World Health Organization

END TB

WHO DR-TB treatment guidelines, BPaL regimen and new definitions

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EURO BPaL webinar
23 April 2021

WHO guidance on treatment and management of drug-resistant TB, June 2020 update

World Health Organization | Health Topics | Countries | Newsroom | Emergencies | Data

15 June 2020 | Departmental news

WHO urges countries to enable access to fully-oral drug-resistant TB treatment regimens

13 January 2020 | Departmental news

WHO announces updates on new molecular assays for the diagnosis of tuberculosis and drug resistance

1 November 2019 | Departmental news

TDR and WHO launch SHOR operational research packa... assess all-oral shorter MDR... treatment regimens

Publications

15 June 2020

WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment

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WHO Operational Handbook on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment

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15 October 2019

Global tuberculosis report 2019

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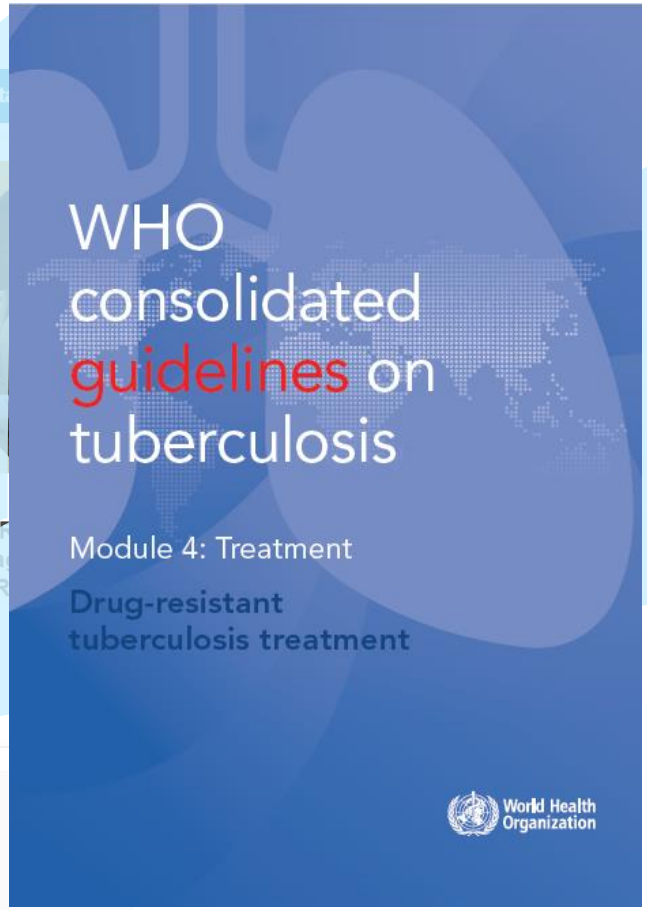
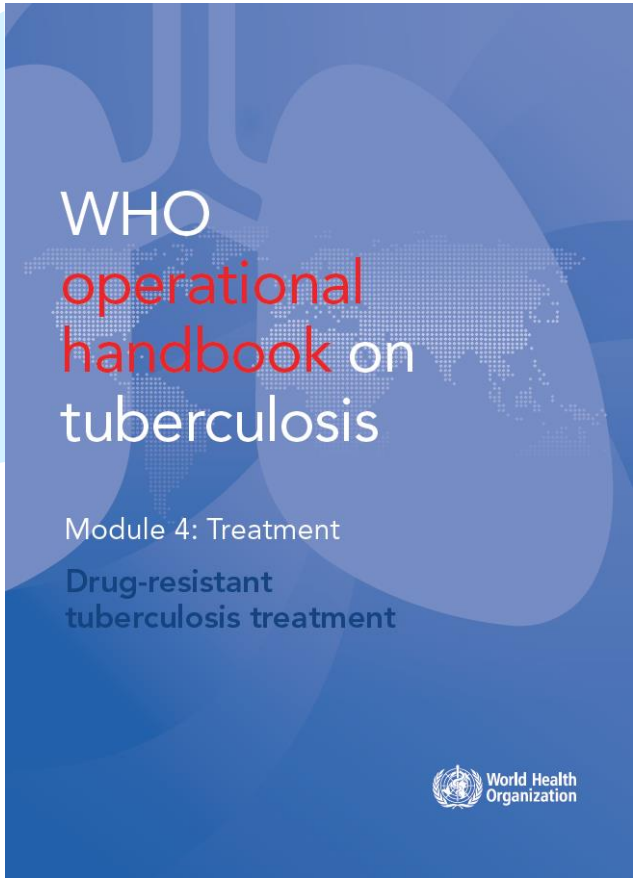




