Overview of WHO consolidated guidelines on TB treatment and care 2025

New DR-TB regimens: evidence and rationale

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TB treatment team
Global Tuberculosis Programme

Joint regional workshops on new WHO policies for TB care
April 2024

World Health Organization

Evolution in treatment of TB disease

- Switch to all-oral regimens
- Introduction of repurposed medicines: quinolones, linezolid, clofazimine
- Discovery and policy on use of new medicines in regimens: bedaquiline, delamanid, pretomanid
- Shorter treatment duration
- Increase in efficacy

DS-TB

6-month 2HRZE/4HR

4-month 2HPMZ/2HPM

1970 … 1996 … 2018 2019 2020 2021 2022 2023 2024 …

DR-TB

18-24-month regimens

9-11-month regimens

All-oral regimens

6-month regimens

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END TB

TB disease treatment in 2022-25: Guidelines & Handbooks

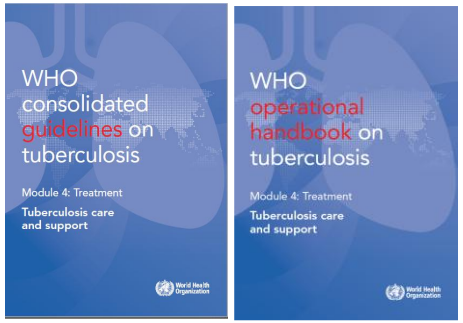
DS-TB

Guidelines & handbook 2022

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

TB Care & Support

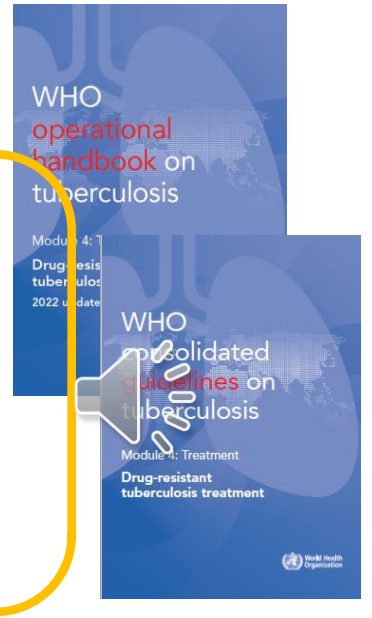
Guidelines & Handbook 2022



DR-TB

Guidelines and handbook 2022-25 update

- **6-month BPaLM regimen,** in patients (aged ≥14 years) with MDR/RR-TB
- **6-month BDLLfxC regimen**, in all patients including children
- **9-month, all-oral, bedaquiline-containing regimens**
- **Longer regimens** for patients with extensive forms of DR-TB



Consolidation of the guidelines (and handbooks) in 2025

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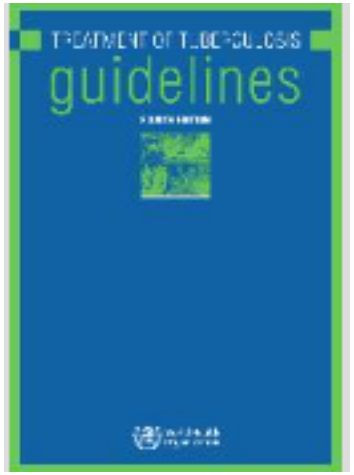
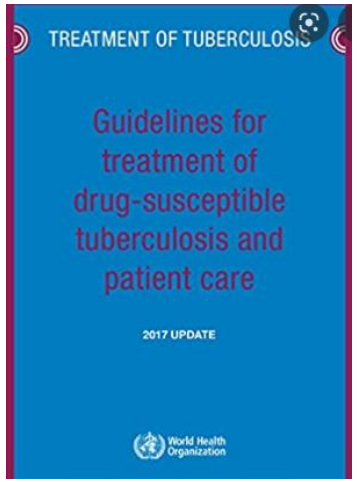
END TB

Chapter 1. Treatment of drug-susceptible TB (DS-TB)

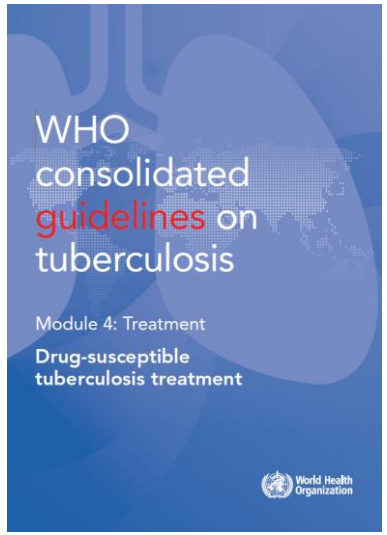
2022 DS-TB Guidelines update



Fourth edition 2010



2017



2022

- **All DS-TB treatment recommendations were consolidated**
- **Redundant recommendations were removed**
- **Nine recommendations remain valid**
- **Two new recommendations were added**
  - **Treatment of drug-susceptible TB using 4-month regimens**

