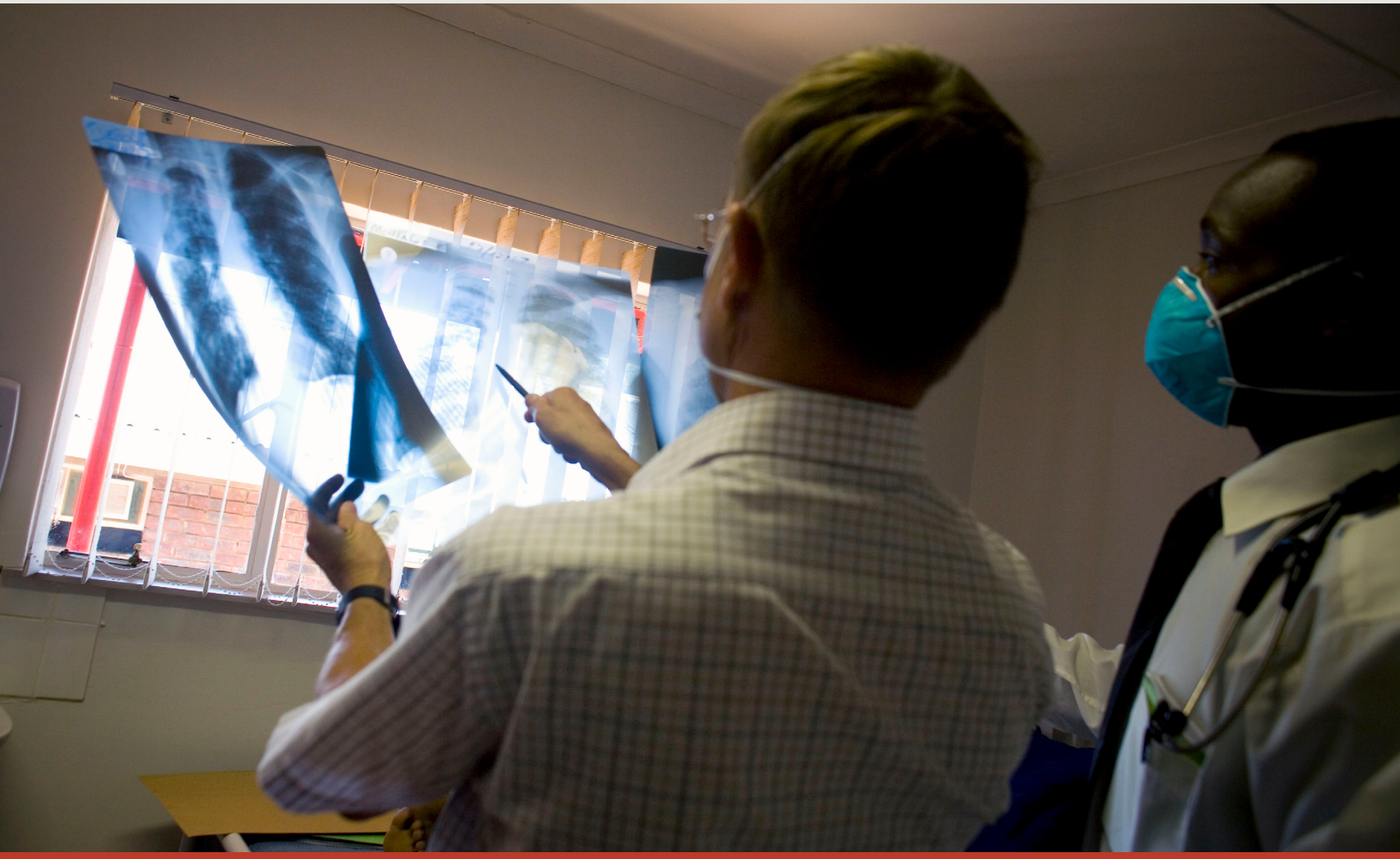
Best Practices for Clinical Management of Tuberculosis with Expanded Resistance

A Field Guide



THE BETTER PROJECT

Building Experience Treating Tuberculosis with Expanded Resistance

First Edition, December 2024

This handbook was developed and written by The Building Experience Treating Tuberculosis with Expanded Resistance Project (The BETTER Project)

Preferred citation: Best Practices for Clinical Management of Tuberculosis with Expanded Resistance: A Field Guide. Cleveland, OH, USA: The BETTER Project, First edition, December 2024

The BETTER Project is a global partnership of researchers, caregivers, and advocates aiming to develop and deploy evidence-based strategies to provide compassionate and comprehensive care for people with all forms of TB, including those whose strains have resistance to newer (bedaquiline, delamanid, and pretomanid) and/or repurposed drugs (linezolid, clofazimine, and the fluoroquinolones). We are a learning network committed to generating and disseminating knowledge and data for immediate action.

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Cover photo courtesy of Justin Ide

The BETTER Project is grateful to and acknowledges the support of Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination (SMART4TB), made possible by the support of the American people through the United States Agency for International Development. SMART4TB supported a meeting of the group in 2024 where issues relevant to this best practices document were discussed. The contents of this guide are the sole responsibility of the BETTER Project and do not necessarily reflect the views of USAID, the United States government, or SMART4TB consortium collaborators or members.

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INTRODUCTION

Background

This is an exciting time in the treatment of rifampicin/multidrug-resistant forms of tuberculosis (RR/MDR-TB). New compounds (bedaquiline, delamanid, pretomanid) have been in clinical use for almost a decade. When combined with re-purposed agents (including linezolid and clofazimine), regimens consisting of these drugs have revolutionized RR/MDR-TB treatment. It is now possible to cure many people who are diagnosed with RR/MDR-TB in 6-9 months using combinations of 3 to 5 of these medications.

As always occurs with antimicrobial agents, however, resistance to these new and repurposed drugs is emerging. It is an urgent priority for people living with RR/MDR-TB, health care providers, and National TB Programs, to identify individuals who are sick with these resistant strains of TB and to offer them optimized care. It will likely be years before the evidence base is built on how best to manage RR/MDR-TB when there is resistance to newer/repurposed agents. Clinicians, however, are seeing these individuals in their clinics right now and need to share best practices for management.

To help support people receiving and providing treatment for these forms of TB, we have developed this "best practices" field guide. The scope of the guide is to provide principles to optimize the care of people with what we refer to as "expanded resistance".

Expanded Resistance

For the purposes of this field guide, we define "expanded resistance" as a strain of *M. tuberculosis* with resistance to rifampicin and to at least one more of the following agents: bedaquiline, linezolid, clofazimine, delamanid, and/or pretomanid. This definition is inclusive of XDR-TB, i.e., TB with resistance to rifampicin, fluoroquinolones, and at least one or more of the Group A agents. However, it also encompasses other resistance patterns, e.g., TB with resistance to rifampicin and bedaquiline and susceptibility to fluoroquinolones. Strains of *M. tuberculosis* with resistance to rifampicin and a fluoroquinolone are defined as "pre-extensively drug-resistant (pre-XDR)" TB by the World Health Organization (WHO) and will be considered in this guide if they also have additional resistance to the drugs mentioned above. However, since the WHO provides guidelines on the management of pre-XDR-TB, we will not focus on those strains in this guide.

The field guide is part of a larger initiative known as the BETTER Project (Building Experience Treating Tuberculosis with Expanded Resistance). The goal of the BETTER Project is to share clinical experiences both receiving and providing care for people with strains of TB that have resistance to bedaquiline, linezolid, the nitroimidazoles, and/or clofazimine. The group is made up of RR/MDR-TB survivors and health care workers living and providing services in countries where resistance to the newer and repurposed agents is increasing. It is meant to share real-world experience and expert opinion about optimized practices. It was possible to reach consensus on most approaches, but when consensus could not be reached, then the rationale for different practices and opinions is described in the text.

The guide focuses on clinical management, but recognizes the need for ongoing social, nutritional, psychological, and emotional support at all stages of care.

Definitions and Abbreviations

The current definitions of various types of RR/MDR-TB used by the WHO have evolved over time. In the past, they were based on the existence of drug resistance that would necessitate a change in management. These current definitions do not suffice, however, to cover all possible scenarios when it comes to resistance to the second-line drugs. For example, a person would be sick with a strain of TB in which there is resistance to bedaquiline and pretomanid but not to moxifloxacin. Such a resistance pattern would necessitate a change in the treatment approach but would not be covered by any of the current WHO definitions of pre-extensively RR/MDR-TB or extensively RR/MDR-TB. Given that these definitions of XDR-TB and pre-XDR-TB will likely require multiple changes over time, we will not be using them in this best practices guide. Rather, we will use the WHO definitions of RR/MDR-TB and then refer to specific drugs by name (i.e. bedaquiline-resistant) or classes (i.e. fluoroquinolone resistance).

The following abbreviations for drugs are used in this best practices guide:

Bdq = bedaquiline	**Emb** = ethambutol	**Lfx** = levofloxacin	**PAS** = Para-aminosalicylic acid
Cfz = clofazimine	**Eto** = ethionamide	**Lzd** = linezolid	**Pza** = pyrazinamide
Cs = cycloserine	**Flq** = fluoroquinolone	**Mfx** = moxifloxacin	**Rif** = rifampicin
Dlm = delamanid	**Inh** = isoniazid	**Pa** = pretomanid	

Evidence Base

In most instances, this best practices guide is based on consensus expert opinion. Whenever possible, however, we have incorporated supporting evidence from trials and observational studies in the discussions. Usually, we suggest an individualized approach to regimen design, taking into account disease severity, comorbidities, and local resistance patterns: however, there are some core backbone regimens that could be considered based on recent trials. For example, the MDR-END regimen was based on a randomized clinical trial assessing a 9-month regimen of Dlm-Lfx-Lzd-Pza against a local standard of care. The study found the Dlm-Lfx-Lzd-Pza regimen to be non-inferior to a longer, conventional, injectable-containing regimen, although there were some challenges with the sample size and study population in this trial (i.e. it did not include people living with HIV). Thus, when there is a patient with Bdq and/or Cfz resistance but preserved susceptibility to the fluoroquinolones and Dlm, this regimen could be considered as a backbone regimen, with potential modifications based on disease severity, resistance patterns, and underlying comorbidities.

The MDR-END Regimen

The MDR-END study was a randomized, controlled trial done in South Korea among people aged 19-85 years with MDR-TB. The study excluded people whose strains of TB had resistance to the fluoroquinolones. The study assessed a 9-month regimen of delamanid, linezolid (600mg), levofloxacin, and pyrazinamide compared with a 20-24 month standard of care regimen. The study enrolled 214 participants, and 168 were included in the modified intention to treat population. Treatment success rates in the experimental arm were 75% compared with 70.6% in the standard of care arm, meeting the threshold of non-inferiority in the modified intention-to-treat population. However, non-inferiority was not achieved in the per-protocol population. Bacteriologic failure or relapse was rare in both groups, and most of the treatment outcome differences were driven by changing or adding newer drugs to the assigned regimen. Safety was comparable between the two groups.

Mok, J., Lee, M., Kim, D., et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. The Lancet 2022, 400: 1522-30.

The endTB Regimens

The endTB study was a randomized, controlled trial done in multiple countries around the world that compared 5 different experimental, 9-month regimens with the locally accepted standard of care. The study used an adaptive trial design and was meant to identify multiple possible regimens for the treatment of RR/MDR-TB. The regimens were:

- endTB regimen 1: bedaquiline, linezolid, moxifloxacin, pyrazinamide
- endTB regimen 2: bedaquiline, clofazimine, linezolid, levofloxacin, pyrazinamide
- endTB regimen 3: bedaquiline, delamanid, linezolid, levofloxacin, pyrazinamide
- endTB regimen 4: clofazimine, delamanid, linezolid, levofloxacin, pyrazinamide
- endTB regimen 5: clofazimine, delamanid, moxifloxacin, pyrazinamide

Each regimen that contained linezolid allowed for dose reduction from 600mg daily to either 300mg daily or 600mg every other day either at the time of side effect development or after four months of therapy.

A total of 754 people were randomized to the different treatment arms and 696 were included in the modified intention to treat population, 14.1% of whom were living with HIV. endTB regimens 1, 2, and 3 were shown to be non-inferior to the standard of care in both modified intention-to-treat and per-protocol populations in terms of efficacy and have been recommended by the WHO. endTB regimen 5 was only non-inferior in the modified intention to treat population and not in the per protocol analysis. Participants receiving this regimen experienced higher rates of treatment failure and amplification of resistance in people who were not bacteriologically cured was more frequent than in regimens 1, 2, and 3. For these reasons, the WHO does not recommend its routine use.

Guglielmetti, L., Khan, U., Velazquez, G., et al. Nine-month, all-oral regimens for rifampicin resistant tuberculosis. *(Preprint)*

It is also important to recognize that although we discuss and define expanded resistance in a general sense, there are important regional variations. Preliminary, unpublished reports suggest that in many parts of southern Africa, for example, Bdq resistance is almost always associated with resistance to Cfz. In some countries in eastern Europe, however, cross-resistance is less common. Some of this may be due to challenges in phenotypic testing for Cfz susceptibility, and more studies are needed to determine if there is real regional variation in Bdq and Cfz cross resistance. In some regions of the world, there are strains of *M. tuberculosis* with resistance to Rif, Bdq, and Cfz but with preserved susceptibility to Lfx and Mfx. Thus, we recognize that no "single" approach will suffice to cover all the complexities seen in care. We thus try to suggest "core" best practices that can then be adapted to country-specific situations.

Although there are many potential issues to address, consensus will first focus on sharing practices in the following areas:

1. Optimizing drug susceptibility testing (i.e. methods, populations who should be tested, frequency, timing, etc.);
2. Principles and practices for informed consent and shared decision making on treatment approaches;
3. Designing regimens (including empiric and definitive regimens) for persons at "high risk" of expanded resistance but in whom resistance has not yet been confirmed;
4. Deploying holistic packages of supportive care;
5. Management considerations in special populations;
6. Practices arounds pre-approval access to novel TB compounds (i.e. telacebec, quabodepistat, ganfeborole, newer generation diarylquinolines);
7. Post-exposure management for household contacts exposed to people with strains of TB that have expanded resistance;
8. Toxicity monitoring and management, including drug substitutions;
9. Operational research in settings of expanded resistance, including collecting common data elements.

1. OPTIMIZING DRUG SUSCEPTIBILITY TESTING

Ideally, all persons diagnosed with RR/MDR-TB should undergo comprehensive baseline drug susceptibility testing (DST). The gap between the development of new drugs and the development of drug susceptibility testing for these drugs is a serious challenge. Often, people diagnosed with RR/MDR and those providing services to them are faced with a situation in which care must be provided in the absence of data on drug susceptibility, and this situation has persisted for far too long. Lifesaving drugs should not be withheld because of a lack of DST, but much more needs to be done to ensure equitable and rapid access to DST.

At a minimum, programs should strive to offer people drug susceptibility testing done for the agents they are going to be prescribed. Chief among the agents to test would be: Bdq, Lzd, Lfx/Mfx, Dlm/Pa, and Cfz. Phenotypic testing provides in vitro susceptibility to these classes of drugs but can take multiple weeks to complete. For this reason, it is not ideal for patient care. Whole genome sequencing (WGS) or targeted next generation sequencing (tNGS) may be more rapid—especially if done on sputum—but not all identified mutations are associated with clinically significant resistance. The data on tNGS and WGS are rapidly improving and there are concerted global efforts to continue to advance the field. While these are being further refined, programs should use whatever methods they have available, either in-country or accessible through a network of national/supra-national laboratory within the region. One important aim is for the most rapid turnaround time possible. There is also a need for advocacy to expand access to rapid DST for all people diagnosed with RR/MDR-TB.

