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Perspective

Update of drug-resistant tuberculosis treatment guidelines: A turning point

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ABSTRACT

In December 2022 World Health Organization released a new treatment for multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) guideline. The main novelty of this update is two new recommendations (i) a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin (BPaLM) is recommended in place of the 9-month or longer (18-month) regimens in MDR/RR-TB patients, now including extensive pulmonary TB and extrapulmonary TB (except TB involving central nervous system, miliary TB and osteoarticular TB); (ii) the use of the 9-month all-oral regimen rather than longer (18-months) regimen is suggested in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Longer (18-month) treatments remain a valid option in all cases in which shorter regimens cannot be implemented due to intolerance, drug-drug interactions, extensively drug-resistant tuberculosis, extensive forms of extrapulmonary TB, or previous failure. The new guidelines represent a milestone in MDR/RR-TB treatment landscape, setting the basis for a shorter, all-oral, more acceptable, equitable, and patient-centered model for MDR/RR-TB management. However, some challenges remain to be addressed to allow full implementation of the new recommendations.

Introduction

Drug-resistant tuberculosis (DR-TB) remains a major global health threat, with an estimated burden of 450,000 (95% CI: 399,000-501,000) new cases of rifampicin-resistant TB (RR-TB) in 2021 [1,2]. Globally DR-TB treatment success rates have increased from 50% in 2012 to 60% in 2019 with 15% of multi DR (MDR)/RR-TB patients still dying from the disease [3].

In December 2022, World Health Organization (WHO) released "The WHO Consolidated Guidelines on Tuberculosis (TB), Module 4: Treatment - Drug-Resistant Tuberculosis Treatment 2022 update" [3], which builds on the previous "Rapid communication" published in 2022 [4] and replaces the 2020 "WHO consolidated guidelines on drug-resistant tuberculosis treatment" [5].

The 2022 WHO DR-TB treatment update includes seven main sections on treatment regimens for MDR/RR-TB and isoniazid-resistant TB (Hr-TB), monitoring patient response to treatment, the timing of starting the antiretroviral therapy in MDR/RR-TB patients living with HIV and use of surgery for patients on MDR/RR-TB treatment [2].

The 2022 update contains two new recommendations (based on a review of new evidence) regarding treatment regimens for MDR/RR-TB: (i) the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month)

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Table 1
Indications/contraindications of the shorter and longer MDR/RR-TB treatment regimens, modified from [10].

Regimen	6-Month BPaLM/BpaL[a]	9-Month all-oral	Longer individualized 18-month
MDR/RR-TB Fluoroquinolones-susceptible	YES (BPaLM)	YES	YES when 6-month and 9-month regimens could not be used
Pre-extensively DR (Fluoroquinolones resistant)	YES (BPaL only)	NO	YES when 6-month regimen could not be used
Extensively DR-TB	NO	NO	YES
Extensive pulmonary TB	YES	NO	YES
Extrapulmonary TB	YES (except TB involving CNS, miliary TB and osteoarticular TB)	YES (except TB meningitis, miliary TB, pericardial TB and osteoarticular TB)	YES
Age <14 years	NO	YES	YES
People living with HIV	YES	YES	YES
Pregnant/breastfeeding	NO	Ethionamide-sparing regimen is recommended	YES
Exposure to any of the drugs composing the regimen for ≥30 days[b]	NO[b]	NO[b]	YES
History of cardiac disease or concomitant drugs that prolong QTc	YES (but must be monitored closely)	YES	YES
Body mass index <17	YES (but must be monitored closely)	YES	YES
Hemoglobin <8 g/dl or platelet <75.000/mm^3	YES (but prefer other regimes)	Linezolid-sparing regimen is suggested	Linezolid-sparing regimen is suggested
Pre-existing peripheral neuropathy of grade III-IV	YES (but prefer other regimes)	Linezolid-sparing regimen is suggested	Linezolid-sparing regimen is suggested

BpaLM: bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin; DR-TB: drug-resistant-tuberculosis; MDR/RR-TB, multidrug-resistant/rifampicin-resistant tuberculosis.
[a] When the regimen is BPaL from the start or is changed to BPaL, it can be extended to a total of 9 months (39 weeks) if sputum cultures are positive between months 4 and 6
[b] When exposure is greater than 1 month, resistance to the specific drugs with such exposure must be ruled out before considering the regimen.

regimens in MDR/RR-TB patients (ii) the use of the 9-month all-oral regimen rather than longer (18-months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones (FQ) has been excluded. Longer regimens remain a valid option in some circumstances (unchanged recommendation). Table 1 summarizes the main indications and contraindications of each treatment regimen.

