WHO recommendations on DR-TB treatment & Update on the Guideline Development Group meeting 2024

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African Regional workshop on DR-TB treatment
2-3 July 2024

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Outline

- Current WHO recommendations on the treatment of drug-resistant TB
  - 6-month regimen – BPaLM
  - 9-month regimens
  - 18-month longer regimens

- Update on the GDG meeting 2024

Guidelines & Handbooks on TB Treatment and Care – 2022 update

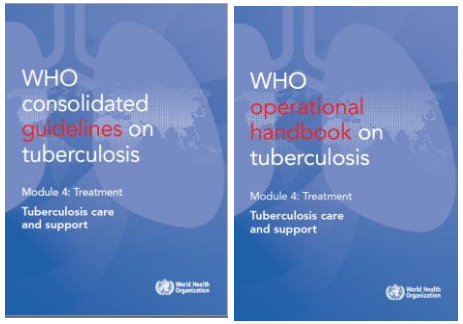
DS-TB

DS-TB guidelines & handbook 2022

- **6-month 2HRZE/4HR** regimen
- **4-month 2HPMZ/2HPM** regimen
- **4-month 2HRZ(E)/2HR** regimen for children and adolescents

TB Care & Support

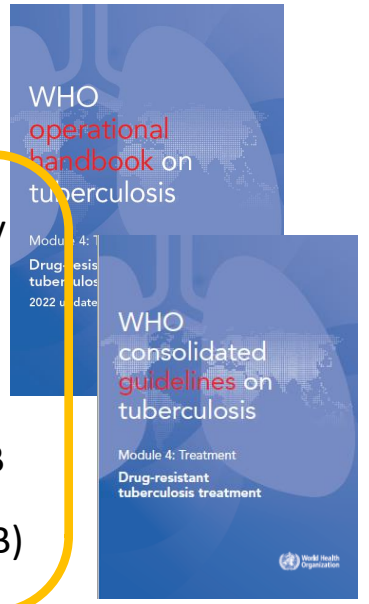
Guidelines & Handbook 2022



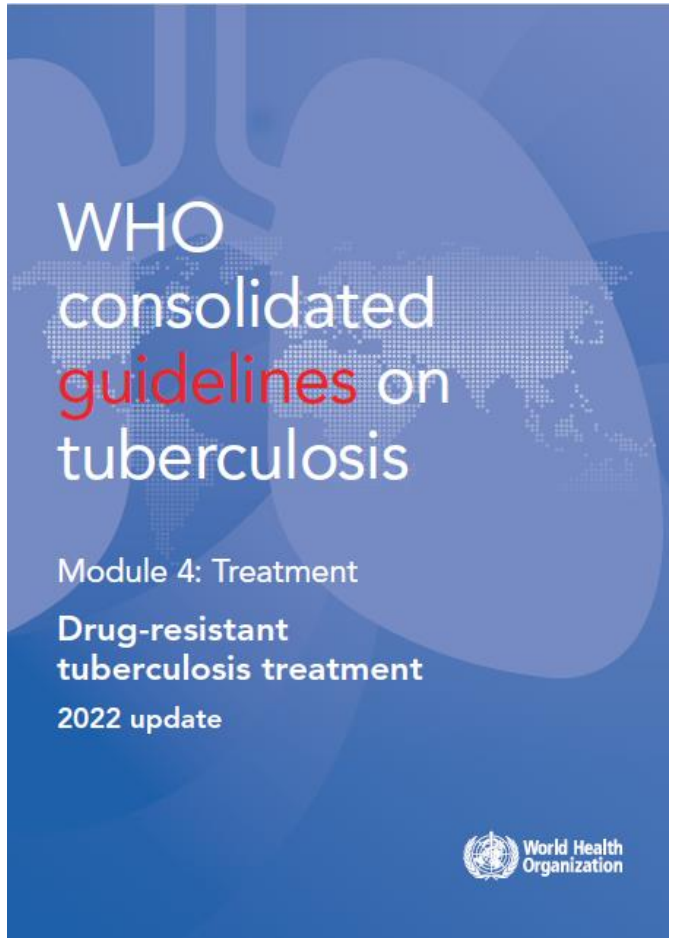
DR-TB

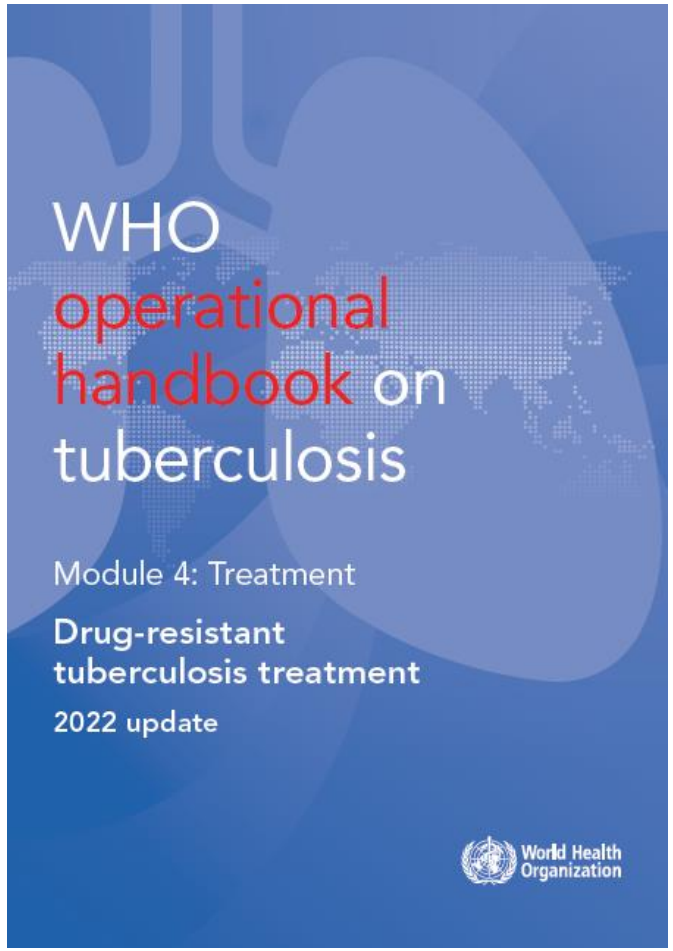
Guidelines and Handbook 2022

- **6-month BPaLM regimen, comprising bdq, Pa, Lzd (600 mg) & Mfx**, may be used programmatically in place of 9-month or longer (>18 months) regimens, in patients (aged ≥15 years) with MDR/RR-TB
- **9-month, all-oral, bedaquiline-containing regimens*** are preferred over the longer (>18 months) regimen in adults and children with MDR/RR-TB
- **Longer regimen** for patients with extensive forms of DR-TB (e.g., XDR-TB)



Treatment of drug-resistant TB (DR-TB)





What are the recommended treatment regimens for patients with MDR/RR-TB?

6-month BPaLM/BPaL regimen (MDR/RR-TB or pre-XDR-TB)

- 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).
- DST to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.
- Cannot be used during pregnancy
- if DST confirms susceptibility can be used in those exposed to B, Pa, or L for more than 1 month