Universal access to drug susceptibility testing for all people with TB is our goal. All persons starting treatment for RR/MDR-TB should have baseline DST done, as primary resistance to the newer and repurposed agents is occurring in all settings. While this is being scaled up, it is considered best clinical practice to prioritize baseline testing for the following individuals:

- Persons with previous exposure to any of the second-line agents (Bdq, Cfz, Dlm, Lzd, Lfx, Mfx, Pa). For drugs such as Lzd or Lfx, most providers consider “previous exposure” to mean 1 or more months of treatment. However, for drugs such as Bdq or Cfz with longer half-lives, even a shorter duration of exposure could result in resistance, so persons even with a shorter exposure should be considered to be at risk for resistance.
- Persons who are contacts of people with strains of TB with known or likely resistance to Bdq, Cfz, Dlm, Lzd, Lfx, Mfx, or Pa;
- Persons who have been previously inpatients in an RR/MDR-TB hospital for any period of time;
- Persons who have been previously treated for RR/MDR-TB and experienced any of the following outcomes: clinical or microbiological failure; loss to follow-up (especially people lost early in treatment or not doing well when they are lost from care); relapse/recurrent TB, or unknown treatment outcome;
- Persons who have had treatment interrupted/missed treatment doses, either because their providers recommending pausing drugs to address adverse events, drugs were not available due to program stock outs, or because of people were not supported enough to overcome challenges with adherence. These missed doses may be even more problematic early in treatment and can compromise outcomes even among people who do not meet the formal WHO definition of “lost to follow up”;
- Persons from other populations that have elevated rates of resistance to Bdq, Cfz, Dlm, Lzd, Lfx, Mfx, Pza, or Pa (e.g., incarcerated individuals, health care providers). These populations are context-dependent and should be determined by local stakeholders.

It is likely there are other groups of people who may be at increased risk for expanded resistance, and they should also be considered to be priority populations for increased access to DST. We recognize that in the past, prioritizing DST for only the groups listed above likely led to missing resistance. Ongoing research is needed to better identify predictors for resistance, but while this is ongoing, baseline resistance testing should be done for at least these populations. Baseline DST should also be done in settings where Bdq, Cfz, Dlm, Lzd, and Flq resistance is known to exist, and transmission of these strains is likely ongoing.

In addition to these individuals who should have baseline samples tested for resistance to these medications, any person who has a positive culture at month 2 or 3 of treatment or later should have that culture sent for resistance testing. It is unclear whether month 2 or 3 is the best time to identify expanded resistance. Some studies show high rates of early culture conversion with the newer and repurposed drugs, and experts feel that conversion should have taken place by month 2. Waiting for month 3 may delay the information needed to offer a more effective treatment regimen. Other experts feel that while the majority of people on newer and repurposed regimens will have culture conversion by month 2, a small percentage of people will convert at month 3 and be successfully treated. Programs will need to consider the optimal timing of culture sampling for DST based on the clinical scenario and the available resources.

Of note, ideally, testing would be done for Bdq, Cfz, Dlm, Pa, Lfx, Lzd, Mfx and Pza. Unpublished data show that while there is often cross-resistance between Bdq and Cfz in some regions of the world (i.e. greater than 90% in southern Africa), in other settings (e.g., Eastern Europe) rates of cross resistance may be lower than 50%. One caveat to interpreting these data is that phenotypic DST for Cfz is notoriously challenging. Incomplete cross-resistance with different geographic patterns may also be seen for other drug classes, such as the fluoroquinolones (i.e. Lfx and Mfx) and the nitroimidazoles (Dlm and Pa).

Finally, in terms of Pza, there are varied opinions about its inclusion even in the presence of resistance. For decades, clinicians and researchers have considered possible synergy between core drugs (i.e. Bdq) and Pza which could contribute to regimen success. In the MDR-END study, the number of people with Pza-resistant strains in the study was low. However, there did appear to be a trend toward worse outcomes in people whose strains of TB had resistance to Pza. In the endTB trial, there was also a trend toward lower rates of success in people who had strains of TB with resistance to Pza, although participants harboring Pza-resistant strains had successful outcomes in more than 80% of cases. Thus, whether or not to include Pza and whether or not to add additional agents should be a topic for shared decision making between providers and people diagnosed with expanded resistance. Pza may be associated with higher rates of liver toxicity, especially when used in combination with other hepatotoxic drugs (i.e. Pa, Mfx, Bdq or others). Pza and Pa should not be used together due to an increased risk of hepatotoxicity.

2. INFORMED CONSENT AND SHARED DECISION MAKING

At the time of this writing, there is not yet a strong evidence base to support any one regimen or approach for TB with expanded resistance. Thus, when regimens are being designed, it is important that the needs, preferences, and values of the person seeking care be considered alongside the recommendations of the providers. This is best accomplished through a process of shared decision making and ongoing consent in which people seeking care and providers are considered active partners in all the treatment decisions.

This is a novel approach for many TB programs and providers who are more accustomed to "telling" patients what to do. With expanded resistance, however, there is no one right answer or clear path forward. Thus, the decisions being made should acknowledge this and be made together, with individual needs considered carefully.

People with forms of TB that have expanded resistance need to be viewed as active partners in their treatment. The first step in making sure this can happen is for the person undergoing treatment to be informed about their options. This process of informed consent is more expansive and ongoing than that typically used in TB care, and it is not a "one-time" event in which a form is signed for legal reasons. Rather, it is a continuous discussion between providers and people undergoing treatment that is grounded in honesty, with frank discussions about risks and benefits of treatment.

When people find out that they have a form of TB with expanded resistance, they may be shocked or overwhelmed, fearing for their lives. This may not be the ideal time to have an educational discussion or ask the person to sign a form authorizing treatment. Rather, it is a time to convey empathy and to emphasize that the person is not in the situation alone. Best practices would utilize a multi-disciplinary team (including peer supporters, nurses, outreach workers, spiritual providers, etc.), assess the needs and values of the person undergoing care, and involve listening as much as sharing information.

Shared decision making does not mean that the onus for deciding on the therapeutic approach rests entirely on the patient or entirely on the providers. Rather, both groups possess specialized knowledge that will help them arrive at an optimal therapeutic approach. There will need to be ongoing discussions throughout treatment regarding the optimal plan going forward. A model of shared decision making is included in Figure 1 below:

Figure 1: Components of Shared Decision Making

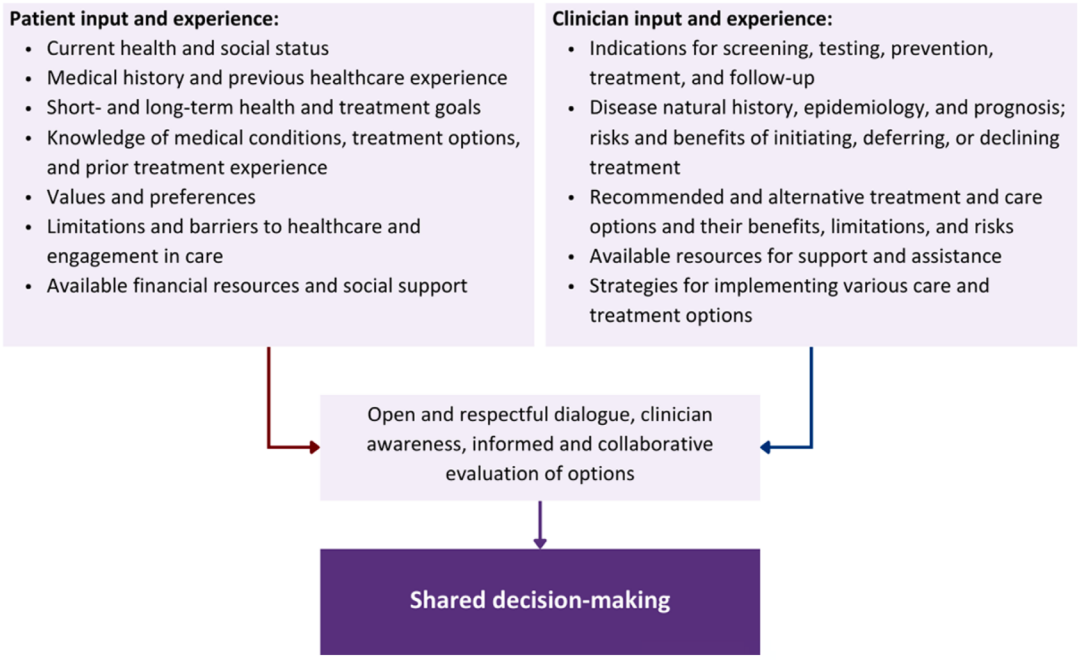


Figure 1 taken from: New York State Department of Health. AIDS Institute HIV Guidelines. Shared Decision Making. August, 2023. Figure reprinted with express written permission from the New York State Department of Health.

There are some decision points in the care of people with TB strains that have expanded resistance where shared decision making could be practiced. For example, in people on the Bdq, Pa, Lzd, and Mfx regimen who are doing well but found to have a strain of TB that has a mutation that *could be* associated with Bdq resistance, shared decision making could be done about continuing the Bdq, Pa, Lzd, Mfx regimen or switching to another treatment. In people who need an individualized regimen, shared decision making could be used to select some of the Group C agents, taking into account the toxicity risks. The location of treatment (community-based or hospital-based) could also be considered in shared decision making as well.

Other issues could be considered in exploring shared decision making best practices in the field of TB. These could be explored in operational research and include:

- What does this overall therapeutic approach mean to patients across different cultural and geographical contexts?
- What does this overall therapeutic approach mean to health providers across contexts?
- What are the challenges/barriers to shared decision making for patients?
- What are the concerns health providers have around shared decision making?
- What is the scope of shared decisions? Where should it be a shared choice?
- What shared decision making models already exist in TB or other disease areas?
- How can we capture narrative evidence of patient experiences of shared decision making?
- What are the common elements of shared decision making across models that seem to work?
- What are the specifics of how shared decision making relates to overall experience in care, improved adherence, quality of life, etc. in different contexts?

3. DESIGNING TREATMENT REGIMENS

Overall, people with forms of TB that have expanded resistance will fall into two main categories: 1) those with risk factors for resistance but where resistance has not (yet) been confirmed and 2) those with demonstrated resistance on DST. There are generally three pathways by which such people come into care:

1. The person had a history of previous treatment with a regimen containing the newer and/or repurposed drugs (e.g., they received Bdq in the past as part of an all-oral, nine-month regimen);
2. The person is currently receiving treatment with a regimen containing the newer and/or repurposed drugs and is not currently improving or is having challenges with missed doses of treatment;
3. The person is currently receiving treatment with a regimen containing the newer and/or repurposed drugs and is doing well but is later found to have a strain of TB with expanded resistance or a mutation of unclear significance that could be associated with expanded resistance on samples that were sent at baseline or during treatment.

Ideally, all persons should have a comprehensive DST done at baseline. In settings where this is not possible due to logistic or financial constraints, in addition to all the populations listed in Section 1 in pathway 1 or 2, comprehensive drug susceptibility testing should be sent if it has not already been. While awaiting the drug susceptible results, a regimen will need to be started, especially since the results can take weeks to obtain.

It is also possible that people with these histories will present in settings where there is no access yet to drug susceptibility testing. They will need to be treated without the benefit of DST, and their regimens can be designed using the principles described below.

3.1 Standardized Approaches

There are some instances in which a standardized regimen could be considered. These include:

- People with a remote (> 2 years ago) history of treatment with the newer or repurposed drugs, and who are at low risk of having a strain with expanded resistance. These include people who were cured or given an outcome of treatment success on the prior regimen. Some people who have an outcome of “lost to follow up” could also be considered to be lower risk for the development of TB with a strain that has expanded resistance, especially people who were in the final months of treatment and who had negative bacteriology and clinical improvement at the time they were lost from care. Such individuals could have a sample sent for DST and be started on the standard shorter regimen being used in their setting while awaiting the results, especially if they have minimal disease and no other comorbidities.
- People with only exposure to Bdq (and not to Lzd or the nitroimidazoles) and in whom there is no resistance detected to the Flq (usually determined on GeneXpert testing) could receive the MDR-END regimen of 9 months of Dlm-Lfx-Lzd-Pza, provided there is no resistance to Lfx. This regimen could be fortified with Cs if there is concern about additional resistance to Pza. It is rare that people will only have had exposure to Bdq.

3.2 Individualized Approaches

Most people, however, will need to be treated with an individualized regimen. The construction of an individualized regimen for a person with TB with risk factors for expanded resistance may initially appear to be a challenging task. TB is always treated with a combination of medications, and for this reason, there may not be specific data about the efficacy of an individual drug. Usually, providers consider the potential efficacy of a drug along with the toxicity and the logistics of administering the drug (e.g., pill burden, need for IV administration) in order to come up with a regimen in a process of shared decision making with the person being treated. Not all TB drugs are equally effective, however, and it is not simply a matter of picking any four or five of them to create a treatment regimen. There are some steps to consider in designing an individualized regimen, and we review them below.

Some general principles to consider in regimen design are:

1. A drug can be counted as effective if there is documented susceptibility to the drug or if the drug (or one it shares cross resistance with) has not been used before. However, in settings where the background prevalence of resistance is known to be high or where ongoing transmission of strains that have resistance to the newer and/or repurposed agents, a drug could be used but not counted as effective;
2. A regimen should consist of a combination of agents that are both bactericidal and sterilizing. Bactericidal drugs are more important in the first weeks/months of treatment, but sterilizing drugs are needed for non-relapsing cure. An effective regimen needs a combination of these two types of drugs. Data regarding the bactericidal and sterilizing effects of many drugs are still being generated. Table 1 below considers the use of TB antimicrobials for bactericidal and/or sterilizing activity.

Table 1: Bactericidal and Sterilizing Roles of Antituberculosis Drugs in Regimens

Drug	Used for bactericidal activity	Used for sterilizing activity
Bedaquiline	+++	+++
Levofloxacin/moxifloxacin	+++	+++
Linezolid	+++	+
Delamanid	++	++
Pretomanid*	+++	+++
Clofazimine	+	+++
Cycloserine	++	+
Amikacin	+++	+
Carbapenem+clavulanic acid	++	+
Pyrazinamide	+	+++
Ethionamide	++	+
PAS	+	+
High-dose INH	++	+

**Has only been assessed in combination regimens and not as a single agent*

3. People with non-severe TB with expanded resistance (isolated lymphadenitis, unilateral and non-cavitary pulmonary TB) could probably receive a regimen of 4 effective drugs (depending on what drugs they are) whereas those with more severe disease (bilateral, cavitary, extrapulmonary TB) should receive at least 5 effective drugs. The actual number of drugs people receive,

however, could be as high as 7-8, as drugs may be used even if they are not counted as effective;

4. The ultimate choice of regimen will be based on preferences, toxicity, availability, and other factors. There is no one-size-fits-all approach.