2020 DR-TB consolidated guidelines

Section 1. Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis

Section 2. Shorter, all-oral, bedaquiline-containing regimen for MDR/RR-TB

Section 3: Longer regimens for MDR/RR-TB

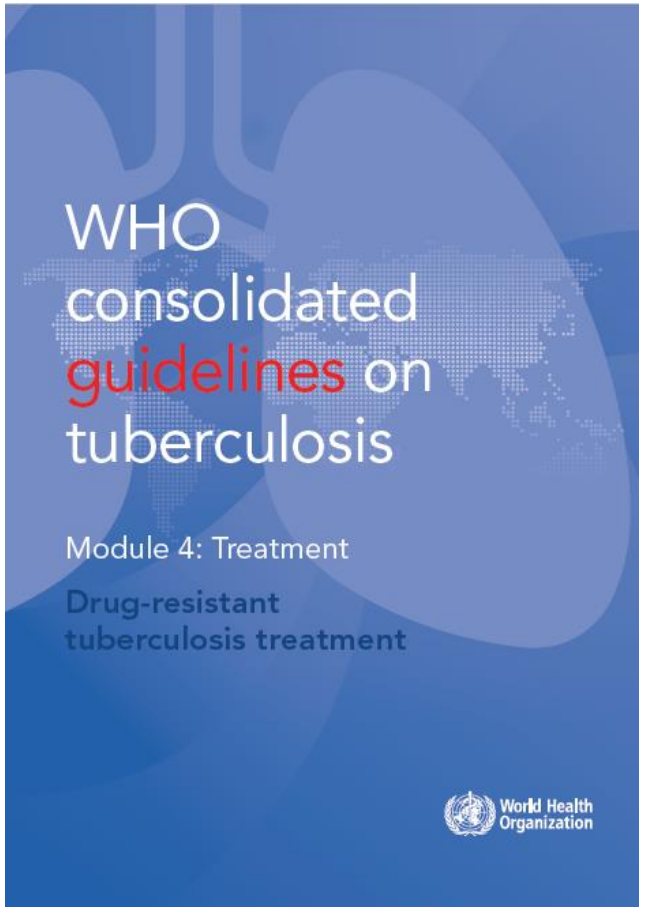
Section 4: The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance

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

Section 6. Start of antiretroviral therapy in patients on second-line antituberculosis regimens

Section 7. Surgery for patients on MDR-TB treatment

Section 8. Care and support for patients with MDR/RR-TB

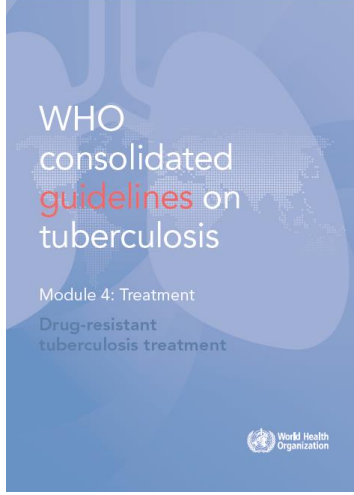


Available on the WHO website from June 2020

Presented and discussed in Regional workshops involving countries of all regions

Russian, Spanish and French translations

DR-TB treatment guidelines 2020



All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, may benefit from effective all-oral treatment regimens, shorter or longer.

1. **For MDR/RR-TB patients without previous exposure to second-line treatment and bedaquiline, without fluoroquinolone resistance and no extensive TB disease or severe extrapulmonary TB**, the preferred treatment option is a shorter, all-oral, bedaquiline-containing regimen. In this group of patients, national programmes can phase out use of the injectable-containing shorter regimen.

4-6 Bdq (6m)-Fq-Cfz-Z-E-Hh-Eto / 5 Fq-Cfz-Z-E

2. **The MDR/RR-TB patients with extensive TB disease, severe forms of extrapulmonary TB, those with resistance to fluoroquinolones or who have been exposed to treatment with second-line drugs** will benefit from an individualized longer regimen designed using the priority grouping of medicines.

