Updated WHO consolidated guidelines on DR-TB treatment 2025

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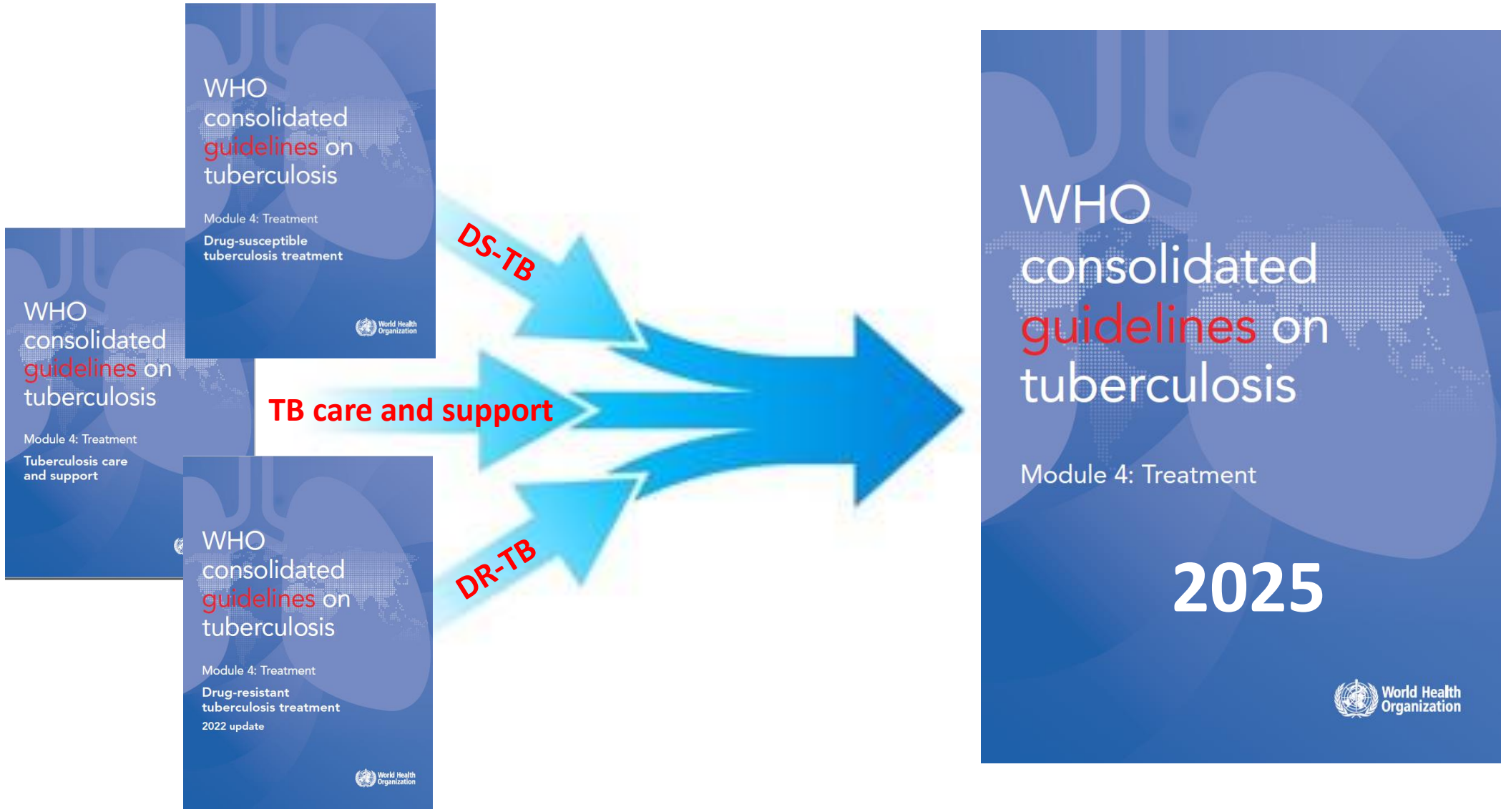
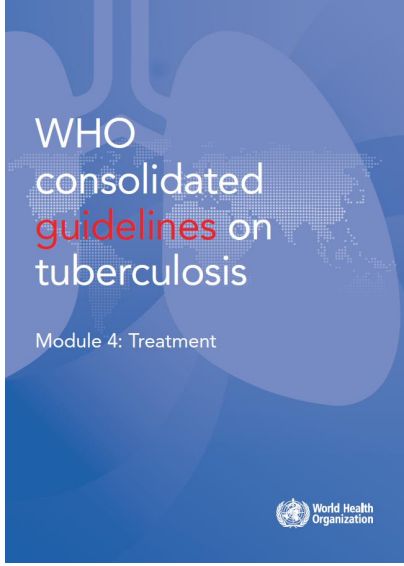
Consolidation of the guidelines (and handbooks) in 2025



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

The 6-month BPaLM regimen: Eligibility

- ✓ MDR/RR-TB or 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
- ✓ Not pregnant 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*

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)*

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

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

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2. 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.
3. 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.

