Workshop

Joint SEAR-WPR workshop to plan the accelerated implementation of new WHO TB policies

1-4 APRIL 2025

Hanoi, Viet Nam

New modified 9-month regimens for treatment of drug-resistant TB

Linh Nguyen

TB treatment team

WHO Global Programme on Tuberculosis & Lung health

Outline

- Source of evidence
- Recommendation
- Eligibility
- Regimen selection
- Composition & duration
- Drug dosage & frequency
- Subgroups
- Implementation considerations
- Treatment monitoring & outcome assignment

Source of evidence – endTB trial

A multi-country clinical trial, five modified 9-month regimens

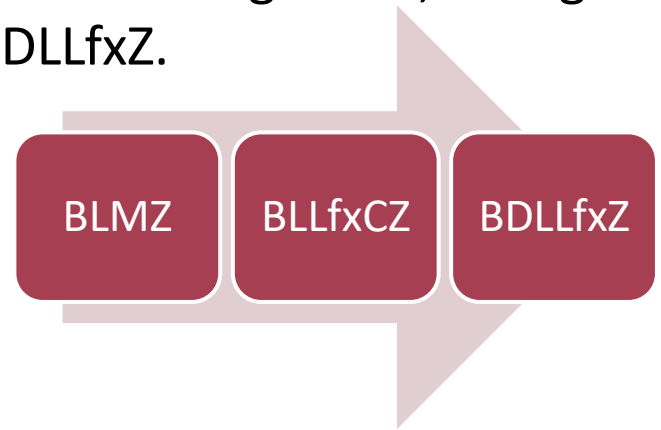
Population	Intervention	Comparator
Patients with microbiologically confirmed pulmonary MDR/RR-TB and without FQ resistance	9Bdq-Lzd-Mfx-Z 9Bdq-Lzd-Cfz-Lfx-Z 9Bdq-Lzd-Dlm-Lfx-Z 9Dlm-Cfz-Lzd-Lfx-Z 9Dlm-Cfz-Mfx-Z	WHO currently recommended longer regimens (18-20 months)

Recommendations

Recommendation 2.2

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)



Recommendation 2.3

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 criteria (Recommendation 2.2)

- MDR/RR-TB without resistance to fluoroquinolones
- All age groups, including children and adolescents
- PLHIV, pregnant and breastfeeding women
- Diagnosed PTB, including extensive PTB disease
- All forms of EPTB - except CNS TB, osteoarticular TB, or disseminated forms of TB with multi-organ involvement
- Less than 1 month of previous exposure to any of the component medicines of the regimen (apart from PZA and FQs); or exposure > 1 month and resistance to the medicine with such exposure has been ruled out
- Children and adolescents without bacteriological confirmation of TB or resistance patterns but with a high likelihood of MDR/RR-TB

Factors to be considered for selection of modified 9-month regimens

Regimen	MDR/RR-TB FQ-susceptible	MDR/RR-TB FQ susceptibility not known	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB disease	Extra-pulmonary TB	Age below 14	Pregnant & breastfeeding woman
6-month regimens								
BPaLM/BPaL	BPaLM	BPaLM	BPaL	No	Yes	Yes[1]	No	No
BDLLfxC/BDLLfx/BDLC	BDLLfx	BDLLfxC	BDLC				Yes	Yes
9-month regimens								
BLMZ	Yes	No	No	No	Yes	Yes[1]	Yes	Yes
BLLfxCZ								
BDLLfxZ								
4–6 $Bdq_{(6m)}$-Lfx/ Mfx-Cfz-Z-E-Hh-Eto or $Lzd_{(2m)}$ / 5 Lfx/ Mfx-Cfz-Z-E)	Yes	No	No	No	No	Yes[1]	Yes	Yes[3]
Longer regimens								
Individualized 18-month regimen	No[2]	No[2]	No[2]	Yes	No	No[2]	No[2]	No[2]

