INT J TUBERC LUNG DIS 26(7):590–591

http://dx.doi.org/10.5588/ijtld.22.0263

EDITORIAL

WHO drug-resistant TB guidelines 2022: what is new?

In May 2022, WHO released "Rapid communication: key changes to the treatment of drug-resistant tuberculosis",[1] a prelude to the much-awaited complete version of the guidelines, to be released towards the end of this year. This document is timely and necessary, as with 500,000 new cases of multidrug- or rifampicin-resistant TB (MDR/RR-TB) each year, only 1 in 3 cases receive treatment. Furthermore, the COVID-19 pandemic may have contributed to the further spread of the MDR/RR-TB strains of *Mycobacterium tuberculosis*.[2–4] The previous consolidated WHO drug-resistant TB guidelines were issued in 2020, incorporating new data from patients on WHO-recommended longer (>18 months) and shorter (<12 months) MDR-TB regimens.[5,6] Although the definition of RR (resistance to rifampicin) and MDR-TB (combined resistance to rifampicin and isoniazid) remain the same, new definitions have been introduced with the addition of pre-XDR-TB (TB caused by MDR/RR-TB strains also resistant to later-generation fluoroquinolones) and a change in the definition of XDR-TB (TB caused by *M. tuberculosis* strains fulfilling the definition of MDR/RR-TB, resistant to later-generation fluoroquinolones and at least one additional Group A drug, bedaquiline or linezolid).[2]

The new WHO 2022 guidelines evaluated the following new regimens: 1) the 6-month regimen based on bedaquiline, pretomanid and linezolid (BPaL) in combination with moxifloxacin (BPaLM), evaluated in the TB-PRACTECAL randomised clinical trial; 2) the 6-month regimens based on the BPaL combination with decreased exposure to linezolid (lower dosing or shorter duration) evaluated in the ZeNix study and 3) the modified all-oral shorter regimens (6–9 months or 9–12 months) containing all three Group A drugs evaluated in the NeXT trial or evaluated using programmatic data from South Africa.[1] Following on from the previous 2020 guidelines,[5] the WHO firmly stresses that all patients with MDR/RR-TB and pre-XDR-TB, can take advantage of the programmatic use of all-oral treatment shorter or longer regimens.

Three regimens are now available, lasting from 6 to 18 months or more as follows (Table):[1] 1) the 6-month BPaLM regimen (bedaquiline [BDQ], pretomanid [Pa], linezolid [LZD] 600 mg and moxifloxacin [MFX]) can be used in programmatic conditions, thus replacing the previous shorter (9-month) or longer (>18 months) regimens in MDR/RR-TB patients aged ≥15 years. No prior exposure to the three drugs for ≥30 days is a precondition for its use. This regimen can be used as BPaL, i.e., without MFX in pre-XDR-TB patients when resistance to fluoroquinolones (FQs) is documented. Drug susceptibility testing (DST) to FQs is therefore strongly encouraged. 2) The 9-month, all-oral, BDQ-containing regimens are preferred over the longer (>18 months) regimen in all patients (adults and children) affected by MDR/RR-TB, with i) no previous exposure to second-line treatment (including BDQ); ii) no FQ resistance; and iii) no extensive pulmonary TB disease (defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography and, in children aged <15 years, as advanced disease with presence of cavities or bilateral disease on chest radiography); or iv) severe extrapulmonary TB (defined as miliary TB or TB meningitis; in children aged <15 years, those are the extrapulmonary forms of disease other than lymphadenopathy, e.g., spinal TB). In these regimens, 2 months of linezolid (at the daily dose of 600 mg) can replace 4 months of ethionamide. Rapid DST to rule out FQ resistance is considered necessary to reduce failure and resistance. 3) The regimen previously known as the longer regimen (≥18 months), which is individualised and based on the drug grouping (A, B, C) according to the 2020 WHO guidelines,[5] is still considered necessary for specific categories of patients, for example, i) those with extensive forms of drug-resistant-TB (e.g., XDR-TB); ii) those who are not eligible for the regimens described above, or iii) those who have previously failed shorter treatment regimens.

Deciding which of the three regimens should be used is based on several factors, including clinical judgement, patient preference, DST results, the patient's treatment history, as well as the risk of adverse events and severity and site of the disease.

Furthermore, the WHO has highlighted the fact that MDR/RR-TB care should be managed using a patient-centred approach, which includes support and informed consent where necessary, under the principles of good clinical practice, active drug safety monitoring and management (aDSM), and regular monitoring of patients and of drug resistance to assess regimen effectiveness.[5,7]

While waiting for the final guidelines to be published, some interesting issues deserve an immediate comment:

- To maximise effectiveness and safety, the daily dose of LZD is 600 mg, which confirms the findings of a previous observational study;[8]

Article submitted 5 May 2022. Final version accepted 5 May 2022.

Table Core regimens to treat MDR/RR-TB

Regimen	Duration (months)	Indications	Contraindications
BPaLM (BDQ, pretomanid, linezolid, MFX) BPaL (without MFX)	6	MDR/RR-TB patients aged 15 years or more; BPaL if documented resistance to FQs	Exposure to any of the drugs composing the regimen for ≥30 days
All-oral, BDQ-containing regimens	9	Adults and children with MDR/RR-TB	Previous exposure to second-line treatment (including BDQ), FQ resistance; extensive pulmonary TB disease; severe extrapulmonary TB
Individualised longer regimen	≥18	Patients with extensive forms of DR-TB (e.g., XDR-TB); or not eligible for the regimens described above or who previously failed shorter treatment regimens	

MDR/RR-TB = multidrug-/rifampicin-resistant TB; BDQ = bedaquiline; MFX = moxifloxacin; FQ = fluoroquinolone; DR-TB = drug-resistant TB; XDR-TB = extensively drug-resistant TB.

- 2 months of LZD (which is a Group A drug) is considered equivalent to 4 months of ethionamide, which is a Group C drug.
- The consistent use of rapid testing for FQ resistance and DST is recommended, as we cannot afford the risk of losing the few drugs we have to manage MDR-/RR-TB while awaiting availability of rapid testing of BDQ, Pa and LZD.
- National TB programmes are expected to work intensively to prepare for the implementation of the new guidelines, solve logistic problems, procure, and implement drug testing and the regimens recommended, while ensuring availability of the second-line drugs necessary to treat with the longer individualized regimens.
- This document accelerates the shift towards shorter regimens to treat drug-susceptible TB in 4 months[9] and MDR-TB in 6–9 months.

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