6-month treatment regimens

Based on the evidence generated by the TB-PRACTECAL [6,7] and ZeNix [8,9] randomized control trials, the Guidelines Development Group (GDG) concluded that BPaLM regimen, composed of bedaquiline, pretomanid, linezolid (600 mg od – 26 weeks) and moxifloxacin, is recommended over the currently recommended longer regimens in patients with MDR/RR-TB. Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but it should not delay treatment initiation; in cases when resistance to fluoroquinolones is documented after the start of BPaLM, moxifloxacin should be stopped, and the regimen continued as BPaL (without moxifloxacin). BPaLM regimen is also recommended over the currently recommended 9-month regimen with 4 months ethionamide or with 2 months linezolid, and over an 18-month longer regimen in patients with pulmonary MDR/RR-TB without fluoroquinolone resistance.

Among the 6-month BPaL-based regimens assessed by the TB-PRACTECAL trial (e.g., BPaL, BPaLM, and bedaquiline, pretomanid, linezolid and clofazimine [BPaLC] containing clofazimine), the BPaLM regimen is preferred, as it led to more treatment success, fewer failures or recurrences and less emerging drug resistance with little difference in adverse events.

BPaLM regimen is suggested for all people with MDR/RR-TB regardless of HIV status, who have not had prior exposure to bedaquiline, pretomanid, and linezolid (defined >1 month exposure). When exposure is >1 month, resistance to the specific drugs with such exposure must be excluded. If resistance to bedaquiline, linezolid, or pretomanid is confirmed or suspected, the BPaLM/BPaL regimen should be stopped, and patients should be referred for a longer individualized regimen [10].

No efficacy data are available yet to propose the use of BPaLM regimen in patients affected by the central nervous system (CNS), osteoarticular, and disseminated (miliary) TB, in those under 14 years of age and in pregnant and breastfeeding women due to limited evidence on pretomanid safety in this population [10,11].

Several different dosing and duration schemes of linezolid were used in the ZeNix trial and data suggested that a daily linezolid dose of 600 mg for 26 weeks was associated with higher levels of treatment success, lower levels of failure and recurrence, and fewer adverse events compared to 1200 mg/day [12,13]. The GDG considered the possibility to reduce the daily dose of linezolid to 300 mg/daily if necessary to mitigate toxicity, even though it is preferable to use linezolid at the dosage of 600 mg/daily throughout the regimen [14,15]. The GDG acknowledged the slight differences in the treatment duration of the BPaLM and BPaL regimens as studied in TB-PRACTECAL and ZeNIX trials and suggested standardizing the treatment duration of BPaLM to 6 months (26 weeks); for BPaL, extension to a total of 9 months (39 weeks) if sputum cultures are positive between months 4 and 6 can be considered. Missed doses of all three or four drugs in the regimen should be avoided; therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.

Additional evaluation of BPaLC regimen was made although evidence was limited due to smaller sample size compared with BPaL; considering the increased pill burden, reduced acceptability because of skin discoloration and other potential adverse effects related to clofazimine use without noticeable benefits, the GDG judged that BPaLC regimen should not be recommended.

9-month all-oral regimen

Another treatment option for people with MDR/RR-TB and without resistance to fluoroquinolones who are not eligible for the BPaLM is the 9-month all-oral bedaquiline-containing regimen. It consists of (i) intensive phase: bedaquiline in combination with FQ (levofloxacin or moxifloxacin), ethionamide (or linezolid at the dosage of 600 mg daily), ethambutol, high-dose isoniazid, pyrazinamide and clofazimine (ii) continuation phase: fluoroquinolones, clofazimine, ethambutol, and pyrazinamide. The intensive phase is

