Practice-Based Recommendations for Implementing the 2018 World Health Organization Recommendations on the Treatment of Rifampicin-Resistant/Multidrug-Resistant Tuberculosis

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I. Introduction

It has been one year since the World Health Organization (WHO) released its Rapid Communication documenting significant changes in the approach to the treatment of rifampicin-resistant/multidrug-resistant tuberculosis (RR/MDR-TB),[1] with the full guidance being released in December of 2018.[2] These recommendations represent a significant shift in RR/MDR-TB management: for the first time, three medications were strongly recommended for the treatment of RR/MDR-TB and all-oral regimens were recommended for a majority of people living with the disease. The guidelines, however, offer several possible therapeutic options for countries and programs treating people living with RR/MDR-TB (see Table 1), creating confusion about the conditions under which each regimen should be prescribed. Country programs and implementation partners have requested advice to guide decision-making and support optimal treatment outcomes for all people living with RR/MDR-TB. The following clinical practice principles were developed based on field experience providing direct care for people living with RR/MDR-TB, engaging with TB programs, and listening to the perspectives from the TB community.

II. WHO Recommended Regimens

Three possible approaches to initial regimen selection are outlined in the 2018 WHO recommendations:

A. The use of all-oral regimens that contain all three strongly recommended Group A drugs (bedaquiline, linezolid and a third-generation fluoroquinolone [either levofloxacin or moxifloxacin]) when possible, along with both Group B drugs (clofazimine and cycloserine/terizidone) for 18-20 months. This is the preferred regimen recommended by WHO;

B. The use of all-oral shorter regimens consisting of 4-5 medications and that contain the Group A drugs bedaquiline, linezolid and a third-generation fluoroquinolone (either levofloxacin or moxifloxacin) and Group B drugs (clofazimine) or Group C drugs (delamanid) for the treatment of RR/MDR-TB but administered for 9-12 months ("modified shorter regimens") under operational research conditions (see section below on principles for operational research);

C. The use of the WHO "standardized shorter regimen"* first recommended in 2016,[3] but given with amikacin instead of kanamycin and accompanied by routine monitoring for hearing loss.

Table 1: Comparison Table for Regimens Recommended in the 2018 WHO RR/MDR-TB Treatment Guidelines

	2018 Longer Regimen	2016 Standardized Shorter Regimen	All-Oral Shorter Regimen
Date of WHO recommendation	2018	2016	2018
Strength of WHO recommendation	Group A drugs§ strongly recommended	Conditionally recommended	Recommended under operational research conditions
Baseline DST necessary	Rifampin resistance and fluoroquinolone resistance at a minimum; consider storage of baseline strains to test for resistance to components of the regimen in the future	Rifampin, fluoroquinolone, and second-line injectable resistance	Rifampin resistance and fluoroquinolone resistance at a minimum; consider storage of baseline strains to test for resistance to components of the all-oral shorter regimen in the future
Evidence for efficacy	Evidence for individual drugs but not for regimen as a whole	Randomized controlled trial showed non-inferiority when compared with the 2016 WHO longer regimen (which is no longer recommended)	Limited evidence from smaller cohorts, largely from South Africa
Efficacy risks	Could have higher rates of loss to follow up given length of regimen	Higher rates of poor bacteriologic outcomes (most benefit is seen in	Could have higher rates of recurrence/relapse, with relapse being

*Four months of clofazimine, moxifloxacin (or levofloxacin), ethambutol, pyrazinamide, high dose isoniazid, ethionamide (or prothionamide), and amikacin, followed by five months of clofazimine, moxifloxacin (or levofloxacin), ethambutol, and pyrazinamide

		reducing loss to follow up)	identified through genetic testing
Safety risks	Largely associated with linezolid; requires clinical and laboratory monitoring that is reasonably easy to access; partially reversible	Hearing loss from injectable; often difficult to monitor; irreversible	Largely associated with linezolid; requires clinical and laboratory monitoring that is reasonably easy to access; partially reversible
Other possible benefits	Lower mortality reported with the use of bedaquiline in some settings	Short-term costs could be lower	Lower mortality reported with the use of bedaquiline in some settings
Other possible risks	Use of medications to which there may be resistance	High pill burden; daily injections; use of medications to which there may be resistance	Use of medications to which there may be resistance
Maximum number of Group A drugs[§]	3/3	1/3	3/3
Maximum number of Group B drugs[§]	2/2	1/2	2/2

[§]Group A drugs: bedaquiline, linezolid, and levofloxacin or moxifloxacin; Group B drugs: clofazimine and cycloserine/terizidone

III. Principles for Regimen Selection

Recently, the WHO and its Civil Society Task Force announced that they "strongly recommend that all countries transition to an all-oral regimen for drug-resistant TB by World TB Day 2020."[4] In light of this, the following best practices are suggested for optimal regimen selection for persons living with RR/MDR-TB:

- All-oral regimens should be given to a MAJORITY of people with RR/MDR-TB and these regimens should include all three of the Group A medications unless there is a non-modifiable clinical contraindication;
- Countries should consider offering all-oral shorter regimens ("modified shorter regimens") under closely monitored conditions that allow them to collect effectiveness and safety data (e.g. operational research), especially in populations that are usually excluded from studies (e.g. children, pregnant women, people living in prisons). These regimens should utilize the Group A drugs (bedaquiline, linezolid, either levofloxacin or moxifloxacin) and Group B drugs (clofazimine, cycloserine/terizidone) or Group C drugs

(delamanid, ethambutol if there is documented susceptibility, pyrazinamide if there is documented susceptibility);

- Injectables should only be used in patients with no other treatment options (e.g. salvage therapy), when there is formal assessment and monthly monitoring of hearing; the person living with RR/MDR-TB has been informed about the risks of the injectable drugs (permanent hearing loss, renal failure, electrolyte abnormalities); and consent is given to receive the medication;
- The 2016 standardized shorter regimen should be phased out in favor of all-oral regimens which are either 18-20 months in duration or shorter and administered under carefully monitored conditions;
- The 2016 standardized shorter regimen should only be given to people who have no documented resistance to the injectable and no documented resistance to the fluoroquinolone since the phase III randomized, controlled study to evaluate the standardized shorter regimen used these criteria.[5] Additionally, it is unethical to expose people to medicines to which they are resistant and carry risks of toxicities without potential benefit. If the shorter regimen is to be given, amikacin should be used, there must be baseline and monthly assessments of hearing, and there must be documented consent that the patient agrees to receive the injectable after being counseled about the risks of permanent hearing loss and renal failure.

IV. <u>All-Oral Regimen Design and Adjustment to Support Optimal Treatment Outcomes</u>

- All countries need to *urgently* scale up laboratory testing to detect resistance to rifampicin and the fluoroquinolones;
- Children over the age of six years can receive bedaquiline and should receive this drug unless it is contraindicated. Children over the age of three years should receive delamanid instead of bedaquiline. Additional dosing and safety data on these drugs in younger children will be forthcoming soon; in the meantime, younger children can receive these drugs on a case-by-case basis;
- There are limited data on the use and safety of all second-line drugs during pregnancy and breastfeeding. Animal studies suggest there are no teratogenic effects of bedaquiline, and delamanid is in the same safety category as most of the other second-line drugs. Since injectable agents are contraindicated in pregnant women, they should receive all-oral regimens. Pregnancy is not a reason to deny women access to drugs with a proven mortality benefit, including bedaquiline, linezolid, and the third-generation fluoroquinolones;
- The 24-week administration period for both bedaquiline and delamanid 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.[6]

Individuals receiving these medications may need to take them for longer than 24 weeks for a variety of reasons, including (but not limited to) toxicity to another medication in the regimen leading to discontinuation of that medication, resistance to one or more of the Group A drugs, delayed culture conversion, or if the person living with RR/MDR-TB has severe disease;

- Initial hesitation to give bedaquiline and delamanid together had to do with a theoretical risk of additive or synergistic cardiotoxicity. Data from observational studies and from a randomized controlled trial show there is no increased risk of cardiotoxicity and therefore bedaquiline and delamanid can be given in combination in patients who need both of these drugs. Data supporting the safe co-administration of bedaquiline and delamanid come from observational cohorts[7]—including the endTB study[8]—and a randomized controlled designed specifically to look at cardiotoxicity of giving bedaquiline and delamanid in combination (ACTG5343);[9]
- All-oral regimens are the preference for a majority of people living with RR/MDR-TB, and some countries may simply wish to use the 2016 standardized shorter regimen and simply replace the injectable with bedaquiline. This regimen, however, includes ethionamide (a drug that is now only recommended for salvage regimens) and only utilizes two of the Group A drugs; additionally, if fluoroquinolone resistance is not ruled out, use of this modification could lead to amplification of resistance to its other components, including bedaquiline and/or clofazimine. Therefore, simply replacing the injectable with bedaquiline may not be ideal;
- Monitoring and management of adverse events associated with the Group A and B drugs is essential to ensure the best possible outcomes for people living with RR/MDR-TB and the programs treating them. This included baseline/monthly monitoring of the complete blood count, visual acuity, and screening for peripheral neuropathy while on linezolid and baseline/monthly monitoring for potassium and the QTcF interval while on bedaquiline, clofazimine, or moxifloxacin;
- If drug adjustments are needed for toxicity, there are several options, including prolongation of bedaquiline, dose adjustments for linezolid, or the use of Group C agents, of which delamanid is preferred given its safety profile.[10]

