The modified 9-month all-oral regimens

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REGIONAL WORKSHOP ON ACCELERATED IMPLEMENTATION OF WHO GUIDELINES
ON TB PREVENTION, DIAGNOSIS, AND DRUG-RESISTANT TB (DR-TB) TREATMENT

Outline

- **Source of evidences**
- **Recommendations**
- **Eligibility criteria**
  - Regimen selection
  - Composition & duration
  - Drug dosage & frequency
- **Implementation considerations**
- **Treatment monitoring & outcome assignment**

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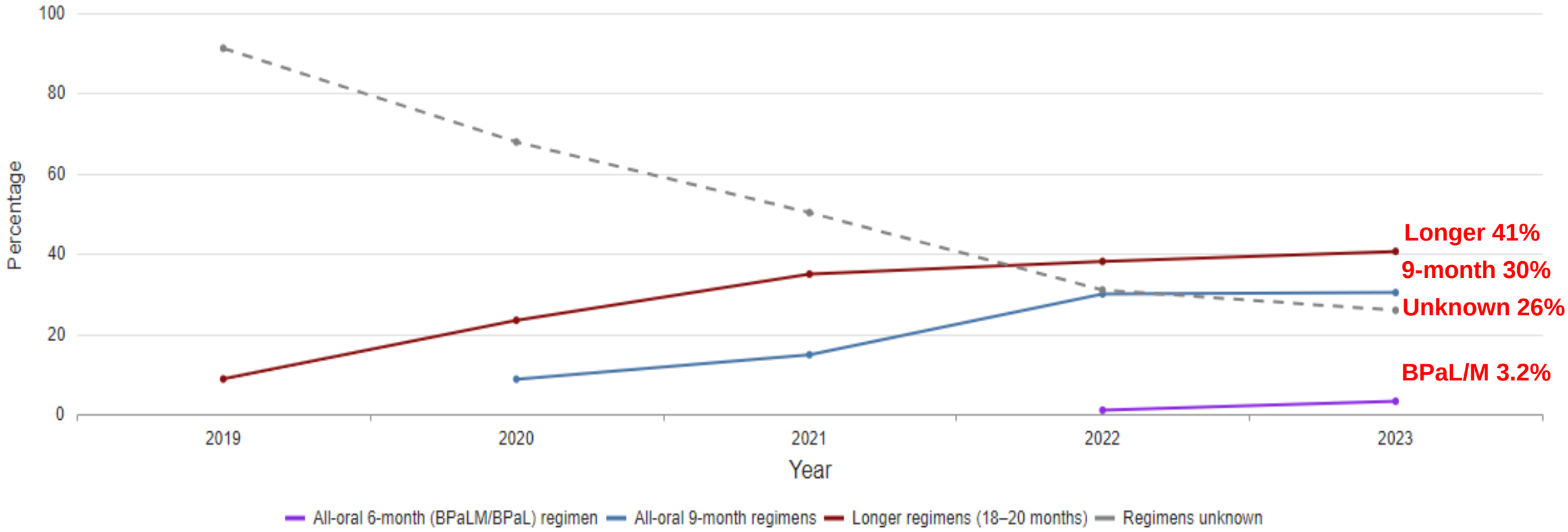
Percentage of MDR/RR-TB people by regimen type, 2019–2023
Global TB Report 2024



BPAL in 58 countries, 9-month regimens in 100 countries

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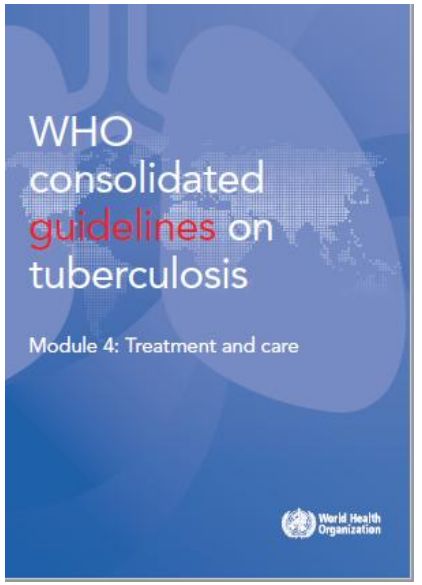
Evidence: The modified 9-month regimens: END-TB trial



