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STATE OF THE ART

Clinical perspectives on treatment of rifampicin-resistant/multidrug-resistant TB

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SUMMARY

Rapid diagnostics, newer drugs, repurposed medications, and shorter regimens have radically altered the landscape for treating rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB). There are multiple ongoing clinical trials aiming to build a robust evidence base to guide RR/MDR-TB treatment, and both observational studies and programmatic data have contributed to advancing the treatment field. In December 2019, the WHO issued their second 'Rapid Communication' related to RR-TB management. This reiterated their prior recommendation that a majority of people with RR/MDR-TB receive all-oral treatment regimens, and now allow for specific shorter duration regimens to be used programmatically as well. Many TB programs need clinical advice as they seek to roll out such regimens in their specific setting. In this Perspective, we highlight our early experiences and lessons learned from working with National TB Programs, adult and pediatric clinicians and civil society, in optimizing treatment of RR/MDR-TB, using shorter, highly-effective, oral regimens for the majority of people with RR/MDR-TB.

KEY WORDS: TB; drug-resistant; oral regimen; MDR-TB; human rights

RIFAMPICIN-RESISTANT TB (RR-TB) and multidrug-resistant TB (MDR-TB) are significant global health problems. Unless far-reaching and urgent action is taken, they will be responsible for one out of every four global deaths caused by antimicrobial resistance by 2050.[1] An estimated 484 000 people develop RR-TB/MDR-TB each year, and of the 156 071 (32.2%) people who receive treatment annually, fewer than 60% are cured.[2] Such poor outcomes are due in part to the use of long (i.e., 18–24 month) regimens with highly toxic medications, most of which have not been assessed in clinical trials[3] and which are administered with only limited patient support.[4]

However, there is cause for optimism, with the introduction of newer medications, repurposed agents, and shorter therapeutic options for the treatment of RR/MDR-TB based on clinical trials, observational studies and data from TB programs.[5–8] The 2019 WHO consolidated guidelines offered three possible therapeutic options for countries and programs treating people with RR/MDR-TB: an all-oral

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longer (18–20 month) regimen; an injectable-containing shorter (9–12 month) regimen; and an all-oral shorter (9–12 month) regimen implemented under operational research conditions. However, country programs and their implementing partners were unclear about which regimens to prioritize. Delays in releasing an updated version of the Companion Handbook for Programmatic Management of RR/MDR-TB further compounded the situation.[9]

In November of 2019, the WHO once again convened an RR/MDR-TB guideline development group to assess additional evidence on several specific clinical topics.[10] These included: 1) the use of all-oral shorter regimens for RR/MDR-TB; 2) the use of the three-drug, 6-month, 'Nix-TB', BPaL regimen; and 3) the use of bedaquiline (BDQ) and delamanid (DLM) in combination or when given for durations longer than 6 months. The group reviewed the evidence from South Africa, where over 4000 individuals were treated with a modified, all-oral shorter regimen consisting of the 2016 standardized regimen with BDQ replacing the injectable (mostly due to baseline hearing loss, baseline renal failure, or the development of injectable toxicity during treatment). In December 2019, the WHO then issued a statement supporting the use of all-oral shorter, BDQ-containing regimens.* The WHO also conditionally recommended the use of an all-oral shorter regimen containing BDQ, higher-dose linezolid (LZD) (1200 mg daily), and the novel nitroimidazole pretomanid (PTM) (the 'BPaL regimen') under operational research conditions for people with fluoroquinolone (FQ) resistant TB/treatment intolerant RR/MDR-TB.

As countries struggle to rapidly transition to all-oral regimens, they need clinical guidance and support to optimize the use of shorter, highly-effective, oral regimens for RR/MDR-TB ('SHORRT' therapy) and the BPaL regimen. Note the term 'highly effective' is based on limited data compared to 2016 WHO recommended longer regimen: it is acknowledged that more data is needed to confirm effectiveness. Such guidance is not yet available globally,[11] and some groups are still erroneously recommending an injectable-containing, shorter regimen for RR/MDR-TB treatment, despite the highly toxic nature of injectable medications.[12] As clinicians, implementing partners, and program managers with early implementation experiences, we are using this Perspective article to provide evidence-based recommendations.

* These recommendations were confirmed in the 2020 WHO Guidelines for the treatment of RR/MDR-TB and the updated Companion Handbook, both of which were released in June of 2020 after this article had gone to press. See https://www.who.int/news-room/detail/15-06-2020-who-urges-countries-to-enable-access-to-fully-oral-drug-resistant-tb-treatment-regimens.

METHODS

The clinical practice principles in this Perspective are based on field experience of providing direct care for people with RR/MDR-TB, engaging with TB programs, and listening to the views of TB-affected communities and civil society. Collectively, the authors have more than five decades experience working on RR/MDR-TB, and have worked extensively in the field since newer drugs and shorter regimens became available, supporting more than 30 countries during this time period. In addition to our robust, direct field experience, several of us have provided evidence for and served as observers and voting members at the 2016, 2018, and 2019 WHO Guideline Development Group Meetings. To ensure our coverage was comprehensive, we carried out a literature review using OVID, MedLINE and PubMED databases from January 1, 2016 to February 1, 2020 using the terms: 'rifampicin-resistant tuberculosis' or 'drug-resistant tuberculosis' with 'bedaquiline', 'delamanid', 'shorter', 'World Health Organization' or 'operational research'. Because there are only limited published data on the use of newer drugs and shorter regimens, expert consensus from the authors was reached if evidence was lacking. The development process differed from that used by some normative bodies (such as the WHO) as it considered practice-based experience in addition to those described in the published literature. For the sake of clarity, we have noted in the text when the perspectives are based on the published evidence and when they are based on the opinion of the authors.

