World Health Organization

Rapid communication: Key changes to the treatment of drug-resistant tuberculosis

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Background

Tuberculosis (TB) remains a threat to global public health and is one of the leading infectious causes of death globally. In 2020, an estimated 10 million people developed TB and 1.5 million died from the disease[1]. Owing to the impact of the coronavirus disease (COVID-19) pandemic, TB incidence could increase globally in 2022 and 2023.[2] About 500 000 new cases of multidrug-[3] or rifampicin-resistant tuberculosis (MDR/RR-TB) are estimated to emerge each year; however, in the latest data (from 2019), only one in three cases were reported to have been treated. In recent years, significant progress in the availability of improved diagnostics and more effective medicines has led to earlier detection and higher treatment success rates among patients with MDR/RR-TB in several countries.[2]

To support countries in responding to the challenges of TB and drug-resistant TB (DR-TB), including extensively drug-resistant TB (XDR-TB) and pre-XDR-TB,[4] the World Health Organization (WHO) Global Tuberculosis Programme (WHO/GTB) regularly issues evidence-based guidelines using the international Grading of Recommendations Assessment, Development and Evaluation (GRADE[5]) approach to assessment of scientific evidence.

The latest WHO consolidated guidelines for the treatment of DR-TB[6] were released in June 2020. Subsequently, new evidence on the treatment of DR-TB became available to WHO through national TB programmes (NTPs), researchers and technical partners, and also from a WHO public call for data[7] issued in June 2021. New data from patients on WHO-recommended multidrug-resistant TB (MDR-TB) regimens – either longer (≥18 months) or shorter (<12 months) regimens – were validated and incorporated into an individual patient dataset to help inform the development of WHO guidelines on DR-TB. Additionally, some new regimens that have not yet been appraised by WHO have recently been tested in trials or used programmatically. These regimens include a new 6-month regimen based on bedaquiline, pretomanid[8] and linezolid (BPaL) in combination with moxifloxacin (BPaLM), evaluated in the TB-PRACTECAL randomized clinical trial;[9] the 6-month regimens based on the BPaL combination with decreased exposure to linezolid (lower dosing or shorter duration) evaluated in the ZeNix study[10] and the modified all-oral shorter regimens (6–9 months or 9–12 months) containing all three Group A

[1] Including people living with HIV

[2] Global tuberculosis report 2021. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240037021).

[3] Defined as combined resistance to rifampicin and isoniazid, the two most important anti-TB medicines.

[4] New definitions agreed by the WHO consultation in October 2020: pre-XDR-TB: TB caused by *Mycobacterium tuberculosis* strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone; XDR-TB: TB caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug.

[5] GRADE working group website: https://www.gradeworkinggroup.org/.

[6] WHO consolidated guidelines on tuberculosis Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240007048).

[7] Public call for individual patient data on treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2021 (https://www.who.int/news-room/articles-detail/public-call-for-individual-patient-data-on-treatment-of-drug-resistant-tuberculosis_06292021).

[8] Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazooxazines. Pretomanid was developed by the TB Alliance as an oral tablet formulation for the treatment of TB in combination with other anti-TB agents.

[9] TB-PRACTECAL is a clinical trial to test a novel shorter, all-oral treatment regimen for MDR/RR-TB or pre-XDR-TB (https://clinicaltrials.gov/ct2/show/NCT02589782).

[10] ZeNix is a study to further test the BPaL regimen (the Nix-TB regimen) with lower exposure of linezolid that holds the potential to be a safer option (https://www.tballiance.org/portfolio/trial/11883). The Nix-TB regimen comprises pretomanid, bedaquiline and linezolid for 6–9 months (https://www.tballiance.org/portfolio/trial/5089).

medicines evaluated in the NeXT trial[11] or implemented by the NTP in South Africa.

Individual patient data were analysed to assess and compare treatment outcomes of the regimens evaluated. WHO convened an independent Guideline Development Group (GDG) in February–March 2022 to assess the results of these analyses using the GRADE process. Detailed recommendations will be presented in a 2022 update of the WHO consolidated guidelines.

This rapid communication aims to inform NTPs and other stakeholders about the key implications for the treatment of DR-TB, to allow for rapid transition and planning at country level.

Key updates

Novel 6-month treatment regimens

Data from the TB-PRACTECAL and ZeNix studies were available to assess whether the BPaLM and BPaL novel treatment regimens comprising bedaquiline, pretomanid and linezolid with or without moxifloxacin can be used in patients aged 15 years or more with MDR/RR-TB or pre-XDR-TB[4] when compared with other regimens conforming to WHO guidelines. For this purpose, the data on the BPaLM and BPaL regimens were compared with internal study controls and with matched records in the individual patient data collected for this purpose.

The data from the ZeNix study made it possible to identify the linezolid dose that offers the best balance in terms of efficacy and safety in patients aged above 14 years. The assessment of evidence from this study suggested that the optimal dosing of linezolid is 600 mg daily and that programmes should strive to maintain this dose throughout the treatment regimen to ensure optimal efficacy, with the possibility of dose reduction in the event of toxicity or poor tolerability.