To design a regimen, a stepwise approach should be considered, as not all drugs are equally effective. The WHO grouping of drugs (A, B, C) was based on an individual patient data meta-analysis which was done to assess the impact of single agents. Of note, interpreting these data can be a challenge since most people are treated with combination regimens. This analysis showed some drugs were associated with improved outcomes and lower mortality, and these are the Group A drugs (Bdq, Lzd, and third-generation Flqs). In the analysis, some drugs were associated with improved outcomes but not a mortality reduction, and those are the Group B drugs (Cs and Cfz). All other drugs were put into Group C. Some Group C drugs were not associated with either improved outcomes or lower mortality, but this may have been due to lack of data (i.e. Dlm). Some Group C drugs were associated with improved outcomes but had a higher rate of toxicity (i.e. Am) or were challenging to administer IV (i.e. carbapenems). Some Group C drugs were not associated with improved outcomes (PAS, Eto). Some Group C drugs may have a synergistic role (Pza), and others should only be used in settings of documented susceptibility (Emb). Some drugs were not grouped (Pa, high-dose Inh). A table summarizing the drugs according to WHO grouping is below. For pediatric dosing, please see the "Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide" available from the Sentinel Project on Pediatric Drug-Resistant Tuberculosis.

Table 2: Possible Drugs and Dosing to Use in Individualized Regimens

Drug	Dose	Standard dosing for 65kg adult	Higher dosing for 65kg adult	Mechanisms of action and cross resistance	Comments
Group A					
Bdq		400mg daily for 14 days followed by 200mg three times a week Or 200mg daily for 8 weeks followed by 100mg daily	500mg daily for 14 days followed by 200mg daily	Diarylquinoline that inhibits synthesis of ATP Cross resistance seen with Cfz	Consider verapamil 120mg twice a day if Rv0678 mutations. This has only been done on a patient-by-patient basis and has not been systematically studied in any way. It should only be done when there are no other options.
Lzd	10mg/kg/day	600mg daily for 12 weeks; can consider dose reduction to 300mg daily or 600mg three times a week in patients doing well or in those who have toxicity. Ultimate decision will need to be made based on individual considerations of regimen composition, risk factors, and toxicity. If patient tolerating the 600mg dose well, can continue this dose. In some studies, higher doses of 1200mg daily of Lzd have been used, but these are associated with very high rates of toxicity.	Not recommended due to increased toxicity	Oxazolidinone that inhibits protein synthesis Cross resistance likely with other oxazolidinones	Consider dose reduction only in patients who have dose-limiting toxicity. Dose reduction likely to be safer after culture conversion. Higher doses of 1200mg daily could be considered only if the toxicity risks are discussed and agreed to as part of a shared decision-making process and there are no other options. Consideration of 1200mg every other day to reduce toxicity could also be considered once the patient has had culture conversion.
Lfx	15-20mg/kg/day	1000mg daily	1500mg daily	Fluoroquinolone that inhibits DNA gyrase Cross resistance likely with other fluoroquinolone agents	Higher doses of 20-30mg/kg/day can be considered

Mfx	7.5-15mg/kg/day	400-600mg daily	800mg daily	Fluoroquinolone that inhibits DNA gyrase Cross resistance likely with other fluoroquinolone agents	Higher doses of 12-15mg/kg/day can be considered
Group B					
Cs	15-20mg/kg/day	750mg daily	1000mg daily	D-alanine analogue that inhibits cell wall synthesis Similar activity to terizidone, complete cross resistance between the two	Terizidone and Cs are considered equivalent in this field guide
Cfz	2-5mg/kg/ day	100mg daily	300mg daily	Riminophenazine that blocks DNA replication Cross resistance possible with Bdq	
Group C					
Dlm		100mg twice a day Or 200mg daily		Bactericidal nitroimidazole that inhibits cell wall synthesis Cross resistance possible with Pa	
Pza	25-35mg/kg/day		2000mg daily	Sterilizing agent whose mechanism of action likely involves interfering with fatty acid synthesis No cross resistance	Doses above 30mg/kg may be associated with increased hepatotoxicity, in particular in association with other hepatotoxic drugs
Emb	15-25mg/kg/day			Bacteriostatic agent whose mechanism of action is unknown No cross resistance	Should only be considered in settings of documented susceptibility

Am	10-15mg/kg/day 25mg/kg three times a week In lieu of IM, doses could be mixed with 200mL of 5% dextrose of 0.9% NaCl and infused slowly over 1 hour	500-750mg daily 1500mg three times a week	1000mg daily 1500mg three times a week	Aminoglycoside that interferes with ribosomal protein synthesis Cross resistance with other aminoglycosides possible	Formal audiometry monitoring necessary, at least 1-2 times per month. Some studies have shown decreased toxicity if given three times a week instead of daily. Can mix with lidocaine for IM administration as this may be less painful
Meropenem		1000-2000 mg twice a day	2000-3000mg twice a day	Carbapenem that interferes with cell wall synthesis Cross resistance with other carbapenems likely. Not effective unless given with clavulanic acid	Must be given with amoxiciilin- clavulanic acid at a dose of 875/125mg orally (dosed 30 minutes prior to each IV administration)
Imipenem		1000mg twice daily		Carbapenem that interferes with cell wall synthesis Cross resistance with other carbapenems likely. Not effective unless given with clavulanic acid	Must be given with amoxicillin- clavulanic acid at a dose of 875/125mg orally (dosed 30 minutes prior to each IV administration)
Ertapenem		1000mg once a day		Carbapenem that interferes with cell wall synthesis Less evidence to support this carbapenem than imipenem or meropenem Cross resistance with other carbapenems likely. Not effective unless given with clavulanic acid	Must be given with amoxicillin- clavulanic acid at a dose of 875/125mg orally (dosed 30 minutes prior to each IV/IM administration) Could be considered for outpatient IM administration after an inpatient course of imipenem or meropenem

Eto	15-20mg/kg/day	500-750mg daily	1000mg daily	Thioamide that inhibits mycolic acid synthesis Cross resistance possible with Inh	Cannot use with *inhA* mutation
PAS		4gm twice a day Some providers prefer to give 8gm every night to decrease GI toxicity but there are more data with twice or thrice daily dosing of PAS	6gm twice a day	Inhibitor of folic acid synthesis No cross resistance	Poorly tolerated and should only be used in "rescue" regimens
Ungrouped agents					
Pa		200mg daily		Sterilizing and bactericidal nitroimidazole that inhibits cell wall synthesis Cross resistance possible with Dlm	
High-dose Inh	10-15mg/kg/day	N/A	600-900mg daily	Bactericidal inhibitor of mycolic acid synthesis Cross resistance possible with Eto	Must be given with pyridoxine; only use if low-level resistance (*inhA* mutation, but no *katG* mutation)

3.2.1 A Stepwise Approach

When designing an individualized regimen for a person with TB who has possible or known expanded resistance, consideration should be given to both the WHO groupings and the bactericidal/sterilizing activity. Regimens need to include a combination of drugs that are bactericidal and drugs that are sterilizing. We suggest the following steps below:

Step 1: Choose as many core drugs as you can

Core drugs are group A drugs that are both sterilizing and bactericidal and include Bdq, Lzd and the third-generation Flqs.

These drugs should be included if susceptibility is documented or uncertain. If low-level resistance has been demonstrated, the third-generation Flqs can be given at higher doses. High-dose Bdq could also be considered. Of note, for high-dose Bdq, there are no clinical studies that demonstrate the effectiveness of this approach. Rather, it is based on modeling data. If high-dose Bdq is given, it should be only done so when there are no other options and when there is close monitoring for toxicity.

Step 2: Choose as many oral agents as you can for their bactericidal activity, including a nitroimidazole (Pa or Dlm) and/or Cs. Depending on the resistance mutations detected, then either high-dose Inh could be given (if only an *inhA* mutation) or Eto (if only a *katG* mutation).

Step 3: Choose from the following oral agents for their sterilizing activity as you need to construct a 5-drug regimen:

Sterilizing: Pza (if susceptible), Cfz

Step 4: Choose as many injectable agents for their bactericidal activity as you need to construct a 5-drug regimen including Am and the carbapenems + clavulanic acid. It is essential that regimens have sufficient numbers of bactericidal agents, especially in the first weeks/months of treatment and thus many individualized regimens will need to have one of these injectable drugs. Of note, some experts would place step 4 above step 3 in the regimen design process to ensure there are adequate bactericidal drugs.

Step 5: Choose other drugs if more are needed to reach a total of at least 5 effective drugs in the regimen

Bactericidal: PAS, Emb (if susceptible), rifabutin (if there is susceptibility to rifabutin demonstrated, although in most settings, testing to this drug is not available nor is the drug).

Step 6: Consider pre-approval access/compassionate use drugs

Please see the section on pre-approval access for more details. Some possible agents that have already completed at least phase 2b include quabodepistat, ganfeborole, and telacebec.

3.2.2 Which Drugs Should be Used in Settings of Uncertainty Regarding Susceptibility?

Some of the core/group A drugs may be given in settings of uncertainty about susceptibility. This is because these drugs are associated with lower mortality and if there is a possibility the drug might work, then the benefit of retaining it may outweigh the risk. Drugs to be considered in this manner include Bdq, Lzd, and the third-generation Flqs. If used, these should not be counted as effective drugs. Whether or not these drugs should be included (even if they are not counted as effective) should also be based on the pill burden and toxicity. If possible, higher doses of these drugs should be used as shown in Table 2.

In the absence of DST confirming or suggesting resistance, the nitromiadzoles could be given (with selection of the nitroimidazole based on exposure) as could Cs. This would depend on local resistance patterns, prior exposure, and toxicity/pill burden considerations.

3.2.3 High-dose Options

Phenotypic drug-susceptibility testing can often be done at both high-doses and low-doses of the drug being tested. Certain mutations detected on genomic sequencing may also be associated with resistance to drugs at lower doses but not at higher doses. Some examples include Lfx, Mfx, and Inh. If there is resistance detected to any of these drugs at lower doses but not at higher doses, then higher end dosing of the drugs could be considered. This includes: 1) high-dose Lfx (30mg/kg) and 2) high-dose Mfx (12-15mg/kg). In persons whose strains of TB have an *inhA* mutation, higher doses of Inh (10-20mg/kg/day) could also be considered, provided there are no other mutations conferring isoniazid resistance (i.e. a *katG* mutation).

Theoretically, Bdq could also be used at both lower and higher doses. There is not yet agreement on the clinical breakpoints for Bdq resistance testing using different methods. Nor is there an understanding of how different breakpoints might affect clinical outcomes. Although there are no data showing that high-dose Bdq is effective, some modeling studies suggest the drug dose of Bdq could be optimized. In persons with no other treatment options, higher doses of Bdq could be considered. This would mean giving Bdq at a dose of 500mg daily for 14 days followed by 200mg daily thereafter. If higher doses of Bdq are used, close monitoring for toxicity (QTcF prolongation, liver toxicity) must be done.

Some drugs are tested at only one dosing level, but in patients with limited treatment options whose strains of TB show susceptibility, higher doses may still be used. This may be done to improve drug penetration into fibrotic/cavitary lesions or to maximize the time the drug levels are above the dose needed to kill TB. These include both Lzd (1200mg daily) and Cfz (300mg daily).

If higher doses of drugs are used, more frequent monitoring should be considered.

Table 3 on the following pages summarizes a stepwise approach of the best practices for designing individualized regimens.

Table 3: Stepwise Approach to Individualized Regimen Design

Steps		WHO Group	Drugs	Comment
1	Choose as many core drugs as you can: Core drugs are group A drugs that are used for their sterilizing and bactericidal activity. They should be added in the regimen even in settings of uncertain or unknown drug susceptibility testing results (but not counted as effective drugs).	A	Bedaquiline	If used before or high-level resistance is ***not*** documented or likely, consider using in higher dose. QTc and liver function (ALT) monitoring should be done more frequently and use of other QTc prolonging drugs minimized. There are no clear breakpoints on when higher dose Bdq might be effective. If there is detection of an *atpE* mutation, then do ***not*** use Bdq at any dose. hBDQ: 500mg loading dose then 200mg daily
			Fluoroquinolones (Lfx, Mfx)	If used before or documented low level resistance, consider high dose. If combined with hBDQ or other QTc prolonging drugs, prefer hLFX. hLFX: 20-30mg/kg; hMfx 12-15mg/kg x 1
			Linezolid	Do not plan systematic dose reduction, if well tolerated. Consider high dose in salvage regimens ***when there are no other options***, if tolerated. Enhanced monitoring of neuropathic adverse events (peripheral and ophthalmic) and myelosuppression is necessary. hLZD: 1200 mg
2	Choose as many oral agents as you can for their bactericidal activity	B, C	Cycloserine/ terizidone	Consider using, especially if not part of the previous regimens.
			Delamanid	Choose one nitroimidazole. Dlm is drug of choice for children and pregnant women/ people. Pa might have better penetration to cavities than Dlm based on animal studies. Pa should ***not*** be used with Pza.
			Pretomanid	
			Ethionamide	Consider using, especially if not part of the previous regimens and if *inhA* mutation not detected.
			Isoniazid	Use high dose and use only in case of susceptibility or if only *inhA* mutation is detected. hINH: 10-15 mg/kg. Higher doses of 15-20mg/kg should be considered if using in combination with cycloserine/terizidone

3	Chose oral agents for their sterilizing activity*	B, C	Clofazimine	Consider using higher doses of Cfz if there is previous exposure to the drug or if it is one of the only effective agents. Enhanced QTc monitoring needed. hCFZ: 300 mg
			Pyrazinamide	Might have synergistic effect with Bdq. Should ***not*** be used together with Pa.
4	Choose injectable agents for their bactericidal activity*	C	Amikacin	Use three times per week at dose 25mg/kg. Can be administered intramuscularly. In case of pain, consider adding lidocaine to the injection. Can also be administered in slow (60min) infusion with 5% glucose. Perform audiometry 2x per month (ideal, but at least once a month). Avoid use in children and pregnant women/people ***unless there are no other options.***
			Carbapenem+ Clavulanic acid	Most experience is with imipenem+ clavulanate and meropenem+ clavulanate. Some programs start with meropenem or imipenem if the person is hospitalized then change to ertapenem + clavulanate at discharge, since ertapenem can be given intramuscularly. There are fewer data supporting the use of ertapenem than the other carbapenems.
5	Choose other drugs to reach 5 effective drugs in the regimen	C	PAS Ethambutol Rifabutin	Emb and rifabutin should only be used if there is documented susceptibility to these agents.
6	Consider compassionate use drugs	N/A	Quabodepistat Ganfeborole Telacebec Newer generation diarylquinolines	See section on pre-approval access to novel compounds.

**Some experts would place step 4 above step 3 since it is essential that a regimen have a sufficient number of sterilizing drugs, especially in the early weeks/ months of therapy. Many individualized regimens will need at least one of these injectable drugs.*

3.2.4 Treatment Regimen Design in the Absence of Resistance Confirmation

Other clinical variables should be taken into account in empiric regimen design. Persons with high sputum smear grade (2+/3+) and with bilateral and/or cavitary disease on chest radiography may be at increased risk of poor outcomes. For these individuals, an empiric regimen with more agents might be needed—including those that could better penetrate into lesions—compared with people who have minimal disease. People with comorbidities—including poorly controlled HIV and those with severe, acute malnutrition—may also need a fortified empiric regimen compared to those without such comorbidities. People who have had adherence challenges and are missing doses of their treatment—especially in the first 4-8 weeks of therapy—may also need to have a new regimen designed while awaiting drug susceptibility testing. Table 4 below includes some risk factors that could be considered in empiric regimen design for these risk groups.