Additional factors to be considered if several regimens are possible

- Patient's age and preferences
- Disease extent and localization
- Drug intolerance or adverse events
- Treatment history, previous exposure to regimen component drugs, or likelihood of drug effectiveness
- Access to and price of the regimen component drugs
- Pill burden

Selecting a modified 9-month regimen

Regimen	Health effect	Cost	Pill burden	Others
BLMZ	Most preferable among the three	Lowest cost	Lowest pill burden	Preferable/equivalent for all other criteria
BLLfxCZ	Slightly preferable to BDLLfxZ	Lower cost than BDLLfxZ	Lower pill burden than BDLLfxZ	More equitable, acceptable, and feasible compared to BDLLfxZ
BDLLfxZ	Similar but less preferable to BLLfxCZ	Significantly higher cost	Higher pill burden	Higher cost likely to negatively affect equity, acceptability, and feasibility

Composition of the regimens

BLMZ

Bedaquiline-linezolid-moxifloxacin-pyrazinamide

BLLfxCZ

Bedaquiline-linezolid-levofloxacin-clofazimine-pyrazinamide

BDLLfxZ

Bedaquiline-delamanid- linezolid-levofloxacin-pyrazinamide

- *Swapping fluroquinolones (Mfx to Lfx or vise versa) is not advisable*

Drug dosage and frequency

Bedaquiline:

- 400mg for first 2 weeks, then 200mg x 3 times a week; or
- 200 mg daily for 8 weeks, then 100 mg daily afterwards

✓ *Either Bdq dosing strategy is acceptable*

Linezolid:

600 mg once daily for 16 weeks then

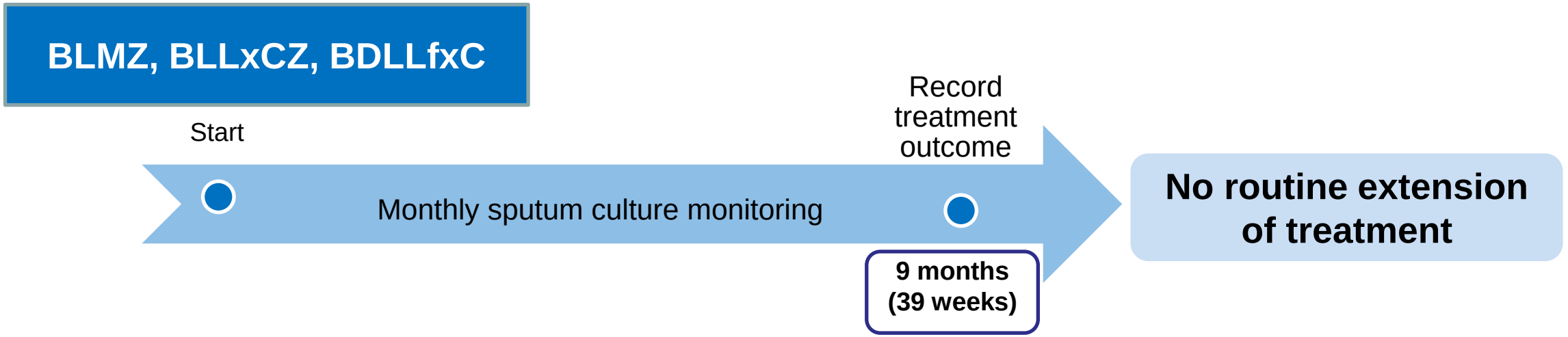
- 300 mg once daily till the end of treatment; or
- 600 mg 3 times a week until the end of treatment

✓ *Either linezolid dose reduction strategy is acceptable as a standard practice*

✓ *Linezolid may be reduced or discontinued earlier if toxicity occurs before 16 weeks, but ideally not before 9 weeks*

Reference: *Annex 4. Dosing of medicines used in TB regimens, adults and children*
WHO consolidated operational handbook on tuberculosis: Module 4: treatment and care

