DRUG-RESISTANT TUBERCULOSIS

Guidelines for MDR-TB: Updates

What changed, why it changed, and how to apply it — WHO 2026 · ATS/CDC/ERS/IDSA 2025 · DACH 2025

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Background

For decades, MDR-TB treatment meant 18–24 months, injectables and poor outcomes

18–24

months of treatment

Individualised longer regimens with many drugs and a high pill burden

Injectables

for months

Aminoglycosides and capreomycin, with permanent toxic effects such as hearing loss

Most people with MDR/RR-TB are still not treated

The 2024 cascade

390 000 developed MDR/RR-TB (estimate)



172 732 detected (MDR/RR + pre-XDR/XDR)



164 545 started treatment — **42%** of estimated cases



Treatment success

50% 2012 cohort

71% 2022 cohort

WHO 2026

Ten years: from injectables to 6-month all-oral regimens

2016

Long regimens Standardised shorter regimen, 9–12 months, still with an injectable (not supported by ERS or ATS)

2018

All-oral regimens prioritised

2019

All-oral 9-month bedaquiline regimen; BPaL under operational research

2022

6-month BPaLM / BPaL for MDR/RR-TB and pre-XDR-TB

2025

6-month BDLLfxC, modified 9-month regimens

2026

Pre-XDR-TB by severity: BPaL or BPaLC

WHO 2026 | ATS/CDC/ERS/IDSA 2025 | DACH 2025

Three guidelines, three lenses on the same evidence

	WHO Module 4	ATS/CDC/ERS/IDSA	DACH consensus
	■ WHO 2026	■ ATS/CDC/ERS/IDSA 2025	■ DACH 2025
Published	2026, 2nd edition	January 2025	November 2025
Method	GRADE, new evidence (GDGs June 2024 and November 2025)	GRADE-ADOLOPMENT of WHO 2022	Expert consensus adapting WHO 2025
Setting	Programmes in high-burden countries	Low incidence, high resources	Germany, Austria, Switzerland
DR-TB scope	6-month, 9-month and longer regimens, Hr-TB, HIV, HCV, surgery	BPaL and BPaLM only	6-month options

The question is no longer “can we shorten?” but “for whom, with what, for how long?”

- **Strength of recommendation**
- **Special populations**
- **Duration and disease severity**

Trial evidence

Nix-TB and ZeNix: BPaL works — and linezolid 600 mg keeps efficacy with less toxicity

Nix-TB

Single-arm, South Africa · BPaL with linezolid 1200 mg, 6 months

~90% favourable outcome

Highly resistant or intolerant disease — but adverse events driven mainly by linezolid 1200 mg

ZeNix

Randomised, partially blinded · n = 181 · linezolid 1200 or 600 mg, for 9 or 26 weeks

91% favourable with 600 mg, 26 weeks — vs 93% with 1200 mg

%

26 weeks	600mg	1200mg
Peripheral neuropathy	24%	38%
Myelosuppression	2%	22%
Optic neuropathy	0	4 patients

Conradie F et al. N Engl J Med 2020;382:893–902 · Conradie F et al. N Engl J Med 2022;387:810–23 (modified intention-to-treat, 26 weeks after treatment)

Trial evidence

TB-PRACTECAL: a 6-month regimen outperformed 9–24-month standard care

Outcome	BPaLM	Standard care
Treatment success	89%	52%
Failure or recurrence	8%	26%
Loss to follow-up	3%	20%
Grade 3–5 adverse events	21%	51%

- Open-label, phase 2/3; stopped early
- 62 vs 66 participants in the BPaLM comparison
- Control arm mixed 9–24-month regimens, some with injectables

WHO 2025 | ATS/CDC/ERS/IDSA 2025

BPaLM became the regimen of choice for eligible patients aged 14 years or older

Eligible

- MDR/RR-TB: BPaLM · pre-XDR-TB: BPaL (moxifloxacin dropped)
- Age 14 years or older, any HIV status
- Pulmonary and most extrapulmonary TB
- Under 1 month of previous Bdq, Lzd, Pa or Dlm — or resistance ruled out