Table 4: Clinical Considerations for Empiric Regimen Design

Clinical Consideration	Impact on Empiric Regimen Design
Extensive pulmonary disease (including high sputum smear grade [2+/3+], bilateral or cavitary lesions)	May need a fortified empiric regimen with additional agents, especially those that are able to penetrate well into cavitary lesions such as Cfz, Mfx, Lfx, Lzd, Pza. Animal models show Pa also penetrates well into lesions.
Poorly controlled HIV (i.e. CD4 count < 200 cells/uL); severe, acute malnutrition; other immunocompromising condition	May need a fortified empiric regimen with additional agents. Care should be taken to avoid (if possible) drugs with overlapping toxicities or known drug-drug interactions.
Extra-pulmonary forms of TB such as central nervous system, pericarditis, osteoarticular	May need longer durations with drugs that penetrate well into the site of disease and, for some localizations, host-directed therapies such as corticosteroids. Drugs that penetrate well into the central nervous system include Lzd, Bdq, Cs, Eto, Inh, Lfx, Mfx, Pza. Animal models show Pa and Dlm penetrate well into the CNS.
Children isolated lymphadenitis or “non-severe” forms of disease	Could be considered for shorter therapy or therapy with fewer agents under closely monitored conditions. Some of this could follow the paradigm set out in the SHINE study, where children with non-severe forms of TB (e.g., unilateral, non-cavitary disease, isolated cervical or intrathoracic lymphadenopathy, etc.) were treated successfully with 3 months of HREZ. Although there is no direct clinical correlation to the care of children with forms of TB that have expanded resistance, the risk-benefit ratio of including certain agents (i.e. injectables) in children with non-severe disease may be different than in children with more severe forms of disease.
People who are pregnant/ breastfeeding	Limited data on optimal drug dosing in this population, and patients may need higher-end doses of drugs due to changes in volume of distribution. Risks of possible teratogenicity (i.e Am, Eto, Pa) must be weighed against the risk of untreated or under-treated TB in pregnancy.
People with low BMIs (< 18.5)	Multiple studies have suggested worse outcomes in this population. They would likely benefit from nutritional support and may need a fortified regimen.

People who have missed doses or treatment interruptions	Persons who struggle with missed doses/treatment interruptions are at higher risk of expanded resistance. They should receive additional treatment support and counseling throughout their care regardless of what is done with their regimen. They could be considered for empiric fortification of therapy, especially if they have extensive lung disease and poorly controlled co-morbidities. However, the risk of making adherence more challenging must also be considered, especially if fortifying the regimen increases pill burden or toxicity.

In addition to these considerations, it is also important to consider factors such as pill burden, time spent in care, and possible toxicity in empiric regimen design. Monitoring and management plans should be made between people receiving care and those providing care.

Additional best practices to consider include:

- Dosing selection should also consider people's weights, as exceeding maximum dosing recommendations could pose additional challenges in people who are underweight.
- There is also some *in vitro* evidence that calcium channel blockers such as verapamil (120mg twice a day) may be able to overcome Bdq resistance that is mediated by efflux pump mechanisms. Theoretically, this is because the verapamil is able to block the efflux pump. No formal clinical studies of verapamil in the treatment of RR/MDR-TB have been done, and the only experience is based on individual patient reports. If verapamil use is considered (dose 120mg twice a day), the potential cardiac toxicity of this drug must be considered in the context of the patient's regimen and other comorbidities, with additional ECG monitoring done for people on the drug.
- Programs need to ensure that injectable drugs (such as Am and the carbapenems) and Group C drugs (including Eto and PAS) are available for people with forms of TB that have expanded resistance. Methods for monitoring and managing the adverse effects associated with these drugs must also be available through TB programs.
- Programs should consider adding newer compounds (i.e. quabodepistat, telacebec, ganfeborole, newer generation diarylquinolines, etc.) through pre-approval access programs. Issues around accessing these drugs are considered later in this document.

3.2.5 Special considerations in the management of persons who are not responding well to an empiric, short-course, all-oral regimen

Most people with RR/MDR-TB will respond well to one of the WHO-recommended short-course, all oral regimens (i.e. Bdq, Pa, Lzd, Mfx; Bdq, Dlm, Lzd, Lfx and/or Cfz, or one of the endTB regimens). Of note, most of these regimens contain Bdq, Lzd, a nitroimidazole (Dlm or Pa), and Lfx/Mfx. Clinical improvement should be well documented by the end of the first 8-12 weeks of treatment. Culture conversion should also be seen in most people by the end of month 2 or 3. In settings where monthly culture monitoring is not possible, at the very least a culture should be sent at the end of month 2 or 3. Culture monitoring is often complicated, however, by the fact that results may not be available for 4-6 weeks, especially if the culture is negative. However, because people whose cultures quickly return as positive (i.e. in 1-2 weeks) likely have a high bacillary load, cultures can be useful in identifying people who are not responding well to a regimen and may be at high risk for acquiring drug resistance. In addition to culture, monitoring for response to treatment for anyone on treatment for RR/MDR-TB should include a number of parameters, including weight, symptoms, and physical examination. Monthly smear examination could also be considered, with positive smears at month 3 triggering additional actions from providers to consider the risks of acquired resistance. This would include reconsidering the backbone regimen, and possibly fortifying the regimen with at least 2 additional agents (although the limitations of smear microscopy must also be considered). Clinicians could also

consider other biomarker monitoring that might be available in the future to guide decisions to switch from an initial regimen to a salvage regimen, although current tools (i.e. C-reactive protein) used on their own are not supported by existing evidence.

In addition to monitoring bacteriologic status, there are other risk factors to consider that indicate a possible non-response to treatment. Chief among these is weight loss or lack of weight gain, as most people with TB who are being effectively treated will gain weight. Symptoms should begin to show some improvement by month 3 as well, although this can take some time in people with more extensive pulmonary involvement. Finally, problems with missed doses of drugs—especially in the first 4-8 weeks of treatment—may be a risk factor for the development of expanded resistance. People may be missing doses because of adherence challenges, drug stock outs, or because providers are holding therapy to manage drug toxicity. Every effort should be made to address the factors leading to missed drug doses. Individuals who are missing doses of treatment should be closely monitored and supported.

In any person where there are missed drug doses, there is no clinical improvement, or there is no culture conversion by the end of month 2/3, a sample should be sent for extended DST and consideration given to an empiric, individualized regimen after the DST sample has been sent (discussed in more detail below). Ultimately, if the assessment of clinical and microbiological evolution seems to indicate treatment is failing, one needs to consider that there is the possibility of resistance to Bdq, Lzd, Lfx/Mfx, and/or the nitroimidazole (Dlm or Pa) the person is receiving. Shared decision making should ultimately guide the timing of initiation of this rescue regimen. Ultimately, however, an individualized regimen in which 4 new agents are added should be the goal once DST is sent. The regimen can be finalized once the DST results are obtained, but the principles discussed in the prior section should also be followed.

Patients should also be given nutritional support and offered ancillary services as needed (e.g., counseling, housing assistance, treatment for comorbid conditions, care for substance use disorder, etc.). People with documented malnutrition should be offered intensive nutritional therapy. These issues are discussed in more detail in the section on holistic packages of care.Surgical assessment should also be done where possible as early as possible if a person does not appear to be responding to therapy.

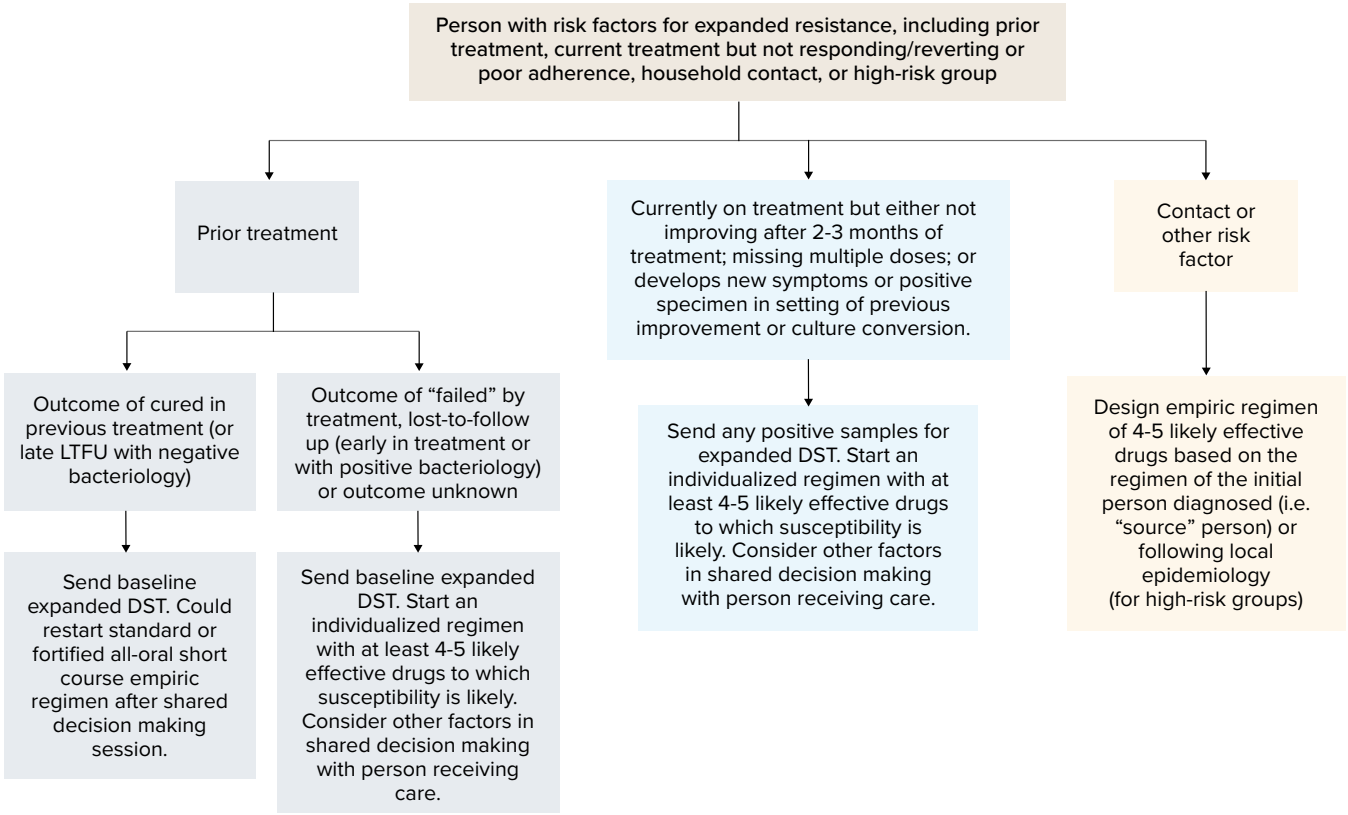
Final regimens can be determined based on DST. If no resistance to Bdq, Lzd, Lfx/Mfx, and the nitroimidazole (Dlm or Pa) is found, then the patient should be given additional psychosocial support and could be put back on a standardized, shorter regimen that includes these drugs. If the person appeared to be having a delayed clinical or microbiological response, then the regimen could be extended for another 3-6 months provided there is no toxicity. If the patient showed improvement and was clinically doing better on the individualized regimen, then there could be a shared decision made to continue the individualized regimen. Nutritional support and co-morbidities should also be addressed.

If additional resistance is confirmed, the individualized regimen will need to be revisited using the principles described above. Drugs should not be given if there is resistance documented, although if there is low-level resistance documented, higher doses could be considered as described above.

When strains show resistance to more than one of the Group A or B drugs, the individualized regimen should last 18-24 months (longer for more extensive disease), depending on culture conversion (12-15 months after culture conversion). This is not based on firm data but rather on historical practice and an absence of evidence showing effectiveness of shorter regimens that do not contain multiple group A and B drugs.

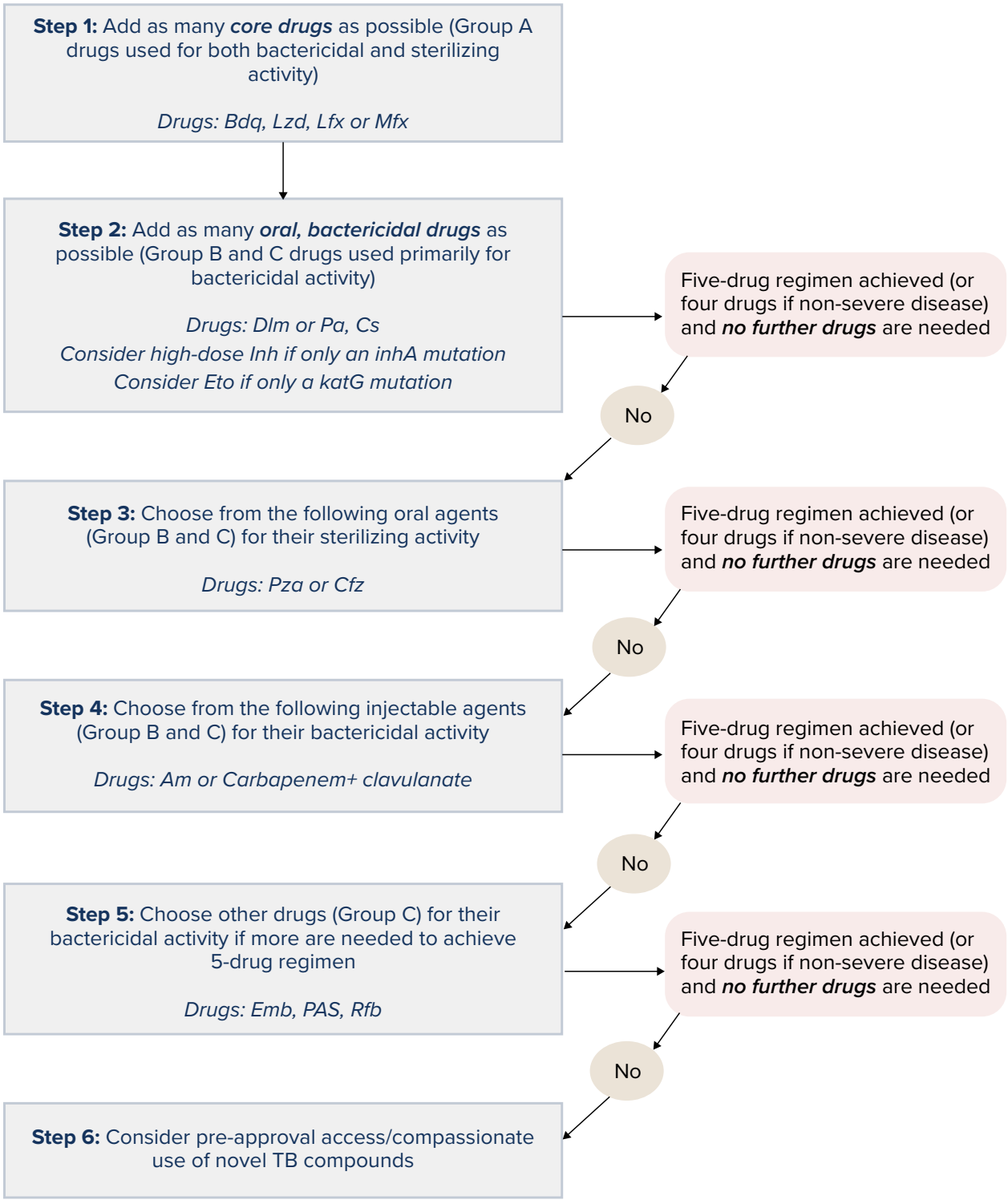
As stated above, the decisions about the "fortified" individualized regimen should be made taking into account the needs and values of the person receiving treatment, and shared decision making must be a core practice. These types of regimens were shown to be successful in a majority of people receiving them in the pre-Bdq era. They were, however, associated with devastating side effects and with multiple negative impacts on quality of life. For this reason, proactive partnerships are a necessary element of treatment. In addition to regimen composition, providers and patients will need to work together to determine the location of treatment (i.e. in the community or in the hospital).