Intervention	Comparator
NEW: Modified 9-month regimens: EndTB trial multicountry: 9-month regimens	
1. **Bdq-Lzd-Mfx-Z** 2. **Bdq-Lzd-Cfz-Lfx-Z** 3. **Bdq-Lzd-Dlm-Lfx-Z** 4. **Dlm-Cfz-Lzd-Lfx-Z** 5. **Dlm-Cfz-Mfx-Z**	WHO recommended longer regimens

- **Treatment of DR-TB TB using 9-month regimens**
  - The 9-month regimen
  - The modified 9-month regimens (NEW)

Population: **Patients with microbiologically confirmed pulmonary MDR/RR-TB w/o FQ resistance**

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Recommendations

BLMZ | BLLfxCZ | BDLLfxZ

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. Among 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 or DCMZ regimens compared with currently recommended longer (>18 months) regimens in patients with Fq-susceptible MDR/RR-TB.

(Conditional recommendation, very low certainty of evidence)

Modified 9-month regimens

What are the eligibility criteria for the modified 9-month regimens?

- People with MDR/RR-TB in whom resistance to fluoroquinolones has been excluded.
- People with PTB, children, adolescents, PLHIV, pregnant and breastfeeding women.
- People with extensive PTB disease and all forms of EPTB, except CNS TB, osteoarticular TB or disseminated forms of TB with multiorgan involvement.
- People with MDR/RR-TB and <1 month of previous exposure to any of the component medicines of the regimen (apart from pyrazinamide and fluoroquinolones). When exposure is > 1 month, resistance should be ruled out.
- children and adolescents without bacteriological confirmation of TB but with a high likelihood of MDR/RR-TB (based on TB symptoms, history of MDR/RR-TB contact and etc)

Modified 9-month regimens

What are the key factors for selecting modified 9-month regimens?

Regimen	Health Effects	Cost	Pill Burden	Other Decision Criteria
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 & 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 & feasibility

DR-TB treatment options

6 month: MDR/RR-TB, pre-XDR

- ≥14 years with MDR/RR-TB w/o exposure to B, Pa &L.
- Not for pregnant woman
- Not for CNS EPTB, osteoarticular, or disseminated TB with multi-organ involvement.

- < 1month of exposure to B,L,D, C.
- PTB, children adolescents, PLHIV, pregnant & breastfeeding women.
- Not for CNS EPTB, osteoarticular, or disseminated TB with multi-organ involvement.

9 month: MDR/RR-TB w/o FQ-R

-PTB, children, adolescents, PLHIV, pregnant & breastfeeding women.
- Extensive PTB disease
- Not for CNS EPTB, osteoarticular, disseminated TB with multi-organ involvement.

-No exposure to 2nd-line treatment
- no extensive PTB or severe EPTB
- can be used in all age groups
- Lzd variation for pregnant women

Longer regimen: XDR

- Last resort regimen
- Those who failed or NE for shorter regimens

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Key factors for MDR-TB treatment regimen selection

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 BLLfxCZ BDLLfxZ	Yes	No	No	No	Yes	Yes[1]	Yes	Yes
4–6 $Bdq_{(6\,m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto or $Lzd_{(2\,m)}$ / 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							

Modified 9-month regimens

What is the composition of the modified 9-month 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*
- *All medicines are administered thought treatment, there is no intensive and continuation phase*
- *PZA can be discontinued*

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Modified 9-month regimens

What is the role of pyrazinamide in the modified 9-month regimens?

PZA susceptibility

- Continue PZA as part of the regimen
  - ✓Monitor for hepatotoxicity and discontinue if severe toxicity occurs

PZA resistance

- PZA can be discontinued

✓PZA resistance does not significantly reduce treatment success.