CLINICAL PERSPECTIVES

Eliminating the injectables

In 2019, the WHO and its Civil Society Task Force announced they 'strongly recommend that all countries transition to an all-oral regimen for drug-resistant TB by World TB Day 2020.'[13] The 2018 WHO guidelines and the 2019 Rapid Communication provide a framework for doing so for the majority of patients (except for those requiring 'salvage' regimens). Countries must move swiftly to ensure that injectables are no longer routinely used for the treatment of RR/MDR-TB, because there is only limited evidence of their efficacy and extensive examples of their toxicity.[14] Continued use of these injectables when safer, more effective treatments are available violates both Good Clinical Practice and the human rights of people with RR/MDR-TB. Under no conditions should kanamycin or capreomycin be used. Although there may be some people with RR/MDR-TB whose strains are highly resistant, or who have received multiple unsuccessful treatment regimens in the past who require amikacin (AMK) therapy (usually as part of 'salvage' or 'rescue

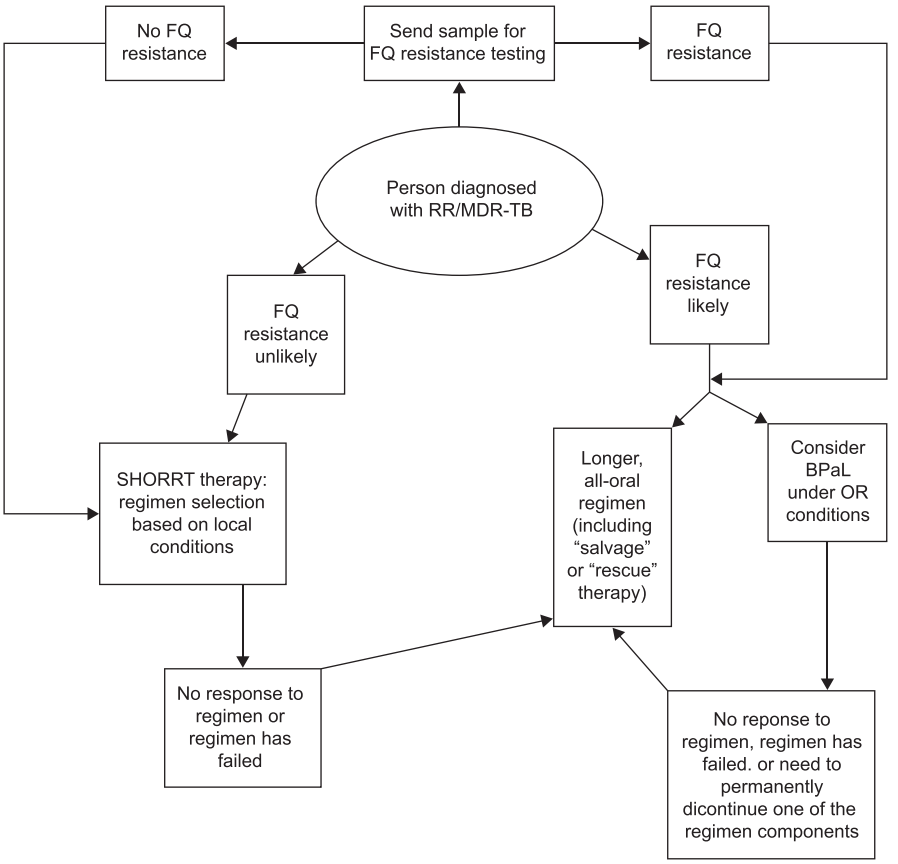

Figure Algorithm for all-oral treatment for RR-TB. FQ = fluoroquinolone; RR-TB = rifampin-resistant tuberculosis; SHORRT = shorter, highly-effective, oral regimens for RR/MDR-TB therapy; OR = operational research.

regimen'), AMK should only be used in people with no other treatment options, and should be accompanied by baseline and routine monitoring for hearing loss. It is the opinion of the authors that countries should not continue using injectables to 'finish their stocks', and major donors (including the Global Fund for AIDS, Tuberculosis and Malaria and USAID) must support immediate transition to all-oral regimens. AMK can be used to treat other serious gram-negative bacterial infections and could be donated to other disease programs in country if needed. It is the opinion of the authors that programs should monitor and report the number of people started on injectable-containing regimens as a basic quality of care indicator. Formal monitoring for adverse drug reactions associated with injectables (hearing loss, renal failure) is required when AMK is used. Of note, although the term 'injectable' as used in this article refers to the aminoglycosides and capreomycin, there has been increased documentation of the successful use of carbapenems in combination with clavulanic acid as part treatment regimens for RR/MDR-TB.[15] These drugs must be administered intravenously (or intramuscularly in the case of ertapenem) and given the limited evidence on their efficacy, the authors suggest they only be administered in longer regimens for patients with limited treatment options.

Duration of therapy

The WHO has recommended an all-oral shorter (9–12 month) regimen for people with RR/MDR-TB who do not have known or likely FQ resistance; severe forms of disease; or other exclusion criteria (see Figure). An all-oral longer (18–20 month) regimen is recommended for people with RR/MDR-TB who have documented or likely FQ resistance, severe forms of disease, or meet other criteria that make them otherwise ineligible to receive a shorter regimen (see Figure). Consequently, all people diagnosed with RR/MDR-TB need to undergo rapid testing for FQ resistance, using a line-probe assay. Other tests may be available in the future, including the expanded Xpert® MTB/RIF cartridge (Cepheid, Sunnyvale, CA, USA),[16] which can also detect resistance to isoniazid (INH), the FQs, and the injectable agents. If FQ susceptibility is not confirmed, people with risk factors for FQ resistance—including those with a prior history of RR/MDR-TB treatment, exposure to a known contact with FQ resistance, or residence in a region where FQ resistance is high (although there is currently no clear

guidance on what is considered to be 'high')—should receive a longer, all-oral regimen.