Groups & steps	Medicine	
Group A: Include all three medicines	Levofloxacin *or* Moxifloxacin	Lfx / Mfx
	Bedaquiline	Bdq
	Linezolid	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	Dlm
	Pyrazinamide	Z
	imipenem–cilastatin *OR* Meropenem	Ipm-Cln / Mpm
	amikacin (*OR* streptomycin)	Am (S)
	ethionamide *OR* Prothionamide	Eto / Pto
	p-aminosalicylic acid	PAS

3. **Novel** BPaL regimen **for MDR-TB with additional quinolone resistance** under operational research conditions

6 Bdq-Pretomanid-Lzd

The BPaL regimen for MDR-TB with additional fluoroquinolone resistance

Recommendation

4.1 A treatment regimen lasting 6-9 months composed of bedaquiline, pretomanid and linezolid (BPaL) may be used under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones who have had no previous exposure to bedaquiline and linezolid for more than two weeks (conditional recommendation, very low certainty in the estimates of effect).

Remarks

- The BPaL regimen may not be considered for routine programmatic use worldwide until additional evidence on efficacy and safety has been generated. However, in individual patients for whom the design of an effective regimen based on existing WHO recommendations is not possible, the BPaL regimen may be considered as a last resort under prevailing ethical standards.
- The evidence reviewed supports the use of this regimen in certain patient sub-groups such as people living with HIV infection.

The BPaL regimen for MDR-TB with additional fluoroquinolone resistance

Implementation considerations and eligibility

- Patient is diagnosed with bacteriologically confirmed pulmonary TB and has laboratory-confirmed resistance to rifampicin and fluoroquinolones with/without resistance to injectable agents; and
- Is at least 14 years of age at the time of enrolment; and
- Weighs 35kg or more; and
- Is willing and able to provide informed consent to be enrolled in the operational research project and to adhere to the follow-up schedule; and
- If the patient is a pre-menopausal woman, she is not pregnant or breastfeeding and is willing to use effective contraception; and
- Has no known allergy to any of the BPaL component drugs; and
- Has no evidence in DST results of resistance to any of the component drugs; or has not been previously exposed to any of the component drugs for two weeks or longer; and
- Has no extra-pulmonary TB (including meningitis, other central nervous system TB, or TB osteomyelitis).

DST results

Essential – rifampicin and quinolones
Important – bedaquiline, linezolid

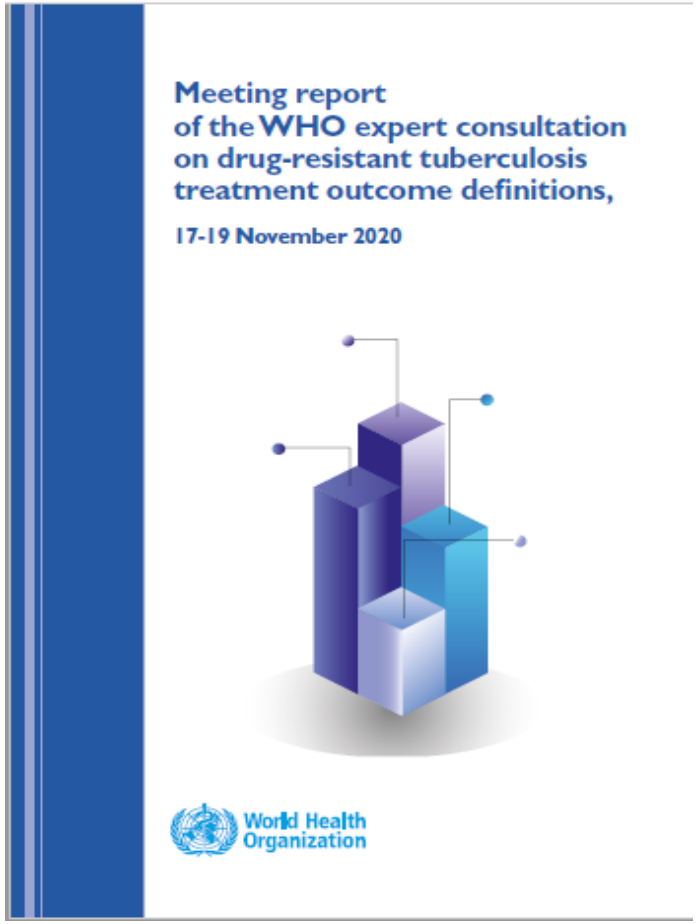
Operational research

National TB Programmes and their stakeholders are encouraged to solicit advice from WHO and technical partners before mounting operational research for modified shorter regimens or the BPaL regimen.