Algorithm 1: Approach to Empiric Regimen Design (Expanded Resistance Possible but not Confirmed)



Algorithm 2: Stepwise Approach for Designing Individualized Treatment Regimens

Note, a drug can be counted as effective if there is documented susceptibility to the drug, if there is no history of previous use of the drug for 1 month or more, of if there are no other risk factors for resistance to the drug (i.e. known contact, cross-resistance, epidemiologic trends).



3.2.6 Treatment Regimen Design upon Detection of Expanded Resistance or Detection of a Mutation of Uncertain Significance

When baseline testing to the new drugs is performed, results will likely only be received after the person has initiated the standard empiric regimen used in the country. Decisions about how to adapt the treatment regimen once genomic or phenotypic DST results are received should take multiple factors into account.

Upon detection of phenotypic resistance or genotypic resistance (defined as a mutation in a candidate drug resistance gene that is classified as associated with resistance (interim) in the WHO mutation catalogue, there is a high likelihood that the drug is not effective. An individualized regimen should thus be designed so that at least 3 effective drugs (and preferably 4 effective drugs) are included in the individualized regimen, with a combination of both bactericidal and sterilizing agents. The principles of designing such regimens are reviewed in the previous sections.

When a mutation of uncertain clinical significance is detected, a phenotypic DST should be requested. Once the phenotypic resistance test results are received, a definitive regimen can be constructed based on those results. While awaiting the pDST results, providers and people being treated must make decisions about the optimal interim treatment regimen. This will require weighing the risks and benefits of continuing the empiric regimen (for which the long-term effectiveness [non-relapsing cure] is not known) versus changing to an individualized regimen (that may have limited evidence regarding its efficacy and may have increased toxicity). Management decisions should consider the following:

- Bacteriological response to treatment. Persons who are smear or culture positive at the time a mutation of uncertain significance is reported may have poor bacteriological response due to resistance conferred by the mutation. If there has been a poor bacteriologic response the person would likely benefit from a change to an individualized regimen. Care should be taken to avoid adding a single drug to a regimen to which the patient is not responding.
- Clinical response to treatment. If the person is responding well to the empiric regimen, then this may be because the mutation of uncertain significance may not be conferring clinical resistance. In such case, the empiric regimen may be continued while awaiting further results. It must be noted that the long-term effectiveness (non-relapsing cure) of an empiric treatment regimen used in the presence of a mutation of uncertain clinical significance is unknown. If there is a poor clinical response, the person would likely benefit from a change to an individualized regimen. Care should be taken to avoid adding a single drug to a regimen to which the patient is not responding.
- Presence of poorly controlled comorbid conditions (i.e. advanced HIV, with CD4 count < 200 cells/uL or detectable viral load or WHO stage 4 disease, uncontrolled diabetes, etc.). Patients with the presence of these comorbidities may require the use of an individualized regimen as they are more likely to have treatment success in the presence of a sub-optimal regimen. Optimizing the management of the co-morbidity is also key to achieving treatment success.
- Timing of the sample. When a mutation of uncertain significance is detected in a baseline sample, a decision could be made to continue the empiric regimen while awaiting the results of the phenotypic DST. In the case of detection of such mutation occurs in a follow-up sample (collected while on treatment), especially in case of culture reversion or persistently positive cultures, an individualized regimen should be considered.
- Presence of heteroresistance. In cases of heteroresistance where the mutation is present as a minor variant (<20% allele frequency), continuing the empiric regimen may be considered. This should only be done after consultation with laboratory specialists. If the empiric regimen is continued, a repeat sample for tNGS should be sent 30 days later (at a minimum) to determine if the allele frequency is increasing. If there is an increase in allele frequency, then an individualized

regimen should be considered, as this likely means the sub-population expressing the mutation is becoming a more dominant strain.

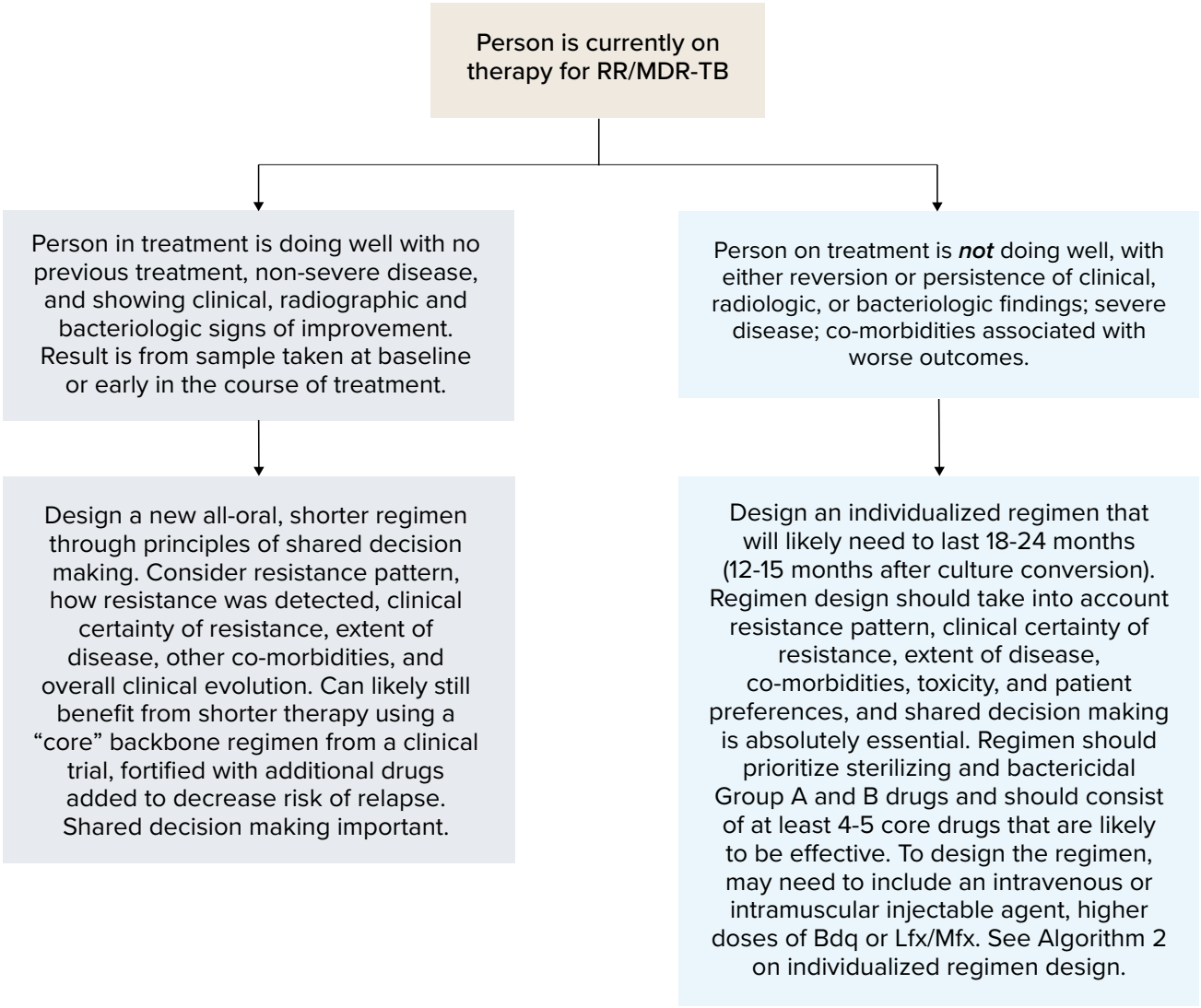
- Treatment decisions for people whose Mtb strains show a mutation of uncertain clinical significance will need to be made on a person-by-person basis. The possible regimen changes should be discussed between providers and persons receiving care ultimately so they can together come to a shared decision about what to do next. If there are any clinical or bacteriological signs of worsening response to treatment, a culture should be sent for extended DST and an individualized, longer "rescue" regimen should be started.

3.2.7 Individualized Regimen Update Once DST Results are Received

People may have their treatment regimens changed or updated once the final DST results are received. The approach should be individualized and include shared decision making as well as an assessment of how the patient has done on the regimen they were given while awaiting the DST results. The approach must also consider the possibility of resistance amplification between the time the DST was take and the time the individualized regimen was started. The possibility of different sub-populations of resistant mycobacteria or heteroresistance must also be considered.

Changes to the regimen upon receipt of the DST will mostly include adding back any drugs to which susceptibility has been confirmed, especially if they are group A drugs. Changes to consider might also include stopping some of the more toxic drugs such as Am. If a person has risk factors for expanded resistance but no expanded resistance is detected, then a standardized, all-oral, shorter regimen could be considered, provided there is low risk of resistance amplification or heteroresistance. This regimen might need to be extended for 9-12 months depending on the clinical evolution and culture conversion of the patient.

Algorithm 3: Approach to Regimen Design when Expanded Resistance is Detected



3.2.8 Practices for the Management of the Carbapenems and the Aminoglycosides (i.e. injectable agents)

Although most people with DR-TB can now be treated with all-oral, shorter regimens, in some instances, injectable agents will need to be used. When this is the case, ongoing discussions of the risks and benefits regarding their use must be a normative practice. There are two main categories of injectable agents; the carbapenems+clavulanic acid and the aminoglycosides (Am). The following best practices have been development around their use:

- The carbapenems consist of imipenem, meropenem, and ertapenem. Both imipenem and meropenem must be given twice a day intravenously, while ertapenem can be given once a day (and can also be given IM). There are less data to support the use of ertapenem compared with imipenem and meropenem. These agents are usually administered through port-a-cath devices or peripherally inserted central catheters (PICC lines). The need for such devices often complicates their use.
- The carbapenems must be given with clavulanic acid, which is currently only available as amoxicillin/clavulanate. An oral tablet should be given 30 minutes prior to the intravenous administration of the carbapenem.
- Optimal duration of the carbapenems is at least 8 weeks, but they can be given for as long as 18 months if needed. Most programs give them for 6 months. Decisions about duration will depend on the other agents used in the regimen, the extent of disease, and the overall clinical response of the patient.
- Am can be considered for use if there is no documented resistance and there is access to formal audiology at baseline and for ongoing monitoring 1-2 times per month. Children under the age of 5 years will need to have special audiometry performed. Capreomycin and kanamycin may be associated with worse outcomes and increased mortality and are no longer recommended for treating any form of TB.
- If Am is to be used, then it could be administered every other day to reduce toxicity (although there are less data on the effectiveness of this approach). It could also be mixed with lidocaine if administered intramuscularly to reduce pain. If patient is in the hospital and receiving IV therapy, IV administration of this agent could be considered as well.
- N-acetyl cysteine could also be considered to reduce the risk of hearing loss associated with amikacin.
- Am should be given for 4-6 months, but longer durations may be needed if there are limited companion drugs. Shorter durations could be considered if there are enough other effective drugs in the regimen or if there is documented toxicity.
- Substitution of the injectables with a drug available through pre-approval access/compassionate use could also be considered.

4. DEPLOYING HOLISTIC PACKAGES OF SUPPORT

Receiving a diagnosis of TB can be devastating and learning that the TB has expanded resistance that makes it more difficult to treat can be overwhelming. Many people facing TB with expanded resistance also face multiple other social, economic, and psychological challenges that make the treatment journey a challenge. Acknowledging and working to address these issues in compassionate, equitable, and comprehensive ways is as important as selecting the right drugs for the treatment regimens. This type of holistic care should not be seen as an optional addition to treatment of TB with expanded resistance but rather as a core part of service provision. Providing such care will mean that TB programs need to collaborate with other arms of government services (e.g., social protection, housing, etc.) as well as non-governmental organizations. Professionalized and paid peer educators/supporters may be a highly effective way to provide many of these support services.

Key issues to consider include:

- Location of care;
- Mental health assessments and services;
- Quality counseling;
- Motivational interviewing from trained and paid peer supporters;
- Nutritional support and services;
- Transportation and travel needs;
- Cash transfers;
- Additional drug safety and sputum monitoring/management costs;
- Support for transitions in care;
- Palliation of symptoms;
- End-of-life considerations;
- Differentiated service delivery;
- Post-TB treatment health challenges and/or disabilities, including for post-traumatic stress disorder.

Location of care is one key consideration that should be discussed between providers and people receiving care. Historically, there has been a tendency to hospitalize all people with resistant forms of TB, and this may be detrimental to both health services and people receiving care. While there may be some logistical challenges to delivering certain medications in the community (e.g., intravenous carbapenems that need to be given multiple times a day), community-based models of service delivery have been developed that can work for many patients. Where prolonged hospitalization is needed for clinical and logistical reasons, people receiving care and their family members should be prepared for this process, with plans made to address the difficulties that can arise during an inpatient stay. Determining the location of care should be done through shared decision making.

Mental health challenges commonly arise before, during, and after treatment for TB with expanded resistance. It is imperative that baseline assessments for depression, anxiety, and substance use be part of the treatment packages. Mental health screening with validated, population-specific questionnaires should be encouraged and used regularly for individuals facing the challenges of expanded drug resistance. Without structured screening, symptoms like anxiety and depression may go unrecognized especially in persons who might downplay or struggle to articulate their emotional state. Untreated mental health issues can worsen adherence to medication, compromise overall recovery and diminish quality of life. Any issues uncovered should be treated with counseling, medication, or other services (e.g., spiritual) provided free of charge. Ongoing routine assessments

for mental health issues should be part of care. Peer support and counseling could supplement other professional services in this area.

Quality counseling must be provided at all stages of care for people with TB that has expanded resistance. Counseling is best done by trained and paired peers who understand the treatment journeys of people with TB. Counseling should be tailored to the situation of expanded resistance and include the following topics: a) DST and waiting for results; b) the need to change regimens; c) possible adverse events and their monitoring/management; d) managing depression, anxiety; e) balancing reality and hope; f) support around injectable agents. Counseling can include family members and other key support people identified by the person undergoing treatment.

Nutritional supplementation should be routinely given to all households where a person has been diagnosed with TB that has expanded resistance. Support should be provided to the household rather than just to the person receiving care, since there may be a tendency–especially for females–to distribute food to children, males, and other household members. Protein and calories should be given preferentially over vitamin tablets/supplements.

Even when medical care is provided free of charge, people with TB that has expanded resistance may incur costs that arise from attending medical appointments. Chief among these are transportation costs and lost wages, especially when frequent follow-up visits are required. Because these transportation costs can be a barrier to remaining engaged in care, ***transportation support*** should be provided to people receiving treatment for TB with expanded resistance.

People with TB that has expanded resistance may come from or find themselves in dire socioeconomic circumstances. Studies support ***cash transfers*** to people with drug-resistant TB as a way to address some of these needs. Cash transfers should also be considered for people with forms of TB that has expanded resistance. Such cash transfers could be used to make up for lost income, provide housing, pay school fees, etc.

When TB with expanded resistance is diagnosed, there will likely be the need for additional sputum testing/monitoring and storage. There will also likely be the need for more drug safety monitoring and management of side effects, as more toxic, less effective drugs will have to be given. Thus, programs will need to ensure they can ***cover the costs required to monitor and manage*** these forms of TB appropriately. This may include obtaining and storing additional sputum (to monitor for acquired drug resistance); testing for additional safety issues (i.e. formal audiometry if Am needs to be given); and management of adverse events seen with some of the agents (i.e. thyroid hormone supplementation for people on Eto and/or PAS).

