



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 the top infectious cause of death globally. In 2018, an estimated 10 million people developed TB and 1.5 million died from the disease¹. About 500,000 new cases of multidrug-² and rifampicin-resistant tuberculosis (MDR/RR-TB) are estimated to emerge annually but only one in three cases were reported by countries to have been treated in 2018.

Significant progress in the availability of improved diagnostics and more effective medicines in recent years has led to earlier detection and higher success rates among patients with MDR/RR-TB in a number of countries. However, these achievements have not been reproduced globally, and the overall treatment success rate reported in 2018 reached only 56% for MDR/RR-TB patients and 39% for patients with extensively drug-resistant TB³ (XDR-TB).

Providing evidence-based guidelines to inform public health service delivery for Member States and other stakeholders is one of the core responsibilities of the World Health Organization (WHO). To support countries in responding to the challenges of TB and drug-resistant TB, the WHO Global TB Programme regularly issues evidence-based guidelines using the international [GRADE](#)⁴ (Grading of Recommendations, Assessment, Development and Evaluation) approach for scientific evidence assessment.

The latest WHO evidence-based guidelines for the treatment of drug-resistant TB were released in December 2018 and incorporated into [Consolidated Guidelines](#) published in March 2019. Subsequently, new evidence on treatment for MDR/RR-TB and XDR-TB became available to WHO through national programmes, researchers and technical partners, and also from an August 2019 WHO [public call for data](#). New data from patients on both longer (≥ 18 months) and shorter (< 12 months) MDR-TB regimens were validated and incorporated into the individual patient dataset (IPD) established previously to help inform development of WHO guidelines on drug-resistant TB (currently containing over 13,000 patient records from 55 different studies in 40 countries)⁵.

International standards for meta-analysis were followed to assess the relative contributions of treatment regimens or combinations of medicines to patient treatment outcomes. WHO convened an independent Guideline Development Group (GDG) on 12-14 November 2019 to assess the results of these analyses using the GRADE system. Detailed recommendations will be presented in a 2020 update of the WHO Consolidated Guidelines and will replace all previous and current WHO guidelines on the treatment of drug-resistant TB.

This Rapid Communication aims to inform national TB programmes and other stakeholders about the key implications for treatment of MDR/RR-TB and XDR-TB in order to allow for rapid transition and planning at country level.

Key updates

Shorter, all-oral, bedaquiline-containing regimen for eligible MDR/RR-TB patients

Data from the South African TB programme were available to assess whether a shorter all-oral bedaquiline containing regimen⁶ safely improves patient outcomes when compared to a standardized shorter regimen with injectables.⁷ The dataset excluded patients with extensive TB disease, severe forms of extrapulmonary TB and included a high proportion (71%) of HIV co-infected individuals.

The comparison showed that replacing the injectable with bedaquiline resulted in significantly better treatment success and a considerable reduction in loss-to-follow up in MDR/RR-TB patients without previous exposure to second-line drugs and with confirmed fluoroquinolone susceptible disease. The outcomes were similar irrespective of HIV status.

The evidence assessment showed that in eligible MDR/RR-TB patients a shorter, all-oral, bedaquiline-containing regimen may be used instead of the standardized shorter regimen with an injectable. Data were not available on the efficacy, safety and tolerability of modifications other than replacement of the injectable with bedaquiline in shorter regimens and require prompt evaluation under operational research conditions.

Novel treatment regimen - BPaL

Data from the single arm, open-label Nix-TB study by the Global TB Alliance were available to assess whether a 6-9-month novel treatment regimen consisting of bedaquiline, pretomanid⁸ and linezolid safely improves treatment outcomes in patients with XDR-TB when compared with other regimens conforming to WHO guidelines. For this purpose, the Nix-TB study data on the BPaL regimen was compared to matched records in the IPD.

The BPaL regimen showed high treatment success when used in XDR-TB patients in South Africa. Limitations in study design and the small number of participants (108), observed adverse events (including blood disorders, liver toxicity, peripheral and optic neuropathy) preclude programmatic implementation of the regimen worldwide until additional evidence has been generated. However, BPaL regimen may be used under operational research conditions conforming to WHO standards (patient-centered care and support, proper patient inclusion, principles of good clinical practice, active drug safety monitoring and management, treatment monitoring, outcome evaluation and comprehensive, standardized data collection).