Some countries are using other criteria to decide who can receive a shorter, all-oral regimen. Because molecular methods may miss some cases where FQ resistance is present, people with documented injectable resistance or with both *inh*A and *kat*G INH resistance mutations could be considered for longer regimens. The especially applies if the shorter regimen contains INH or ethionamide (ETH)—unless FQ susceptibility can be documented. This is because the presence of both these INH mutations in *M. tuberculosis* strains may be a marker for FQ resistance.[17]

Pregnant and breastfeeding women, people with HIV, people with underlying liver disease, people who are incarcerated, people who are migrants/refugees/asylum seekers, and other vulnerable populations are all eligible to receive shorter regimens. Children are a population who should be prioritized for shorter regimens, but the duration of therapy in the pediatric population should be determined by the extent of disease.[18]

Regimen design: 'SHORRT' therapy

The 2019 WHO Rapid Communication recommends giving the 2016 WHO-recommended regimen but replacing the injectable agent with BDQ. Thus, the recommended regimen (the number of months the drug is administered in parentheses) is: BDQ (6)+ETH (4–6)+high-dose INH (4–6)+levofloxacin (LVX) (9)+clofazimine (CFZ) (9)+pyrazinamide (PZA) (9)+ethambutol (EMB) (9). Because the regimen has numerous limitations, concerns have been raised about its use. First, the regimen contains seven drugs and is a substantial pill burden for people with the disease. Second, the regimen contains EMB and PZA for which no routine drug susceptibility testing (DST) is available in most settings: also these drugs may be of limited utility given the high rates of resistance seen among the *M. tuberculosis* strains of people with RR/MDR-TB and prior use of these two agents.[19] Third, the regimen continues to utilize ETH, a drug with multiple adverse drug reactions, which can lead to treatment intolerance, especially nausea and vomiting. Furthermore, in the meta-analysis that informed the 2018 WHO recommendations, ETH use was associated with worse treatment outcomes, even among people whose strains were susceptible to the drug, leading to a conditional recommendation for the medication to only be used in 'salvage' or 'rescue' regimens.[20] Fourth, a simple BDQ substitution in the 2016 shorter regimen means that people will not be treated with all three group A drugs—drugs that have been associated with improved treatment outcomes and lower mortality rates—since LZD is not included in the regimen. Fifth, there are concerns that in settings where FQ resistance is common, a simple BDQ substitution could amplify resistance, especially since results for FQ DST may be delayed for weeks to months (notably with people with smear-negative RR/MDR-TB). This concern is amplified in settings where there is limited experience performing and interpreting line-probe assay (LPA) results. Finally, there has been inconsistent experience with the dose and selection of the FQs used in the injectable containing shorter regimens, with some studies using moxifloxacin (MFX) at 'high doses' and some at standard doses.[21] Of note, the regimen reviewed by the Guideline Development Group in 2019 utilized LVX at a dose of 15–20 mg/kg/day.

There are several alternative all-oral shorter regimens being used globally, and it is the opinion of the authors that countries should consider countrywide implementation of an all-oral regimen suitable to their local context. It is likely the WHO will review data from these regimens in the next 12 to 18 months, and there is regional and country-wide experience using the regimens described below:

1) The 2016 shorter regimen in which the injectable is replaced by BDQ and ETH is replaced by LZD, at least until results from FQ resistance testing are available. This regimen includes all three Group A drugs and is first-line therapy for all people living with RR/MDR-TB in South Africa, where it has been given to thousands of individuals under enhanced monitoring implementation conditions. Its limitations include the continued use of PZA, EMB, and INH which have unclear efficacy in the context of treatment for RR/MDR-TB, increase the pill burden and are associated with adverse events. The combined use of INH and LZD—both of which can cause peripheral neuropathy—is especially problematic, most notably in other populations with risk factors for neuropathy, including people living with diabetes, people who use alcohol, and people living with HIV, although this risk could be mitigated by using LZD for a shorter duration (i.e., 8 weeks or less).

2) One of the 'endTB' regimens. The endTB project is funded by Unitaid and carried out by the humanitarian organizations Interactive Research & Development, Médecins Sans Frontières, and Partners In Health. It has an observational study component[22] and two randomized clinical trials: endTB (NCT02754765) and endTB-Q (NCT03896685). The observational cohort data—which included people who received newer drugs (BDQ and/or DLM), people who received repurposed drugs, and some people who received 'salvage' regimens that included injectable agents—were presented at the 50th Union World Conference on Lung Health. The treatment success was 77.6% among people receiving newer drugs and 84.8% in the subset of patients who received all-oral regimens ($n = 259$).[23] The endTB trial is assessing several different regimens for patients with RR/MDR-TB and confirmed FQ susceptibility, each lasting 9 months and containing different combinations of the drugs BDQ, LZD, LVX/MFX, DLM, CFZ, and/or PZA. Two of the regimens are being used in program

settings. The first contains BDQ, LZD, LVX, CFZ and PZA. This regimen uses all three group A drugs as well as one of the group B drugs plus PZA. The second regimen being used programmatically consists of BDQ, LZD, DLM, LVX, and PZA. This regimen contains all three group A drugs as well as PZA and DLM. Results from the endTB trial are expected in 2022. The endTB-Q study has recently begun enrolling and uses a regimen of BDQ, DLM, LZD and CFZ for people with FQ-resistant RR/MDR-TB.