- no TB meningitis, osteoarticular or disseminated TB

9-month regimens (MDR/RR-TB)

- 2 months of linezolid (600 mg) can be used as an alternative to 4 months of ethionamide.
- no previous exposure to second-line treatment (including bedaquiline),
- no fluoroquinolone resistance and
- no extensive pulmonary TB disease or severe extrapulmonary TB.
- rapid DST for ruling out fluoroquinolone resistance is required.
- can be used in all age groups
- regimen with linezolid can be used in pregnant women

Longer regimens (18-month, individualized, mostly in XDR-TB)

- Last resort regimen
- Those who failed or not eligible for two shorter regimens
- XDR-TB patients
- Individualized based on current recommendations

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The 6-month BPaLM regimen

Recommendation:

WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients.

(Conditional recommendation, very low certainty of evidence)

Eligibility

- ✓ MDR/RR-TB without or with resistance to fluoroquinolones (pre-XDR-TB)
- ✓ PTB or extrapulmonary TB (except TB involving the CNS, osteoarticular or disseminated/miliary TB)
- ✓ 14 years and older
- ✓ regardless of HIV status
- ✓ no pregnancy or breastfeeding
- ✓ < 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid; or drug resistance is ruled out for the medicines with >1-month exposure

Same regimen – two options

BPaLM	**BPaLM should be used for MDR/RR-TB patients** with • *confirmed susceptibility to fluoroquinolones* • *result of fluoroquinolone DST is never determined or not done*
BPaL	**Omit Mfx and use the BPaL when** • *FQ resistance is confirmed or highly likely* • *the patient is a close contact of a FQ-resistant case or* • *in a setting with a high prevalence of FQ resistance and in the absence of FQ-DST*

