SHORTER REGIMEN FOR RR-TB IN ADULTS

JULY 2020. VERSION 1

Based on the Management of Rifampicin-Resistant Tuberculosis: A Clinical Reference Guide, November 2019, 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 or LPA reported as rifampicin-resistant

Send sample for "DR-TB reflex DST testing"
(includes smear, culture, first-line & second-line LPA & phenotypic DST)

- History of previous treatment with second-line TB medicines for more than 1 month
- Complicated EPTB (meningitis, osteoarticular, pericarditis, abdominal)
- Contact with XDR or pre-XDR TB
- Younger than 6 years
- Extensive disease on chest X-ray
- Both INH mutations (inhA and KatG) on LPA

None of these

One or more of these

Hb ≥ 8g/dL at diagnosis or after transfusion

No

Yes

Hospitalise

Start individualised LONG COURSE

First smear microscopy

Negative

Sample will be sent for culture and only first-line LPA will be attempted on the negative smear sample. If the culture is positive then second-line LPA will be carried out on the cultured isolate

Positive

1st and 2nd line LPA will be done on smear and sent for culture. Additional phenotypic tests can be done if required

Start SHORT COURSE

4-6 months (Intensive Phase):

LZD (2 months only) + BDQ (total 6 months) + hdINH (4-6 months) + LFX + CFZ + PZA + EMB

5 months (Continuation Phase):

LFX + CFZ + PZA +EMB

Note: Give pyridoxine 50 mg/day to adults to prevent peripheral neuropathy while receiving INH

	2 MONTHS	4 MONTHS	6 MONTHS	9 MONTHS
LZD	2 months only, due to toxicity			
hdINH	Extend for another 2 months, if smear positive at month 4*			
BDQ	Continue to 9 months in some patients, as explained in exceptions			
LFX, CFZ, PZA, EMB				

*If smears remain positive at month 4, begin extended workup for treatment failure while INH is continued

EXCEPTIONS

⇒ BDQ may be extended from 6 to 9 months:
- If there is no 2nd-line DST result available
- If the patient is slow to smear or culture convert
- If there is extensive disease
- If there is delayed clinical response

⇒ If either PZA or EMB needs to be discontinued, no drug substitution is needed

⇒ If both PZA and EMB need to be discontinued, then drug substitution could include BDQ extension or LZD extension

⇒ If other medications need to be stopped, the patient should switch to a longer regimen—contact PCAC or NCAC

Present all pregnant patients to NCAC

Review LPA and phenotypic DST results

Special situations:

Xpert positive and RIF resistant, but second-line LPA results are pending: Assess clinical risk factors and, if no exclusion factors start on shorter regimen. If no LPA results within 30 days, submit repeat sample. If no 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

FIRST-LINE LPA RESULT	ACTION
Rifampicin resistant	Continue shorter RR-TB regimen, modify according to other LPA results
InhA or katG mutation only	Continue shorter RR-TB regimen, modify according to other LPA results
Both InhA and katG mutations	Switch to longer regimen, follow up 2nd-line LPA results and phenotypic DST results
INH susceptible	Continue shorter RR-TB regimen, modify according to other LPA results. If phenotypic DST confirms INH susceptible reduce INH dose to normal dose
SECOND-LINE LPA RESULT	**ACTION**
Susceptible to FLQs	Continue shorter RR-TB regimen with 2 months of linezolid. Follow up phenotypic DST for levofloxacin, or moxifloxacin
Resistant to FLQs	Switch to a longer regimen, follow up phenotypic DST for LZD, BDQ & CFZ
Susceptible to INJ	Continue shorter RR-TB regimen (if also susceptible to FLQs)
Resistant to INJ	Switch to a longer regimen, follow up phenotypic DST for LFX, LZD, BDQ and CFZ

INCLUSION CRITERIA

1. Individuals with RR-TB <u>without</u> prior exposure (>1 month) to second line RR-TB treatment, including:
   - RR-TB: resistance to at least rifampicin, based on initial GXP result, while awaiting further genotypic first- and second-line LPA results
   - Rifampicin mono-resistant TB: resistance to rifampicin but susceptibility to isoniazid
   - MDR-TB: resistance to both rifampicin and isoniazid (with either inhA or katG mutation but not both) and susceptibility to both the fluoroquinolones and the injectable agents
2. Uncomplicated extra-pulmonary RR-TB, including lymphadenopathy or pleural effusion

Of note, children 6 years and older, pregnant women, and persons with HIV, regardless of CD4 count, can all receive the shorter regimen if they do not meet any exclusion criteria

EXCLUSION CRITERIA

1. A history of previous treatment (>1 month) with any second-line RR-TB treatment regardless of treatment outcome
2. RR-TB with resistance to FLQs, INJs, or both
3. MDR-TB with both inhA and katG mutations
4. RR-TB with additional resistance to BDQ, LZD and/or CFZ
5. RR-TB with suspected resistance to second-line drugs, even if susceptibility is demonstrated on DST:
   - Contacts of persons with RR-TB and additional resistance to second-line drugs or both INH mutations
   - Contacts of persons not successfully treated for RR-TB
6. Persons with RR-TB meningitis, pericarditis, abdominal or osteoarticular RR-TB disease. Children of all ages should be prioritized for all-oral regimens on the extent of disease
6. Persons with extensive disease (i.e. bilateral, cavitary disease with significant fibrosis, scarring or cavities in three or more lung zones)
7. Children under the age of 6 years (BDQ dosing and safety is not confirmed yet)
8. Any other situation in which the clinician is uncertain of the patient's eligibility for the shorter regimen
10. Hb < 8g/dl or neutrophils < 0.75 or platelets < 50 at diagnosis or following transfusion