Treatment of extensively drug-resistant forms of TB presents multiple challenges to clinicians and national TB programmes both due to the limited range of medicines available and the life-threatening nature of the disease. The experience in the use of BPaL for treatment of XDR-TB patients is limited and the data from patients treated prospectively using all-oral longer regimens based on a WHO recommended revised priority classification of drugs⁹ is not yet available for comparison. Nevertheless, in individual patients for whom design of an effective regimen based on existing recommendations is not possible, the BPaL regimen may offer benefits despite potential harms and may be considered under prevailing ethical standards. In such patients the use of BPaL should be accompanied by individual consent, adequate counselling on potential benefits and harms and active monitoring and management of adverse events. Patients should also be advised that reproductive toxicities have been observed in animal studies¹⁰ and that the potential effects on human male fertility have not been adequately evaluated at this point in time.

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.

- MDR/RR-TB patients with extensive TB disease, severe forms of extrapulmonary TB, those with resistance to fluoroquinolones or who have been exposed to treatment with second-line drugs will benefit from an individualized longer regimen designed using the WHO priority grouping of medicines recommended in 2018.
- For MDR/RR-TB patients without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and no extensive TB disease or severe extrapulmonary TB, the preferred treatment option is a shorter, all-oral, bedaquiline-containing regimen. In this group of patients, national TB programmes are advised to phase out use of the injectable-containing shorter regimen.
- Access to rapid drug susceptibility testing, especially for ruling out fluoroquinolone resistance, is required before starting the shorter, all-oral, bedaquiline-containing MDR-TB regimen.
- In settings with a high probability of, or patients with confirmed resistance to other medicines in the regimen, further modifications of the shorter, all-oral, bedaquiline-containing regimen using priority grouping of

second-line TB medicines may be implemented. However, the efficacy, safety and tolerability of such modifications to regimens <12 months are unknown and should therefore be evaluated under operational research conditions.

- The BPaL regimen may be used under operational research conditions in patients with XDR-TB who have not had previous exposure to bedaquiline and linezolid (defined as less than two weeks). This regimen may not be considered for programmatic use worldwide until additional evidence on efficacy and safety has been generated. However, in individual patients for whom design of an effective regimen based on existing recommendations is not possible, BPaL regimen may be considered as a last resort under prevailing ethical standards.
- Decisions on appropriate regimens should be made according to patient preference and clinical judgement, also considering the results of susceptibility testing, patient treatment history 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 patient monitoring to assess regimen effectiveness.

Next steps

- The 2020 Consolidated Guidelines on treatment of drug-resistant TB will replace all previous and current WHO guidelines on the treatment of drug-resistant TB and will include updated recommendations and detailed results of the evidence review for all questions that guided the analysis. These will include use of bedaquiline for longer than 6 months and concurrent use of bedaquiline and delamanid.
- The 2020 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.
- National TB Programmes and their stakeholders are encouraged to solicit advice from WHO and technical partners before mounting operational research for modified shorter regimens or the BPaL regimen. To facilitate such research, the Special Programme for Research and Training in Tropical Diseases (TDR) in close collaboration with the Global TB Programme at WHO and technical partners is developing ShORRT¹¹ (Short, all-Oral Regimens For Rifampicin-resistant Tuberculosis), an implementation/operational research package to assess the effectiveness, safety, feasibility, acceptability, cost and impact (including on quality of life) of the use of all-oral shorter drug regimens for patients with drug-resistant TB.
- WHO will convene a Global Consultation in 2020 to inform Member States, technical partners, donors and civil society on the key changes in the updated guidelines. The meeting will aim to support countries to update their national guidelines, inform programme budgets and enable monitoring systems to facilitate rapid transition to more effective treatment regimens for drug-resistant TB patients.

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¹ Global Tuberculosis Report 2019 https://www.who.int/tb/publications/global_report/en/

² Defined as combined resistance to rifampicin and isoniazid, the two most important anti-TB medicines.

³ Defined as MDR-TB with additional resistance to a fluoroquinolone plus a second-line injectable agent

⁴ <http://www.gradeworkinggroup.org/>

⁵ For more details on data sources: [9 November 2019 GTB Newsflash](#)

⁶ Regimen used in South Africa: 4-6 Bdq[6]-Lfx[Mfx]-Eto-E-Z-Hh-Cfz / 5 Lfx[Mfx]-Cfz-Z-E, bedaquiline was replacing the injectable drug and used for 6 months.

⁷ Regimen as recommended in previous WHO guidelines: 4-6 Am-Mfx-Eto[Pto]-Cfz-Z-Hh-E / 5 Mfx-Cfz-Z-E

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

⁹ Table 2.1 of the WHO Consolidated Guidelines for Drug Resistant Tuberculosis Treatment.

¹⁰ Pretomanid caused testicular atrophy and impaired fertility in male rats.

¹¹ Additional information on ShORRT research package https://www.who.int/tdr/research/tb_hiv/shortt/en/