- *DST for fluoroquinolones is strongly encouraged in people with MDR/ RR-TB, although it should not delay initiation of the BPaLM*
- *FQ-DST result guides the decision on whether Mfx can be retained or should be dropped from the regimen – in case of documented resistance to fluoroquinolones, BPaL (without Mfx) would be initiated or continued*

Composition and Dosing

BPaLM is a combination of bedaquiline, pretomanid, linezolid and moxifloxacin

Drug	Dose
Bedaquiline (100 mg tablet)	**400 mg** once daily for 2 weeks, then **200 mg** 3 times per week OR **200 mg** daily for 8 weeks, then **100 mg** daily
Pretomanid (200 mg tablet)	**200 mg** once daily
Linezolid (600 mg tablet)	**600 mg** once daily
Moxifloxacin (400 mg tablet)	**400 mg** once daily

Dosing of Bedaquiline

- **400 mg daily** for 2 weeks, then 200 mg three times per week ***(Product label)***

OR

- **200 mg daily** for 8 weeks followed by 100 mg daily ***(ZeNix trial)***
  - *an alternative way to dose Bdq that allows for daily dosing of all drugs throughout the regimen*
  - *may be more convenient for patients and health care providers*

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Dosing of Linezolid

The recommended dose of linezolid is 600 mg once daily for BPaLM/BPaL

Lzd 600 mg
preferred for the entire duration, at least the first 9 weeks

Reduce to Lzd 300 mg (after 9 weeks) in case of toxicity
with possible drug interruption for 1–2 weeks before dose reduction

Potential permanent suspension
due to significant AEs

Duration

- ✓ **BPaLM:** 6 months (26 weeks) - standardized treatment duration
- ✓ **BPaL:** 6 to 9 months (39 weeks)

  Extension to 9 months applies if sputum culture is positive months 4 – 6

Missing doses:

- ➢ *All medicines to be used throughout treatment duration*
- ➢ *Ideally, missing doses of all three or four drugs in the regimen should be avoided*
- ➢ *If doses are missed, any interruption of >7 days should be made up for by extending the treatment duration (for the number of missed doses)*

9-month all-oral regimen for MDR/RR-TB

Recommendation:

WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

(Conditional recommendation, very low certainty of evidence)

Eligibility

- ✓ patients with MDR/RR-TB and without resistance to fluoroquinolones
- ✓ without extensive TB disease and without severe extrapulmonary TB
- ✓ children of all ages
- ✓ regardless of HIV status
- ✓ no resistance to bedaquiline, clofazimine, or ethionamide or linezolid
- ✓ < 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; resistance has been ruled out when >1 month exposure to the specific medicines
- ✓ pregnant women use the regimen with linezolid instead of ethionamide

Regimen composition & duration

	Ethionamide variation	Linezolid variation
Initial phase	4-6 Bdq(6m)-Eto-Lfx/Mfx-Cfz-Z-E-Hh	4-6 Bdq(6m)-Lzd (2m)-Lfx/Mfx-Cfz-Z-E-Hh
Continuation phase	5 Lfx/Mfx-Cfz-Z-E	5 Lfx/Mfx-Cfz-Z-E

- *Eto & High-dose H can be dropped after initial phase*
- *Lzd is only given the first 2 months of treatment.*

- *If sputum remains positive at month 4, initial phase is extended to 6 months*
- *Bdq can be extended to 9 months*

What factors to be considered while choosing 9-month regimens?

Factors/conditions	Ethionamide variation	Linezolid variation
Any sign of optic neuritis	Yes	No
Severe or mild peripheral neuropathy	Yes	No
Hemoglobin (> 8 g/dl) **neutrophils** (> 0.75 X 10^9/L) **and platelets** (>150 × 10^9/L)	Yes	Yes
Pill burden	Eto for 4 months	Lzd only for 2 month
Use during pregnancy & breastfeeding	No	Yes
Other factors to be considered:		

- *preferences of patients and clinicians*
- *feasibility of monitoring for drug adverse effects*
- *availability of blood transfusion or ophthalmology services*

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What factors to be considered when modifying 9-month regimen?