Not eligible

- Pregnancy and breastfeeding (limited pretomanid safety data)
- Children under 14 years
- CNS, osteoarticular or disseminated multi-organ TB

Linezolid 600 mg daily · WHO: conditional, very low certainty · ATS/ERS: strong, very low certainty

WHO 2025 DACH 2025

But BPaLM leaves key patients behind

Children under 14

Pretomanid data limited or absent

Pregnancy and breastfeeding

Limited pretomanid safety data

Intolerance or prior exposure

Over 1 month of key drugs without proof of susceptibility

Access

Pretomanid cost and a licensed indication out of step with guidance

Trial evidence

BEAT-Tuberculosis: a pretomanid-free 6-month strategy for all ages, including pregnancy

Design	Phase 3, open-label, pragmatic, non-inferiority (margin 10 points)
Setting	2 sites, South Africa, 2019–2022
Population	n = 403, age 6 or older; HIV 50.9%; pregnant women and FQ-resistant TB included
Comparator	South African standard: 9 months; longer if FQ-resistant

TRIAL STRATEGY · 6 MONTHS

B · D · L

bedaquiline, delamanid, linezolid 600 mg

+ levofloxacin and/or clofazimine, adjusted to the fluoroquinolone result

Trial evidence

BEAT-Tuberculosis was non-inferior

Successful outcome at week 76

86.1% 6-month strategy

86.0% Standard care

Adjusted difference −0.2 points (95% CI −6.9 to 6.5)

Grade ≥3 adverse events	**31.2% vs 37.0%**
Deaths	**10 vs 10**
Recurrence	**5.0% vs 2.0%**
Aged 8–17 years (n = 30)	**all successful**
Pregnant at enrolment (n = 9)	**all live births**

Conradie F et al. N Engl J Med 2026;394:2429–39 (intention-to-treat, both arms for the subgroups)

WHO 2025

BDLLfxC is adapted to fluoroquinolone susceptibility

FQ RESULT UNKNOWN

Start BDLLfxC

All five drugs while waiting — testing must not delay treatment

Fluoroquinolone-susceptible

BDLLfx — stop clofazimine

Fluoroquinolone-resistant

BDLC — stop levofloxacin

Daily dosing · extend to 9 months if culture conversion is not sustained by week 16

WHO 2025, recommendation 1.2 (conditional, very low certainty)

Trial evidence

endTB: five 9-month regimens tested against a standard of care

754

randomised in 7 countries, age 15 or older, fluoroquinolone-susceptible

5 × 9 m

combinations of B, D, L, Lfx/M, C and Z vs mostly 18–24-month regimens

80.7%

favourable outcome with standard care

Phase 3, open-label, Bayesian response-adaptive randomisation · primary end point at week 73 · non-inferiority margin –12 points · cavitation 57% · pyrazinamide resistance 54%

Guglielmetti L et al. N Engl J Med 2025;392:468–82

Trial evidence

Three bedaquiline-containing 9-month regimens were non-inferior

Regimen	Favourable	Difference (95% CI)	Non-inferior?
Standard care	80.7%	—	—
BLLfxCZ	90.4%	+9.8 (0.9 to 18.7)	Yes
BLMZ	89.0%	+8.3 (−0.8 to 17.4)	Yes
BDLLfxZ	85.2%	+4.6 (−4.9 to 14.1)	Yes
DCMZ	83.2%	+2.5 (−7.5 to 12.5)	Not per protocol
DCLLfxZ	78.8%	−1.9 (−12.1 to 8.4)	No

Guglielmetti L et al. N Engl J Med 2025;392:468–82 · modified intention-to-treat, week 73 · BLLfxCZ = BCLLfxZ in the trial report

