Updated WHO consolidated guidelines on DR-TB treatment 2022

Fuad Mirzayev

TB treatment team
Global Tuberculosis Programme

IAS webinar
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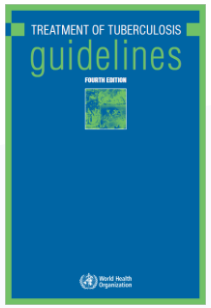
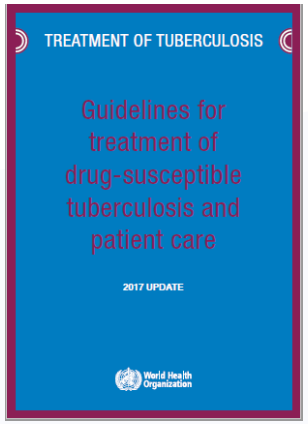
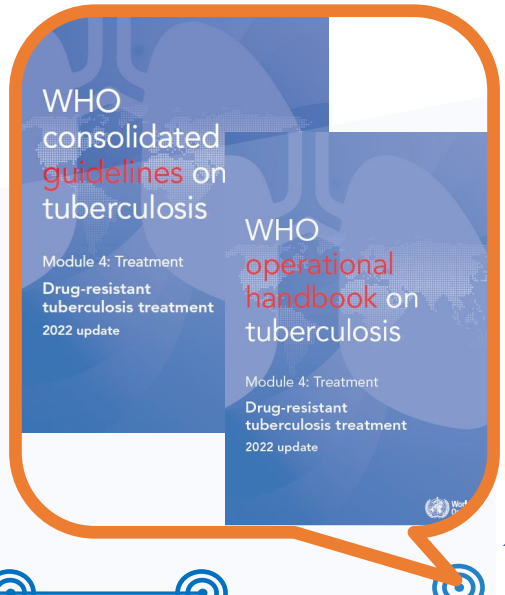
World Health Organization

Guidelines and derivative documents on TB treatment: Guidelines and handbooks

DS-TB

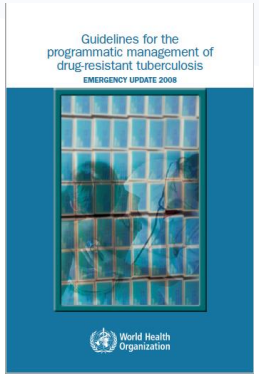






1997 2003 2008 2010 2011 2016 2017 2018 2019 **2020** **2022**

DR-TB



New developments in 2022: Guidelines & Handbooks

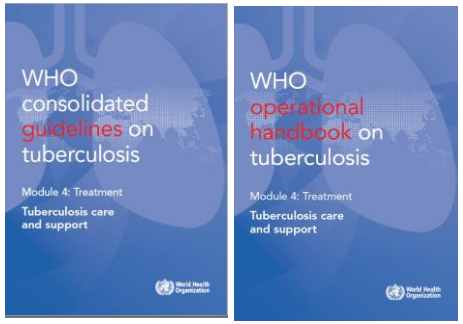
DS-TB

DS-TB guidelines & handbook 2022

- **4-month 2HPMZ/2HPM** regimen
- **4-month 2HRZ(E)/2HR** regimen for children and adolescents
- Consolidating all recommendations on DS-TB (2022)

TB Care & Support

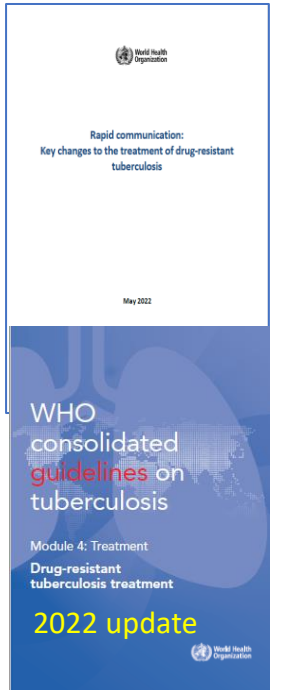
Guidelines & Handbook 2022



DR-TB

Guidelines and handbook 2022 update

- **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)



Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

1. TB PRACTECAL Trial (sites: Uzbekistan, South Africa, Belarus)

- **Investigational regimens in Stage 1**
  - Arm 1: bedaquiline (B) + pretomanid (Pa) + linezolid (Lzd) + moxifloxacin (Mfx) for 24 weeks (**BPaLM**)
  - Arm 2: bedaquiline + pretomanid + linezolid + clofazimine for 24 weeks (**BPaLC**)
  - Arm 3: bedaquiline + pretomanid + linezolid for (**BPaL**) 24 weeks

- **Investigational regimen in Stage 2** (selected after stage 1)
  - Arm 1: bedaquiline (B) + pretomanid (Pa) + linezolid (Lzd) + moxifloxacin (Mfx) for 24 weeks (**BPaLM**)

- **Comparator: Standard of care**
  - Locally approved standard of care which is as much as possible consistent with WHO recommendations for RR/MDR-TB (9-month and 18-month regimens depending on the site)

Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

2. ZENIX - trial (sites: Georgia, Moldova, Russia, and South Africa)

BPaL regimen with different doses and duration of linezolid

- Bedaquiline and pretomanid at standard doses
- One of the following oral daily linezolid doses:
  1) 1200mg 26 weeks (primary analysis)
  2) 1200mg 9 weeks
  3) 600mg 26 weeks
  4) 600mg 9 weeks
- **No SoC comparator regimen included in the trial**

Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

3. South African - 2019 regimen

- Programmatic data
- 9-month regimen containing linezolid
  - 4-6-month intensive phase: **Lzd(2m)-Bdq(6m)-Lfx-Cfz-Hh-Z-E**
  - 5-month continuation phase: **Lfx-Cfz-Z-E**

- 9-month regimen containing ethionamide
  - 9-month regimen containing Eto: **Bdq(6m)-Lfx/Mfx-Eto-Cfz-Hh-Z-E**
  - WHO recommended longer regimens

Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

4. Public call - data from multiple countries

- Intended use as external comparators where relevant and possible
- Programmatic data on the use of the WHO-recommended 9-month regimen (data from South Africa) and
- Programmatic data on the WHO-recommended longer regimens (data from country programs in Belarus, Georgia, India, the Republic of Moldova, Mozambique, Papua New Guinea, the Russian Federation, and Somalia);
- data from fieldwork in multiple countries from Médecins Sans Frontières (MSF); and cohorts from the EndTB project provided by MSF and Partners in Health.

2022 DR-TB Guidelines update

Section 1. **The 6-month bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) regimen for MDR/RR-TB (new)**

Section 2. **The 9-month all-oral regimen for MDR/RR-TB (new)**

Section 3: **Longer regimens for MDR/RR-TB**

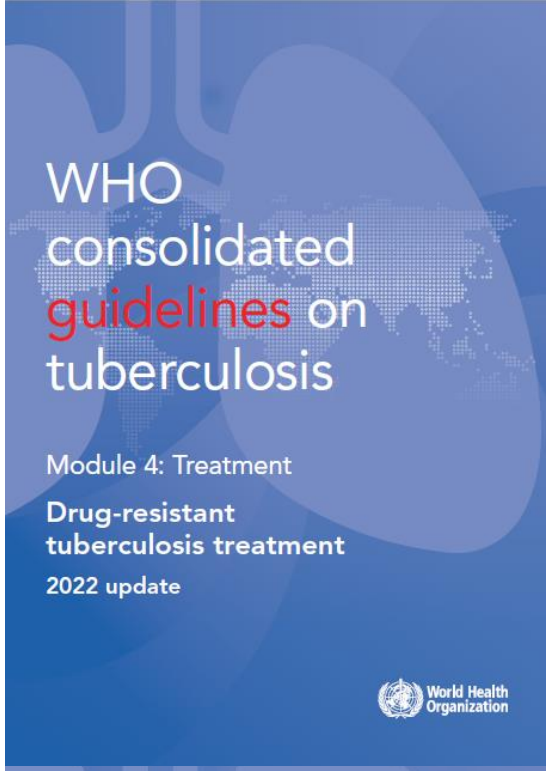
Section 4: **Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis**

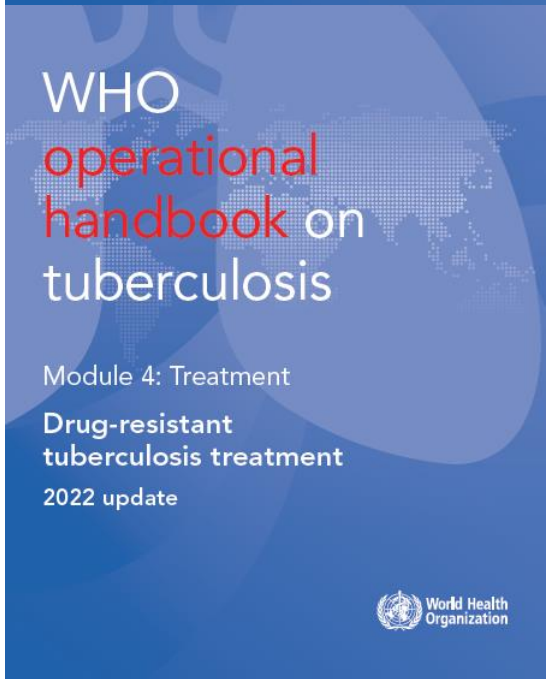
Section 5. **Monitoring patient response to MDR/RR-TB treatment using culture**

Section 6. **Start of antiretroviral therapy in patients on MDR/RR-TB regimens**

Section 7. **Surgery for patients on MDR/RR-TB treatment**

DR-TB handbook was updated in parallel





2022 DR-TB guidelines - key recommendations

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB

2022 DR-TB key recommendations

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB

1.1 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)

Remarks

1. Drug susceptibility testing (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.
2. This recommendation applies to the following:
    a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
    b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.
    c. Adults and adolescents aged 14 years and older.
    d. All people regardless of HIV status.
    e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.
4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.