3) A novel regimen lasting 9–12 months consisting of the five group A and B drugs: BDQ, LZD, LVX, CFZ, and cycloserine: this regimen is being assessed under operational research conditions in some settings (i.e., Ukraine, the Philippines). The rationale for using this regimen is that it uses all the drugs recommended by the WHO for treatment of RR/MDR-TB that have been associated with improved treatment outcomes. Some programs are also considering the use of a 9–12-month regimen which adds DLM to the group A and B drugs above, but there has been limited implementation experience with this regimen and it is unclear why six drugs would be needed at treatment initiation.

In each of these examples, LVX is used instead of MFX because the regimens contain at least two other medications that prolong the corrected QT interval calculated using the Fridericia formula (QTcF interval) (BDQ and CFZ or DLM) and LVX has fewer effects on the QTcF interval. Of note, these regimens may also utilize BDQ for the entire duration of therapy, as published studies and the 2019 WHO review did not identify any increase in adverse drug reactions when BDQ is given beyond 24 weeks. Except for the endTB-Q study, these regimens are only recommended for people in whom FQ resistance has been ruled out or is unlikely (i.e. no previous FQ exposure for >1 month, no exposure to a person with known FQ resistance, no other risk factors for FQ resistance as described in the Figure). The duration of therapy is usually 9–12 months and dependent in some regimens on the smear status at month 4 or on the completion of a certain number of doses. While there is a theoretical concern for continued exposure to BDQ after treatment completion give its long half-life, the clinical implications of this are unclear.

The authors' clinical opinions on SHORRT therapy are summarized in Tables 1, 2 and 3. Table 1 compares the advantages and disadvantages for each of these regimens. Clinical perspectives on monitoring for and managing adverse drugs reactions are included in Table 2. Considerations for special populations are included in Table 3.

Regimen design: longer regimens and fluoroquinolone resistance

If FQ resistance is documented or likely, then the patient does not qualify for SHORRT therapy and will likely need to be treated with a longer, all-oral regimen lasting 18 to 20 months. The principles of regimen construction for such individuals should follow the WHO groupings and the regimens should include at least five drugs. In practice, regimens for people with FQ-resistant RR/MDR-TB almost always contain DLM, since this drug appears to be safe and has shown effectiveness in the treatment of RR/MDR-TB. All efforts should be made to avoid injectables in the longer regimens if equally effective and safer alternatives are available. For a subset of patients, however, a carbapenem such as meropenem or imipenem in combination with clavulanic acid (available only as amoxicillin-clavulanate) or AMK (if there is susceptibility to this drug and formal audiological assessments are available) may be needed to construct a regimen with enough effective drugs. Data on the safety of BDQ and DLM use in combination, both from observational cohorts[24–27] and from a randomized controlled trial,[28] has shown that giving these two drugs together does not lead to an excess increase in QTcF prolongation. The 24-week administration period for both BDQ and DLM was selected so clinical trials could be completed in a shorter time period, not because of any evidence of cumulative toxicity or risk if either drug is administered for longer than 24 weeks.[29] It is the opinion of the authors that patients on longer regimens will likely also need DLM and/or BDQ extended for the entire duration of therapy, a clinical practice that is supported by observational cohort studies, which show no increase in adverse events with prolonged administration.[30] Policy makers and programs need to budget for such prolongation and work to define an oversight mechanism by which such extensions can be supported in their local settings. Monitoring for adverse events is essential when BDQ and/or DLM are given for longer than 24 weeks to continue to build the database on the safety and efficacy of this practice.

Some countries may consider using the BPaL regimen under operational research conditions (see section on principles for operational research) for certain patients with FQ-resistant RR/MDR-TB and among those for whom designing an effective regimen based on existing WHO recommendations is not possible. As noted above, the BPaL regimen consisting of 6–9 months of BDQ, higher-dose LZD (1200 mg daily) and the novel nitroimidazole PTM was recently approved under the 'Limited Population Pathway for Antibacterial and Antifungal Agents' by the FDA.[31] This is a new regulatory approval pathway that is intended for treatment of diseases associated with high mortality and for which limited therapeutic options exist. The evidence required for approval using this mechanism is less rigorous than for medication approved through other FDA pathways.[32] The FDA did not grant approval to any of the single agents in the BPaL regimen and only recommended the entire

Table 1 Comparison of SHORRT therapy being used in programmatic settings and the BDQ+PTM+LZD regimen