Duration of regimens



- All medicines to be used throughout treatment duration (9 months or 39 weeks) and no routine extension of treatment
- Missed doses should be made up to complete all doses within an 11-month timeframe

Modification or discontinuation of treatment

- **Lack of treatment response**

✓ Month 4 : No clinical/bacteriological improvement → Investigate for drug resistance

✓ Month 6: Persistent smear/culture positivity or no clinical improvement → Switch to a longer regimen

- **Acquired drug resistance**

✓ If fluoroquinolone resistance or resistance to any component drug (except PZA) develops → Declare treatment failure and start a new regimen

- **Adverse events**

✓ Stopping PZA or Lzd may be possible while continuing treatment

✓ If more than one drug must be discontinued → Switch to an alternative treatment

Subgroup considerations

Breastfeeding women

- **BLMZ preferred** due to fewer drugs & history of prior drug use in breastfeeding women

✓*Drug transfer in breast milk to infant is minimal, but more evidence is needed*

✓*Infection control measures are required*

Pregnant women

- **BLMZ preferred** due to fewer drugs & the drugs have been used in pregnancy

✓*Limited data (pregnant patients were excluded from the endTB trial)*

✓*Requires close monitoring on safety and efficacy*

Children

- **BLMZ regimen preferred** as of low pill burden & child-friendly formulations available

✓*Not included in the endTB trial but similar drugs/combinations have been used safely in children*

✓*Close monitoring required for **Lzd toxicity** (e.g. blood disorders, neuropathy, vision issues)*

Subgroup considerations

PTB

- Modified 9-month regimens can be used for **all forms of PTB**
  - All PTB forms were included in the trial
  - Patients with cavities or high-grade sputum smears had lower overall success rates but still better than in the control arm

EPTB

- The trial enrolled only a few patients with EPTB and **no patients with severe forms of extrapulmonary TB**
- Efficacy of the regimens in treating severe forms of EPTB (e.g. CNS TB, osteoarticular TB or disseminated TB) **remains unproven**

Subgroup considerations - comorbidities

Diabetes Mellitus

- Modified 9-month regimens **can be used in DM patients**
- **Close monitoring** required for neuropathy in patients on Lzd
- **Treatment of DM** should be provided alongside DR-TB treatment

Hepatic Dysfunction

- Patients with **moderate to advanced liver disease** may require an alternative regimen (due to high risk of **PZA hepatotoxicity**)
- **ALT level >3x:** Modified 9-month regimens not recommended

HIV

- All three modified 9-month regimens showed good outcomes for PLHIV

Implementation considerations in relation to PZA

PZA susceptibility

- PZA be used as part of the regimen

✓Monitor for hepatotoxicity and discontinue if severe toxicity occurs

PZA resistance

- PZA can be discontinued

✓Regimens remain effective, but careful monitoring is required

PZA DST unknown

- PZA should be used

✓Monitor for hepatotoxicity and adjust treatment if needed

World Health Organization

END TB

Treatment monitoring

The same monitoring as for other DR-TB regimens is applied to modified 9-month regimens

- **Monitoring treatment response**
  - Monthly sputum smear microscopy and culture to evaluate bacteriological response, DST in case of poor response
  - Regular clinical examinations to evaluate clinical improvement
  - Radiological assessments at baseline & end of treatment
- **Monitoring safety**
  - Clinical and laboratory examinations

Treatment monitoring examinations

(For all DR-TB regimens)

