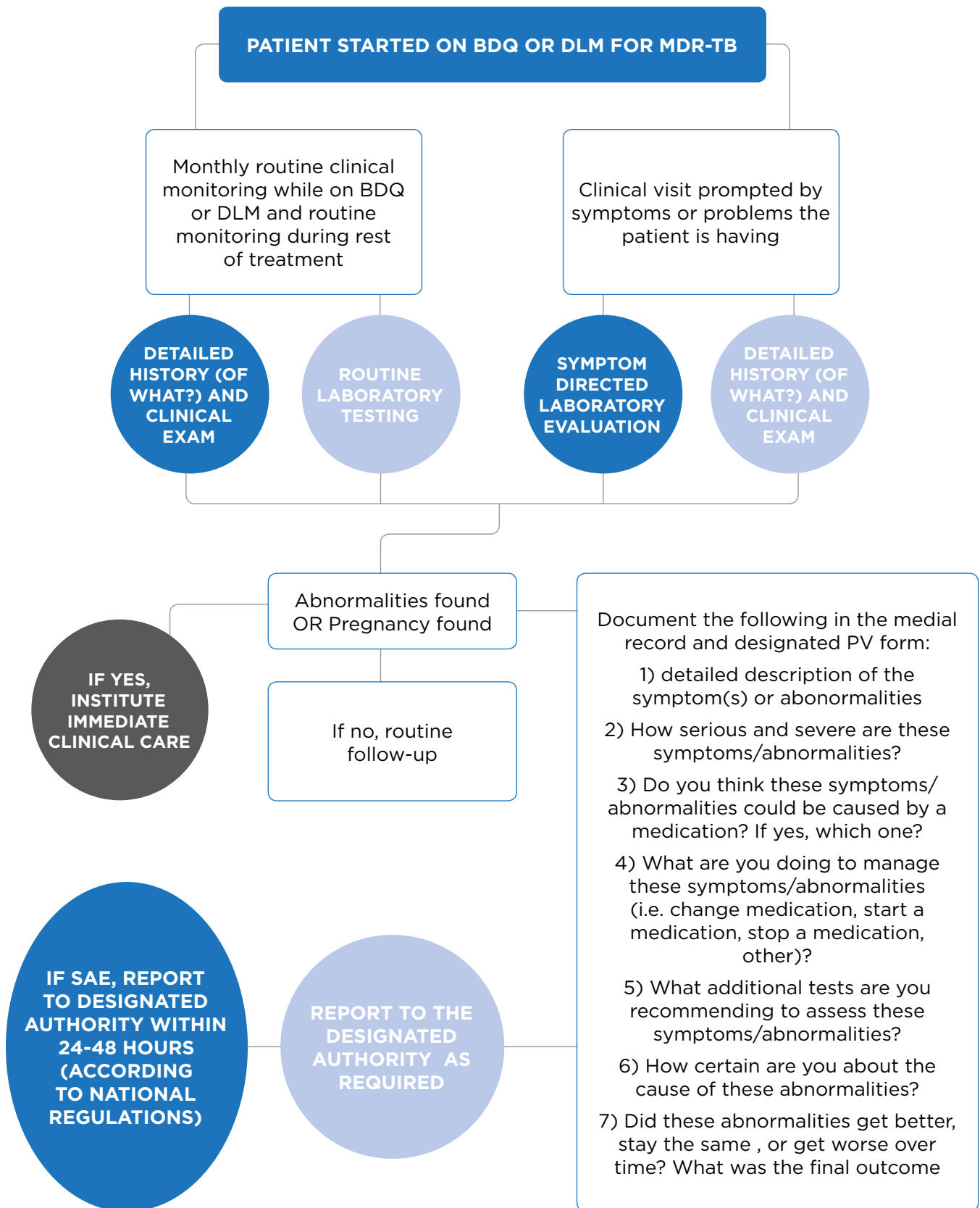
Once the clinical provider has captured the information in the medical record, transcription or entry of the data in an electronic database is needed on an ongoing basis by data entry staff at the health facility. Some other activities take place at a more central level. These include:

- Formal assessments of severity and causality.
- Transmission of the data to an identified central level for analysis.
- Reporting of trends noted at the central level back to the field.
- Recommended guidance for adverse event management when a concerning trend is noted.