People with TB that has expanded resistance will also need ***support for transitions in care***. This may include movement between inpatient and outpatient care; transition from treatment to post-treatment follow up; and planning for resumption of social, professional, and education activities. TB that has expanded resistance disrupts people's lives: planning on how to return to valued activities can be an important motivator to engaging in treatment. Thus, support in planning for transitions is an important part of care. This should also include any follow up assessments and management for post-TB lung disease, including post-traumatic stress disorder.

In addition to the focus on treatment that will cure the TB, care also needs to focus on alleviating any symptoms people may have. This includes pain, shortness of breath, nausea/vomiting, anxiety, weakness, and other problems for which palliation is necessary. ***Palliative care*** is aimed at alleviating suffering and should be offered to all people with TB with expanded resistance.

While all efforts should be made to offer curative therapy to people with TB that has expanded resistance, there are some people who will not have an option for cure. These individuals should be

offered ***end-of-life support*** so that they can make the most of their remaining time. Working with a multidisciplinary team–including spiritual care providers–can mean that people are able to face death with dignity. Their families should also be offered support to manage the loss, including possible financial support for funeral costs.

Detailed guidance on palliative and end-of-life care have been developed by several organizations and can be found in the WHO Review on palliative care with focus on 18 high tuberculosis priority countries.

The WHO has developed a series of recommendations on social protection for people with TB that can provide additional guidance on holistic support. For people with TB that has expanded resistance, support needs might be more acute than with other forms of TB. We therefore recommend that all the services discussed above be offered to all people being treated and that they be given the option to opt out of the types of support they do not wish or need to receive. It is also recommended that these services be offered as part of ***differentiated service delivery packages***, as there is no "one-size-fits-all" approach that will work for each person undergoing therapy.

5. MANAGEMENT CONSIDERATIONS IN KEY AND VULNERABLE POPULATIONS

There are multiple reasons a population could be considered as needing special consideration when it comes to forms of TB with expanded resistance. Some populations may be at increased risk for transmission of strains of TB with expanded resistance (e.g., those living in congregate settings, such as people who are incarcerated, people who are without a fixed address, people who are migrants in their own country or another country). Some populations may need different dosing considerations or may not be able to receive certain medications (e.g, children, pregnant women/people). Some populations may have co-morbid conditions that need additional management or consideration of drug-drug interactions or overlapping toxicities (i.e. people living with HIV, people living with diabetes, etc.). Finally, the issue of drug penetration into TB lesions must also be considered, so people with extra-pulmonary forms of TB that has expanded resistance also require special considerations.

Working with outreach teams to both identify and serve special populations is an essential part of care. Each setting will have to define their own populations needing special considerations, according to their own situations in the field. Some common populations include:

- Children;
- Pregnant or lactating women/people;
- People who are incarcerated;
- People who do not have a fixed address;
- Refugees/migrants (regardless of the reason);
- The elderly;
- People who use substances;
- People with occupational exposures (i.e. mine workers, textile workers, health care workers);
- People who have malnutrition;
- People living with HIV;
- People living with hepatitis B/C;
- People living with diabetes mellitus;
- People with extra-pulmonary TB;

- People with disabilities;
- People without legal guardians.

Most of the second-line drugs have been used in ***pediatric and pregnant populations***, with the exception of Pa. Thus, the best practices discussed in this document can be applied to children of all ages and to pregnant women/people and for people who are breastfeeding. Ideally, however, these populations should receive Dlm as the nitroimidazole of choice, with Pa only considered in situations where there is resistance documented to Dlm but not to Pa. Special care should be taken when considering Am in these groups, given its harmful effects on the fetal ear and the harmful consequences of hearing loss in children and adolescents of all ages.

For ***women/people who are breastfeeding***, there are studies documenting that Bdq is concentrated in the breastmilk and achieves concentrations in the infant that are similar to those seen in primary therapy. While some providers feel this might offer protection to the infant, counseling and shared decision making around optimal feeding practices should be done. Cfz may also concentrate in the breastmilk. There is limited information about the safety of most of the second-line agents used in treatment of TB and breastfeeding and additional studies are needed. There are no data around the safety of Pa during breastfeeding.

For additional considerations in pregnant and peri-partum women/people, please see the "Management of Drug-Resistant Tuberculosis in Pregnant and Peri-partum Women/People: A Field Guide" available from the Sentinel Project on Pediatric Drug-Resistant Tuberculosis. Pregnant people/women should also be considered for baseline DST to the full complement of drugs in order to quickly identify and manage resistant strains, given the increased risks to them and their unborn babies.

For ***children***, it will be important to review the weight-based dosing of all the medications. Studies have also shown that children with non-severe forms of TB (i.e. TB that is isolated to the cervical or intra-thoracic lymph nodes or that involves only unilateral pulmonary infiltrates without any cavities) may need less intensive treatment in terms of composition and/or duration. Many children will not have bacteriologic confirmation of TB with expanded resistance, but they will be close contacts of people who have these forms of TB. In such situations, all efforts should be made to obtain samples from the child for bacteriologic confirmation, as there are not always 100% concurrent DST patterns seen within households. Child-friendly formulations should be used in young children whenever possible, and such formulations exist for almost all of the second-line drugs.

Because the roll out of Bdq was delayed in ***children***, there is some experience using Bdq-free regimens in the pediatric population. Most of these regimens, however, do utilize Cfz and it is important to consider the possibility of cross-resistance between Bdq and Cfz. Some examples of Bdq-free, shorter, all-oral regimens that have been used successfully in children include:

- 9 months of Dlm, Lfx, Lzd, Cfz, and Pza
- 9 months of Dlm, Lzd, Cfz, Cs, and Pza

Both of these regimens could be used in children with known or possible resistance to Bdq provided there is no resistance (known or likely) to the other agents used in the regimens.

For additional pediatric considerations, please see the "Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide" available from the Sentinel Project.

In terms of management of ***people with co-morbid conditions***, it is important to consider drug-drug interactions as well as overlapping toxicities. While there are limited data on drug-drug interactions with many of the second-line TB drugs, the issues in the following table should be considered.

Table 5: Considerations for Management of People with Co-morbid Conditions

Drug	Condition	Risk	Recommended Action
Bdq and efavirenz	HIV	Drug interaction with efavirenz	Do not use Bdq and efavirenz in combination
Lzd and AZT	HIV	Bone marrow suppression	More frequent monitoring
Lzd	Diabetes mellitus	Peripheral neuropathy and optic neuropathy	More frequent monitoring
Am	Diabetes mellitus	Renal complications	More frequent monitoring
Pa or Pza	Hepatitis B/C or Alcohol use	Liver toxicity	More frequent liver function monitoring

Coordination between TB services and other agencies providing care to these populations will be key. For example, if care is being provided to people who are incarcerated, it will be essential to work with government agencies responsible for health in prisons. For people with co-morbid conditions, integration of services with the other health providers are essential. For example, people with substance use disorder will need to have treatment for their substance use offered by experts alongside their care for TB that has expanded resistance.

6. PRACTICES AROUND PRE-ACCESS TO NOVEL TB COMPOUNDS

Persons with strains of TB that have extended resistance will often need to access newer agents as part of effective therapy. This will need to be done via compassionate use (CU) or expanded access (EA) pre-approval access programs. Companies should begin developing these programs as soon as their agents are in phase 2 of clinical testing, with the goal to make the drugs available through CU/EA programs after phase 2b trials show promising data for safety and efficacy. TB programs will also need to make sure they proactively explore developing or strengthening CU/EA programs in their settings. These programs should be universally available, transparent, be flexible enough to integrate into a variety of regulatory environments. Finally, these programs should be funded as part of the development of new drugs by drug companies and funders, rather than developed hastily after the fact.

There are currently many gaps in TB research–especially related to the needs of people with expanded drug resistance. Unfortunately, many of the newer agents that are further along in development (e.g., telacebec, quabodepistat) are not yet being widely offered via these mechanisms. Furthermore, the research networks studying new drugs for use in RR/MDR-TB are, at least initially, studying them alongside a Bdq, Dlm, or Pa backbone. This situation must be addressed urgently, as persons with RR/MDR-TB that have expanded resistance have the right to benefit from science and their needs are urgent. People with strains of TB with expanded resistance require novel drugs to be studied in novel combinations and not in conjunction with agents that their TB strains are resistant to. Additionally, it is important to include people with TB strains with expanded resistance and people with complicated disease and comorbidities in clinical trials. Without these steps, we will not have the evidence base necessary to inform guidelines and the best clinical practices.

The following practices should be considered when accessing newer compounds via CU/EA programs:

- Newer compounds should not be added as single drugs to failing regimens. Ideally, they would

be given with at least 2-3 other agents that are known or likely to be effective;

- Combination regimens should use agents with different mechanisms of action whenever possible;
- Combination regimens should consider cross-resistance, overlapping toxicities, and drug-drug interactions;
- Informed consent and shared decision making should be key practices when accessing newer drugs via CU/EA programs. Patients needing these drugs may be vulnerable and need additional support to understand potential risks and benefits associated with the drugs;
- Drug developers, policy makers, impacted communities, and care providers should work together to ensure there is equity and transparency in access to newer compounds and that the lessons learned from using these drugs benefits people impacted by TB;
- Access for vulnerable populations who have historically been excluded from CU/EA programs (children, pregnant women/people, people who are incarcerated, etc.) should also be prioritized.

Some possible agents to consider for CU/EA are summarized in Table 6 below.

Table 6: Potential Drugs for CU/EA Use

Drug	Category/ Mechanism of Action	Current Development Phase	Dosing
Telacebec	Inhibitor of the mycobacterial cytochrome bc1 complex	Phase 2a trial completed	100mg, 200mg, and 300mg daily
Quabodepistat	Inhibitor of decaprenylphosphoryl-β-D-ribose-2′-oxidase, an essential enzyme for Mycobacterium tuberculosis to synthesize key components of its cell wall	Phase 2b/c trial completed (in combination with Dlm and Bdq in drug-susceptible TB)	10, 30, and 90mg
Ganfeborole	Benzoxaborole inhibiting the Mycobacterium tuberculosis leucyl-tRNA synthetase	Phase 2a trial completed; phase 2b trial to begin in 2025	5, 15, and 30mg daily
TBAJ-876	Diarylquinoline that may be effective in strains of TB with Bdq resistance	Phase 2b trial ongoing	3.125, 6.25, 12.5 mg/kg daily

In addition to accessing newer antituberculosis drugs, there may be other adjunct therapies that could benefit people with TB that has expanded resistance. These include what are known as “host-directed” therapies, including immune modulators and/or therapeutic vaccines. As more becomes known about these types of adjunct treatments, they should also be offered to persons through CU/EA programs.

A series of 10 key principles have been elaborated by the BETTER Project as best clinical practices for CU/EA programs. These include:

1. **Free, equitable access to novel TB compounds** through **transparent mechanisms** prior to their regulatory approval but **as soon as early efficacy and safety data** have been demonstrated in the treatment of *M. tuberculosis* in phase 2b or later studies.
2. Access for people with strains of TB that have expanded resistance to these novel compounds **both as single agents and as part of regimens that combine multiple new drugs.** Single drugs cannot be used on their own in failing regimens, and some people with certain strains of expanded resistance may require access to more than one new drug to form an adequate regimen. Other people, however, may only need one new drug to construct an adequate treatment regimen if other approved TB drugs can be given in combination with the single novel medication. Drug sponsors, being private, public or product development partnerships, must collaborate with one another and with front-line providers and people needing treatment to

ensure this range of options is available. When more than one novel compound is required to form an adequate regimen, the real risk of poor treatment outcome and/or death must outweigh potential risks stemming from absence of evidence to support concomitant use.

3. Access to these novel compounds must encompass **all drug-resistant forms of TB**, with the drug provided for the duration of therapy recommended by the treating clinicians. Although some new drugs are currently being assessed only for fully drug-susceptible TB as part of shorter regimens (i.e. lasting for 4 months or less), this does not preclude their use in people with drug-resistant TB for longer durations. The new drugs may be of greater benefit to people with drug-resistant forms of TB (compared with susceptible strains) since those individuals have limited treatment options. Unless there is a compelling reason to believe there will be unacceptable toxicity with a higher cumulative exposure, **the new drug should be given for as long as it is deemed necessary** by the front-line provider in consultation with global experts and the person undergoing treatment. Pre-approval access/compassionate use programs may have the added value that safety and efficacy data can be systematically collected on new drug use beyond the short courses drug developers and trialists are studying. Pre-approval access for people with limited treatment options—alongside to post-marketing surveillance or individual off-label use which may take place after drug registration—is an additional setting in which to better monitor longer durations of the necessary drug. Once a drug has been shown to be effective against *M. tuberculosis*, the maximum duration of therapy for people with TB who have limited treatment options should be determined by attending clinical care providers in discussion with a clinical expert/review committee (see point #5 below) and people receiving treatment through a shared decision-making process that includes **regular monitoring for adverse events**.
4. **All populations must be able to access new drugs, and there are no groups or individuals who should be systematically excluded** from pre-approval access/compassionate use programs. This includes (but is not limited to) children/adolescents; pregnant women/people; people who are incarcerated; and people who have substance use disorders. These vulnerable populations are often "protected" from enrolling in research studies since they may be subject to additional risks. When they have forms of TB with expanded resistance, however, the risk-benefit ratio of receiving a new drug once data from phase 2b trials are available must be considered on a person-by-person basis since limited treatment options are available. Prior delays seen with new drugs access for these populations are unacceptable in the current TB landscape. In addition to these groups, people who have had adherence challenges in the past should not be excluded from pre-approval access/compassionate use programs. Unless there is a clinical indication for hospitalization, **flexible models of service delivery** should also be provided, including community-based care.
5. The decision regarding whether a person qualifies to receive a drug via a pre-approval access/compassionate use program should not be made by a drug developer or those working for drug developers. Rather, **an independent body** of clinical providers, civil society organizations, impacted community members, and other relevant specialists should review the clinical files of people needing access to novel compounds via pre-approval access/compassionate use and make a recommendation on the optimal treatment regimens.
6. People needing access to novel compounds and the TB clinicians and programs requesting them should not have to pay for any part of the pre-approval access/compassionate use programs. Rather, **the costs of the drugs as well as the shipping and importation expenses should be covered by the drug developers**. These costs are likely to be minimal in the context of overall drug development and should be planned for in budgeting and grant requests.

7. Systematic and standardized safety, effectiveness, and other **data on the use of new drugs through pre-approval access/compassionate use programs should be collected, anonymized, and shared** with relevant stakeholders (including product developers and regulatory authorities). Standardized data should also be collected on **resistance to new drugs**, including at baseline and throughout treatment to ensure the drugs are being used in an optimized way that does not drive selection of resistance. This will require access to the drug compounds and sharing of methods for resistance testing. As with bedaquiline, such implementation research will prepare scale-up once the new drug is more widely recommended. Methods for compiling and sharing data and lessons learned should also be explored as part of pre-approval access programs.
8. **Ongoing informed consent** that emphasizes true understanding and **shared decision making** should supersede complicated "one-off" consent forms that were designed to minimize liability for drug developers. Consent must be robust and meaningful and protect vulnerable people living with TB that has expanded resistance. Consent language must clearly explain potential risks but should do so using terminology and a style that is appropriate for people receiving care.
9. Counseling, mental health screening, psychosocial support, nutritional support, and other forms of **socioeconomic support** needed to minimize suffering for people undergoing treatment with new drugs as part of pre-approval access/compassionate use programs must be provided as an integral part of pre-approval access programs. These services would preferably be funded by the global community and provided by local groups who are trained and paid to provide this essential work.
10. **Pharmacovigilance requirements** for new drugs should build upon the structures and processes that were put into place in TB programs over the past decade (including past experiences gained through previous pre-approval access/compassionate use programs) rather than creating new systems that are unique to the different drug developers.