✓Regimen remains effective, but careful monitoring is required

PZA DST unknown

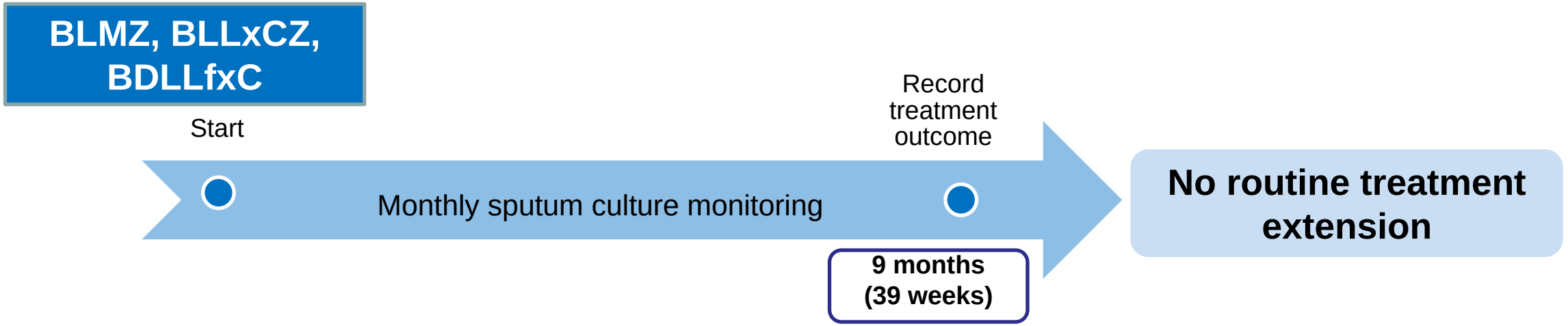
- Regimens can still be used if DST is unavailable or pending.

✓Monitor for hepatotoxicity and adjust treatment if needed.

✓Decisions on discontinuation should be based on severity of liver toxicity

The modified 9-month regimens

What is the duration of the modified 9-month regimens?



- All medicines to be used throughout treatment duration
- **Missed doses**:
- If missed < 7 days and < 1 month , doses should be made up
- If missed early in treatment, more harmful, DST may be needed to determine regimen effectiveness

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Modified 9-month regimens

What is the dosage and frequency of the modified 9-month regimens?

Medicine	Dose
Bedaquiline (100 mg)	**400 mg** once daily for 2 weeks, then **200 mg 3x** per week till the end **OR** **200 mg daily** for 8 weeks, then **100 mg daily** afterwards
Linezolid (600 mg)	**600 mg once daily** for 16 weeks then **300 mg once daily** or **600 mg 3X** a week until the end of treatment.

✓*Either* ***Lzd dose reduction strategy*** *is acceptable & standard practice*

✓***Linezolid may be reduced or discontinued*** *before 16 weeks, but ideally not before 9 weeks.*

➢*Early discontinuation requires a good clinical response (culture conversion, symptom resolution, or no radiological worsening)*

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

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Modified 9-month regimens & comorbidities

Diabetes Mellitus	• **Higher risk** of renal disease and peripheral neuropathy. • **Close monitoring** required for neuropathy in patients on linezolid. • **Normalization of H**bA1C should occur alongside MDR-TB treatment
Hepatic Dysfunction	• **PZA hepatotoxicity** may require alternative regimens in moderate to advanced liver disease. • **ALT levels >3x:** Modified 9-month regimens not recommended. • **Hepatitis C:** DAAs can be co-administered with MDR/TB treatment unless there is advanced liver damage
HIV	• The three modified 9-month regimens showed good outcomes for PLHIV • Subgroup analysis found any effect modification compared to overall population

Modified 9-month regimens & comorbidities

Breastfeeding woman

- **BLMZ preferred** due to prior use in breastfeeding.

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

✓ *Breastfeeding remains ideal; infection control measures are crucial.*

Pregnant woman

- **BLMZ preferred** due to fewer drugs and prior pregnancy use.

✓ *Limited data; caution advised with MDR/RR-TB treatment.*

✓ *Requires individualized risk-benefit assessment*.

Children

- **BLMZ regimen preferred** for low pill burden & child-friendly formulations.

✓ *Not included in the endTB trial but have used similar regimens safely.*

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

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The 9-month regimens

What is the composition and duration of 9-month regimens?

Ethionamide variation:

4-6 Bdq-Eto-Lfx/Mfx-Cfz-Z-E-Hh / 5Lfx/Mfx-Cfz-Z-E

- Eto & High-dose H can be dropped depending on smear status

Continuation phase:

5Lfx/Mfx-Cfz-Z-E

-Bdq may extend to 9 m

Linezolid variation:

4-6 Bdq–Lzd-Lfx/Mfx-Cfz-Z-E-Hh / 5Lfx/Mfx-Cfz-Z-E

- Lzd is only given the first 2 months
- High-dose H can be dropped depending on smear status

Continuation phase:

5Lfx/Mfx-Cfz-Z-E

-Bdq may extend to 9 m

- If SS remains (+) at month 4, initial phase is extended to **6 months**
- Duration of continuation phase is fixed **at month 5**

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The 9-month regimens

What factors need to be considered when modifying 9-month regimens?