Figure 8 summarizes a field approach to aDSM for new and repurposed drugs and the shorter regimen.

Figure 8 summarizes a field approach to active PV for new and repurposed drugs.

Figure 8: Implementation Tool: Pharmacovigilance/aDSM for DR-TB Clinical Providers



Case Example 13: aDSM

HS is a 42-year-old woman with DR-TB that is resistant to INH, RIF, EMB, Sm, and Ofx. She is started on a treatment regimen of Km-Eto-Cs-PAS-Z-Amoxicillin/CLV. In her third month of treatment, she remains smear positive and complains of buzzing in her ears and decreased hearing. Her medical team notes this in her medical record, and because the hearing loss is interfering with her ability to work and take care of her children, a decision is made to stop the injection, as the Km is most likely to be causing the hearing problems. Her country has recently procured several new and re-purposed agents, and after review by the clinical expert team it is determined that HS meets the criteria to start on BDQ. Given that she is still smear and culture positive and has not gained weight, her team is concerned about a simple substitution and decide to start her on LZD-BDQ-CFZ and to continue her Eto-C-PAS-and PZA.

Her team is worried about needing to do “aDSM”, but upon review of their standard initiation and follow-up forms, they note that they already collect most of the information needed for aDSM, except for formal severity and causality ratings. They obtain a severity rating scale from an international organization. Although they have no formal PV center in the country, it is determined that all data will be reported to the NTP and analyzed monthly by the NTP while awaiting development of a national PV monitoring system. Special plans are made for reporting serious adverse events within 24-48 hours using a standard form.

HS does well on the new regimen, converts her smear and culture in month four and gains 2 kg. She is unhappy that her skin is a more orange color and reports this to her physicians. They deem the skin discoloration is moderate and give it a grade of 2 based on their grading system. They note in the chart that they believe this is due to CFZ but that they will continue the drug given that this adverse event is reversible.

HS was not on any birth control as she thought she was “too old to get pregnant.” She thinks she is missing her period because of menopause. However, after 3 missed periods she undergoes a pregnancy test and is found to be pregnant. Her medical team notes the pregnancy in the chart and calls the NTP the next day to let them know about this event. The NTP asks the team to record this in the aDSM section of the medical forms and after review with the clinical review committee, they decide to continue the current treatment.

10. ETHICAL ISSUES AND INFORMED CONSENT

There are several important ethical issues to consider in the use of new and re-purposed drugs for the treatment of DR-TB. These include informing patients about the potential risks and benefits of the new and re-purposed drugs, as well as issues such as equity in access, fair drug pricing, and developing patient-provider relationships. In general, the introduction of new and re-purposed agents offers the DR-TB community a chance to improve communication with patients on all levels.

Most DR-TB patients sign a general informed consent that states they agree to be treated. While there may be some details in the informed consent about the risks and benefits of the medications given, information is usually limited. No specific recommendations have been made regarding the use of informed consent and LZD or CFZ and it is recommended that routine treatment consent procedures be followed for persons treated with the shorter

regimen. For BDQ and DLM, the WHO requires that a “due process” be followed for patients receiving the drugs, although specific details on “due process” are not provided. In general, an open, transparent, and ongoing process of communication should take place for all patients receiving DR-TB treatment, no matter what the specifics of the regimen may be.