Examination	Baseline	2nd week (for Lzd-containing regimens)	Monthly	End of treatment	6 and 12 months post-treatment
Clinical evaluation	✓	✓	✓	✓	✓
Bacteriological tests					
Smear microscopy	✓		✓	✓	✓
TB culture	✓		✓	✓	✓
DST **Xpert MTB/XDR or** **First- and second-line LPA** **Phenotypic DST**	✓ ✓		If culture remains positive at month 4 of treatment in cases of culture reversion or culture positivity during post-treatment follow-up		
Diagnostic tests					
Chest X-ray (every 6 months)	✓			✓	✓
ECG **(Bdq, Dlm, Pa, Mfx, Lfx or Cfz)**	✓		pre-existing cardiac disease or symptoms	✓	
Visual acuity&colour vision tests (Lzd or E)	✓	✓	✓	✓	
peripheral neuropathy screening **(ILzd, H, Cs, Trd, Lfx, Mfx, or Am)**	✓	✓	✓	✓	
Mental health screening (PHQ-9)	✓		✓ (ICs or Hh)	✓	

Treatment monitoring examinations (cont)

Examination	Baseline	2nd week (for Lzd cont. regimens)	Monthly	End of treatment	6 and 12 months post-treatment
Blood chemistry, haematological & immunological tests					
ALT and AST (Z, H, Pa, Bdq, Eto/Pto, Cs/Trd or PAS)	✓		✓	✓	
CBC with platelet count (if regimen contains Lzd, Mpm, H or Pa)	✓	✓	✓	✓	
Fasting blood sugar and/or glycosylated haemoglobin	✓				
Serum potassium	✓				
Creatinine (monthly Am, S)	✓		✓		
TSH (If Pto/Eto or PAS; then 3-monthly)	✓				
Albumin (Dlm)	✓				
Pregnancy test (reproductive age)	✓				
HIV screening	✓				
CD4 count (latest test for PLHIV)	✓				
HBsAg and anti-HCV	✓				

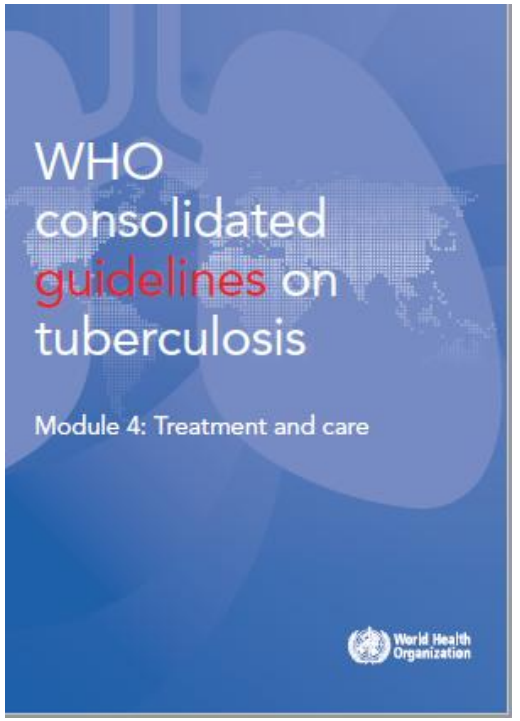
Source: ***Annex 2. Table A2.2. Recommended schedule of baseline, routine and post-treatment monitoring examinations and tests for patients receiving DR-TB treatment.*** **WHO consolidated operational handbook on tuberculosis: Module 4: treatment and care**

