

Key updates to the treatment of drug-resistant tuberculosis

Rapid communication

June 2024

Background

Tuberculosis (TB) remains a threat to global public health and is one of the topmost infectious causes of death in the world. In 2022, an estimated 10.6 million people developed TB, and 1.3 million died from the disease. About 410,000 new cases of multidrug-resistant¹ or rifampicin-resistant tuberculosis (MDR/RR-TB) were estimated to occur in 2022. While all of these would have been eligible for a second-line TB treatment regimen, only 175,650 enrolments on treatment were reported by countries in the same year. Significant improvements in the availability of enhanced diagnostics and more effective medicines have occurred in recent years and have led to earlier detection and higher success rates among patients with MDR/RR-TB in a number of national programs. In the last ten years, reinvigorated research into new medicines and regimens to treat TB has paved the way for the development and evaluation of several novel regimens. The evidence generated by this research provided a solid scientific basis for the World Health Organization (WHO) to update its policy, which was gradually adopted by countries. The use of new and repurposed medicines like bedaquiline, pretomanid, linezolid, and delamanid and the shift away from older injectable-based regimens has led to incremental improvements in the treatment success rate for people with MDR/RR-TB. Globally in 2022, in MDR/RR-TB patients who started treatment in 2021, the treatment success rate was 63%, reflecting a steady improvement from 50% in 2012².

The latest evidence-based guidelines for the treatment of TB and drug-resistant TB, including MDR/RR-TB and pre-XDR-TB,³ were published by WHO in May 2022 – “*WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment*”⁴, in August 2022 – “*WHO consolidated guidelines on tuberculosis: module 4: treatment: tuberculosis care and support*” and in December 2022 – “*WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment*”⁵. All the developments were performed according to the requirements of the WHO Guidelines Review Committee, using the *Grading of Recommendations Assessment, Development and Evaluation approach (GRADE)*.

Access to the most efficacious treatment regimens and medicines is necessary to optimize treatment outcomes while minimizing adverse events, improving tolerability, enhancing quality of life, and preventing the acquisition of additional drug resistance. Several novel drugs and shorter (4- or 6-month) regimens have emerged in recent years and are recommended by WHO for use in TB and DR-TB treatment. A new and efficacious regimen (BPaLM) is now recommended for patients with or without additional resistance to fluoroquinolones, although with some eligibility limitations. Patients affected by strains exhibiting resistance to fluoroquinolones and at least another Group A medicine (XDR-TB) must currently be treated with longer (≥ 18 months) regimens with potentially poorer efficacy and tolerability.

Over the past several years, researchers have been testing combinations and durations of medicines to treat MDR/RR-TB that a WHO-convened Guideline Development Group has not yet appraised. These regimens include a new 6-month regimen based on bedaquiline (B), delamanid (D), and linezolid (L) in combination with either levofloxacin (Lfx) or clofazimine (C) or both (BEAT-Tuberculosis clinical trial in South Africa, NCT04062201) and a group of 9-month regimens for the treatment of patients with MDR/RR-TB without fluoroquinolone resistance (endTB clinical trial,

¹ Combined resistance to both rifampicin and isoniazid, the two most important first-line anti-TB drugs.

² Global tuberculosis report 2023. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO <https://iris.who.int/handle/10665/373828>

³ Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020. Geneva: World Health Organization; 2021. CC BY-NC-SA 3.0 IGO <https://iris.who.int/handle/10665/338776>

⁴ WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. <https://iris.who.int/handle/10665/353829>

⁵ WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO <https://iris.who.int/handle/10665/365308>

NCT02754765). The evidence from these trials has been shared with WHO, and a guideline development group (GDG) was convened on 24-27 June 2024 to review this new evidence on the treatment of MDR/RR-TB and pre-XDR-TB, to ensure access to the latest treatment options for eligible patients.

Methods

The evidence was assessed and synthesized following the GRADE method. Evidence summaries in standard GRADE format were prepared in GRADEpro. The outcomes in the tables were those relevant to the PICO questions. Preference was given to outcomes scored as “critical” or “important” by the GDG.