	BDQ substitution regimen	South African regimen	endTB regimens	Group A and B drugs regimen	BPaL regimen
Conditions of WHO recommendation	2019 recommended	Carefully monitored national program conditions	Operational research conditions	Operational research conditions	Operational research conditions
Regimen composition*	HD-INH (4–6), ETH (4–6), BDQ (6), LVX, CFZ, EMB, PZA (9–11)	LZD (2), HD-INH (4–6), BDQ (6), LVX, CFZ, PZA, EMB (9–11)	BDQ, LZD, LVX, CFZ, PZA (9–11) BDQ, LZD, DLM, LVX, PZA (9–12)	BDQ, LZD, LVX, CFZ, CS/TRD (9–12)	BDQ, higher-dose LZD (1200 mg a day), PTM
Duration (note: duration is for the entire regimen: BDQ could be given the entire time), months	9–11	9–11	9–11	9–11	6–9
Baseline drug susceptibility testing necessary	RIF resistance and FQ resistance at a minimum; consider storage of baseline strains to test for resistance to components of the regimen in the future	RIF resistance and FQ resistance at a minimum; consider storage of baseline strains to test for resistance to components of the regimen in the future	RIF resistance and FQ resistance at a minimum; consider storage of baseline strains to test for resistance to components of the regimen in the future	RIF resistance and FQ resistance at a minimum; consider storage of baseline strains to test for resistance to components of the regimen in the future	RIF resistance and FQ resistance at a minimum; if previous CFZ exposure, should document susceptibility to BDQ prior to using this regimen
Evidence for efficacy	Evidence for individual drugs from randomized trials and individual patient data meta-analyses; data from South Africa showing greater efficacy compared with injectable-containing shorter regimen	Evidence for individual drugs from randomized trials and individual patient data meta-analyses; currently the standard of care regimen in South Africa, planned analysis in 2020	Evidence for individual drugs from randomized trials and individual patient data meta-analyses; data from observational cohorts likely to be analyzed in 2021 and trial data available in 2022	Evidence for individual drugs from randomized trials and individual patient data meta-analyses; data from observational cohorts likely to be analyzed in 2021	Data from 109 participants enrolled in a single-arm, uncontrolled trial
Efficacy risks	Could have higher rates of recurrence/relapse compared with regimens lasting longer than 12 months; could lead to resistance amplification in people with FQ resistance	Could have higher rates of recurrence/relapse compared with regimens lasting longer than 12 months, amplification of resistance	Could have higher rates of recurrence/relapse compared with regimens lasting longer than 12 months	Could have higher rates of recurrence/relapse compared with regimens lasting longer than 12 months	Could have higher rates of recurrence/ relapse compared with regimens lasting longer than 12 months
Safety risks	Use of multiple drugs to which resistance is likely in a substantial population of patients (including PZA and EMB); QTcF prolongation due to BDQ, CFZ. MFX; hepatitis due to PZA and INH; skin discoloration due to CFZ	Largely associated with LZD and include bone marrow toxicity, optic neuritis, and peripheral neuropathy (although this risk may be lower given that LZD is only given for 8 weeks); requires clinical and laboratory monitoring that is reasonably easy to access; QTcF prolongation due to BDQ, CFZ, MFX; hepatitis due to PZA and INH; skin discoloration due to CFZ	Largely associated with LZD and include bone marrow toxicity, optic neuritis, and peripheral neuropathy; requires clinical and laboratory monitoring that is reasonably easy to access; QTcF prolongation due to BDQ, CFZ, MFX; skin discoloration due to CFZ	Largely associated with LZD and include bone marrow toxicity, optic neuritis, and peripheral neuropathy and with CS/TRD (psychosis, seizures); requires clinical and laboratory monitoring that is reasonably easy to access; QTcF prolongation due to BDQ, CFZ, MFX; skin discoloration due to CFZ	Liver toxicity, testicular toxicity (seen in animal studies but not yet assessed in humans) due to PTM; bone marrow toxicity, optic neuritis, peripheral neuropathy due to higher-dose LZD; QTcF prolongation due to BDQ
Other possible benefits	Lower mortality reported with the use of BDQ in most settings	Lower mortality reported with the use of BDQ and LZD in most settings	Lower mortality reported with the use of BDQ and LZD in most settings	Lower mortality reported with the use of BDQ and LZD in most settings	Lower mortality reported with the use of BDQ and LZD in most settings
Other possible risks	Use of medications to which there may be resistance, high pill burden	High pill burden; use of medications to which there may be resistance	Use of medications to which there may be resistance	Use of medications to which there may be resistance	
Maximum number of Group A drugs†	2/3	3/3	3/3	3/3	2/3
Maximum number of Group B drugs†	2/2	1/2	Either 0 or 1 of 2	2/2	0/2

* Number of months in parentheses.
† Group A drugs: bedaquiline (BDQ), linezolid (LZD), and levofloxacin (LVX) or moxifloxacin (MFX); Group B drugs: clofazimine (CFZ) and cycloserine/terizidone CS/TRD); Group C drugs: delamanid (DLM), pyrazinamide (PZA)
SHORRT = shorter, highly-effective, oral regimens for RR/MDR-TB therapy; PTM = pretomanid; HD-INH = high-dose isoniazid; ETH = ethionamide; LVX = levofloxacin; EMB = ethambutol; RIF = rifampin; FQ = fluoroquinolone; RR/MDR-TB = rifampin-resistant/multidrug-resistant tuberculosis.

Table 2 Adverse events and suggested monitoring tools for people on all-oral therapy for RR/MDR-TB

Adverse event	Potentially causative medications	Recommended monitoring	Program tools	Ancillary medications for management
Peripheral neuropathy	LZD, HD-INH, CS	Monthly clinical assessments with standardized symptom screening and physical examination	Brief peripheral neuropathy screening tool,* reflex hammer, mono-filament (especially useful for children)	Gabapentin, pregabalin
Optic neuritis/neuropathy	LZD, EMB	Monthly clinical assessment with standardized visual acuity and color vision testing	Snellen chart, Ishihara color plates	Prednisone may be given, but there is little evidence documented to support its use
QTcF prolongation	BDQ, CFZ, MFX, DLM, LVX	Baseline and monthly ECG	Handheld ECG app, 12 lead ECG, QTcF calculator, laboratory testing for potassium	Potassium, magnesium; levothyroxine supplementation if TSH is elevated
Hepatotoxicity	Pretomanid, BDQ, CFZ, PZA, HD-INH; of note, any drug can cause hepatotoxicity	Monthly liver function tests	Laboratory testing for transaminases, bilirubin, protocols for management of hepatotoxicity	TB medications that can be used in liver-sparing regimens
Skin hyperpigmentation	CFZ	Ongoing counseling and support, especially around inadvertent disclosure		Use of sunscreen or avoidance of direct sunlight