intended as 4-month long (except bedaquiline, which is always 6-month long, and linezolid, which is maximum 2-month long), but it may be extended to 6 months when bacteriological conversion is not seen at the end of the fourth month of treatment, while the continuation phase remains of 5 months; hence, if extended, the entire regimen may last 11 months instead of 9. The two regimens are as follows: 4-6 $Bdq_{(6m)}$-FQ-Cfz-Z-E-Hh-Eto/5 FQ-Cfz-Z-E (known as ethionamide variation) and 4-6 $Bdq_{(6m)}$-$Lzd_{(2m)}$-FQ-Cfz-Z-E-Hh/5 FQ-Cfz-Z-E, also known as linezolid variation [11]. 9-month regimens represent the preferred treatment option over the longer regimens for patients without previous exposure to second-line treatment (including BDQ), except in case of extensive pulmonary disease, severe extrapulmonary, CNS, military, and osteoarticular TB where longer treatment is still recommended.

While the lack of safety data on pretomanid in children aged below 14 years makes the BPaLM not recommended in this age group, the 9-month all-oral regimen can be suggested to children of all ages, in consideration of the recommendation for bedaquiline use in children even below 6 years of age [14]. Furthermore, considering the contraindication to the use of ethionamide in pregnancy and the consolidated data on using linezolid during pregnancy, the 9-month regimen with linezolid is recommended instead of ethionamide for pregnant and lactating women. Regarding the choice of fluoroquinolones, although levofloxacin and moxifloxacin have shown similar efficacy for treating DR-TB, levofloxacin is often preferred because of moxifloxacin's higher potential for cardiotoxicity even if levofloxacin has been associated with musculoskeletal disorders in pediatric populations [15]. The 9-month regimen can be a preferred option over the longer regimens in newly diagnosed patients not eligible for the 6-month BPaLM/BPaL; an informed decision-making process, including clinical judgment, DST results, and patient preference should be made.

Longer regimens for multidrug-resistant/rifampicin-resistant tuberculosis

The last treatment section of the guidelines is dedicated to longer regimens (18-20 months), based on the WHO drug grouping A, B, and C*. This option, with no changes compared to 2020 WHO guidelines, is still considered when the BPaLM/BPaL or 9-month all-oral regimen cannot be used (e.g., severe extrapulmonary TB; additional resistance to key medicines of the BPaLM/BPaL regimen -except moxifloxacin- or the 9-month all-oral regimen; lack of response to shorter treatment regimens; drug intolerance to the component medicines of the 6-month or 9-month regimen; pregnant and lactating women or children aged below 14 years). Longer treatment, preferably all-oral, should be individualized based on DST and treatment history and it must include an intensive phase with at least four likely to be effective TB agents (three of Group A and at least one of Group B), and a continuation phase of at least three drugs. If four likely effective drugs cannot be achieved with agents from Group A and Group B, Group C agents are added to complete it. When Group C agents are included in the regimen, the number of drugs may exceed four, to reflect the uncertainty about the efficacy of some of these medicines. Due to the long duration of therapy and the potential side effects, the GDG agreed that reducing the pill burden to the minimum effective one is the best strategy to minimize the risk of treatment failure. Bedaquiline should be included in all age groups, even in pregnancy and in those aged below 6 years; in addition, evidence supports its safe use beyond 6 months in selected patients, under "off-label" use [16]. Although the GDG did not give recommendations on the effectiveness of the co-administration of bedaquiline and delamanid, owing to lack of evidence data, both medicines may be used in patients who have limited treatment options. Recent data presented from the DELIBERATE trial highlighted that the QTc effects of co-administration of bedaquiline and delamanid were not more than additive and they were not associated with grade 3 or 4 QTc prolongation [17]. Balancing desirable and undesirable effects, GDG judged that it would probably be feasible to use delamanid in children of all ages (using the 25 mg dispersible delamanid formulation in children below 3 years of age) [18]. The total duration of longer regimens is 18-20 months (15-17 months after culture conversion) that may be modified according to treatment response.

All regimens (BPaLM, BPaL, 9-month, and longer treatments) can be safely recommended in people living with HIV, with careful evaluation of drug-drug interactions and in those with CD4+ cell count $< 100/mm^3$.

Discussion

The long-awaited new DR-TB treatment guidelines represent a clear push toward the utilization of all-oral, shorter regimens for most patients with MDR/RR-TB.