WHO 2025 | Trial evidence

Without bedaquiline, short regimens fail

endTB regimen	Failure or recurrence	Amplified resistance
Standard care	2.5%	0%
BLMZ	3.4%	0%
BLLfxCZ	6.1%	1.6%
BDLLfxZ	1.6%	0%
DCLLfxZ — no bedaquiline	11.0%	4.0%
DCMZ — no bedaquiline	11.2%	6.7%

WHO 2025, GRADE analysis of endTB (WHO outcome definitions), p. 107

WHO 2026

WHO 2026: new data on pre-XDR-TB, analysed by disease severity

New data · 2025 call for patient data

- TB-PRACTECAL updated dataset: 507 participants, 108-week outcomes, genome sequencing of failures and recurrences
- endTB-Q (247, BDLC) pooled with BEAT-Tuberculosis (403, BDLLfx/C)
- Programmatic cohorts without comparator — Belarus 722, Uzbekistan 425, Italy 25 — as supporting evidence

How it was analysed

- Within-trial comparisons, each arm split into severe and non-severe pulmonary pre-XDR-TB
- Six outcomes, including amplified drug resistance
- New in 2025: outcome-specific decision thresholds — effects per 1000 judged trivial, small, moderate or large

Severe pre-XDR-TB: cavities on chest X-ray with smear 1+ or higher, or smear 2+ or higher even without cavities · **all new recommendations conditional, very low certainty**

WHO 2026

Why each pre-XDR-TB recommendation changed

Pre-XDR-TB	Comparison (n)	Key result	WHO 2026
Non-severe	TB-PRACTECAL, 108 weeks: BPaLC 45 vs BPaL 46	Failure or recurrence 20% vs 2.2%; adverse events 33% vs 24%	**B1.1a: BPaL — clofazimine adds no benefit**
Severe	TB-PRACTECAL, 108 weeks: BPaLC 70 vs BPaL 65	Failure or recurrence 10% vs 17%; amplified resistance 0% vs 4.6%; adverse events 30% vs 20%	**B1.1b: BPaLC**
Non-severe	BEAT-Tuberculosis + endTB-Q: BDLC 87 vs longer 61	Failure or recurrence 11.2% vs 10.9%; deaths 1.1% vs 3.1%	**B1.2a: BDLC, 6 instead of 18 months**
Severe	BEAT-Tuberculosis + endTB-Q: BDLC 114 vs longer 58	Failure or recurrence 12.3% vs 1.7%; amplified resistance 9.6% vs 3.4%	**B1.2b: against BDLC — longer regimen**

B1.1 and B1.2 updated accordingly: BPaLM stays first choice for MDR/RR-TB; BDLLfx/C stays the option for those who cannot receive BPaLM

WHO 2026, Module 4, 2nd ed., pp. 77, 79, 103, 105 · recommendations B1.1–B1.2b

WHO 2026

WHO 2026: the regimen depends on the fluoroquinolone result and, in pre-XDR-TB, on severity

	MDR/RR-TB, FQ-SUSCEPTIBLE	PRE-XDR-TB, NON-SEVERE	PRE-XDR-TB, SEVERE
14 years or older, not pregnant	**BPaLM** B1.1	**BPaL** B1.1a	**BPaLC** B1.1b
Cannot receive BPaLM — children, pregnancy, no pretomanid	**BDLLfx** B1.2	**BDLC** B1.2a	**≥18 months** Not BDLC (B1.2b)

FQ result unknown: start BPaLM or BDLLfxC, then adjust to the result

No 6-month option, FQ-susceptible: 9 months, BLMZ › BLLfxCZ › BDLLfxZ — unchanged (B2.2)

WHO 2026, Module 4, 2nd ed., recommendations B1.1–B1.2b, B2.2 · conditional, very low certainty

WHO 2026 DACH 2025

One guideline for all? Know your epidemiology

Regimen	WHO 2026	DACH 2025
BPaLM / BPaL, 6 m	Recommended (14 years or older); pre-XDR: BPaL or BPaLC by severity	Option 1
BDLLfx / BDLC, 6 m	Recommended, all ages and pregnancy; not BDLC in severe pre-XDR	Option 2, equal rank
Modified 9-month	Recommended, ranked	Not favoured
Longer, individualised	When short regimens are not possible	18 months or more, at least 4 effective drugs