Same regimen – three options

BDLLfxC	**Should be used for MDR/RR-TB patients** • *Unknown susceptibility to fluoroquinolones*
BDLLfx	**Omit clofazimine** • *FQ susceptibility is confirmed*
BDLC	**Omit levofloxacin** • *FQ resistance is confirmed*

- *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 Lfx or clofazimine can be retained or should be dropped from the regimen*

The 6-month BDLLfxC regimen: Eligibility

- ✓ MDR/RR-TB or pre-XDR-TB
- ✓ PTB or extrapulmonary TB (except TB involving the CNS, osteoarticular, or disseminated/miliary TB)
- ✓ All ages, pregnant or breastfeeding
- ✓ Regardless of HIV status or extent of disease on the chest X-ray
- ✓ < 1-month previous exposure to bedaquiline, linezolid, or delamanid; or drug resistance is ruled out for the medicines with >1-month exposure
- ✓ Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB

Duration of BDLLfxC

- ✓ **BDLLfxC:** 24 weeks
- ✓ Can be extended 9 months (39 weeks) *if sputum culture is positive at 4 months*

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)*

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?

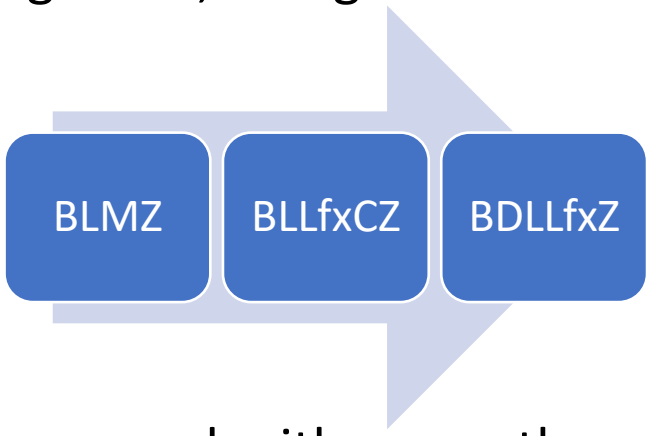
Population	Intervention	Comparator	Outcome
Patients with microbiologically confirmed pulmonary MDR/RR-TB and without FQ resistance	endTB 1 regimen[a]: **9 Bdq-Lzd-Mfx-Z** endTB 2 regimen[b]: **9 Bdq-Lzd-Cfz-Lfx-Z** endTB 3 regimen[c]: **9 Bdq-Lzd-Dlm-Lfx-Z** endTB 4 regimen[d]: **9 Dlm-Cfz-Lzd-Lfx-Z** 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: 2.3-2.4 (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)

Eligibility

- MDR/RR-TB without resistance to fluoroquinolones;
- Diagnosed pulmonary TB, including children, adolescents, PLHIV, pregnant and breastfeeding women.
- 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
- When exposure is greater than one month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out
- Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB

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

Recommendation: 2.1

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)

Remarks

1. The 9-month all-oral regimen 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 treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).
2. A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.

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Eligibility

- ✓ patients with MDR/RR-TB and without resistance to fluoroquinolones
- ✓ without extensive TB disease and 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

Two regimen options

Bedaquiline (6m), Lfx/Mfx, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide, clofazimine (4m), with the possibility of extending to 6m if the patient remains sputum smear+ at the end of 4m), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). **Ethionamide can be replaced by 2 months of linezolid (600 mg daily).**	*Eto*	**Should be used for MDR/RR-TB patients** • *Confirm susceptibility to fluoroquinolones* • *Can be used in children* • *Cannot be used during pregnancy due to ethionamide-related risks*
	Lzd	**Should be used for MDR/RR-TB patients** • *Confirm susceptibility to fluoroquinolones* • *Can be used in children* • *Can be used during pregnancy with caution*

Longer regimens

Recommendations: 3.1-3.17

In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective and that 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.

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.

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

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

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, adding a choice of regimens with fewer component medicines to the group of **9-month regimens**
- **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.