2022 DR-TB key recommendations – 6-month BPaLM/BPal regimen

Patient selection

High-level summary of main inclusion and exclusion criteria: TB-PRACTECAL and ZeNix trials

	TB-PRACTECAL	ZeNix *(22)*
Inclusion	• Aged 15 years and older • Confirmed TB and RR-TB • Regardless of HIV status	• Aged 14 years and older • Confirmed MDR/RR-TB or pre-XDR-TB • Regardless of HIV status
Exclusion	• Known resistance to Bdq, P, Dlm or Lzd • More than 1 month prior use of Bdq, P, Dlm or Lzd • Pregnant or breastfeeding • Liver enzymes 3 times the upper limit of normal • QTcF >450 ms and other risk factors for QT prolongation (excluding age and gender) or other risk factors for tdp • History of cardiac disease, syncopal episodes, significant symptomatic or asymptomatic arrhythmias (with the exception of sinus arrhythmia) • Moribund • Taking any medications contraindicated with the medicines in the trial • Any baseline laboratory value consistent with Grade 4 toxicity • TB meningoencephalitis, brain abscesses, osteomyelitis or arthritis	• Documented resistance to Bdq, P, Dlm or Lzd • More than 2 weeks of Bdq, Dlm or Lzd • Pregnant • Liver enzymes 3 times the upper limit of normal • BMI <17 • QTcF interval on ECG >500 msec, history of congenital QT prolongation, history of tdp, bradyarrhythmia • Karnofsky score <60 • Peripheral neuropathy of Grade 3–4 • Not expected to survive for more than 6 months • Uncontrolled diabetes or cardiomyopathy, extrapulmonary TB requiring extended treatment, cancer that could affect survival • Abuse of alcohol or illegal drugs • CD4+ count <100 • Use of zidovudine, stavudine or didanosine, use of MAO Inhibitors

6-month regimen BPaLM/BPaL can be used for:

- ✓ People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB)
- ✓ People with confirmed pulmonary TB and all forms of extrapulmonary TB except TB involving the CNS, osteoarticular or disseminated (miliary) TB
- ✓ 14 years and older
- ✓ regardless of HIV status
- ✓ less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimen if resistance to the specific medicines with such exposure has been ruled out

Not recommended during pregnancy owing to limited evidence on the safety of pretomanid

2022 DR-TB guidelines - key recommendations
2. 9-month all-oral regimen for MDR/RR-TB

2022 DR-TB key recommendations
2. 9-month all-oral regimen for MDR/RR-TB

2.1 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)

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.
3. This recommendation applies to :

    a. people with MDR/RR-TB and without resistance to fluoroquinolones.

    b. patients without extensive TB disease and without severe extrapulmonary TB.

    c. patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;.

    d. All people regardless of HIV status.

    e. children (and patients in other age groups) who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

2022 DR-TB key recommendations

2. 9-month all-oral regimen for MDR/RR-TB

Patient selection

9-month regimen can be used for:

- ✓ patients with MDR/RR-TB and without resistance to fluoroquinolones;
- ✓ patients without extensive TB disease and without severe extrapulmonary TB;
- ✓ patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;
- ✓ regardless of HIV status;
- ✓ children and patients in other age groups who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

- ➢ 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
- ➢ **NEW.** In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used.

2022 DR-TB guidelines - key recommendations
3. 18-month all-oral regimen for MDR/RR-TB

2022 DR-TB key recommendations
3. 18-month all-oral regimen for MDR/RR-TB

3.1 Recommendation

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.

(Conditional recommendation, very low certainty of evidence)

2022 DR-TB key recommendations

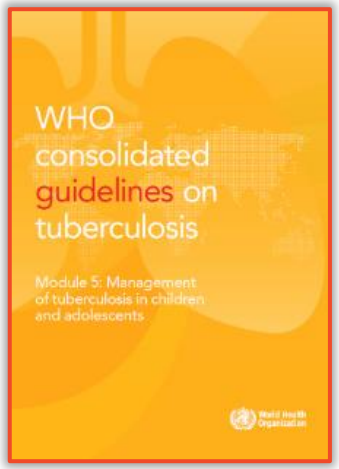
3. 18-month all-oral regimen for MDR/RR-TB

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

NEW. In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used.

NEW. In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens.



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.

MDR/RR-TB regimen selection

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

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

In summary:

- New and shorter treatment regimens for MDR/RR-TB treatment – BPaLM/BPaL and the 9-month regimen
- Longer, 18-20 months regimen – the “last resort” individualized regimen
- The duration of MDR/RR-TB treatment can be the same as of DS-TB treatment
- DST, age and other factors to be considered for MDR/RR-TB regimen selection

Acknowledgements

- Experts participating in the guideline development groups and global consultation meetings
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Thank you

World Health Organization

20, Avenue Appia
1211 Geneva

Switzerland