World Health Organization

END TB

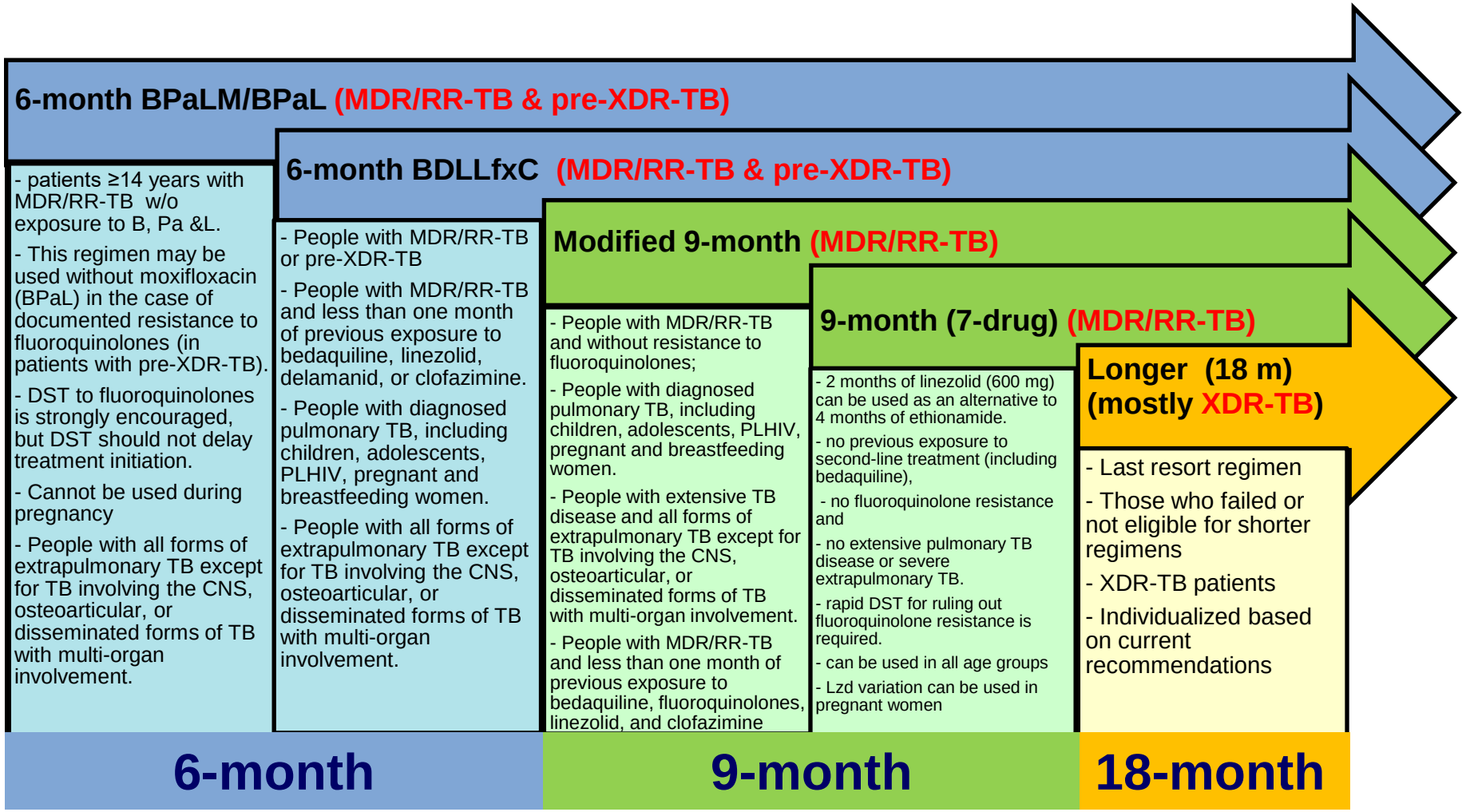
Treatment outcome definitions

Outcome	Definition
Treatment failed	A patient whose treatment regimen needed to be terminated or permanently changed[a] to a new regimen or treatment strategy.
Cured	A patient with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response[b] and no evidence of failure.
Treatment completed	A patient who completed treatment as recommended by the national policy but whose outcome does not meet the definition for cure or treatment failure.
Died	A patient who died[c] before starting treatment or during the course of treatment.
Lost to follow-up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned.[d]
Treatment success	The sum of all patients cured and treatment completed.
An optional definition was also proposed for use in operational research only	
Sustained treatment success	An individual assessed at 6 months (for DS-TB and DR-TB) and at 12 months (for DR-TB only) after successful TB treatment, who is alive and free of TB.