7. POST-EXPOSURE MANAGEMENT FOR HOUSEHOLD CONTACTS EXPOSED TO TB WITH EXPANDED RESISTANCE

Post exposure management is a package of care that should be offered to all close and household contacts of persons exposed to RR/MDR-TB, including those with expanded resistance. Persons exposed to TB strains with expanded resistance must be a priority group for post exposure activities for the important reasons that: 1) early identification is likely associated with better outcomes and 2) treatment of infection (i.e. "preventive therapy) could be offered to prevent contacts from developing disease.

The first person in the household diagnosed with RR/MDR-TB with expanded resistance should receive disclosure counseling. Special consideration may be needed for disclosing information about strains of TB with expanded resistance given the possible risks associated with these types of TB in the absence of effective treatment. Efforts should be made to identify and evaluate all close contacts. All persons with high-risk exposure to RR/MDR-TB with expanded resistance should be evaluated for RR-TB disease. If no evidence of disease is found they should be offered counseling and health education on RR/MDR-TB with expanded resistance, nutritional support, treatment of infection and follow up care.

The WHO now recommends 6 months of Lfx for treatment of infection of close and household contacts exposed to RR/MDR-TB where there is presumed or known fluoroquinolone susceptibility. High-dose Inh (6 months) preventative therapy also remains a preferred option for persons exposed to strains of TB with *inhA* mutations, although most people would recommend using Lfx instead given that there is a stronger evidence base to support the use of Lfx. How best to manage household contacts exposed to strains of TB with katG Inh resistance and resistance to Lfx or Mfx is unclear. There are ongoing trials assessing Dlm and Bdq, respectively, for this purpose, but they are not likely to yield results anytime soon.

For household contacts of people with expanded resistance, using shared decision making to come up with a plan for post-exposure care is ideal. Some family members and their providers may wish to proceed with medication therapy such as Dlm even while awaiting the results of clinical trials. Others may wish to have close clinical follow up so that any disease can be identified and treated quickly, although the risks of doing so must be fully explored when making this decision.

All persons exposed to RR/MDR-TB with expanded resistance in the household should be given a package of nutritional support. This is based on the RATIONS study which showed that the provision of modest nutritional support (i.e. 750 kCal, 23 gm of protein, and micronutrients) to household contacts of people with TB lowered their risk of developing TB disease.

8. TOXICITY MONITORING AND MANAGEMENT, INCLUDING DRUG SUBSTITUTIONS

People who have TB with expanded resistance will usually require the use of regimens that contain medications that may be associated with increased toxicity, including injectable agents. They may also require higher doses of some of the more commonly used drugs, which could increase the risk for toxicity. In addition to the use of these agents, there may be a need to continue drugs that are causing toxicity if there are limited or no other treatment options. As with all aspects of care for people with TB that has expanded resistance, the decision about whether or not to continue a medication that is causing side effects should be made in partnership with providers and patients

If a drug is causing side effects, a short therapeutic break from the medication could be considered. Monitoring for and management of side effects must be an essential part of treatment for forms of TB that have expanded resistance (see Table 7). Alleviating suffering caused by treatment is part of a comprehensive palliative care program that should be offered to all people with TB that has expanded resistance. These services should be provided free of charge and may be associated with improved outcomes.

Table 7: Drug Toxicity Monitoring and Management

Drug	Toxicity	Monitoring	Management
Bdq	QTcF prolongation	Baseline ECG, monthly ECG	More frequent ECG monitoring if on high doses and on other QTcF prolonging drugs
Lzd	Bone marrow suppression, peripheral neuropathy, optic neuritis	Baseline full blood count, monthly full blood count, baseline and monthly visual acuity, baseline and monthly brief peripheral neuropathy screening	Transfusion, consider dose reductions
Lfx	QTcF prolongation, arthritis, arthralgia	Baseline ECG, monthly ECG	More frequent ECG monitoring if on high doses and on other QTcF prolonging drugs Physical therapy, non-steroidal anti-inflammatories
Mfx	QTcF prolongation	Baseline ECG, monthly ECG	More frequent ECG monitoring if on high doses and on other QTcF prolonging drugs Physical therapy, non-steroidal anti-inflammatories
Cs/terizidone	Psychosis, hallucinations, seizures, depression, anxiety	Formal screening for depression and anxiety at baseline and each visit	Counseling and support

Dlm	QTcF prolongation, hallucinations, psychosis	Baseline ECG, monthly ECG, formal screening for depression and anxiety at baseline and each visit	More frequent ECG monitoring if on high doses and on other QTcF prolonging drugs Counseling and support
Pa	Liver toxicity	Baseline liver function (ALT), monthly liver function (ALT)	Discontinue if LFTs increased to 3x upper limit of normal
Am	Hearing loss, renal failure, other cranial nerve VIII toxicity, injection site pain	Formal audiometry twice per month (minimum once per month); children need special audiometry if under age 5, baseline creatinine, monthly creatinine	Three times a week dosing (25mg/kg); Administer with lidocaine
Carbapenem+ clavulanate	Need to be given IV, liver toxicity, seizures, diarrhea, rash	Baseline liver function (ALT), monthly liver function (ALT), support for administration	Nursing and other support for administration
Eto	Nausea, vomiting, hypothyroidism	Baseline thyroid stimulating hormone, every three months thyroid stimulating hormone	Anti-emetics Thyroid hormone replacement
Inh	Peripheral neuropathy, liver toxicity	Baseline liver function (ALT), monthly liver function (ALT), baseline and monthly visual acuity, baseline and monthly brief peripheral neuropathy screening	Administer with pyridoxine (50mg) for prevention
Cfz	QTcF prolongation, skin hyperpigmentation, nausea, vomiting, diarrhea	Baseline ECG, monthly ECG, counseling about skin changes	More frequent ECG monitoring if on high doses and on other QTcF prolonging drugs
Pza	Liver toxicity, arthralgia, arthritis	Baseline liver function (ALT), monthly liver function (ALT)	Discontinue if LFTs increased to 3x upper limit of normal
Pas	Nausea, vomiting, diarrhea, hypothyroidism	Baseline thyroid stimulating hormone, every three months thyroid stimulating hormone	Administer with yogurt or other acidic food Anti-emetics Thyroid hormone replacement

Drug substitution of single agents may be necessary either due to toxicity or due to stock-outs. If a person needs to stop taking a medication or if a medication is not available, then clinicians and people receiving treatment will need to take action to ensure a full regimen is provided.

The approach to drug substitution will depend on where the patient is in the treatment course and how s/he is doing. If the substitution happens later in the course of therapy when the patient is doing well, then single drug substitutions should be considered to be relatively safe. Drug substitutions should utilize Group A drugs (if there are any not being used), Group B drugs, and then Group C drugs. If a single drug within the same class can be substituted, this would be ideal (i.e. if there is a Pa shortage or toxicity, then Dlm should be considered the optimal switch). If the patient is early in treatment or has worrisome clinical, microbiologic, or other signs, then care must be taken to avoid changing a single drug in a failing regimen. For example, if Lzd or Bdq needs to be stopped prior to culture conversion, then a new regimen should be considered. This new regimen should be designed as if the person has a strain of TB that is resistant to the medication that needs to be stopped.

Lzd toxicity remains a challenge in the field, particularly its bone marrow suppression and association with anemia. Many people with untreated or undertreated TB will have a low hemoglobin (Hb) at baseline due to their TB. Often, this actually improves with Lzd treatment. A blood transfusion may be given at baseline for people with Hb < 8g/dL. However, a low baseline Hb is a risk factor for future Lzd toxicity, and people with low Hb at baseline started on Lzd merit close monitoring with more frequent full blood counts. If a person develops a low Hb while on Lzd, there is no clear consensus about how best to manage this. In general, the Lzd can be held and transfusion considered, especially with an Hb< 8g/dL or if the person is symptomatic. Other factors potentially contributing to the anemia should also be addressed. Lzd may be re-introduced at a lower dose (either 300mg daily or 600mg three times a week). However, in the first 8-12 weeks of treatment Lzd may play a more crucial role and full-dose re-introduction should be considered. In patients with limited treatment options, ongoing transfusions could be considered, although the risks and benefits must be considered as part of shared decision making. Of note, planned Lzd dose reductions in people receiving treatment for expanded resistance should ***not*** be routinely done.

In some instances of toxicity due to other drugs, re-introduction of the causative agent may be considered, depending on the type of toxicity experienced and provided this can be done safely. As with all other regimen changes, ongoing informed consent for treatment changes is a necessary part of therapy with shared decision making between the person receiving care and the providers. Documentation of any interruptions in treatment as well as the reason is essential.

One possible consideration for managing toxicity could be to consider substituting agents available via pre-approval access. For example, to avoid or manage the toxicity associated with injectable agents, quabodepistat could be considered.

In recent high-quality trials, RR/MDR-TB regimens have been tested as regimens and stopping any one component was considered an “unfavorable” outcome for the experimental regimen in most trials. For this reason, there is limited experience or data to guide regimen construction and/or duration in the case of a single drug substitution. Having multiple regimens as options for therapy is thus an exciting development in the treatment of RR/MDR-TB, and countries should ensure they do not offer only a single regimen.

It is important to closely monitor and manage anti-TB medicine stock to avoid compromising the efficacy/effectiveness of a treatment regimen. The following best practices can help avoid medicine stock-out:

- Regular monthly stock check with the central medical store in consideration of expiry date;
- Timely ordering of medicine and tracking of pending orders;

- Use of standardized quantification and forecasting tools;
- Consultation with experts in drug procurement (i.e. through the Stop TB Partnership's Global Drug Facility [GDF]);
- Beware of failed national tenders and plan for impacts on drug supplies (based on ordering schedules)
- Development of community systems for monitoring and reporting stock outs.

In situations where stock shortages are likely to happen, emergency measures should be put into place to order and receive stock. This can be done via the GDF or via in-country suppliers. If timely receipt of medicine is not expected, borrowing stock from a neighboring country may be needed, but this should only be done in emergency situations. Within a country, tracking the stock status across health facilities and shifting to the facilities with stock-out may be required. Having telecommunication groups (e.g., "WhatsApp") within health facilities is a good community forum for such assistance. People receiving care should also be able to access these groups. In settings of possible stock out, providing shorter durations of therapy may also be considered (e.g. every two weeks through treatment supporter instead of monthly) if new stock is expected within a short time frame. In any situation of stock shortages, people receiving treatment should be informed of the shortage as rapidly as possible. Situational assessments of factors leading to the stock out must be done with urgent actions to remediate any modifiable factors as quickly as possible.

9. OPERATIONAL RESEARCH CONSIDERATIONS

While clinical trials to definitively gather evidence on optimal approaches for expanded resistance are important, there are not likely to be clinical trial results in the near future to guide the management of people with expanded resistance. For this reason, it is important that countries and programs are systematic in their approaches to care and that they offer enhanced monitoring for people on treatment with these forms of TB. Impacted communities should take the lead in developing an operational research agenda in partnership with providers, programs and donors.

There are two key areas for operational research. The first includes surveillance of drug susceptibility patterns and trends in different settings. The most important aspect of DST is to inform patient care, but countries can also establish systems for monitoring trends in drug resistance. These trends can help inform local and regional treatment best practices. It is important to note, however, that when these systems were developed previously (i.e. in the 1990s), there was only limited impact on patient care. Thus, any newly established systems should be built taking the lessons learned from previous experience into account. The second includes the development of observational cohorts of people receiving treatment for TB with expanded resistance. These cohorts could include people who agree to participate and monitor effectiveness, safety, tolerability, and quality of life among people on therapy. In addition to standard quantitative measure, such observational cohorts could include qualitative assessments to better describe the experiences and needs of people with strains of TB that have expanded resistance. Findings from these cohorts could be shared with impacted communities, researchers, policy makers, and funders to develop informed care and research agendas that are relevant to stakeholders at all levels.

Special attention should also be given to people who have undergone treatment for TB with expanded resistance even after they have completed their therapy. It will be important to monitor them for post-TB lung disease, especially since many have had prolonged experiences in care, either due to delays in diagnosis or ineffective treatment. People may also have notable mental health challenges—including post-traumatic stress disorder—depending on what their treatment journeys were like. These issues all deserve attention and follow-up.

Collecting Common Data Elements

Most TB programs have standardized data collection forms and variables that they use for recording/reporting and for monitoring/evaluation. These forms should also be used in the care of people with forms of TB that have expanded resistance, but they may need to be modified or supplemented to collect additional information to guide patient care. In addition to their important roles in service provision, data collected in the care of patients could be used to guide future management strategies and recommendations.

Many of the program-specific outcomes may not provide sufficient information on the care of people with forms of TB that have expanded resistance. For example, in people receiving individualized regimens there may need to be multiple regimen changes made to accommodate toxicity management or new DST results. These changes are not necessarily associated with bacteriologic or clinical failure and in people with forms of TB that have expanded resistance, they should not be counted as such. There is also some value in collecting additional information on interruptions to treatment that do not meet standard definitions of "lost to follow up" as defined by the World Health Organization. In order to maximize the potential for learning from the experiences caring for people with TB that has expanded resistance, a number of additional data elements are suggested below.

People receiving care should be informed of this potential use of their health information and asked if they consent to have de-identified data monitoring and reported in this way. Countries will need to follow their policies and practices for ethical review for inclusion of human participants in such types of operational research monitoring. Knowledge gained from such monitoring should also be shared with the participants and other impacted communities.

In addition to standard outcome measures, it is important that some measures of quality of life and the subjective experience of undergoing treatment for TB that has expanded resistance should be included in data collection. Some instruments that could be considered for use to assess quality of life include the WHO Quality of Life Scale or the Quality of Life Short Form-36. These measures, however, are not specific to TB and should be supplemented with additional questions/measures that ask about what the experience of being treated for these types of TB is like.

In order to facilitate the sharing of information from different programs and countries, we suggest information should be captured on the following variables:

1. Sex
2. Age/Date of birth
3. BMI
4. Co-morbidities (HIV—including CD4 count, VL, and current ART regimen; DM; hepatitis C; substance use disorder, other)
5. Prior treatment (dates, outcomes, drugs received)
6. Prior drugs received (check box list, > 14 days)
7. Currently on treatment? If yes, with what regimen?
8. Smear, culture, Xpert, LPA data (dates, results, samples)
9. Resistance to any of the following (drug name, method tested, date of sample, date of resistance result):
10. Chest imaging/radiology
11. Extrapulmonary TB site (list site)

12. Regimen recommendations for new regimen ("BETTER" regimen including components and dates)—could be done using the drug-o-gram approach (see Annex B);
13. Drug changes and dates from the initial treatment regimen started;
14. Monitoring on new regimen (smear, culture, CXR, interruptions in treatment, reasons for interruptions, outcome)
15. Adherence (specifying how this was done, as adherence may be very difficult to measure and record)
16. Adverse events (including date of onset, grade, outcome, date of outcome)
17. Other (as determined by the program)

In addition, collecting more detailed information on the following variables is considered a best clinical practice:

Treatment failure

- Bacteriological failure, no interruption in treatment
- Bacteriological failure, interruption in treatment
- Clinical failure: poor clinical response resulting in a decision to change the treatment regimen

Treatment interruption

- Patient who interrupted treatment for 2 to 6 months before returning to care
- Loss to follow up
- Patient who does not start treatment following (within x months of) diagnosis
- Patient who did not return to care (within x months of the last clinic visit)

Treatment refusal

- Initial treatment refusal
- Treatment refusal resulting in premature end of treatment episode

Death

- Death between diagnosis and treatment initiation
- Death during treatment, no interruption in treatment
- Death during treatment, interruption in treatment
- Death between last clinic visit and assignment of LTFU

Initial treatment success

- Completes treatment for the intended duration (regimen as per national guidelines)
    - With or without changes made in response to AE
- Documented bacteriological conversion
    - Includes patients diagnosed with rapid molecular test who are culture negative at diagnosis and remain culture negative
- No bacteriological reversion
- Good clinical response
    - Is treatment success based solely on clinical response acceptable in settings where there is no access to culture facilities?