* Mehta S, et al. Implementation of a validated peripheral neuropathy screening tool in patients receiving antiretroviral therapy in Mombasa, Kenya. Am J Trop Med Hyg 2010; 83(3): 565–570.
RR/MDR-TB = rifampin-resistant/multidrug-resistant tuberculosis; LZD = linezolid; HD-INH = high-dose isoniazid; CS = cycloserine; EMB = ethambutol; BDQ = bedaquiline; CFZ = clofazimine; MFX = moxifloxacin; DLM = delamanid; LVX = levofloxacin; ECG = electrocardiogram; TSH = thyroid stimulation hormone; PZA = pyrazinamide.

regimen for people with extensively drug-resistant TB (XDR-TB—RR/MDR-TB with resistance to both an injectable and a FQ), pre-XDR-TB (i.e., RR/MDR-TB with resistance to either a FQ or injectable), or treatment intolerant/non-responsive RR/MDR-TB. This regimen should not be given to people who have been previously treated with two or more weeks of BDQ, LZD, or DLM (given the possibility of cross-resistance between DLM and PTM), unless there is DST documenting susceptibility to these agents. In

Table 3 Considerations for vulnerable populations

Population	Special considerations
People living with HIV	Cannot use BDQ with efavirenz as efavirenz lowers BDQ concentrations; Dolutegravir-based regimens preferred; Monitor for overlapping toxicities (i.e., linezolid/zidovudine)
Children	BDQ recommended in children ages 6 years and above; Delamanid recommended in children ages 3 years and above; Children under these age cut-offs should be considered on a patient-by-patient basis; Child-friendly formulations should be used; Must be included in operational research so data can be obtained
Adolescents (10–19 years)	No physiological reason to exclude them from early trials or from receiving SHORRT or other shorter regimens; May need additional support for diagnosis and adherence
Pregnant and breastfeeding women	Limited experience with most second-line drugs in this population; Robust regimens most likely to result in treatment success; Must be included in operational research so data can be obtained
Hepatitis B or C	Should receive treatment for viral hepatitis as part of RR/MDR-TB therapy; May wish to avoid PZA- and INH-containing regimens
People who use alcohol or other substances	Counseling and harm reduction should be offered as an essential part of treatment; Abstinence is not required for RR/MDR-TB treatment; May wish to avoid PZA- and INH-containing regimens
Incarcerated individuals	Must be included in operational research as part of equity and human rights approach to RR/MDR-TB; May be more likely to benefit from shorter regimens; Transition to civilian sector is a vulnerable time during which additional support is needed.
Migrants/refugees/asylum seekers	Must be included in operational research as part of equity and human rights approach to RR/MDR-TB; May be more likely to benefit from shorter regimens

BDQ = bedaquiline; SHORRT = shorter, highly-effective, oral regimens for RR/MDR-TB therapy; RR/MDR-TB = rifampin-resistant/multidrug-resistant tuberculosis; PZA = pyrazinamide; INH = isoniazid.

people with a history of having received CFZ, BDQ susceptibility should be confirmed as there can be cross-resistance between BDQ and CFZ.[33]

Given the very limited experience with the BPaL regimen and the need to collect additional data, it is the opinion of the authors that patients on this regimen be monitored closely during treatment and for at least 24 months after treatment. Furthermore, given the adverse events seen with PTM in other controlled trials (especially hepatotoxicity[34,35]) and the limited clinical evidence of PTM's independent contributions towards the efficacy of the BPaL regimen, it should be rolled out to the populations specified by the FDA. It is the opinion of the authors that the BPaL regimen should not be considered for broader use among populations with RR/MDR-TB until additional evidence is generated, especially since there are multiple treatment options that now exist for individuals with all forms of RR/MDR-TB.

Clinicians treating people under the Nix-TB protocol had significant leeway in the management of individuals on the regimen, including those who developed toxicity to one or more of the three medications. As per the FDA approved package insert for PTM,[36] it is strongly recommended that all people on the BPaL regimen have routine (i.e. monthly) and systematic screening for peripheral neuropathy (using standard assessment tools and grading systems), optic neuritis, liver toxicity and bone marrow suppression. LZD-related toxicity developed in a high proportion of people who received the BPaL regimen, and some patients required the initiation of chronic medical therapy to manage adverse events, most notably those with peripheral neuropathy. In some instances of toxicity, the LZD was held and then reintroduced at a lower dose (either 300mg or 600mg daily). In other instances, LZD was completely discontinued (usually after 2 months) and the remainder of the regimen completed with just two drugs—BDQ and PTM. If either BDQ or PTM needs to be discontinued, however, the patient should be transitioned to a 'salvage' or 'rescue' regimen in some instances. The ongoing 'Ze-Nix' trial (NCT03086486) will assess different doses of LZD to see if lower rates of adverse drug reactions can be achieved.[37] Results of this study are expected in 2020.

It is the opinion of the authors that countries may also consider using DLM as the nitroimidazole of choice in a BDQ and LZD-containing regimen (as is being done in the endTB study, the endTB-Q study, the BEAT TB study in South Africa, NCT04062201 and the SMART KIDS IMPAACT 2020 study); however, there have been no head-to-head comparisons of DLM and PTM to assess the comparative efficacy and safety of these two nitroimidazoles, including in the context of the BPaL regimen. DLM has an excellent safety profile and can be given to children; however, in a phase III randomized, placebo-controlled trial, DLM failed to reach its primary efficacy endpoint.[38] It is the opinion of the authors that a trial comparing these two nitroimidazoles is a priority in RR/MDR-TB clinical research. Countries may also consider using the regimens being assessed in the Unitaid-sponsored 'endTB-Q' study as SHORRT regimen options for people whose *M. tuberculosis* strains have known or possible FQ resistance. This regimen consists of BDQ, DLM, LZD and CFZ given daily for 9–11 months.[39]