There are a few summary points to consider when thinking about informed consent, including:

- These new and repurposed drugs are being recommended for use under program conditions and not as a clinical trial, and the informed consent process should take this into account;
- Many existing consent forms for DR-TB are more about reducing liability as opposed to truly informing the patient. Thus, caution should be taken when adapting existing forms to program conditions;
- Informed consent is stressed with BDQ and DLM based on the small numbers of patients included in the clinical trials;
- Informed consent is stressed with BDQ and DLM because of the lack of long-term safety data, but could also apply to LZD;
- Specific ethical concerns have been raised about the higher mortality rate seen with BDQ compared with placebo in the registration trial, although increased mortality has NOT been reported during the rollout of programmatic use of the drug;
- These ethical concerns must be placed in the context of current treatment of MDR-TB, including poor outcomes and high rates of adverse events;
- The informed consent process should ensure that information of the new and repurposed drugs is provided, but the drugs should not be “exceptionalized” in terms of the real risks presented by the existing medications;
- Ensure that the process of obtaining informed consent facilitates patient understanding;
- Ideally, obtaining informed consent is an ongoing process and dialogue between providers and patients;
- Samples of possible consent forms are shown in Figure 9A and 9B.

Box 6: Symptom-Based Informed Consent

A symptom-based approach to obtaining consent is recommended over a drug-based approach, as patients will be much more able to relate to symptoms they may experience. For an example of a symptom-based approach, please see the companion workbook on “Living with DR-TB: Making the Most of Your Treatment Experience” also developed by the SWIFT Project

Developing patient information

A key part of the informed consent process is making sure the patient understands and can contextualize the potential risks and benefits of therapy and can ask questions. Most models of informed consent do not allow sufficient time for this, and patients are asked to take in an incredible amount of information and “sign that they agree to treatment” at a very vulnerable moment. While there can be an urgency to start therapy, providers must ensure that patients are able to share concerns and questions that may come up within the days and weeks after treatment has started. Directly observed therapy provides an ideal time for this, as it requires that patients and providers spend some time together each day; alternately, treatment supporters can be counseled to encourage patients to share questions and concerns with their providers.

It is essential that materials about the new and re-purposed drugs for patients with DR-TB be developed. These materials should not copy and paste lengthy strings of possible side effects and risks from existing clinical trials documents, but rather should take into account the needs of patients taking the drugs in routine programmatic conditions. An example of a patient information brochure on BDQ developed by TB Proof is included in the Annex.

When developing information for patients being provided new and repurposed drugs for DR-TB, the following points should be considered:

General points to include on newer drugs:

- Information needs to be culturally appropriate, available in local languages, and developed with the input of patients and the community;
- An explanation of the reason the drug is being offered, such as resistance or intolerance means a sufficiently strong regimen cannot be constructed;
- Any additional monitoring needed while on a new re-purposed drug, such as ECGs;
- Avoid “laundry lists” of possible adverse events, but rather help patients contextualize the risks and benefits of new and repurposed drugs;
- Keep in mind the goal of the consent process: to ensure the patient understands the role of the new or re-purposed drug and can ask questions and have them answered.

BDQ considerations:

- BDQ is a new TB drug that has been shown to increase cure rates in patients who received the drug compared with those that did not;
- Side effects can include problems with the liver and problems with the rhythm of the heartbeat;
- In one clinical study, patients who received BDQ had a higher death rate than those who did not, but this was felt not to be due to the drug;
- To date more than 8000 patients globally have received BDQ.

DLM considerations:

- DLM is a new TB drug that has been shown to increase cure rates in patients who received the drug compared with those that did not;

- Side effects can include problems with the liver and problems with the rhythm of the heartbeat;
- To date more than 500 patients globally have received DLM.

LZD considerations:

- LZD is a drug commonly used for the treatment of infections other than TB;
- It is a drug that has shown success in groups of patients with DR-TB who received it, but no comparison group was included to show how much success;
- Side effects can include problems with the nerves as well as with the cells that make blood and clotting factors.

CFZ considerations:

- Cfz is a drug commonly used in the treatment of infections other than TB, such as leprosy;
- The drug has shown success in groups of patients with DR-TB who received it compared with those who did not;
- Side effects can include reversible changes in skin color and moisture, problems with the rhythm of the heart, and abdominal pain.