To facilitate initiation of operational research by country programs, the Special Programme for Research and Training in Tropical Diseases (TDR) in close collaboration with the Global TB Programme at WHO and technical partners has developed ShORRT (Short, all-Oral Regimens For Rifampicin-resistant Tuberculosis), an operational research package to assess the effectiveness, safety, feasibility, acceptability, cost and impact of the use of shorter drug regimens for patients with DR-TB.

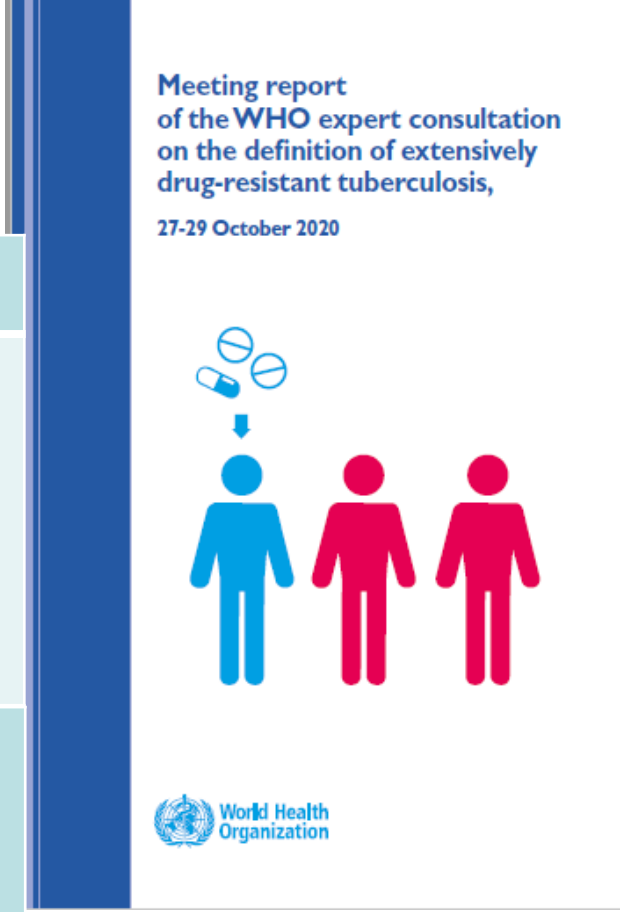
Other normative documents

- XDR definition 2021
- Outcome definitions 2021



2021 XDR-definition

Definition	Meaning	Considerations
MDR/RR-TB	RIF and INH resistance RIF resistance	• resistance to most potent FLDs • important to keep multi- label in the general context of AMR • well established and useful communication/advocacy • rapid DST available widely • indicates need of second-line treatment • unchanged for the moment may require adjustment if/when results of Study 31 will translate into policy recommendations
Pre-XDR	MDR/RR-TB + FQL*	• FQL* - potent Group A drugs • rapid DST for FQL is available (not yet for BDQ and LZD) • if study 31 results make it into recommendations, FQL may be part of first-line TB treatment • indicates change in treatment pathway (no for shorter regimen but yes for longer regimens and BPaL)
XDR	MDR/RR-TB + FQL + (at least one other drug from Group A, BDQ or LZD)	• evidence on potential use of LZD in shorter regimen soon to be available, will make both LZD and BDQ present in all MDR regimens • not singling out BDQ or LZD makes it future-proof • definition will remain relevant as condition with very limited treatment options • 14 yrs of advocacy and messaging is not lost • importance for AMR agenda



*Quinolones as listed in the current WHO guidelines

Summary new outcome definitions for DS and DR-TB

TREATMENT FAILED
A patient whose treatment regimen needed to be terminated or permanently changed[1] to a new regimen option or treatment strategy.

CURED
A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response[2] and no evidence of failure.

TREATMENT COMPLETED
A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failure.

DIED
A patient who died[3] before starting 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[4].