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
- 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 patient with CM: see ART guidelines
- Initiate TLD as first-line ART if patient ≥ 10 years of age and weight ≥ 35kg, provided adequate renal function. Use ABC if TDF contraindicated. If DTG 50mg not available, contact the hotline to discuss

Re-starting ART
- History of ART interruption on ART TEE: Initiate a second-line PI based regimen e.g. TDF + FTC + LPV/r. Address adherence and repeat VL after 6 months. After LZD is completed or withdrawn, the ART regimen can be switched to AZT + 3TC + DTG once the Hb is > 10 g/dL
- If previously on first-line TLD restart same regimen. Use ABC if TDF contraindicated
- If previously on second-line ART with a PI: address adherence and restart the same regimen, replacing AZT with either TDF or ABC. Repeat viral load after 3 months

Modifications in patients on ART when RR-TB treatment is initiated
- VL < 50 on 1st-line: switch to TLD, if renal function allows it
- VL < 50 on 2nd-line with PI: continue, but switch AZT to TDF or ABC. Can switch back to AZT once linezolid completed and Hb > 10 g/dL
- VL ≥ 1000 on 1st-line: switch to PI-based 2nd-line. While on LZD use TDF or ABC/3TC/PI. Once linezolid completed and Hb > 10 g/dL can switch to AZT/3TC/DTG
- VL ≥ 1000 on 2nd-line, continue 2nd-line and address adherence. While using linezolid, use TDF or ABC instead of AZT. Follow guidance for geno-typing if VL remains unsuppressed
- VL between 50 and 1000: discuss with expert

DOSAGE AND ADVERSE EFFECTS

Drug/Formulation	Target dose	Dosage	Adverse Effects
Bedaquiline (BDQ) 100 mg tab	Once daily loading dose then thrice weekly dosing	≥ 30 kg: 400 mg once daily for 2 weeks followed by 200 mg three times per week (Monday, Wednesday, Friday)	QT prolongation, liver toxicity, nausea and vomiting
Clofazimine (CFZ) 100 mg gel caps	2-5 mg/kg daily	≥ 30 kg: 100 mg once daily	Skin discoloration, QT prolongation, nausea and vomiting
Ethambutol (EMB) 400 mg tab	15-25 mg/kg daily	30-45 kg: 800 mg once daily ≥ 46 kg: 1200 mg once daily	Impaired vision
High Dose Isoniazid (hdINH) 100/300 mg tab	10-15 mg/kg daily (Use 15 mg/kg in CNS disease)	30-45 kg: 450 mg once daily ≥ 46 kg: 600 mg once daily	Peripheral neuropathy, liver toxicity, seizures and psychosis
Levofloxacin (LFX) 250 mg disp tab, 500 mg tab	15 - 20 mg/kg daily	30-45 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 kg: 600 mg once daily	Peripheral neuropathy, myelosuppression, impaired vision and diarrhoea
Pyrazinamide (PZA) 500 mg tab	20-30 mg/kg daily	30-35 kg: 1000 mg once daily 36 -70 kg: 1500 mg once daily > 70 kg: 2000 mg once daily	Liver toxicity, arthritis / arthralgia / osteo-articular pain

MONITORING FOR SHORTER COURSE MEDICINES

	Baseline	Short regimen: intensive phase (4-6 months)				Short regimen: continuation phase (5 months)				
MONTH	0	1	2	3	4	5	6	7	8	9
FBC and neutrophil count	X	Week 2 and 4	X	Repeat monthly, or more often as required, while on LZD						
ECG	X	X	X	X	X	X	X			X
Audiometry	X			X	Available if required for any patient in need					
Peripheral neuropathy	X	X	X	While on LZD						
Visual acuity	X	X	X	Assess visual acuity using Snellen chart as required when on LZD/EMB monthly or more often, if required						
ALT	X	When symptomatic								
K+ and Mg2+	X	If QTcF prolonged or vomiting/diarrhoea/clinically unwell								

This publication was supported under funding provided by the Global Fund to Fight AIDS, Tuberculosis and Malaria through the National Department of Health of South Africa and the NDoH
Pharmacovigilance Centre for Public Health Programmes. Its contents are solely the responsibility of the authors and do not neces-sarily represent the official views of the Global Fund or the National Department of Health of South Africa

3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ARV = antiretroviral; AZT = zidovudine; CM = cryptococcal meningitis; DR-TB = drug-resistant tuberculosis; DST = drug sensitivity testing; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EPTB = extrapulmonary tuberculosis; FBC = full blood count; Hb = haemoglobin; HIV = human immunodeficiency virus; INJ = injectable; K^+= potassium; LPVr = lopinavir/ritonavir; MDR-TB = multidrug resistant tuberculosis; Mg^{2+} = magnesium; NCAC = National Clinical Advisory Committee; 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; TEE = tenofovir+emtricitabine+efavirenz; TLD = tenofovir+lamivudine+dolutegravir; VL = viral load; XDR = extensively drug resistant