The evidence assessment suggested that the 6-month BPaLM regimen – comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin – may be used programmatically in MDR/RR-TB patients without previous exposure to these medicines in place of the 9-month regimen (described below) or the longer (≥18 months) regimen. The BPaLM regimen showed favourable efficacy and safety when compared with the regimens given in the control arm of the TB-PRACTECAL trial. The evidence assessment also suggested that the BPaL combination (with 600 mg linezolid) retains sufficient efficacy and allows the regimen to be used without moxifloxacin in the case of documented resistance to fluoroquinolones (i.e. in patients with pre-XDR-TB). In this group of patients receiving the BPaL combination, where there is a slow response to therapy, an extension of 3 months (bringing the total regimen to 9 months) is possible.

The BPaLM and BPaL regimens showed high treatment success. The evidence from the available studies suggests that these regimens may be used in eligible patients with MDR/RR-TB and pre-XDR-TB[4] regardless of their HIV status. The available evidence was limited to patients aged above 14 years and there were no data on the use of these regimens during pregnancy or in severe forms of extrapulmonary TB (e.g. TB meningitis). Thus, the evidence provided by the TB-PRACTECAL and ZeNix studies will support new recommendations for the programmatic use of the two regimens.

New data on the safety of pretomanid based on hormone evaluations in four clinical trials and a paternity survey were also assessed; these data have largely alleviated previous concerns on reproductive toxicities observed in animal studies,[12] suggesting that adverse effects on human male

[11] The NeXT study is a clinical trial conducted in South Africa to test a novel regimen – 6-9 Bdq-Lzd-Lfx-Z-Eto/Hh/Trd – for treatment of MDR/RR-TB without fluoroquinolone resistance (https://clinicaltrials.gov/ct2/show/NCT02454205).

[12] Pretomanid has been shown to cause testicular atrophy and impaired fertility in male rats.

fertility are unlikely. A study assessing semen in men undergoing treatment that includes pretomanid is in progress and will address any remaining concerns.

9-month treatment regimens

Routine data from the South African NTP were available to assess whether a 9-month all-oral regimen[13] containing bedaquiline, fluoroquinolones and linezolid (600 mg) combined with other medicines may be used in MDR/RR-TB patients without resistance to fluoroquinolones and without previous exposure to second-line drugs. This regimen was compared with the currently recommended 9-month, all-oral, bedaquiline-containing regimen[14] (which contains ethionamide instead of linezolid) or longer regimens in the same group of patients. The dataset excluded children aged under 6 years, and patients with extensive pulmonary TB disease[15] and severe forms of extrapulmonary TB;[16] it included mostly adult patients (96%) and a high proportion of people living with HIV (67%).

The comparison showed that replacing 4 months of ethionamide with 2 months of linezolid in this regimen resulted in similar treatment efficacy and safety. The outcomes were similar, irrespective of HIV status.

The evidence assessment showed that in eligible MDR/RR-TB patients the 9-month all-oral regimens[17] may be used instead of the longer regimens, and that linezolid can be used as an alternative for ethionamide within this regimen.

Summary

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, stand to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under programmatic conditions.

- 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 ≥15 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). Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.
- The 9-month, all-oral, bedaquiline-containing regimens[13,14] are preferred over the longer (≥18 months) regimen in adults and children with MDR/RR-TB, without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and with no

[13] This regimen has been used in South Africa since mid-2018: 4-6 Bdq[6]-Lfx[Mfx]-Lzd[2]-E-Z-Hh-Cfz / 5 Lfx[Mfx]-Cfz-Z-E, with 2 months of linezolid replacing 4 months of ethionamide.
[14] This regimen is recommended in current WHO guidelines: 4-6 Bdq[6]-Lfx[Mfx]-Eto-E-Z-Hh-Cfz / 5 Lfx[Mfx]-Cfz-Z-E.
[15] Extensive (or advanced) pulmonary TB disease is the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.
[16] Severe extrapulmonary TB is the presence of miliary TB or TB meningitis. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe.
[17] A regimen that consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months); followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine and ethambutol. Ethionamide can be replaced by 2 months of linezolid (600 mg).

extensive pulmonary TB disease or severe 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-TB[4]) or those who are not eligible for or have failed shorter treatment regimens will benefit from an individualized longer regimen designed using the priority grouping of medicines recommended in current WHO guidelines.[6]
- Decisions on appropriate regimens should be made according to clinical judgement and patient preference, considering results of DST, patient treatment history, risk of adverse events, and severity and site of the disease.
- All treatment should be delivered under WHO-recommended standards, including patient-centred care and support, informed consent where necessary, principles of good clinical practice, active drug safety monitoring and management, and regular monitoring of patients and of drug resistance to assess regimen effectiveness.

Next steps

- The 2022 WHO consolidated guidelines on the treatment of drug-resistant TB will replace all previous and current WHO guidelines on this topic, and 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 BPaLM and BPaL regimens, the 9-month regimens and patient eligibility.
- The 2022 WHO consolidated guidelines will be accompanied by an update of the companion handbook, with further details on patient selection, regimen design, medicine dosing, patient management, and programmatic monitoring and evaluation.

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