Methods for delivering patient information

Current approaches for teaching patients about the new and re-purposed drugs and providing the informed consent process usually involve a one-on-one conversation with patients and providers. However, this is only one means of conveying information, and other modes are needed to ensure the patient and his or her family are provided with the information they need to stay involved in and supportive of the patient's DR-TB care. Multiple other methods for delivering information to patients and their family can be employed, including:

- Peer educators
- Videos
- Role playing exercises
- Waiting room educational sessions
- Community health workers
- Social media

Box 7: Directly observed treatment (DOT) and the Informed Consent process

As a final point, DOT is considered an essential cornerstone in the management of patients with DR-TB, although emerging data show that DOT may place undue burdens on patients and result in lower rates of adherence. DOT is likely to remain a key part of TB treatment for the near future; if DOT is modified and used as a daily opportunity to answer questions, interact with patients, and provide information, the entire process could be transformed in a way that is more meaningful for both patients and the providers that serve them.

Case Example 14: Informed Consent

PJ is a 27-year-old male who was diagnosed with XDR-TB after failing MDR-TB treatment. He has resistance to INH-RIF-EMB-SM-KM-LFX-Eto. He was previously treated with a regimen of KM-LFX-PZA-Eto-CS-PAS and developed severe neuropathy. He is depressed and very frightened to find out he has “the most resistant TB possible.”

PJ’s physicians want to start him on a new regimen for XDR-TB consisting of BDQ-LZD-CFZ-CS-PAS-PZA. They tell him if he doesn’t start this regimen, not only will he die, but he will also “infect everyone in his community.” He agrees to try the new regimen as he is very worried.

His doctors and nurses explain to him that he needs to give permission for them to treat him, just like when he was treated for MDR-TB. However, they explain he will need to sign an additional informed consent to receive one of the drugs—BDQ—as this drug has not been used very much and has been shown to cause heart problems and even to cause higher rates of death in people.

PJ does not understand why his doctors and nurses want to treat him with this new drug. It sounds like an experiment to him, and he already has enough problems with his lungs and feet that he does not need another problem with his heart now. He also thinks that since the new drug could kill him, it would be better to die of his TB. A nurse explains that the new drug may help him, but PJ is completely overwhelmed and decides not to sign the form. The nurse gives him some material to take home and read, but he is too ashamed to tell her that he cannot understand most of the words. The doctor comes out and tells him he must sign the form to take the new drug or he cannot have any treatment and he will die.

PJ feels like they are pushing him to join an experiment and he decides to leave. Two months later he dies from XDR-TB.

CONCLUSIONS

This is an exciting time in the treatment of MDR-TB, with multiple novel therapeutic approaches being recommended to both improve treatment outcomes and limit the toxicity associated with the conventional MDR-TB regimen. WHO has recommended these innovations for use in programmatic settings and will continue to update recommendations and guidelines as data evolve. There is a need, however, for more detailed clinical guidance for providers in the field and the programs within which they work, and this field guide is meant to provide such implementation advice.

It is no longer acceptable to treat MDR-TB without using novel drugs, repurposed drugs, and shorter regimens, and countries need to move quickly to make sure all persons in need of these medications and regimens can access them. At the same time it is crucial that countries and providers use local knowledge to optimize use of these interventions and that they share the lessons they have learned with one another. As a global community, there is now a stated commitment to ending all forms of TB by 2030, including drug-resistant TB. New drugs and therapeutic agents are key in achieving this goal.

Figure 9: Examples of Consent Forms for Patients and Providers

A. Due Process for Informed Consent: Checklist for Patients

Due process is considered to have been followed when the answers to points 1,2,3,4 and 5 are answered yes. Bedaquiline can be administered when points 1,2,3,4,5,6,7, and 8 are answered yes.

1) Were you provided with information about your current health status, your diagnosis, and the reason you are being started on treatment for TB?