ATS/CDC/ERS/IDSA 2025 | DACH 2025 | Trials

Linezolid dosing: different answers to the same toxicity problem

ATS/ERS

600 mg throughout

Drug monitoring; after 9 weeks, may stop if not tolerated

DACH

600 → 300 mg

Reduction allowed after 16 weeks in 6-month regimens

endTB

Lower from week week 16

Linezolid toxicity less common than with standard care

BEAT-Tuberculosis

600 mg, no reduction

Interruptions only; 10.3% stopped linezolid

WHO 2026 | ATS/CDC/ERS/IDSA 2025 | DACH 2025

Duration details matter: 24 or 26 weeks, and when to extend

	Standard length	When to extend
ATS/ERS · BPaL(M)	26 weeks (as in ZeNix)	Up to 39 weeks if response is slow (culture conversion after 8 weeks), after full resistance testing
DACH · BPaL(M)	6 months	9 months if culture still positive at month 4; 9 or 18 months in severe disease, by expert board
WHO · BDLLfxC	6 months (24 weeks)	9 months if conversion not sustained by week 16

All extension rules rest on expert opinion or trial protocols — none was tested as a strategy.

WHO 2026 | ATS/CDC/ERS/IDSA 2025 | DACH 2025

Severe extrapulmonary TB remains outside the short regimens

Excluded in all three guidelines

- Central nervous system TB
- Osteoarticular TB
- Disseminated, multi-organ TB

→ individualised longer regimens

WHO 2026 | DACH 2025 | Trial evidence

Pyrazinamide resistance: reason to reject the 9-month regimens?

DACH consensus

Most MDR/RR strains in the region are resistant to pyrazinamide — and all modified 9-month regimens contain it

→ 9-month regimens not favoured

endTB

54% pyrazinamide-resistant at baseline

Yet 85–90% favourable outcomes with the bedaquiline regimens. WHO: lower efficacy with pyrazinamide resistance — but still above longer regimens.

Drop pyrazinamide only if resistance is reliably confirmed; keep it where testing is unavailable. Its role remains a research gap.

Lange C et al. Pneumologie 2026;80:160–7 · Guglielmetti L et al. NEJM 2025;392:468–82 · WHO 2026, recommendation B2.2

WHO 2026 | DACH 2025 | Trial evidence

Extensive disease and pre-XDR-TB: one duration may not fit all

endTB-Q

pre-XDR-TB · BDLC

Shortened BDLC was inferior to longer individualised treatment in extensive disease

BEAT-Tuberculosis

6-month strategy

Recurrence 5.0% vs 2.0%; possibly poorer outcomes with cavities (exploratory)

Individual patient data

RR-TB meta-analysis

People with extensive disease may benefit from longer treatment

DACH: consider longer treatment in extensive disease or immunosuppression — decided by an expert board, on treatment response, not at baseline

WHO 2026: in pre-XDR-TB, severity now decides the regimen — BPaLC rather than BPaL, and no BDLC, if severe;

Guglielmetti L et al. Lancet Respir Med 2025;13:809–20 · Conradie F et al. NEJM 2026 · Campbell JR et al. Thorax 2024 · Lange C et al. 2026 · WHO 2026, B1.1b, B1.2b

A practical algorithm for 2026

RR-TB confirmed
Rapid FQ test, in parallel

Testing never delays treatment — every recommended regimen can start before the fluoroquinolone result

6-month regimen possible?

Yes →

14 YEARS OR OLDER, NOT PREGNANT
BPaLM
FQ-resistant: BPaL, or BPaLC if severe

ANY AGE, PREGNANCY
BDLLfx
FQ-resistant: BDLC, non-severe only

No

FQ-susceptible?