- **9-month regimen should be implemented as a standardized package**

- **A few possible exceptions:**
  - ✓ Bedaquiline can be extended from 6 to 9 months if initial phase prolonged from 4 to 6 months.
  - ✓ Prothionamide may be used instead of ethionamide.
  - ✓ Levofloxacin (with ECG monitoring) may be used instead of Moxifloxacin.
  - ✓ If full dose (600mg) of Linezolid is not tolerated for the first full 2 months (apart from occasionally missed doses), then **switch to a new regimen.**
  - ✓ If bedaquiline, levofloxacin/moxifloxacin, linezolid/ethionamide or clofazimine needs to be stopped early → **switch to a new regimen.**
  - ✓ In case of intolerance of pyrazinamide or ethambutol, one of them (only one) can be dropped during continuation phase **without switch to a new regimen.**

18-month all-oral regimen for MDR/RR-TB

Grouping of medicines recommended for use in longer MDR-TB regimens

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

- All three Group A agents and at least one Group B agent should be included
  - ✓ Treatment starts with at least four TB agents likely to be effective
  - ✓ At least three agents are included for the rest of the treatment if bedaquiline is stopped
- If only one or two Group A agents are used, both Group B agents are to be included
- If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

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MDR/RR-TB regimen selection and factors to be considered

Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualized 18-month	Yes[a]/No	Yes[a]/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug-resistant TB.

[a] When 6-month BPaLM/BPaL and 9-month regimens could not be used.

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An update on the Guideline Development Group (GDG) Meeting on treatment of drug-resistant TB

24-27 June 2024

Evidence reviewed by the GDG

BEAT-TB trial : 6-month regimen
South Africa Bdq-Lzd-Dlm-Lfx/Cfz/both

endTB trial: 9-month regimens

1. Bdq-Lzd-Mfx-Z
2. Bdq-Lzd-Cfz-Lfx-Z
3. Bdq-Lzd-Dlm-Lfx-Z
4. Dlm-Cfz-Lzd-Lfx-Z
5. Dlm-Cfz-Mfx-Z

PICO questions

1. Should a 6-month regimen using bedaquiline, delamanid, and linezolid with or without the addition of levofloxacin or clofazimine or both (BDLLC) be used in patients with pulmonary RR-TB (with or without fluoroquinolone resistance) over the currently recommended 9-month regimen?

2. Should any 9-month endTB trial regimens be used in patients with pulmonary RR-TB (without fluoroquinolone resistance) over the currently recommended longer regimens?

English

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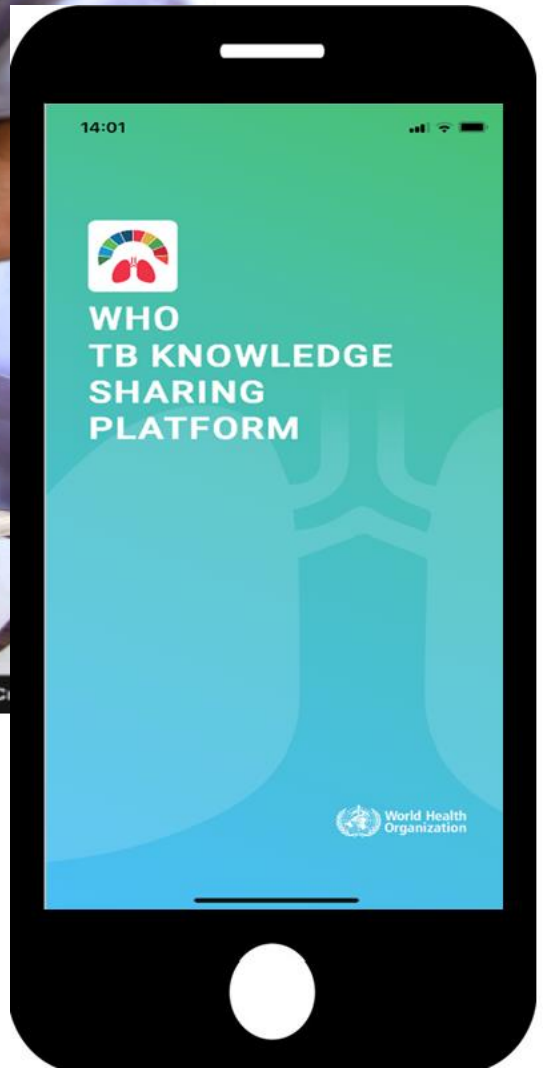
About Us

The WHO's Global Tuberculosis Programme works towards the goal of a world free of TB, with zero deaths, disease and suffering due to the disease. The team's mission is to lead and guide the global effort to end the TB epidemic through universal access to people-centered prevention and care,



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Thank you

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