- Yes No

2) Were you offered the opportunity to meet with a nurse or counselor to review the treatment that is being offer to you as well any problems or symptoms that may arise during treatment?

- Yes No

3) Were you given an opportunity to ask and have answered any questions you might have about your health status and the treatment you are being offered?

- Yes No

4) Were you given the name of a person to contact and information about how to contact that person should you have any questions about your health status and the treatment that is being offered to you?

- Yes No

5) Do you agree to receive the treatment recommended for you by your health care providers?

- Yes No

6) Are you being offered treatment with a drug called bedaquiline?

- Yes (if yes, answer 7 and 8) No (if no, skip to point 9)

7) If yes, were you given specific information about the symptoms of problems this drug might cause?

- Yes No

8) Do you agree to receive treatment with the drug called bedaquiline?

- Yes No

9) By signing this form, I consent to receive treatment for TB

Print name of patient

Signature of patient

Date

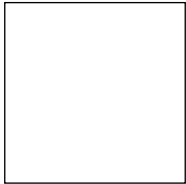
If patient unable to read or write fluently in the language in which the information was provided and used in this form, fill in the following section

I designate _____
to read this information to me and to sign on my behalf. I also place my thumbprint here to verify this.

Print name of witness

Signature of witness

Date

Thumbprint 

Verification by person reviewing education materials with the patient (counselor)

Print name of counselor

Signature of counselor

Date

B. Due Process for Informed Consent: Checklist for Counselors/Providers

Due process is considered to have been followed when the answers to points 1,2,3,4, and 5 are answered yes. Bedaquiline can be administered when points 1,2,3,4,5,6,7 ,and 8 are answered yes.

1) Did you provide the patient with information about his/her current health status, diagnosis, and the reason he/she is being started on treatment for TB?

- Yes No

2) Did you provide an opportunity to meet with the patient to review the treatment that is being offered to him/her as well any problems or symptoms that may arise during treatment?

- Yes No

3) Did you give the patient an opportunity to ask and have answered any questions he/she might have about his/her health status and the treatment he/she being offered?

- Yes No

4) Did you give the patient the name of a person to contact and information about how to contact that person should he/she have any questions about his/her health status and the treatment that is being offered to him/her?

- Yes No

5) Did the patient agree to receive the treatment recommended for him/her by his/her health care providers?

- Yes No

6) Is the patient being offered treatment with a drug called bedaquiline?

- Yes (if yes, answer 7 and 8) No (if no, skip to point 9)

7) If yes, did you give the patient specific information about the symptoms of problems this drug might cause?

- Yes No

8) Did he or she agree to receive treatment with the drug called bedaquiline?

- Yes No

9) By signing this form, I verify that this information was provided to the patient. to receive treatment for TB

Print name of counselor

Signature of counselor

Date

Verification by patient receiving education materials (or by designated appointee if patient is not fluent in the language in which the information was provided)