Yes →

9 months
BLMZ › BLLfxCZ › BDLLfxZ
Check local pyrazinamide resistance first

No

Otherwise →

18+ months
Individualised · at least 4 effective drugs · Groups A › B › C
XDR-TB · severe pre-XDR-TB without BPaLC option · intolerance · severe extrapulmonary TB · prior exposure

Severe pre-XDR-TB: cavities on chest X-ray with smear ≥1+, or smear ≥2+ (or molecular equivalent) even without cavities (WHO 2026).

Synthesis of WHO 2026 and ATS/CDC/ERS/IDSA 2025

WHO 2026 | ATS/CDC/ERS/IDSA 2025 | DACH 2025

Drug susceptibility testing is the gatekeeper

Fluoroquinolones

At baseline, always — but never delaying treatment

Bedaquiline and linezolid

At baseline (above all if FQ-resistant), no conversion by month 4, recurrence

Sequencing

Detects mutations for drugs without rapid tests; confirm molecular FQ results phenotypically

Pirazinamid

Confirm resistance

WHO 2026 | Trial evidence

Bedaquiline resistance is the threat that could undo the gains

A long half-life

Any interruption leaves bedaquiline alone: functional monotherapy

Seen in the trials

BEAT-Tuberculosis: resistance at failure (3 vs 5) and at relapse (2), more often in FQ-resistant disease

Loss to follow-up

Leaving care while culture-positive on bedaquiline raises the risk

NO SAFETY NET

No regimen with phase 3 evidence exists for bedaquiline-bedaquiline-resistant TB

Conradie F et al. NEJM 2026 · WHO 2026 · Ndjeka N et al. Lancet Infect Dis 2022;22:1042–51 · Marais BJ et al. Lancet Microbe 2026

ATS/CDC/ERS/IDSA 2025

Short regimens need intensive monitoring

What	When (BPaL / BPaLM)
Sputum smear and culture	Weekly to smear conversion, every 2 weeks to culture conversion, then monthly
ECG (QTcF)	Baseline, weeks 2, 12 and 24; monthly with moxifloxacin or clofazimine
Blood count	Every 1–2 weeks for 6–8 weeks, then monthly on linezolid
Vision and neuropathy	Acuity, Ishihara and neuropathy screen monthly on linezolid
Liver, kidney, electrolytes	Baseline and monthly
After treatment	Clinical review, sputum and imaging at 3, 6, 12, 18 and 24 months

ATS/CDC/ERS/IDSA 2025, Table 8 (joint panel opinion)

Trial evidence

Each regimen has its own safety signature

Linezolid

BEAT-Tuberculosis, 6-month vs standard

Anaemia 16.3% vs 14.5%
Optic neuropathy 3.5% vs 1.0%
Linezolid stopped 10.3%

Liver

endTB, grade 3 or higher

18.3% BLMZ

vs 7.1% with standard care; pyrazinamide in every 9-month regimen

QT interval

endTB and BEAT-Tuberculosis

QTcF above 500 ms uncommon (2.5–3.5%); in endTB only with clofazimine plus bedaquiline or moxifloxacin

Systematic review, 35 studies: short all-oral regimens caused fewer adverse events and less hearing loss than injectable-based care; grade 3–4 QTc prolongation more frequent with bedaquiline, without severe ventricular arrhythmias.

Conradie F et al. NEJM 2026;394:2429–39 · Guglielmetti L et al. NEJM 2025;392:468–82 · Lopes et al. Breathe 2025;21:240232

WHO 2026 DACH 2025

Shorter regimens still need people-centred care

WHO models of care

- Mainly ambulatory, rather than hospital-based
- Decentralised rather than centralised
- Education and counselling for every patient
- Adherence package: material and psychological support, tracers, video-supported treatment