- **Treatment outcome definitions are the same for DS &DR TB**

Treatment options for MDR/RR-TB patients



World Health Organization

END TB

9-month regimen options

	Regimen	Duration	Core Drugs (months)	Variable/ Additional Drugs (months)	Key Features
Modified 9-month regimens (4–5 drugs)	9BLMZ	9 months	B, L, M, Z	-	All-oral regimen for fluoroquinolone-susceptible MDR/RR-TB.
	9BLLfxCZ		B, L, Lfx, Z	C	All-oral regimen for fluoroquinolone-susceptible MDR/RR-TB.
	9BLLfxDZ		B, L, Lfx, Z	D	All-oral regimen for fluoroquinolone-susceptible MDR/RR-TB.
9-month regimen (7 drugs)	**Ethionamide variation** 4–6 $B_{(6m)}$-Lfx/ M-C-Z-E-Hh-Eto / 5 Lfx/M-C-Z-E **Linezolid variation** 4–6 $B_{(6m)}$-Lfx/ M-C-Z-E-Hh-$L_{(2m)}$ / 5 Lfx/M-C-Z-E	9–11 months	B (6), Lfx/M (9–11), Z (9–11), C (9–11), E (9–11), Hh (4–6)	Eto (4–6), L (2)	All-oral regimen for fluoroquinolone-susceptible MDR/RR-TB. Ethionamide and linezolid are used for specific durations; duration depends on treatment response at month 4.

