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**
  - 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)

**DR-TB**
- **Guidelines and handbook 2022 update**
  - 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
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**

- 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
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.

Data reviewed by the WHO Guideline Development Group GDG meeting in February - March 2022
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

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

---

**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).

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

- NEW. 9-month regimen with linezolid instead of ethionamide may be used in **pregnant women**, unlike the regimen with ethionamide.
2022 DR-TB guidelines - 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

<table>
<thead>
<tr>
<th>Groups and steps</th>
<th>Medicine</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Include all three medicines</td>
<td>Levofoxacin or</td>
<td>Lfx</td>
</tr>
<tr>
<td></td>
<td>moxifloxacin</td>
<td>Mfx</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline$^{bc}$</td>
<td>Bdq</td>
</tr>
<tr>
<td></td>
<td>Linezolid$^{d}$</td>
<td>Lzd</td>
</tr>
<tr>
<td>Group B:</td>
<td>Clofazimine</td>
<td>Cfz</td>
</tr>
<tr>
<td>Add one or both medicines</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycloserine or</td>
<td>Cs</td>
</tr>
<tr>
<td></td>
<td>terizidone</td>
<td>Trd</td>
</tr>
<tr>
<td>Group C:</td>
<td>Ethambutol</td>
<td>E</td>
</tr>
<tr>
<td>Add to complete the regimen and when medicines from</td>
<td>Delamanid$^{a}$</td>
<td>Dlm</td>
</tr>
<tr>
<td>Groups A and B cannot be used</td>
<td>Pyrazinamide$^{f}$</td>
<td>Z</td>
</tr>
<tr>
<td></td>
<td>Imipenem–cilastatin or</td>
<td>Ipm–Cln</td>
</tr>
<tr>
<td></td>
<td>meropenem$^{g}$</td>
<td>Mpm</td>
</tr>
<tr>
<td></td>
<td>Amikacin (or streptomycin)$^{h}$</td>
<td>Am (S)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide or</td>
<td>Eto</td>
</tr>
<tr>
<td></td>
<td>prothionamide$^{l}$</td>
<td>Pto</td>
</tr>
<tr>
<td></td>
<td>$^{a}$P-aminosalicylic acid$^{l}$</td>
<td>PAS</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>MDR/RR-TB \nfluoroquinolone susceptible</th>
<th>Pre-XDR-TB</th>
<th>XDR-TB</th>
<th>Extensive pulmonary TB</th>
<th>Extrapulmonary TB</th>
<th>Age &lt;14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month BPaLM/BPal</td>
<td>Yes (BPaLM)</td>
<td>Yes (BPal)</td>
<td>No</td>
<td>Yes</td>
<td>Yes – except TB involving CNS, miliary TB and osteoarticular TB</td>
<td>No</td>
</tr>
<tr>
<td>9-month all-oral</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes – except TB meningitis, miliary TB, osteoarticular TB, and pericardial TB</td>
<td>Yes</td>
</tr>
<tr>
<td>Longer individualized 18-month</td>
<td>Yes³/No</td>
<td>Yes³/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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.

³ 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
• NTPs, researchers and partners who shared data for the WHO guideline updates
• Fuad Mirzayev, Medea Gegia, Linh Nguyen, Samuel Schumacher, Zignol Matteo and other colleagues in Global Tuberculosis Programme, WHO

Thank you