Up to 25%

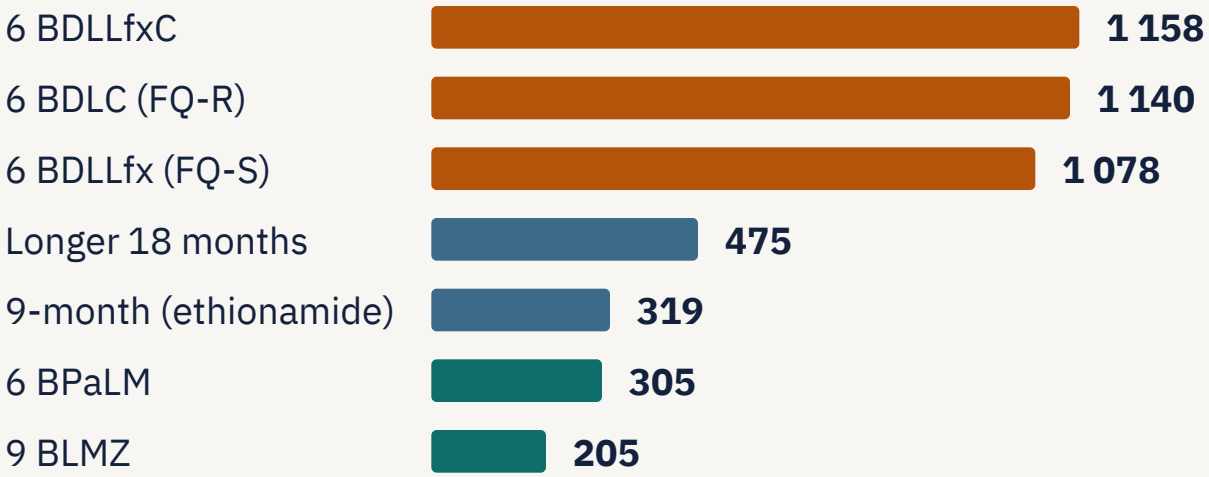
missing outcomes with long regimens in Germany (transfer or interruption)

Low case numbers → treatment in, or with, specialised centres and expert boards

WHO 2026 DACH 2025

Cost and access shape which regimen patients actually receive

Estimated drug price per regimen (US$, GDF, July 2026)



Beyond the drug price

- TB-PRACTECAL: US$14 868 saved per patient for providers and US$172 for patients; 1.28 DALYs averted — driven by fewer inpatient days
- Pretomanid: cost and label limit access, even in Europe
- At GDF prices, BPaLM (US$305) and BLMZ (US$205) are now the cheapest 6- and 9-month options

WHO 2026, Module 4, 2nd ed., Table 2.8 (GDF, July 2026) · Sweeney S et al. PLoS Glob Public Health 2022 · Lange C et al. 2026

Critical appraisal

How strong is the evidence behind the revolution?

Very low certainty

for every regimen recommendation

Small, open-label trials

one stopped early; heterogeneous control arms

Concentrated in South Africa

Nix-TB, BEAT-Tuberculosis, much of ZeNix and TB-PRACTECAL

Key groups excluded or few

children, pregnancy, severe extrapulmonary TB, older adults

And yet: consistent results across trials, a strong comparator in endTB, and programmatic data that reproduce them

WHO 2026 · research gaps

Open questions for the next guideline cycle

1. Which companion drugs best protect bedaquiline?
2. What regimen for bedaquiline-resistant TB?
3. Optimal duration in severe disease?
4. What is the role of pyrazinamide when resistance is common?
5. Optimal linezolid dose and duration, in adults and children
6. Do results hold outside South Africa and in excluded groups?

From one regimen for all to the right regimen, the right duration, the right patient

The strain

Fluoroquinolone, bedaquiline and pyrazinamide susceptibility

The person

Age, pregnancy, HIV, hepatitis C, prior drug exposure

The disease

Extent, cavities, site, response to treatment

TAKE-HOME MESSAGES

1. **Six months, all oral,** is now the standard for most people with MDR/RR-TB
2. **BDLLfxC** opens short treatment to children and pregnant women
3. **Nine months is the safety net** — BLMZ first, always with bedaquiline
4. **Testing and monitoring** are not optional: they make short regimens safe
5. **Protect bedaquiline** — it is the anchor, and there is no backup