- **9-month shorter all-oral regimen should be implemented as a standardized package.**
- **A few possible exceptions:**

✓ **Bedaquiline** can be extended from **6 to 9 months** if initial phase prolonged from 4 to 6 months.

✓ **Prothionamide** may be used instead of ethionamide.

✓ **Moxifloxacin** (with ECG monitoring) may be used instead of levofloxacin.

✓ **If full dose** (600mg) **of Linezolid** is not tolerated for the first full 2 months (apart from occasionally missed doses), then switch to a new regimen.

✓ In case of **intolerance of pyrazinamide or ethambutol**, one of them (only one) can be dropped during continuation phase without switch to a new regimen.

✓ **If bedaquiline, levofloxacin/moxifloxacin, linezolid/ ethionamide or clofazimine** are stopped early

⟶ switch to a new regimen.

Treatment monitoring examinations

Examination	Baseline	2nd week (for Lzd cont. 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	✓				

Reference: ***Annex: Table A2.2. Recommended schedule of baseline, routine and post-treatment monitoring examinations and tests for patients receiving DR-TB treatment***

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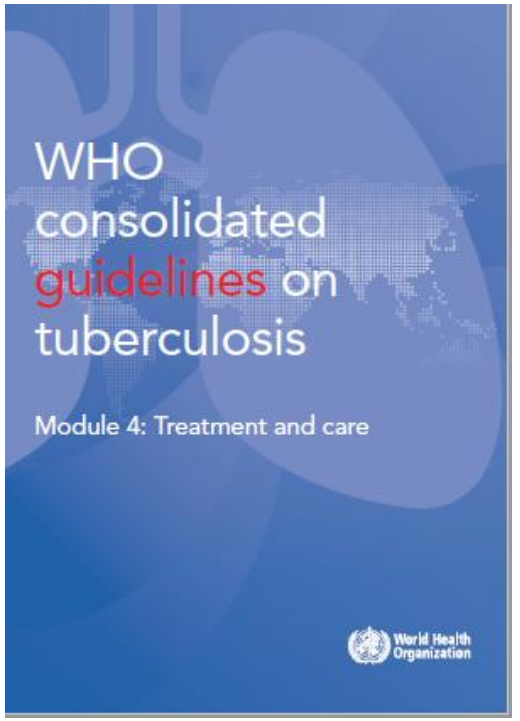
Treatment outcome definitions

What are the definitions of treatment outcomes for modfied 9-month regimens?

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**

Modified 9-month regimens: Outcome definitions

- **Lack of Improvement**

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

✓ Month 6: Persistent smear/culture positivity → Switch to longer regimen

- **Drug Resistance**

✓ If fluoroquinolone resistance or resistance to any 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.

Main messages

- While 6-month regimens are the preferred choice for patients with MDR/RR-TB , 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 in pregnant and breastfeeding woman

✓ have less medicines compared to 9-month regimens

DST, extent of TB disease and other factors to be considered for choosing the shorter regimens.

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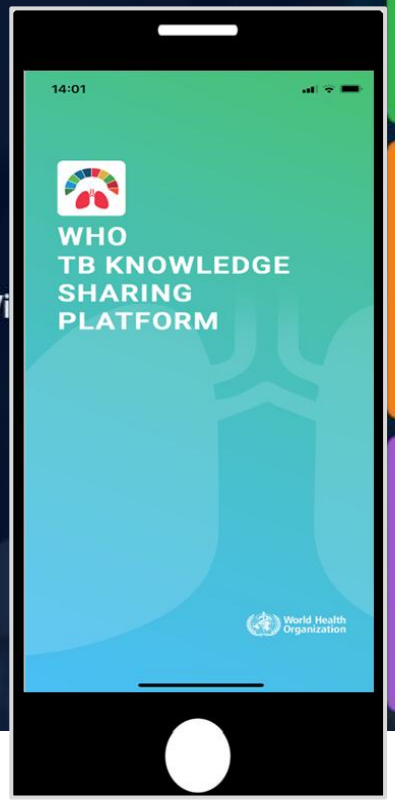

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