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2022 DS-TB Guidelines update

Summary of Recommendations

New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR

Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy

In new PTB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended

The use of fix-dose combination (FDC) is recommended over separate drug formulations in treatment of patients with DS-TB

In all patients with DS PTB, the use of 3x dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen 2HPMZ/2HPM

In children and adolescents, 3month-16years, with non-severe TB, a 4- month treatment regimen 2HRZ(E)/2HR should be used

It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients.

ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.

In patients with TB meningitis, an initial adjuvant corticosteroids with dexamethasone or prednisolone tapered over 6-8 wk should be used

In patients with TB pericarditis, an initial adjuvant corticosteroids may be used

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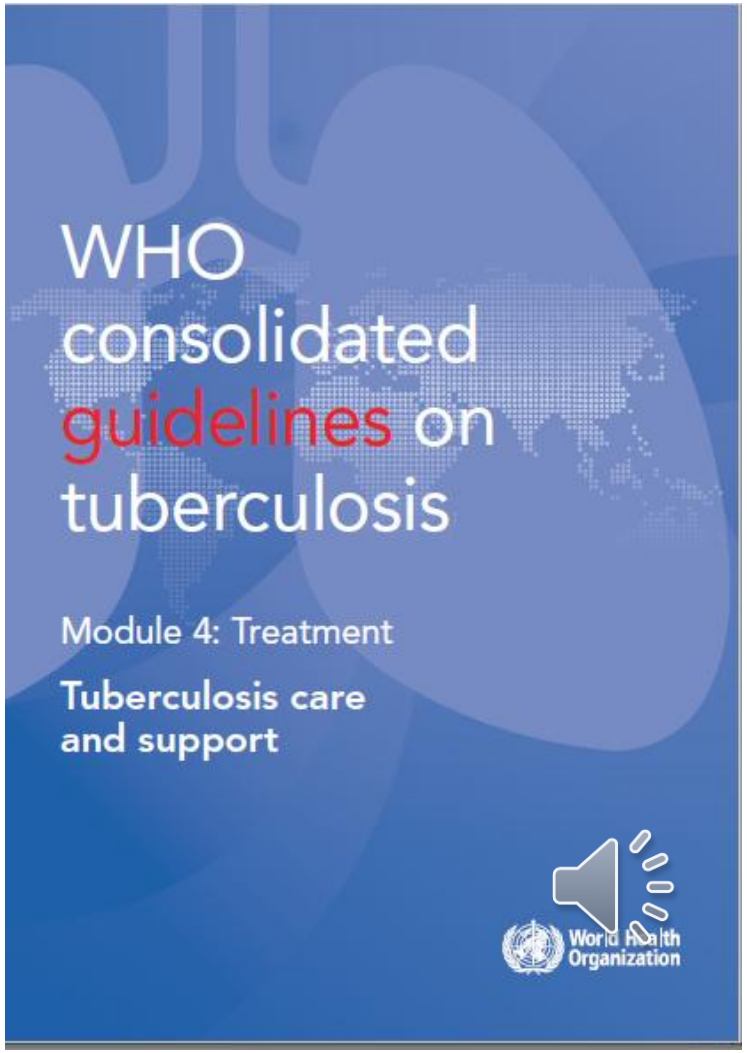
Chapter 3: Tuberculosis care and support

2022 Guidelines - TB care and support

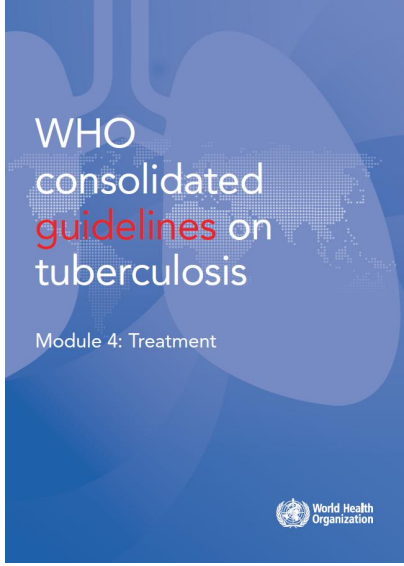
Recommendations on:

1. Care and support interventions for all people with TB
2. Models of care for people with DR-TB
3. Models of care for children and adolescents