V. Principles for Operational Research

- Operational research is **not** meant to replicate clinical trials but rather to help countries answer questions about optimal implementation in the populations they are treating in every day practice;
- Sample protocols for modified, all-oral shorter regimens have been developed by multiple groups, including the WHO Tropical Diseases Research (TDR) Program, the US Agency for International Development (USAID), and the Harvard Medical School Dubai

Center for Global Health Delivery and these can be adapted to local country settings with support for planning, implementing and analyzing the results of such protocols provided by in-country partners, including academic institutions;

- While there are multiple, ongoing clinical trials to assess all-oral, shortened RR/MDR-TB regimens,[11] there is also a need to collect and analyze data on the implementation of such regimens under field conditions;[12]
- 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.[13,14]
- Table 2 below reviews the medications that should be prioritized in all-oral shorter regimens.

Table 2: Priority Medications for All-Oral Shorter Regimens

Drug	Phase completed and regulatory approval status	Summary of study results	Adverse events	Drug-drug interactions and overlapping toxicities	Access and pricing[15]	Ongoing trials[16]
Bedaquiline [17,18,19,20]	2B US, Europe, South Africa, multiple other countries	Significantly faster time to culture conversion, significantly higher rates of culture conversion, and significantly improved treatment outcomes when compared with placebo	QTc prolongation (moderate), hepatitis	Cannot use with efavirenz or rifampin Use with protease inhibitors results in increased bedaquiline levels but clinical significance not clear Caution when used with other QTc prolonging agents	USD 66.6 per month via Global Drug Facility (GDF)	endTB, endTB-Q, PRACETCAL, NiX-TB, STREAM-2, NeXT TB, ZeNiX
Clofazimine [21]	3 No registered TB indication, approved for treatment of leprosy	Significantly faster time to and higher rates of culture conversion, significantly improved treatment outcomes, non-placebo-controlled studies	Skin discoloration, QTc prolongation	Caution when used with other QTc prolonging agents	USD 30.00 per month via GDF	endTB, STREAM-2

Delamanid [22,23,24,25,26,27]	3 Europe, Japan, South Africa, limited number of additional countries	Faster time to culture conversion (p=0.052) compared with placebo: no differences in final outcomes, but study not powered to detect these	QTc prolongation (mild), generally well tolerated	No significant drug-drug interactions	USD 283.20 per month via GDF	endTB, MDR-END
Levofloxacin	2 No registered TB indication, approved for treatment of other bacterial infections	Considered a core drug in the treatment of RR-TB based on observational studies	QTc prolongation (mild), tendinitis, tendinopathy, generally well tolerated	No significant drug-drug interactions	USD 12.00 per month via GDF	endTB, NeXT, Opti-Q, MDR-END,
Linezolid[28,29]	2B, 3 No registered TB indication, approved for treatment of other bacterial infections	Significantly higher rates of and faster times to culture conversion and improved outcomes in delayed-start trial and non-placebo-controlled trials	Bone marrow toxicity, peripheral neuritis, optic neuritis	Caution when used in persons on AZT due to overlapping bone marrow toxicity Caution when given with other drugs causing peripheral neuropathy (i.e. INH) or causing optic neuritis or neuropathy (i.e. ethambutol)	USD 39.00 per month via GDF	endTB, NiX-TB, PRACTECAL, ZeNiX

VI. Programmatic Considerations

- Countries will need to ensure they have adequate stocks of newer drugs (bedaquiline and delamanid) as well as other companion drugs (clofazimine, linezolid, levofloxacin, and possibly moxifloxacin);
- While identifying and managing adverse events during treatment are crucial activities, systems for reporting serious, severe, and other adverse events of interest should be developed or strengthened within the country to serve all persons living with RR/MDR-TB regardless of their treatment regimen. This active Drug Safety Monitoring and Management should be done according to WHO principles[30] and national guidelines;
- While countries may consider rolling out all-oral shorter regimens or "modified shorter regimens" in selected locations or provinces, scale-up of all-oral shorter regimens

containing group A and B medications needs to take place on a national level and implementation plans must be in place for equitable and widespread access.

The WHO Guideline Development Group will be meeting at the end of 2019 to update recommendations on the treatment of RR/MDR-TB, including the use of all-oral shorter regimens. It is anticipated that these new recommendations will be available in the second quarter of 2020. More frequent updates to the WHO recommendations are anticipated in the coming years as more evidence emerges. This is a welcome development that reflects the improving science in RR/MDR-TB treatment and is common in other diseases/WHO guidelines such as for HIV management. Countries should develop systems to rapidly update their national guidelines and implementation plans as better treatment data emerges; this is necessary to "End TB" and to ensure that a patient-centered, human right-based approach to RR/MDR-TB is available to all affected by the disease.

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