TREATMENT SUCCESS

The sum of cured and treatment completed

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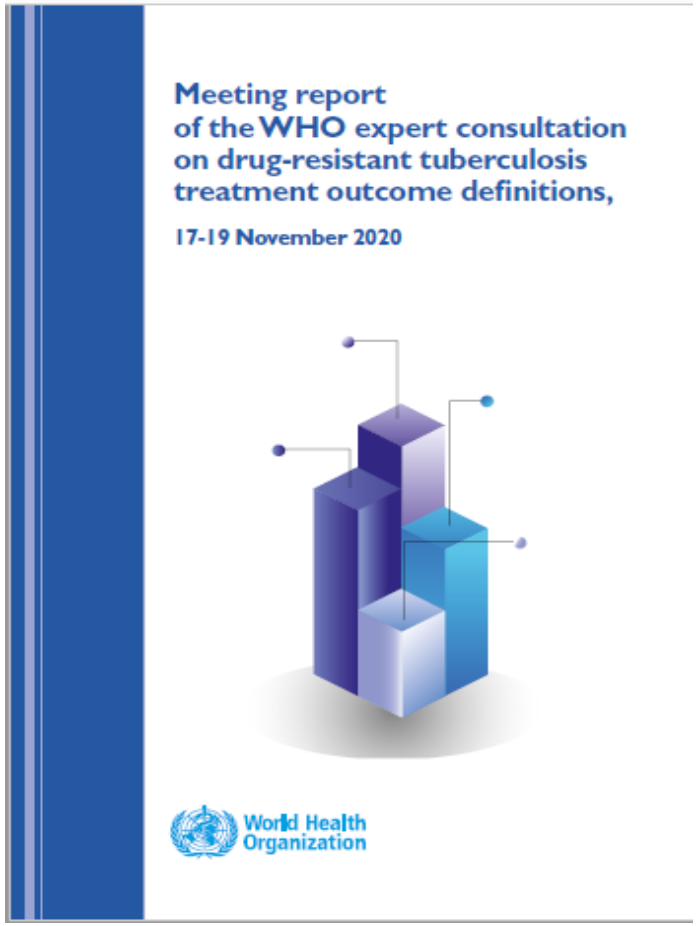
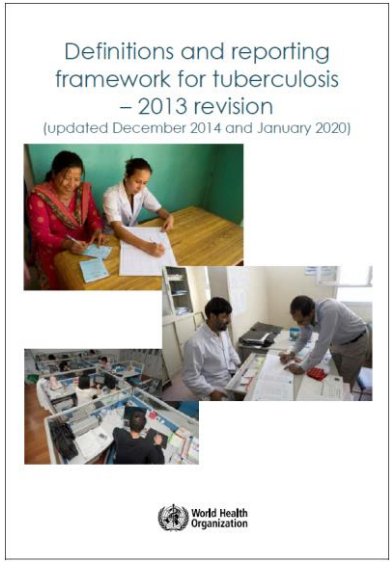
and an optional definition

SUSTAINED TREATMENT SUCCESS *(for use in operational research only)*

An individual assessed at 6 months (DS-TB and DR-TB) and 12 months (DR-TB) after successful TB treatment who is alive and TB free.





To be featured in the updated Definitions and reporting Framework Expected to be released in 2021

Plan for new developments in 2021:

Guidelines

DS-TB

DS-TB guidelines 2021 (update)

- 4-months quinolone-based regimen

Public call for data on DR-TB treatment (Q2 2021)

DR-TB

DR-TB guidelines 2022 (update)

- Review PRACTECAL trial data (BPaLM)
- Update on the all-oral shorter regimens for MDR/RR-TB
- Update on BPaL for pre-XDR-TB (use, duration of components and dosing)
- Revisit Bdq use for longer than 6 months and Bdq-Dlm concurrent use
- DR-TB and HCV treatment co-administration
- Use of new medicines in DR-TB treatment in pregnancy

Plan for new developments in 2021:
Handbooks and other normative documents

DS-TB

DS-TB handbook 2021 (new)

- Selection of treatment regimen (depending on outcomes of GDG)
- Dosing of component medicines in DS-TB regimens (sys review)
- Definition of TB disease severity

Updated Target TB treatment Regimen Profiles (2022)

Updated Definitions and reporting framework 2021

DR-TB

DR-TB handbook 2022 (update)

- Update on the implementation aspects for all sections where guidelines were updated

DR-TB training modules 2021 (KNCV collaboration)

Thank you

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