Based on available data, the 6-month BPaLM/BPaL regimens can achieve successful outcomes even in case of extensive pulmonary and extrapulmonary (except CNS, miliary and osteoarticular TB) MDR/RR-TB, representing the shortest regimens ever proposed for this difficult-to-treat condition. While the evidence around BPaLM/BPaL regimens is highly promising, some aspects must be addressed soon to allow their smooth roll-out.

Firstly, access to drug susceptibility tests and second-line drugs remains the major issue for National TB Programs, and only a third of estimated MDR/RR-TB patients have been enrolled on treatment globally [1]. Once MDR/RR-TB is identified, the limited global access to rapid bedaquiline and linezolid molecular testing and the lack of pretomanid rapid molecular testing to exclude baseline resistance are major concerns, especially in consideration of the rise of bedaquiline resistance [19]. BPaLM regimen, including only four drugs, and even more BPaL, are likely to be inadequate in case of baseline resistance to one or more drugs included in the regimen, with a high risk of treatment failure. While resistance testing to FQ is available, its global coverage remains low (being only 50% in 2021) [3], and universal access to rapid fluoroquinolone-DST should also be pursued, to allow appropriate regimen selection (i.e., BPaL instead of BPaLM) and avoid unnecessary and potentially toxic drugs administration in case of resistance.

In addition, the high cost of bedaquiline, pretomanid, and linezolid, together with issues regarding pretomanid availability in some countries, limit the access to these medicines for many patients, not only in low resources but also in middle and high-income countries, and should be urgently addressed.

Besides diagnostic and treatment capacity, there are also some practical aspects that need to be clarified (i) BPaLM only considers moxifloxacin use, and not levofloxacin: further studies are needed to show if levofloxacin can be a safe substituted with same outcomes; (ii) the GDG allowed the reduction of the daily linezolid dose to 300 mg to mitigate linezolid-related side effects (e.g., anemia, peripheral neuropathy); it is our opinion that the reduced dose should be given only if therapeutic drug monitoring and minimal inhibitory capacities are available; (iii) evidence is needed to understand if BPaLM/BPaL can be continued (and how) without linezolid in case of drug interruption/early discontinuation or, rather, if the entire regimen should be stopped; (iv) the 6-month BPaL regimen might be prolonged to 9 months in case of positive sputum cultures between months 4 and 6. However, when the evidence of culture conversion is not available at 6^{th} month, we wonder if other elements (i.e., previous failure, smear microscopy results, chest X-ray picture or computer-aided detection score) could be considered to predict response to treatment and, in case of likely poor response, clinicians might decide to prolong the treatment to 9 months.

BPaLM is not supposed to be prolonged beyond 6 months; however, we wonder if the same elements listed above suggesting a poor response to treatment could guide the decision to prolong it to 9 months as well. Although limited data on the BPaLC regimen are available, in the case of FQ resistance, adding clofazimine to BPaL might be considered to reinforce the regimen and protect against bedaquiline resistance onset.

Last, but not least, future guidance in the following areas would be very useful for National TB Programs in view of BPaLM/BPaL roll-out: BPaLM/BPaL adherence monitoring plan, with details on adherence methods/digital technologies utilization; BPaL/BPaLM treatment monitoring schedule (beside culture monitoring); post-treatment follow-up data recording and reporting, to inform about the sustained treatment success and risk of relapse.

In conclusion, the updated DR-TB treatment guidelines represent a turning point in MDR/RR-TB treatment evolution, offering multiple all-oral, shorter, and more patient-centered options, and setting the basis for a new, more acceptable, equitable, and cost-effective model for MDR/RR-TB management [20,21]. Massive efforts in terms of capacity building, strengthening of diagnostic capacity, actions to ensure new drugs and shorter regimens access and generation of further evidence around new regimens are urgently needed to expand the MDR/RR-TB treatment coverage and achieve actual implementation of the new guidelines at a global level.

Group A = levofloxacin or moxifloxacin, bedaquiline, and linezolid; • Group B = clofazimine, and cycloserine or terizidone; and • Group C = ethambutol, delamanid, pyrazinamide, imipenem–cilastatin or meropenem, amikacin (or streptomycin), ethionamide or prothionamide, and p-aminosalicylic acid.