Standard methods were used to describe and analyze the aggregated and individual data. Estimates of effect were expressed as risk ratios, odds ratios, or hazard ratios with their 95% confidence limits. The absolute risk was also calculated where possible. During the virtual discussions and the physical GDG meeting in June 2024, the GDG members formulated successive drafts of the recommendations based on their assessment of the evidence. The GRADEpro “evidence to decision” template guided this process. Several factors determined the direction and strength of the recommendations (e.g., strong or conditional), including the certainty in the estimates of effect (“quality of the evidence”), values and preferences, how substantial the anticipated desirable and undesirable effects were, certainty on the balance of the benefits and harms, resource implications, health equity, acceptability, and feasibility.

The GDG made recommendations about which populations required a particular treatment and its conditions, outlining considerations for implementation when possible. All GDG decisions were reached by discussion and consensus on the recommendations, including their strength and, where appropriate, the conditions to be attached to them.

Key updates

6-month treatment regimens

Final results from the BEAT-Tuberculosis clinical trial on the use of a new 6-month regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) were available to assess whether this new regimen can be used for patients with MDR/RR-TB or pre-XDR-TB when compared with the currently WHO-recommended regimens. The trial used an approach in which either levofloxacin or clofazimine was dropped from the regimen depending on fluoroquinolone drug susceptibility testing (DST) results - BDLLfxC initiated without delay in case of unknown FQ-resistance at the time of RR-TB diagnosis (and continued with both levofloxacin and clofazimine if FQ-DST results could not be obtained); BDLLfx continued for FQ-sensitive TB; BDLC for FQ-resistant TB. Within the trial, all of these regimens were compared with the recommended all-oral, bedaquiline-containing regimens (most of the control group received a 9-month linezolid-containing regimen). The dataset included patients with severe TB disease, people living with HIV, children, adolescents, and a small group of pregnant women. The summary of the evidence is in Table 1.

The Guideline Development group concluded that the 6-month regimen may be used programmatically in MDR/RR-TB patients without prior exposure to these medicines (defined as > 1-month exposure)⁶ in place of the previously recommended 9-month or longer (≥18 months) regimens. The BDLLfxC regimen showed favorable efficacy and safety when compared with the regimens given in the control arm of the BEAT-Tuberculosis trial.

⁶ When exposure is greater than one month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out.

The following recommendation was agreed upon:

WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance (conditional recommendation, very low certainty of evidence).

The 6-month BDLLfxC regimen showed high treatment success and is composed of medicines that have been recommended and used widely in all patient groups. The trial's evidence suggests that this regimen may be effectively and safely used in eligible patients with MDR/RR-TB and pre-XDR-TB regardless of their HIV status. The available evidence included children, adolescents, pregnant and breastfeeding women, flagging the possible use of the regimen in these population groups. Thus, the evidence provided by the study will support new recommendations for the programmatic use of the regimen in many population groups.

9-month treatment regimens

Final results from the endTB clinical trial on the use of five different 9-month regimens were available to assess whether these all-oral regimens comprising different combinations of bedaquiline, levofloxacin or moxifloxacin (M), linezolid, clofazimine, delamanid, and pyrazinamide (BLMZ, BLLfxCZ, BDLLfxZ, DCLLfxZ, and DCMZ) may be used in MDR/RR-TB patients without resistance to fluoroquinolones and no previous exposure to second-line drugs (defined as > 1-month exposure)⁶ when compared with the WHO-recommended longer (≥18 months) regimens. Within the trial, each of these regimens was compared with the currently recommended longer (≥18 months), all-oral, bedaquiline-containing regimens. The dataset included patients with severe TB disease, people living with HIV, adolescents, and a small group of pregnant women. The evidence provided by the study will support new recommendations for the programmatic use of the regimens in many population groups, including children, adolescents, pregnant and breastfeeding women. The summary of the evidence is in Tables 2-4.

The Guideline Development group concluded that in eligible MDR/RR-TB patients with confirmed drug susceptibility to fluoroquinolones, three (BLMZ, BLLfxCZ, and BDLLfxZ) of the five 9-month all-oral regimens studied may be effectively and safely used instead of the longer (≥18 months) regimens. The review suggested against using DCLLfxZ and DCMZ regimens that were associated with high rates of treatment failure/relapse and acquired drug resistance.