Table 4 Operational research considerations for all-oral treatment of RR/MDR-TB

1	Operational research is usually recommended when there is clinical rationale or emerging evidence favoring the use of a drug or regimen, but the WHO has not been able to formally assess select regimens due to insufficient data for review
2	Operational research is not meant to replicate or replace clinical trials but rather to help countries answer questions about optimal implementation in the populations they are treating in everyday practice
3	Operational research should focus on the populations of people with RR/MDR-TB who receive care within national programs: as such, children, pregnant women, breastfeeding women, people who are incarcerated, migrants/refugees/asylum seekers, and people who use/abuse substances (including alcohol) should be included
4	While there are multiple, ongoing clinical trials of SHORRT therapy,* there is also a need to collect and analyze data on the implementation of and how such regimens perform under field conditions.† Well-conducted observational cohort studies have been used to support policy change at both national and international levels and have the added benefit of assessing feasibility as well as effectiveness of drugs and regimens‡,§
5	One potential benefit to carrying out operational research is that it is an opportunity to strengthen country and program data collection and routine monitoring systems, although additional financial and human resources must be put toward this task. This higher quality data can then be shared with local, national and international bodies, including the WHO, to better inform future policy decisions for the treatment of RR/MDR-TB at all levels
6	Countries—and the donors supporting them—should feel comfortable utilizing regimens under operational research conditions as part of health systems strengthening and closely monitored implementation rather than separate, 'stand alone' research projects

* RESIST-TB. Clinical Trials Progress Report. http://www.resisttb.org/?page_id=1602.
† Cox HS, et al. The need to accelerate access to new drugs for multidrug-resistant tuberculosis. Bull World Health Organ 2015; 93(7): 491–497.
‡ Khan F, et al. Effectiveness and safety of standardized shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analysis. Eur Respir J 2017; 50: 1700061.
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RR/MDR-TB = rifampin-resistant/multidrug-resistant tuberculosis; SHORRT = shorter, highly-effective, oral regimens for RR/MDR-TB therapy.

Principles for operational research and programmatic considerations

WHO recommendations on the treatment of RR/MDR-TB over the past several years have routinely recommended novel treatment regimens, including SHORRT regimens, be implemented under 'operational research conditions.' Table 4 reviews the authors' opinions regarding important considerations for operational research on RR/MDR-TB. The authors' opin-

Table 5 Programmatic considerations for all-oral treatment of RR/MDR-TB

1	The top priority for TB programs is to halt the routine use of injectable agents and begin offering all oral regimens for people with RR/MDR-TB, unless they are in need of salvage therapy.
2	All countries need to urgently scale up laboratory testing to detect resistance to rifampin and the fluoroquinolones with further plans to develop and implement drug susceptibility testing for BDQ, LZD, CFZ, and DLM
3	Countries will need to ensure they have adequate stocks of newer drugs (BDQ and DLM) aligned with supply of companion drugs (CFZ, LZD, levofloxacin, and possibly moxifloxacin)
4	There is a critical need for improved counseling on a number of topics and social support—including a genuine approach to 'patient-centered care'—for these regimens to be successful
5	As with any treatment for RR/MDR-TB, identifying and managing adverse drug reactions during treatment are priority activities (see Table 2). In addition to this, systems for reporting serious, severe, and other adverse events of interest should be developed or strengthened within the country to serve all people with RR/MDR-TB regardless of their treatment regimen. Active Drug Safety Monitoring and Management (aDSM) should be done according to WHO principles* and national guidelines: countries must make available the necessary human and financial resources to implement quality aDSM
6	As part of roll out of all-oral regimens, countries need to strengthen their monitoring and evaluation systems so local data can be used to make decisions about optimizing treatment
7	While countries may consider rolling out some of the regimens described above in selected locations or provinces, scale-up of all-oral RR/MDR-TB treatment needs to take place on a national level and implementation plans must be in place for equitable and widespread access
8	Capacity building in the management of RR/MDR-TB is paramount for a successful implementation of the newer guidelines using the above agents.

* World Health Organization. Active drug-safety monitoring and management: framework for implementation. Geneva, Switzerland: WHO, 2015.
RR/MDR-TB = rifampin-resistant/multidrug-resistant tuberculosis; BDQ = bedaquiline; LZD = linezolid; CFZ = clofazimine; DLM = delamanid.

ions on programmatic considerations for implementation of SHORRT therapy and all-oral regimens for FQ-resistant RR/MDR-TB are reviewed in Table 5.

CONCLUSION

For the first time, the WHO has recommended an all-oral therapy for the majority of people living with RR/MDR-TB. AMK-based regimens should only be used for people in need of 'salvage' or 'rescue' therapy. The WHO has recommended that people for whom FQ-resistant TB has been ruled out or is unlikely should receive a BDQ-containing 9–12-month regimen. Given the concerns with the WHO recommended 2016 shorter regimen, (with BDQ given instead of the injectable agent) there are a number of other 'SHORRT' regimens being used under program conditions that, in the opinion of these authors, could be considered for monitored implementation by countries. People with likely or documented FQ resistance will likely need longer, all-oral regimens, although in some settings with rigorous monitoring, the 6-month BPaL regimen or endTB-Q regimen could be considered (See Table 6