Print name of patient/representative

Signature of patient/representative

Date

SELECTED REFERENCES

World Health Organization

1. World Health Organization. A 2016 review of available evidence on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Geneva, Switzerland, 2017. WHO/HTM/TB/2017.01. Available at http://www.who.int/tb/publications/2017/GDGreport_Bedaquiline/en/. Accessed April 20, 2017
2. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. 2016.
3. World Health Organization (WHO). WHO treatment guidelines for drug resistant tuberculosis: 2016 update. Geneva, World Health Organization; 2016. WHO/HTM/TB/2016.04
4. World Health Organization. Active Tuberculosis Drug Safety Monitoring and Management (aDSM): a framework for implementation. 2015. WHO/HTM/TB/2015.28
5. *Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis* (WHO/HTM/TB/2014.11). Geneva: World Health Organization; 2014.
6. *Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008*. (WHO/HTM/TB/2008.402). Geneva, World Health Organization. 2008. Available from: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf
7. *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 Update*. (WHO/HTM/TB/2011.6). Geneva, World Health Organization. 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf.
8. *The use of bedaquiline in the treatment of multidrug-resistant tuberculosis, Interim policy guidance*, Geneva, World Health Organization. 2013; Available from: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf.
9. *Definitions and reporting framework for tuberculosis – 2013 revision* (WHO/HTM/TB/2013.2) [Internet]. Geneva, World Health Organization; 2013. Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf
10. *Minimum Requirements for a functional Pharmacovigilance System*, World Health Organization and Global Fund 2010. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficiency/PV_Minimum_Requirements_2010_2
11. *Policy Implementation Package for the Introduction of New TB Drugs in Countries*. . Geneva, World Health Organization. 2014.
12. World Health Organization. Interim guidance on the use of delamanid to treat MDR-TB. Geneva: World Health Organization; 2014. WHO/HTM/TB2014.23.
13. World Health Organization. The contribution of bedaquiline to the treatment of MDR-TB: synthesis of publicly available evidence. January, 2013. http://www.who.int/tb/challenges/mdr/BF_BDQ_Summary.pdf
14. World Health Organization: *Global Tuberculosis Report 2016* (WHO/HTM/TB/2014.08). Geneva: World Health Organization; 2016.

United States Centers for Disease Control and Prevention

1. Mase, S., Chobra, T., Lobue, P. and Castro, K. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. MMWR 62(RR09): 1-12. 2013. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm>.

Partners In Health

1. *The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis, Second Edition*. Partners In Health Boston, USA. USAID TB CARE II. 2013

ERS/WHO Consilium

1. Blasi, F., Dara, M., van der Werf, M., and Migliori, G. Supporting TB Clinicians Managing Difficult Cases: the ERS/WHO Consilium. *European Respiratory Journal* 41(3): 491-4, 2013. Doi 10.1183/09031936.00196712.
2. Esposito S, D'Ambrosio L, Tadolini M, et al. ERS/WHO Tuberculosis Consilium assistance with extensively drug-resistant tuberculosis management in a child: case study of compassionate delamanid use. 2014 Sep;44(3):811-5. doi: 10.1183/09031936.00060414. Epub 2014 May 15.

Curry International Tuberculosis Center

1. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2011. <http://currytbcenter.ucsf.edu/drtb/>

General

1. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* 2005;307(5707):223-7.
2. Cariem R, Cox V, de Azevedo V, Hughes J, Mohr E, Durán LT, Ndjeka N, Furin J. The experience of bedaquiline implementation at a decentralised clinic in South Africa. *Public Health Action*. 2016 Sep; 6(3):190-192. PMID: 27695682.
3. Chang, K., Leung, C., Yew, W., et al. Pyrazinamide may improve fluoroquinolone-based treatment of multi-drug resistant tuberculosis. *Antimicrobial Agents and Chemotherapy* 56(11): S465-S475, 2012.
4. Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2012 Apr;16(4):447-54.
5. Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrobial Agents & Chemotherapy*. 56(6):3271-6, 2012 .
6. Dooley KE, Obuku EA, Durakovic N, Belitsky V, Mitnick C, Nuermberger EL; Efficacy Subgroup, RESIST-TB. World Health Organization group 5 drugs for the treatment of drug-resistant tuberculosis: unclear efficacy or untapped potential? *J Infect Dis*. 2013 May 1;207(9):1352-8. Epub 2012 Jul 17.
7. Gler MT, Skripconoka V, Sanchez-Garavito E, Xia H, et al. Delamanid for multidrug resistant pulmonary tuberculosis. *New Engl J Med* 2012. 366(23):2151-60.
8. Gras, J., et al.. Bedaquiline for the treatment of pulmonary, multidrug-resistant tuberculosis in adults. *Drugs Today (Barc)*. 2013 Jun;49(6):353-61.
9. Gugliemetti, L., Le Dû, D., Jachym, M., et al. Compassionate use of bedaquiline for the treatment of MDR- and XDR- tuberculosis: an interim analysis of a French cohort. *Clinical Infectious Diseases*, 2014 doi: 10.1093/cid/ciu786.
10. Gugliemetti, L., Jaspard, M., Le Du, D., et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *European Respiratory Journal* 2016, DOI: 10.1183/13993003.01799-2016
11. Gugliemetti L, Hewison C, Avaliani Z, Hughes J, Kiria N, Lomtadze N, Ndjeka N, Setkina S, Shabangu A, Sikhondze W, Skrahina A, Veziris N, Furin J. Examples of bedaquiline introduction for the management of multidrug-resistant tuberculosis in five countries. *Int J Tuberc Lung Dis*. 2017 Feb 01; 21(2):167-174. PMID: 28234080.
12. Hafkin J FM, Hesseling A, Garcia-Prats AJ, Schaaf HS, Gler M, Hittel N, Welld C, Geiter L, Mallikaarjun S. . Pharmacokinetics and safety of delamanid in paediatric MDR-TB patients, ages 6-17 years. *ICAAC; San Diego, California*2015.

