SHORTER RR-TB REGIMEN (BPaL-L) IN PATIENTS ≥ 15 YRS

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Based on Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide, September 2023 and Circular 2/23: Implementation of BPaL-L regimen, South African National Department of Health

NEED HELP?

Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline

0800 212 506 /021 406 6782

Alternatively "WhatsApp" or send an SMS or "Please Call Me" to 071 840 1572

www.mic.uct.ac.za

Xpert, TB-NAAT or culture reported as rifampicin-resistant

Send second sample for "DR-TB reflex DST testing"
(includes smear, culture, Xpert MTB/XDR & phenotypic DST)

- Severe EPTB (meningitis, osteoarticular, pericarditis, abdominal or disseminated/miliary disease)
- Younger than 15 years
- Documented resistance to BDQ or LZD or Pa or DLM
- If pregnant and would be eligible for BPaL-L then Pa may be substituted with DLM

None of these

One or more of these

Hb ≥ 8g/dL at diagnosis or after transfusion

No

Yes

Hospitalise

Start individualised LONG COURSE

Microscopy and MGIT culture

Negative

Positive

Submit new sample for DR-TB reflex testing

Xpert MTB/XDR on clinical isolate. Additional phenotypic tests will be done if required based on Xpert MTB/XDR results

Start SHORT REGIMEN BPaL-L

6 months:

BDQ + Pa + LZD (minimum 2 months) + LFX

Extend to 9 months:

Patients with extensive pulmonary disease i.e. bilateral, cavitary disease with significant fibrosis, scarring or cavities in 3 or more lung zones

All drugs should be continued throughout treatment if tolerated. LZD can be temporarily interrupted if there is toxicity (whilst continuing the remainder of the regimen) and can then be restarted to give a total LZD duration of at least 8 weeks.

Review Xpert MTB/XDR and phenotypic DST results

GENOTYPIC RESULTS	ACTION
INH resistant: InhA or katG mutation or both	Continue BPaL-L regimen, modify according to other genotypic and phenotypic susceptibility results
INH susceptible	Continue BPaL-L regimen, modify according to other genotypic and phenotypic susceptibility results
Susceptible to FLQs	Continue BPaL-L
Resistant to FLQs	Continue BPaL and stop levofloxacin
Susceptible or resistant to INJ	Continue BPaL-L
Resistant to EtO	Continue BPaL-L
PHENOTYPIC RESULTS	**ACTION**
Susceptible to BDQ and LZD	Continue BPaL-L
Resistant to BDQ and/or LZD	Switch to individualised long regimen and request EDST. Discuss with PCAC/NCAC or expert if unsure.
Individualised extended phenotypic DST	Use results to construct individualised long regimen

Special situations:

Xpert MTB/RIF Ultra positive and RIF resistant, but Xpert MTB/XDR results are pending: Assess clinical risk factors and, if no exclusion factors start on shorter regimen. If no results within 30 days, submit repeat sample. If no resistance testing results available, continue shorter regimen and follow up closely to monitor both clinical and bacteriological response

Discrepant phenotypic and genotypic test results: Phone laboratory to discuss discrepancies. In general, treatment should be based on the "most resistant" scenario; consult with PCAC or NCAC

Inform NCAC of all pregnant patients, but permission to initiate not required.

INCLUSION CRITERIA

- Individuals with RR-TB: resistance based on initial genotypic result, while awaiting further susceptibility results. This includes prior exposure to BDQ, Pa or LZD for longer than 1 month, but resistance to BDQ and LZD must be excluded
- Non-severe extra-pulmonary RR-TB, including lymphadenopathy or pleural effusion
- Extensive pulmonary disease (i.e. bilateral, cavitary disease with significant fibrosis, scarring or cavities in 3 or more lung zones)—TB treatment should be extended to 9 months
- Patients who received <28 days of another regimen who are eligible for BPaL-L may switch to it. The treatment start date will not change

EXCLUSION CRITERIA

- Documented resistance to bedaquiline or linezolid
- RR-TB with additional resistance to pretomanid or delamanid
- XDR-TB (resistance to the fluoroquinolones and bedaquiline or linezolid)
- Severe extra-pulmonary RR-TB meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease
- Children under the age of 15 years (pretomanid safety not yet confirmed in this population)
- Pregnant women (pretomanid safety not yet confirmed in this population, may replace Pa with DLM)

HIV AND RR-TB CO-INFECTION

All people co-infected with RR-TB and HIV should receive ART

Important drug interactions

- EFV is contraindicated with BDQ and Pa
- Co-trimoxazole can be given regardless of CD4 count and can be given with LZD: monitor FBC and neutrophils
- AZT and LZD should not be used together as both drugs can cause bone marrow suppression and thrombocytopenia