Table 6 Summary of authors' recommendations

Type of RR/MDR-TB	Treatment options	WHO guidance	Authors' guidance	Comments
RR/MDR-TB without: 1) FQ resistance, risk factors for FQ resistance, or 2) osteoarticular/meningeal TB (3 treatment options)	1) WHO-recommended all-oral BDQ-containing shorter regimen	Preferred option	Discouraged, although still preferable to injectable-containing shorter regimens	The regimen is the older shorter RR/MDR-TB regimen, with AMK replaced by BDQ No other modifications are allowed Does not use all three Group A drugs Uses EMB and PZA, which may have resistance Uses ethionamide, which is associated with poorer outcomes in some analyses and intolerance
	2) All-oral individualized longer regimen (18–20 months)	Acceptable option	Acceptable option	Uses all three Group A drugs Increased monitoring for LZD adverse effects is requited See Table 2 for the Hierarchy of TB drugs
	3) All-oral modified regimens ('SHORRT' Regimens) under OR conditions	Acceptable option	Preferred option	Has the advantage of being short and using all three Group A drugs Increased monitoring for LZD adverse effects is required See text and Table 3 for the choice of SHORRT regimens
RR/MDR-TB with FQ resistance, risk factors for FQ resistance or osteoarticular/meningeal TB (3 treatment options)	1) Individualized, longer regimen (majority can still be all-oral)	Preferred option	Preferred option if unable to do OR in the country	This regimen has been used most frequently and has good outcomes in multiple countries
	2) BPaL regimen under OR conditions	Acceptable option but not for osteoarticular/meningeal TB	Acceptable option if able to do OR	Concerns on adverse events and the high dose of LZD Pretomanid not widely registered Limited experience with use
	3) All-oral modified regimens ('SHORRT' Regimens) such as the regimen being used for the endT-Q study under OR conditions	WHO does not give an opinion	Preferred option if able to do OR in the country	Has the advantage of being short Limited experience with use

RR/MDR-TB = rifampin-resistant/multidrug-resistant tuberculosis; FQ = fluoroquinolone; BDQ = bedaquiline; AMK = amikacin; EMB = ethambutol; PZA = pyrazinamide; LZD = linezolid; SHORRT = shorter, highly-effective, oral regimens for RR/MDR-TB therapy; OR = operational research.

for a summary of the authors' recommendations). It is essential that pregnant women, children, and people living with HIV be prioritized for all-oral regimens. There is no reason they—or other vulnerable populations—should be excluded. An exception to this is PTM-containing regimens, until reproductive toxicity studies are completed. Finally, programmatic issues must be addressed to ensure rapid and equitable access to these innovative treatments, but also to the support people require to successfully complete the regimens.

The WHO Guideline Development Group will continue to meet and review additional evidence on improving RR/MDRTB treatment. This is common practice in the response to other epidemics and is a welcome development that reflects the strengthened science to support RR/MDR-TB management. In addition to clear, unequivocal recommendations, practice-based solutions are needed to help countries decide on the optimal treatment strategies for their settings. Countries should develop systems to rapidly update their national guidelines and implementation plans as better treatment data becomes available. Strong, programmatic leadership and flexibility is essential to 'End TB' and to ensure that a patient-centered, human rights-based approach to RR/MDR-TB is available to everyone affected by this disease.

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RÉSUMÉ

Les diagnostics rapides, les nouveaux médicaments, les médicaments recyclés et les protocoles plus courts ont radicalement altéré le paysage du traitement des formes de TB résistantes à la rifampicine et multirésistantes (RR/MDR-TB). Il y a de nombreux essais cliniques en cours visant à créer une solide base de données pour guider le traitement de la RR/MDR-TB ; les études d'observation ainsi que les données des programmes ont contribué à faire progresser le domaine du traitement. En décembre 2019, l'OMS a publié son deuxième « Rapid Communication » relatif à la prise en charge de la RR-TB ; l'OMS a réitéré sa recommandation antérieure—que la majorité des personnes atteintes de RR/MDR-TB reçoive des protocoles de traitement uniquement oraux—et autorise maintenant les protocoles spécifiques de plus courte durée pour être utilisés également par les programmes. De nombreux programmes TB ont besoin de conseils cliniques quand ils veulent lancer de tels protocoles dans le contexte spécifiques de leur pays. Cette perspective fournit des expériences précoces et des leçons apprises des Programmes Nationaux TB, des partenaires, des cliniciens adultes et pédiatriques de RR/MDR-TB et de la société civile pour optimiser le traitement de la RR/MDR-TB, en utilisant des protocoles oraux, plus courts, hautement efficaces pour une majorité de personnes atteintes de RR/MDR-TB.

RESUMEN

Los métodos de diagnóstico rápido, los nuevos fármacos, los medicamentos destinados a un nuevo uso y los esquemas terapéuticos acortados han modificado totalmente el panorama del tratamiento de las formas de TB resistentes a rifampicina y multirresistentes (RR/MDR-TB). En la actualidad, están en curso múltiples ensayos clínicos encaminados a obtener una evidencia sólida para orientar el tratamiento de la RR/MDR-TB y, tanto los estudios observacionales como los datos programáticos han aportado avances en materia de tratamiento. En diciembre del 2019, la OMS emitió su segunda "Comunicación rápida" sobre el manejo de la RR-TB; la OMS reiteró su recomendación anterior de que la mayoría de las personas con RR/MDR-TB deberían recibir pautas de tratamiento de administración oral exclusiva y ahora, permite además la administración de tratamientos acortados específicos en el marco programático. Muchos programas de TB necesitan asesoramiento clínico en el momento de desplegar estos regímenes en los entornos propios de su país. La perspectiva del presente artículo comunica las experiencias iniciales y las enseñanzas aprendidas a partir de los Programas Nacionales de TB, los asociados, los médicos que se ocupan de la RR/MDR-TB en los adultos y los niños y la sociedad civil, con el propósito de optimizar el tratamiento de la RR/MDR-TB con regímenes acortados de administración oral exclusiva y de gran eficacia, dirigidos a la mayoría de las personas con estas formas de TB.