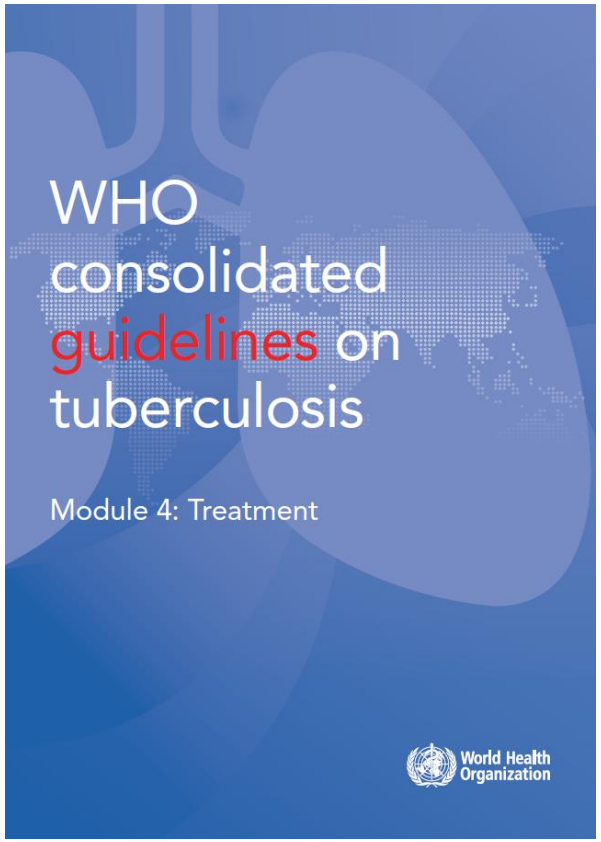
World Health Organization

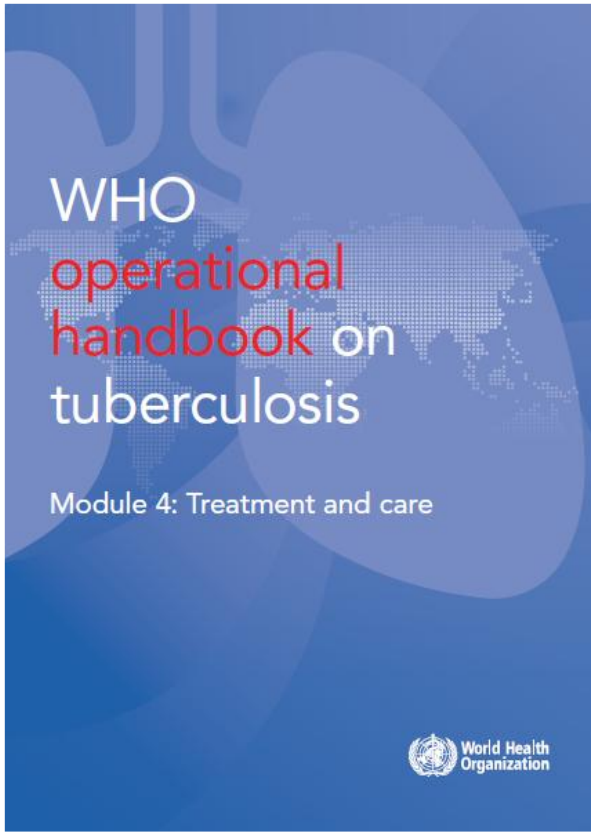
END TB

Main messages

- While 6-month regimens are the preferred choices for patients with MDR/RR-TB without FQ resistance, the modified 9-month regimens are considered as good alternatives with some limitations
- Modified 9-month regimens:
  - ✓ are applicable for all age groups
  - ✓ can be used for pregnant and breastfeeding women
  - ✓ have less medicines compared to the 9-month regimen containing 7 medicines

WHO consolidated guidelines on tuberculosis
Module 4: Treatment and care (2025)





https://iris.who.int/handle/10665/380799

World Health Organization

END TB

World Health Organization

Consolidated Guidelines | Operational Handbooks | Training Catalogue | Research and Innovation | English | Log in

WHO TB Knowledge Sharing Platform

Access the modular WHO guidelines on tuberculosis, with corresponding handbooks and training materials.

Quick search

Search for information about TB

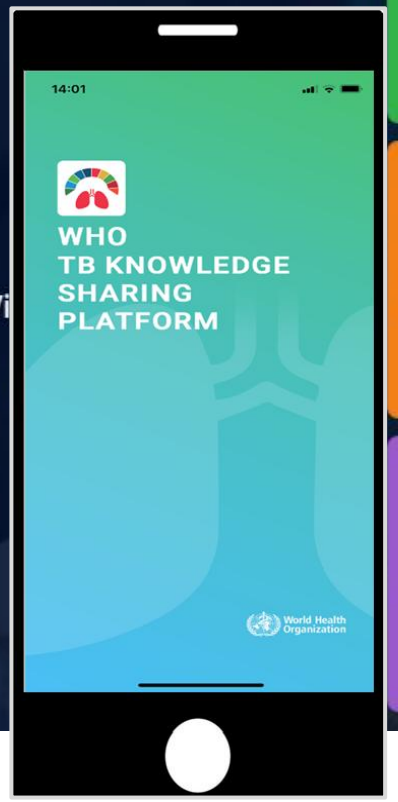
Drug Dosage Finder

Download WHO TB Knowledge Sharing Platform Application

Desktop Version

Mobile Version

https://tbksp.who.int



Consolidated Guidelines

WHO guidelines provide the latest evidence-informed recommendations on TB prevention and care to help countries achieve the Sustainable Development Goals (SDGs) and the targets of the End TB Strategy.

Learn more →

Operational Handbooks

The WHO Operational Handbooks on tuberculosis provide users with practical "how to" guidance, with details essential for the proper implementation of the corresponding WHO guidance.

Learn more →

Training Catalogue

The WHO Training Catalogue on tuberculosis consists of online eLearning courses and other training materials to help users implement the corresponding WHO guidance.

Learn more →

Research and Innovation

WHO normative guidance on tuberculosis research and innovation seek to shape the research agenda and innovation landscapes to bette prevent and respond to tuberculosis.

Acknowledgements

- National TB programmes, research partners, civil society representatives and experts who contributed to the update of WHO guidelines and operational handbooks on TB treatment and care

- Fuad Mirzayev, Medea Gegia, Francesca Conradie, Samuel Schumacher, Matteo Zignol and others at the WHO Global Programme on Tuberculosis & Lung Health

World Health Organization

END TB