ART-naïve patients

- In ART-naïve patients, initiate ART within 2 to 8 weeks of starting RR-TB treatment. Patients with CD4 < 50: initiate ART within 2 weeks. If RR-TB meningitis, initiate ART after 4-6 weeks to decrease the risk of IRIS. If RR-TB patient with CM: see ART guidelines
- Initiate TLD as first-line ART if patient weight ≥ 30 kg, provided adequate renal function. Use ABC if TDF contra-indicated. If DTG 50 mg not available, contact the hotline to discuss

Re-starting ART

- Re-initiate on TLD as for ART-naïve patients
- Provide adherence support and do VL after 3 months

Modifications in patients on ART when RR-TB treatment is initiated

- Patients on the following regimens qualify for a same day switch to TLD regardless of VL:
  - Any EFV or NVP-based regimens
  - AZT/3TC/DTG
  - Any PI-based regimen for < 2 years
- Patients with VL < 1000 on a PI-based regimen may also switch to TLD with adherence support and a repeat VL after 3 months
- Patients with 2 VLs ≥ 1000 two or more years after starting a PI regimen and confirmed adherence < 80% can switch to TLD
- Patients with 2 VLs ≥ 1000 two or more years after starting a PI regimen and confirmed adherence > 80% should remain on the PI with consideration for a resistance test

Consult the 2023 ART Clinical Guidelines for more detailed information

DOSAGE AND ADVERSE EFFECTS

Drug/Formulation	Target dose	Dosage	Adverse Effects
Bedaquiline (BDQ) 100 mg tab	If treatment interrupted for > 2 weeks, call hotline.	200 mg daily for 8 weeks, then 100 mg daily	QT prolongation, liver toxicity, nausea and vomiting
Delamanid (DLM) 50mg tab		30—45.9 kg: 50 mg twice daily ≥ 46 kg: 100 mg twice daily	Nausea, vomiting, headache, insomnia, hypokalaemia, QT prolongation
Levofloxacin (LFX) 250 mg disp tab, 500 mg tab	15 - 20 mg/kg daily	30—45.9 kg: 750 mg once daily ≥ 46 kg: 1000 mg once daily	QT prolongation, but less than with moxifloxacin, rarely causes: liver toxicity, seizures, psychosis and arthritis / arthralgia / osteo-articular pain
Linezolid (LZD) 600 mg tab	10 mg/kg daily	30—35.9 kg: 300 mg once daily ≥ 36 kg: 600 mg once daily	Peripheral neuropathy, myelosuppression, impaired vision and diarrhoea
Moxifloxacin (MFX) 100 mg disp tab, 400 mg tab	LFX may be substituted with MFX if LFX is not available	≥ 30 kg: 400 mg once daily	QT prolongation, rarely causes: liver toxicity, seizures, psychosis and arthritis / arthralgia / osteo-articular pain
Pretomanid (Pa) 200 mg tab		≥ 30 kg: 200 mg daily	Nausea, vomiting, headache. Can cause QT prolongation, but currently lacks evidence for a risk of TdP when taken as recommended

MONITORING FOR SHORTER COURSE MEDICINES

	Baseline	Standard duration 6 months. May be extended to 9 months								
MONTH	0	1	2	3	4	5	6	7	8	9
Smear and culture	X	Week 2 and 4	X	X	X	X	X	X	X	X
FBC, neutrophil count and platelets	X	Week 2 and 4	Week 6 and 8	Repeat monthly, or more often as required, while on LZD						
ECG	X	Week 2 and 4	X	X	X	X	X	X	X	X
Peripheral neuropathy	X	Assess monthly and intervene early as per guidelines to avoid permanent damage								
Visual acuity	X	Assess visual acuity using Snellen chart as required when on LZD monthly or more often, if required								
ALT	X	When symptomatic								
K+ and Mg2+	X	If QTcF prolonged or vomiting/diarrhoea/clinically unwell								

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3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; AZT = zidovudine; CM = cryptococcal meningitis; DR-TB = drug-resistant tuberculosis; DST = drug sensitivity testing; DTG = dolutegravir; ECG = electrocardiogram; EDST = extended drug sensitivity testing; EFV = efavirenz; EPTB = extrapulmonary tuberculosis; EtO = ethionamide; FBC = full blood count; FLQs = fluoroquinolones; Hb = haemoglobin; HIV = human immunodeficiency virus; INJ = injectable; K^+= potassium; Mg^{2+}= magnesium; MGIT = Mycobacteria growth indicator tube; MTB = Mycobacterium tuberculosis; NCAC = National Clinical Advisory Committee; NVP = nevirapine; TB-NAAT = TB nucleic acid amplification test; PCAC = Provincial Clinical Advisory Committee; PI = protease-inhibitor; QTcF = corrected QT interval using Fridericia's formula; RR-TB = rifampicin-resistant tuberculosis; TB = tuberculosis; TDF = tenofovir; TdP = Torsades de Pointes; TEE = tenofovir+emtricitabine+efavirenz; TLD = tenofovir+lamivudine+dolutegravir; VL = viral load; XDR = extensively drug resistant