Chapter 2: Treatment of drug-resistant TB (DR-TB)

2025 Guidelines DR-TB chapter



- **Treatment of drug-resistant TB using 6-month regimens.**
  - **Recommendation 1.1 The 6-month bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) regimen**
  - **Recommendation 1.2 The 6-month bedaquiline, delamanid, linezolid, levofloxacin and clofazimine (BDLLfxC) regimen (NEW)**
- **Treatment of drug-resistant TB using 9-month regimens**
  - **The 9-month all-oral regimen for MDR/RR-TB**
  - **The modified 9-month all-oral regimens for MDR/RR-TB (NEW)**
- **Treatment of drug-resistant TB using longer regimens**
- **Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis**
- **Monitoring patient response to MDR/RR-TB treatment**
- **Start of antiretroviral therapy in patients on MDR/RR-TB regimens**
- **Surgery for patients on MDR/RR-TB treatment**
- **Hepatitis C virus (HCV) and MDR/RR-TB treatment co-administration (NEW)**

Recommendation 1.1 – The 6-month BPaLM regimen

Recommendation 1.1

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 or pre-XDR TB patients.

(*Conditional recommendation, very low certainty of evidence)*

Remarks

- DST for fluoroquinolones is strongly encouraged in people with MDR/ RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.
- This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.
- The recommended dose of linezolid is 600 mg once daily for BPaLM/BPaL

MDR/RR-TB regimen groups, 2022 guidelines

6-month regimen - BPaLM/BPaL regimen (MDR/RR-TB and 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

6-month

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

9-month

18-month - longer regimens, 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

18-month

World Health Organization

Clinical trials reviewed during 2024 GDG

Comparator

BEAT-TB trial in South Africa: 6-month regimen

MDR/RR-TB or pre-XDR-TB

6m Bdq-Dlm-Lzd-Lfx/Cfz/both

- Recommended 9-month regimen (with Lzd) for Fq-susceptible
- Longer regimens for Fq-resistant

EndTB trial multicountry: 9-month regimens

MDR/RR-TB

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

Recommended longer regimens

PICO 1 – BEAT-TB trial

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

Population	**Intervention**	**Comparator**	**Outcome**
Patients with microbiologically confirmed pulmonary MDR/RR-TB and with or without FQ resistance	BDLLfx/C regimen[a]: **6 Bdq-Dlm-Lzd-Lfx/Cfz (and/or)**	BEAT-Tuberculosis comparator regimens: • **9 Bdq(6)-Lzd(2)-Lfx-Cfz-Hh-Z-E (for Fq-susceptible)** • **WHO currently recommended longer regimens (18-20 months) (for Fq-resistant)**	• Sustained treatment success • Failure and recurrence • Death • Lost to follow up • Adverse events • Amplification (acquisition) of drug resistance

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END TB

Recommendation 1.2 – The 6-month BDLLfxC regimen

Recommendation 1.2 (new)

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).

Remarks

1. When resistance to fluoroquinolones is unknown, the regimen can be started as BDLLfxC and then adjusted based on the DST results. In cases of quinolone susceptibility, the regimen can include four medicines— bedaquiline, delamanid, linezolid and levofloxacin (BDLLfx). In cases of resistance to fluoroquinolones, the regimen with bedaquiline, delamanid, linezolid and clofazimine (BDLC) can be used.
2. During the randomized controlled trial, the BDLLfxC regimen group was compared to the group of participants who received either a previously recommended 9-month shorter regimen with linezolid or the longer(>18 months) WHO-recommended regimens. The majority of controls were on the 9-month regimen.

PICO 2 – endTB trial

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

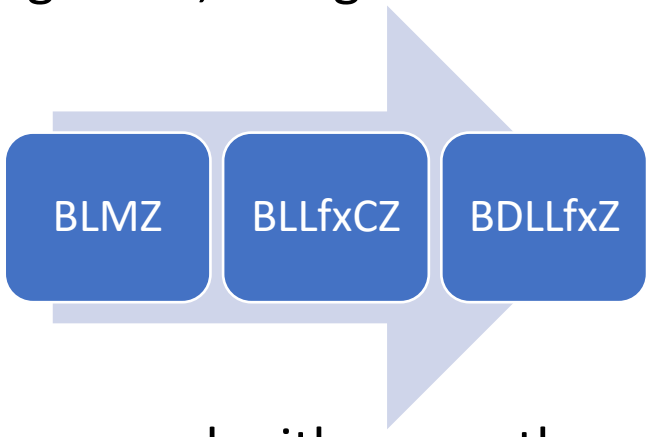
Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB and without FQ resistance	endTB 1 regimen[a]: **9 Bdq-Lzd-Mfx-Z** endTB 2 regimen[b]: **9 Bdq-Lzd-Cfz-Lfx-Z** endTB 3 regimen[c]: **9 Bdq-Lzd-Dlm-Lfx-Z** endTB 4 regimen[d]: **9 Dlm-Cfz-Lzd-Lfx-Z** endTB 5 regimen[e]: **9 Dlm-Cfz-Mfx-Z**	**WHO currently recommended longer regimens (18-20 months)**	• Sustained treatment success • Failure and recurrence • Death • Lost to follow up • Adverse events • Amplification (acquisition) of drug resistance