The following recommendation was agreed upon:

WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over using BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ (conditional recommendation, very low certainty of evidence).

Summary

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, need to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under programmatic conditions. The 2022 update of the DR-TB treatment guidelines added and prioritized a new 6-month regimen – BPaLM⁷, as a treatment of choice for eligible patients. The new BDLLfxC regimen can expand the use of the 6-month regimens to additional patient groups, like children, adolescents, and pregnant women, who could not benefit from the currently recommended BPaLM

⁷ BPaLM/BPaL regimen is composed of bedaquiline (B), pretomanid (Pa), linezolid (L) and moxifloxacin (M). Moxifloxacin may be dropped in case of the documented resistance to fluoroquinolones.

regimen (due to the absence of safety and dosing data for pretomanid). Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation with regimens that are also effective in patients with pre-XDR-TB.

- The 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin, may be used programmatically in place of 9-month or longer (≥ 18 months) regimens, in patients (aged ≥ 14 years) with MDR/RR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure). This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB).
- The 6-month BDLLfxC regimen, composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine, may be used programmatically in place of 9-month or longer (≥ 18 months) regimens, in all patients with MDR/RR-TB who have not had previous exposure to bedaquiline, delamanid and linezolid (defined as >1 month exposure). The regimen may be used without either levofloxacin or clofazimine depending on fluoroquinolone DST results - BDLLfxC can be initiated without delay in case of unknown FQ-resistance at time of diagnosis of RR-TB (and may be continued with both levofloxacin and clofazimine if FQ-DST results cannot be obtained); BDLLfx is continued for FQ-sensitive TB; BDLC for FQ-resistant TB. The available evidence included children, adolescents, pregnant and breastfeeding women, flagging the possible use of the regimen in these population groups.
- The use of the modified 9-month, all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) is preferred over currently recommended longer (18-month) regimens in patients with MDR/RR-TB who have not had previous exposure to bedaquiline, delamanid and linezolid (defined as >1 -month exposure) and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ. Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on one of these regimens.
- The 9-month, all-oral, bedaquiline-containing regimens⁸ are preferred over the longer (≥ 18 months) regimens in adults and children with MDR/RR-TB, without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and with no extensive pulmonary TB disease or severe forms of extrapulmonary TB. In these regimens, 2 months of linezolid (600 mg) can be used as an alternative to 4 months of ethionamide. Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on one of these regimens.
- Patients with extensive forms of DR-TB (e.g., XDR-TB4) or those who are not eligible for or have failed shorter treatment regimens will benefit from individualized longer (≥ 18 months) regimens designed using the priority grouping of medicines recommended in current WHO guidelines.
- Decisions on appropriate regimens should be made according to clinical judgement and patient preference, considering DST results, treatment history, risk of adverse events, and severity and site of the disease.
- All treatment should be delivered under WHO-recommended standards, including patient-centered care and support, informed consent where necessary, principles of good clinical practice, active drug safety monitoring and management, and regular monitoring of patients and drug resistance to assess regimen effectiveness.

Next steps

- The 2025 WHO consolidated guidelines on the treatment of TB, drug-resistant TB and patient care

⁸ BEtoLfx/MCZEhh and BLLfx/MCZEhh

and support will be released in the first quarter of 2025.

- The 2025 WHO consolidated guidelines on the treatment of TB, drug-resistant TB and patient care and support will replace all previous and current WHO guidelines on TB treatment and care. They will include updated recommendations and detailed results of the evidence review for all questions that guided the analysis. The guidelines will include recommendations and related reviews on the use of the 6-month regimens, the 9-month regimens, and patient eligibility.
- The 2025 WHO consolidated guidelines will be accompanied by an update of the companion handbook, which will provide further details on patient selection, regimen design, medicine dosing, patient management, and programmatic monitoring and evaluation.
- Prior to the release of the 2025 WHO consolidated guidelines on the treatment of TB, drug-resistant TB and patient care and support, which will include all the evidence and methods used in the development of this new policy, the evidence and methods can be requested from the WHO Global Tuberculosis Program Prevention, Care and Innovation unit.

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