13. Harausz EP, Garcia-Prats AJ, Seddon JA, Schaaf HS, Hesselning AC, Achar J, Bernheimer J, Cruz A, D'Ambrosio L, Detjen A, Graham SM, Hughes J, Jonckheere S, Marais BJ, Battista Migliori G, McKenna L, Skrahina A, Tadolini M, Wilson P, Furin J. New/Repurposed Drugs for Pediatric Multidrug-Resistant Tuberculosis: Practice-Based Recommendations. *Am J Respir Crit Care Med*. 2016 Nov 17. PMID: 27854508.
14. Harausz, E., Cox, H., Rich, M., et al. QTc prolongation and the treatment of multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 2015. <http://dx.doi.org/10.5588/ijtld.14.0335>.
15. Lange, C., Abubakar, I., Alffenaar, J., et al. Management of patients with multidrug-resistant/ extensively drug-resistant tuberculosis in Europe. A TBNET consensus statement. *European Respiratory Journal* 44(1): 23-63. doi: 10.1183/09031936.00188313. 2014.
16. Lee M, Lee J, Carroll MW et al. . Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med*. 2012 Oct 18;367(16):1508-18.
17. Migliori GB, Eker B, Richardson MD, et al; TBNET Study Group. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J*. 2009 Aug;34(2):387-93. Epub 2009 Mar 12.
18. Ndjeka, N., Conradie, F., Schnippel, K. et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *International Journal of Tuberculosis and Lung Disease* 19(8): 979-85, 2015
19. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, Cirule A, Leimane V, Kurve A, Levina K, Geiter LJ, Manissero D, Wells CD. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J*. 2013 Jun;41(6):1393-400.
20. Sotgiu G, Centis R, D'Ambrosio L, et al.. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J*. 2012 Dec;40(6):1430-42. Epub 2012 Apr 10.
21. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, Hewison C, Centis R, Schaaf HS, Marais BJ, Ferreira H, Caminero JA, Jonckheere S, Sinha A, Herboczek K, Khaidarkhanova Z, Hayrapetyan A, Khachatryan N, Urtkmelidze Ia, Loreti C, Esposito S, Matteelli A, Furin J, Varaine F, Migliori GB. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. *Eur Respir J*. 2016 Sep; 48(3):938-43. PMID: 27338197; PMCID: PMC5007219.
22. Tang, S., Yao, L., Hao, X., et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, randomized multicentre controlled study in China. *Clinical Infectious Diseases*, January 20, 2015. doi: 10.1093/cid/civ027.
23. Udawadia, Z., Amale, R., and Mullerpatan, J., Initial experience of bedaquiline use in a series of drug-resistant tuberculosis patients from India. *International Journal of Tuberculosis and Lung Disease* 18(11): 1315-8.
24. Zumla, A., Gillespie, S., Hoelscher, M., et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances and future prospects. *The Lancet Infectious Diseases* March 24 :49-62. 2014. <http://dx.doi.org/10.1016/>