Modified 9-month all-oral regimens for MDR/RR-TB

Recommendation: 2.2 (new)

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)



Recommendations: 2.3 (new)

WHO suggests against using 9-month DCLLfxZ and DCMZ regimens compared with currently recommended longer (>18 months) regimens in patients with fluoroquinolone-susceptible MDR/RR-TB.

(Conditional recommendation, very low certainty of evidence)

MDR/RR-TB regimen groups, 2025 guidelines

6-month regimen - BPaLM/BPaL regimen (MDR/RR-TB and 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
- People with all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular, or disseminated forms of TB with multi-organ involvement.

6-month BDLLfxC (MDR/RR-TB and pre-XDR-TB)

- People with MDR/RR-TB or pre-XDR-TB
- People with MDR/RR-TB and less than one month of previous exposure to bedaquiline, linezolid, delamanid, or clofazimine.
- People with diagnosed pulmonary TB, including children, adolescents, PLHIV, pregnant and breastfeeding women.
- People with all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular, or disseminated forms of TB with multi-organ involvement.

6-month

Modified 9-month regimens (MDR/RR-TB)

- People with MDR/RR-TB and without resistance to fluoroquinolones;
- People with diagnosed pulmonary TB, including children, adolescents, PLHIV, pregnant and breastfeeding women.
- People with extensive TB disease and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular, or disseminated forms of TB with multi-organ involvement.
- People with MDR/RR-TB and less than one month of previous exposure to bedaquiline, fluoroquinolones, linezolid, and clofazimine

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

9-month

18-month - longer regimens, 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

18-month

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Implementation challenges with the new regimens

- ✓ Diagnostic barriers
- ✓ High price of some medicines
- ✓ Medicines availability and procurement
- ✓ Programmatic implementation barriers:
  - previous regimens in use,
  - innovation doubts,
  - regulatory barriers,
  - policy updates or local research

Expected new evidence from treatment trials*

End-stage trials on DR-TB treatment

Next-TB, MDR-End, Stream 1 and 2	Nix, ZeNix	TB PRACTECAL, endTB, BEAT-Tuberculosis	endTB Q
Trials that used de-recommended SoC as comparator or already recommended intervention – important contribution to the knowledge on TB but cannot be used for new policy	no comparator, contributing to the knowledge and supporting regulatory approval but challenge to match the policy development process	Contributed to the policy development	only phase 3 trial that may contribute to the policy in the next couple of years, depending on the results

A wave of phase 2 trials is ongoing and may contribute new products for further research under phase 3 trials in the next 5 years

SMART4TB Consortium

UNITE 4TB IMI AMR Accelerator

PAN-TB PROJECT TO ACCELERATE NEW TREATMENTS FOR TUBERCULOSIS

~ $600 million research investment

World Health Organization

*not including host-directed therapies or stratified medicine

END TB

Main messages

- **Shorter, 6-month BPaLM/BPaL** is the preferred choice for patients with MDR/RR-TB or pre-XDR-TB above 14 years of age
- **6-month BDLLfxC** is a 6-month alternative for those not eligible for BPaLM, and it can be used in all patients (including children and pregnant women)
- **Modified 9-month regimens** can also be used for patients with MDR-RR-TB (but no FQ resistance), adding a choice of regimens with fewer component medicines to the group of **9-month regimens** (including currently recommended)
- **Longer, 18-20 months regimens remain** the “last resort” individualized regimens
- The duration of MDR/RR-TB treatment can be the same as DS-TB treatment for most patients, including children and during pregnancy.

In summary:

- In 2025 - consolidation of several guidelines and handbooks in Module 4: Treatment
- DS-TB: 3 regimens, two shorter, 4-month regimens for and 6-month regimen remains recommended
- DR-TB: 7 shorter treatment regimens – 6-month BPaLM/BPaL and BDLLfxC, 3 new modified 9-month regimens and 2 previously recommended 9-month regimens
- Longer, 18-20 months regimens – the “last resort” individualized regimens

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