Declaration of competing interests

Tiberi S. is an employee of GSK, all opinions are his own and not that of the company. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Transparency declaration

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References

[1] World Health Organization *Global tuberculosis report 2022*. Geneva: World Health Organization; 2022.
[2] Migliori GB, Tiberi S. WHO drug-resistant TB guidelines 2022: what is new? *Int J Tuberc Lung Dis* 2022;**26**:590–1. doi:10.5588/ijtld.22.0263.
[3] World Health Organization *WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update*. Geneva: World Health Organization; 2022.
[4] World Health Organization *Rapid communication: key changes to the treatment of drug-resistant tuberculosis*. Geneva: World Health Organization; 2022.
[5] World Health Organization *WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment*. Geneva: World Health Organization; 2020.
[6] Berry C, du Cros P, Fielding K, Gajewski S, Kazounis E, McHugh TD, et al. TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II–III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis. *Trials* 2022;**23**:484. doi:10.1186/s13063-022-06331-8.
[7] Nyang'wa BT, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2022;**387**:2331–43. doi:10.1056/NEJMoa2117166.
[8] Esmail A, Oelofse S, Lombard C, Perumal R, Mbuthini L, Goolam Mahomed A, et al. An all-oral 6-month regimen for multidrug-resistant tuberculosis: a multicenter, randomized controlled clinical trial (the NExT Study). *Am J Respir Crit Care Med* 2022;**205**:1214–27. doi:10.1164/rccm.202107-1779OC.
[9] Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022;**387**:810–23. doi:10.1056/NEJMoa2119430.
[10] World Health Organization *WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update*. Geneva: World Health Organization; 2022.
[11] World Health Organization *WHO consolidated guidelines on drug resistant tuberculosis treatment*. Geneva: World Health Organization; 2019.
[12] Migliori GB, Eker B, Richardson MD, Sotgiu G, Zellweger J-P, Skrahina A, et al. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J* 2009;**34**:387–93. doi:10.1183/09031936.00009509.
[13] Imperial MZ, Nedelman JR, Conradie F, Savic RM. Proposed linezolid dosing strategies to minimize adverse events for treatment of extensively drug-resistant tuberculosis. *Clin Infect Dis* 2022;**74**:1736–47. doi:10.1093/cid/ciab699.
[14] World Health Organization *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents*. Geneva: World Health Organization; 2022.
[15] Briasoulis A, Agarwal V, Pierce WJ. QT prolongation and torsade de pointes induced by fluoroquinolones: infrequent side effects from commonly used medications. *Cardiology* 2011;**120**:103–10. doi:10.1159/000334441.
[16] Zhurkin D, Gurbanova E, Campbell JR, Menzies D, Setkina S, Hurevich H, et al. Safety of prolonged treatment with bedaquiline in programmatic conditions. *ERJ Open Res* 2022;**8**:00685–2021. doi:10.1183/23120541.00685-2021.
[17] Dooley KE, Rosenkranz SL, Conradie F, Moran L, Hafner R, von Groote-Bidlingmaier F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. *Lancet Infect Dis* 2021;**21**:975–83. doi:10.1016/S1473-3099(20)30770-2.
[18] Tyeku N, Apolisi I, Daniels J, Beko B, Memani B, Cengani L, et al. Pediatric delamanid treatment for children with rifampicin-resistant TB. *Int J Tuberc Lung Dis* 2022;**26**:986–8. doi:10.5588/ijtld.22.0264.
[19] Kaniga K, Hasan R, Jou R, Vasiliauskienė E, Chuchottaworn C, Ismail N, et al. Bedaquiline drug resistance emergence assessment in multidrug-resistant tuberculosis (MDR-TB): a 5-year prospective in vitro surveillance study of bedaquiline and other second-line drug susceptibility testing in MDR-TB isolates. *J Clin Microbiol* 2022;**60**:e0291920. doi:10.1128/JCM.02919-20.
[20] van de Berg SEJ, Pelzer PT, van der Land AJ, Abdrakhmanova E, Ozi AM, Arias M, et al. Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients. *BMC Public Health* 2021;**21**:1404. doi:10.1186/s12889-021-11427-y.
[21] Akkerman OW, Tiberi S, Alffenaar JW. Shortening MDR-TB treatment: is treating more patients with fewer drugs better? *Int J Tuberc Lung Dis* 2021;**25**:419–20. doi:10.5588/ijtld.21.0146.