Sustained treatment success

- An individual who is alive and free of TB 12 months after initial treatment success

Bacteriological failure, no client interruption in treatment

- No culture conversion by month 3 (?) of treatment or culture reversion after conversion
- Independent of whether the treatment regimen was changed
- Sequencing (and/or pDST) shows no amplification of resistance

Bacteriological failure, client interruption in treatment

- No culture conversion by month 3 (?) of treatment or culture reversion after conversion
- Independent of whether the treatment regimen was changed
- Sequencing (and/or pDST) shows no amplification of resistance

Clinical failure

- Lack of weight gains and/or lack of symptom resolution and/or lack of improvement in general condition
- Proof of bacteriological response (if available)
- Leads to a decision to change the treatment regimen

ANNEXES

Annex A. Selected References

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Annex B. Drug-O-Gram

The “drug-o-gram” approach is used by many providers to give a visual representation of treatment for people with forms of TB that have expanded resistance. This example was provided by Médecins Sans Frontières.

In the “drug-o-gram” drugs that have results that confirm or suggest resistance are written in red. Drugs that have results that confirm susceptibility are written in green. Drugs that are unknown or uncertain are written in blue. Months in which the sputum is positive are shaded red. Months in which the sputum is negative are shaded green. The doses of each drug are written in each month in red (resistant), green (susceptible) or blue (unknown). A “drug-o-gram” like this can be created in a Word or Excel file for each patient and modified based on data available in the program (i.e. if phenotypic testing is used, this information can be included instead of the mutations).

Drug	Gene	Genomic position	Codon change	AA change	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
H	katG	2155168	agc315acc	S315T						
R	rpoB	761155	tcg450ttg	S450L						
E	embB	4247496	gat328ggt	D328G						
Z	pncA	2289040	tgg68ggg	W68G						
Lfx	gyrA	7581	gac94tac	D94Y						
Mfx 0.25	gyrA	7582	gac94tac	D94Y						
Mfx 1.0	gyrA	7583	gac94tac	D94Y						
Lzd					600	600	600	600	600	600
Bdq	rv0678	779182	delG	frameshift	200	200	200	200	200	200
Pa										
Cfz	rv0678	779182	delG	frameshift						
Cs					750	750	750	750	750	750
Dlm					200	200	200	200	200	200
Km	rrs	1473246	a1401g	n/a						
Cm	rrs	1473247	a1401g	n/a						
Ami	rrs	1473248	a1401g	n/a						
S	rpsL	781687	aag43agg	K43R						
Pto/Eto					750	750	750	750	750	750
PAS										
Ipm (Clv)					2000	2000	2000	2000	2000	2000

Annex C. Patient Scenarios

Scenario 1: PY is a 37-year-old male who was diagnosed with RR-TB based on a WHO-recommended rapid molecular test. He is drinks alcohol daily. His chest radiograph reveals bilateral upper lobe cavitary lesions. He is started on a 6-month regimen of Bdq, Pa, Lzd, and Mfx but he misses multiple doses in the first month of therapy. He is counseled by a peer supporter and undergoes specific alcohol counseling using the SBIRT tool. He is also provided with nutritional support. He does not miss any additional doses, but he remains febrile, fails to gain weight, and his month 2 culture remains positive as does his month 3 smear.

His care providers are concerned about his lack of clinical improvement and his persistently positive bacteriology. Because he missed multiple doses in the first weeks of treatment, they speak to him about sending a drug susceptibility test to look for resistance to the components of his regimen. They also talk with him about possible changes to his regimen while awaiting DST.

A rapid test for FLQ resistance using the Xpert XDR cartridge does not reveal any resistance to the FLQs. A regimen is therefore constructed using the steps described above for an individualized regimen.

- **Step 1:** Lfx is added and counted as effective since there is no resistance documented. He is also continued on Bdq and Lzd, but these drugs are not counted as effective.
- **Step 2:** Dlm is added but not counted as effective given his prior exposure to Pa. Cs is added and counted as effective.
- **Step 3:** Cfz is not offered as there is an almost complete cross-resistance between Bdq and Cfz in his setting. Pza is added and counted as effective since rates of Pza resistance are lower in his setting (less than 50%).
- **Step 4:** Am is offered but the patient declines this option, since he has already lost the hearing in his left ear due to occupation exposure. Imipemen and clavulanic acid are offered, and the patient agrees to be admitted to the hospital while awaiting his DST results.
- **Step 5:** No additional drugs are needed since he now has an effective regimen.

His regimen is Bdq, Lzd, Lfx, Dlm, Cs, Pza, and imipenem-clavulanic acid. He remains on this regimen for 4 weeks, and his targeted NGS returns showing mutations that are associated with resistance to Bdq. No other resistance is detected. He also feels better clinically and his smear one month after starting this regimen is negative.

Given these results, he is transitioned to an all-oral regimen of Lzd, Lfx, Dlm, Pza, and CS, which is given for 12 months after his culture conversion. He also receives additional counseling, nutritional support, and transportation support to come to the clinic once a month. He does well and completes his treatment cured.

Scenario 2: PS is a 7-year-old male child whose mother died of TB while being treated with the Bdq, Pa, Lzd, Mfx regimen. Her cultures persisted as positive through treatment, and a phenotypic DST done on her month 5 culture showed resistance to Bdq, Lfx, Cfz, and Inh. PS presents with cough and on chest radiograph has a right-sided infiltrate and right peri-hilar lymph node enlargement. A stool sample is sent for Xpert MTB/RIF Ultra testing and is positive for Rif resistance. Multiple sputum samples are sent for culture and targeted NGS given his contact history. After discussion with his father and baseline counseling, he is started on nutritional support. Because he has non-severe disease, he is given a regimen based on the DST of his mother. The regimen is designed using the following steps:

- **Step 1:** Lzd is given and counted as effective.
- **Step 2:** Dlm is given and counted as effective as is Cs.
- **Step 3:** Pza is given and counted as effective.

Since he has non-severe disease and no comorbidities, his regimen is considered to be adequate with four drugs. He and his family are all assessed for active TB, and nobody else has any signs of disease. They are all offered nutritional support and Dlm treatment of infection. His cultures all result as negative. He gains weight and returns to school after 2 weeks on therapy. He is monitored closely for adverse events. As he gains weight, his doses are adjusted. He completes 6 months of therapy and is cured of his TB with expanded resistance.

Scenario 3: GH is a 47-year-old woman who was diagnosed with RR-TB in 2016 and treated with a regimen of Bdq, Lfx, Cfz, Lzd, high-dose Inh, Emb, and Pza. She completed 9 months of this treatment and was declared to be a treatment success. She now presents more than 8 years later with weight loss and cough, and she again has a WHO-recommended rapid molecular test showing resistance to Rif. She is living with HIV and has a CD4 count of 347 cells/uL with an undetectable viral load. She is offered a treatment regimen of Bdq, DLm, Lzd, Lfx, and Cfz, as her prior treatment was multiple years ago and she had a successful outcome. Given her previous treatment, her sputum is sent for targeted NGS as well as for testing with the Xpert XDR cartridge. There is no additional resistance found on the Xpert XDR test. After discussion with her providers, she remains on the Bdq, Dlm, Lzd, Lfx, and Cfz while awaiting the NGS results. After the NGS results come back with no additional resistance mutations, she is continued on Bdq, Dlm, Lzd, and Lfx and completes six months of therapy.

Scenario 4: HG is a 32-year-old woman with poorly controlled diabetes who was diagnosed with RR-TB 18 months ago. She had a large right upper lobe cavitary lesion and nodular disease in the left upper lobe. She was initially started on a regimen of Bdq, Lzd, Lfx, Cs, and Cfz. She continued to have symptoms as well as a positive culture. Her diabetes was poorly controlled as she was unable to afford insulin. She also developed peripheral neuropathy and her Lzd was held and not reintroduced. In the setting of her positive cultures, Dlm and Pza were added to the regimen. She continued to have symptoms and a positive culture and ended up stopping therapy for 2 months due to depression. A peer supporter convinced her to come back to therapy, and she was restarted on the same regimen of Bdq, Lfx, Cs, Cfz, Dlm, and Pza. She had two months where here cultures were negative, but they reverted to positive, and she began to have hemoptysis. She is referred to a central hospital for further management. Unfortunately, there is no access to phenotypic or genotypic testing for second-line drugs in her setting.

A meeting is held with her and her husband, and they state they would like to try a new regimen. They would like her to be cured but also want her to be free of pain. The care providers begin to plan a regimen for her with the following steps:

- **Step 1:** Lzd is not offered given her neuropathy. She has not improved on Bdq and there is a chance of resistance, so she is offered a higher dose of Bdq. She is offered Mfx instead of Lfx. Neither Bdq nor Mfx is counted as effective, but they are included given their association with lower mortality.
- **Step 2:** Pa is considered as a nitroimidazole for her. It is not counted as effective since she has received Dlm. Given her limited treatment options, she is offered Pa even though she is not being given Bdq and Lzd. Cs is not offered given her prior treatment with the drug. She is offered Eto since she has not received this drug in the past.
- **Step 3:** Pza is considered as a possible sterilizing agent for her, but since she is receiving Pa, Pza is not recommended since the two agents cannot be used together.
- **Step 4:** Both Am and meropenem-clavulanic acid are recommended. She is offered both of

these medications IV. The Am is dosed at 25mg/kg three times a week. If a drug is available via pre-approval access/compassionate use, this could be considered as a substitute for one of the injectable agents.

- **Step 5:** PAS is offered since she has not been exposed to it in the past.

She and her husband are told about the multiple potential side effects with her recommended regimen (hBdq, Mfx, Pa, Ethio, Am, meropenem-clavulanic acid, and PAS) but agree they want to try the regimen. She is also placed in an intensive insulin regimen for her diabetes. Baseline audiometry is normal. She has nausea and vomiting daily for the first 10 days of treatment, and these are relived with ondansetron. She becomes depressed being in the hospital and is offered counseling. Her month 1 smear is positive, and the culture returns positive after 14 days as well. She and her husband decide to continue with the regimen, but her audiometry at week 6 shows some high-frequency hearing loss. After an intensive counseling session, she and her husband determine they no longer wish to continue treatment. She wishes to go home, and a community health worker from her community does a home visit. There is a separate room where she can stay, and her husband wishes to care for her there. The family is offered nutritional support, and she is taken home in a private car (funded by a charitable group at the hospital). She is given anti-emetics and pain medications. The hospital is informed that she has died three weeks after she is discharged.

Scenario 5: TR is a 52-year-old male living with HIV (CD4 is 452 cells/uL, VL is undetectable) who is diagnosed with RR-TB based on Xpert MTB/RIF testing. He is in a country where all people with RR-TB have samples sent for targeted NGS, so his sample is sent. He is started on the Bdq, Pa, Lzd, Mfx regimen. He is doing well on the regimen, with less cough and weight gain. However, 9 weeks into treatment, his NGS results return showing mutations associated with resistance to Bdq and Cfz. His month 1 and 2 smears are negative, his month 1 culture is positive, and his month 2 culture is pending. He and his treatment supporter are told about the results of the sample. They want to know what options they have for his treatment. A phenotypic DST for Bdq resistance was sent, but the culture is contaminated. The option of staying on his current regimen is reviewed, but the providers note that the resistance to Bdq could decrease the chance of non-relapsing cure. He is told about the possibility of a Bdq-free regimen with Dlm, Lzd, Lfx, and Pza, but his providers note that no people with HIV were included in the study. Together, the patient and his providers determine that a regimen consisting of a backbone of Dlm, Lzd, Lfx, and Pza with additional Cs added offers him the best chances of culture. This regimen is recommended for 9 months from the time it is started. He is also offered nutritional support. He does well on the regimen, with no positive smears or cultures and is declared cured after 11 total months of treatment, 9 of which are on the new regimen.

Scenario 6: IJ is a 43-year-old female who was diagnosed with RR-TB and started on a regimen of Bdq, Lzd, Lfx, Dlm, and Cfz. She has no other health problems and has right-sided cavitary lung involvement in the upper and middle lobes. She initially does well on her regimen, but 3 months into treatment, her health center has a stock out of Bdq. She stays on a regimen of Lzd, Lfx, Dlm, and Cfz, but she loses faith in her care and starts to miss appointments so she can go into work. Although her initial smears and cultures converted at month 2, her month 5 culture returns positive. The culture is sent for DST to the FLQs, Bdq, and Lzd and she is continued on her regimen of Lzd, Lfx, Dlm, and Cfz. She loses weight and her smears once again become positive as does her month 6 culture. She also develops optic neuritis and her Lzd is stopped, with Eto started in its place. Her providers learn that her phenotypic DST was contaminated and send another culture. In the meantime, however, they consider starting her on a new regimen. Bdq is now back in stock, and they design her regimen using the following steps:

- **Step 1:** Bdq is chosen but not counted as effective since she received it in the past. The dose of her Lfx is increased to 30mg/kg but not counted as effective since she received it in the past. Lzd is not given due to her optic neuritis.

- **Step 2:** Cs is chosen and counted as effective since she has not received it in the past. High-dose Inh is also selected given that she has not received it in the past. There is no access to the nitroimidazoles in her setting.
- **Step 3:** Pza is selected given that it has not been used in the past. It is not counted as effective since rates of Pza resistance in her setting are above 70%.
- **Step 4:** Both Am and imipenem-clavulanate are selected since neither has been used in the past. If a drug is available via pre-approval access/compassionate use, this could be considered as a substitute for one of the injectable agents.
- **Step 5:** PAS is selected since she has not received it in the past.

After counseling, she and her sister agree to try the new regimen. The regimen is Bdq, high-dose Lfx, Cs, high-dose Inh, Pza, Am, imipenem-clavulanate, and PAS. She is hospitalized at the start of the new regimen, but a plan is made to transition her to ertapenem-clavulanate after the first month of treatment. Her baseline ECG and audiometry are normal, but after 14 days on treatment, her QTcF is found to be prolonged, and it does not correct with medical management, so her Lfx dose is decreased to 15mg/kg. She is anxious about her treatment and has daily counseling with a trained peer supporter.

Three weeks into her treatment, her phenotypic DST returns. It shows resistance to the FLQs at all doses and to Lzd, but there is no resistance detected to Bdq. The information is shared with the patient and her sister. The treating team recommends stopping the Lfx entirely and adding Cfz to the regimen. They also recommend stopping the Pza and the PAS. However, the patient is complaining of some loss of balance, so the decision is made instead to stop the Am. Her definitive regimen is Bdq, CS, Cfz, imipenem-clavulanic acid, and high-dose Inh. She stays in the hospital for another 3 weeks and then is transitioned from imipenem-clavulanate to ertapenem-clavulante IM. She begins to slowly improve and has a negative culture 3 months into treatment with her new regimen. Dlm is now available in her setting, and after discussions between the patient and the treating team, ertapenem is stopped and Dlm started. She stays on her regimen of Bdq, Dlm, Cs, Cfz, and high-dose Inh for an additional 15 months after she has culture conversion and completes treatment with an outcome of cured.