RRTB / MDRTB 9-11 month Short Regimen
Adults, Adolescents and Children ≥ 6 years & ≥ 16kg

WHO CAN BE INITIATED ON THE SHORT REGIMEN

- Patients ≥ 6 years with RRTB (>16kg) / MDRTB single mutation / Rif Mono
  - AND Uncomplicated EPTB, including lymphadenopathy or pleural effusion
- Includes Pregnant women (inform NCAC)

WHO MAY NOT BE INITIATED ON THE SHORT REGIMEN

- Possible resistance to other 2nd line DRTB drugs
  - Prior exposure to 2nd line anti-TB agents >1 month
  - When additional 2nd line drug resistance is suspected (even if susceptible on DST) E.g. Close contact with XDR / PreXDR / MDR Dual mutation / Second line treatment failure (request eDST)
- MDRTB with dual mutation (both inhA and Kat G)
- FLQ and / or Injectable resistance (PreXDR / XDR)
- MDRTB with additional resistance to BDQ, CFZ or LZD
- Complicated Disease
  - Complicated / Severe EPTB (CNS / osteo-articular / pericardial effusion / Abd TB / TBM)
  - Extensive disease e.g. bilateral, cavitary pulmonary RRTB disease with significant fibrosis, scarring or cavities in three or more lung zones
- HB <8g/dl or neutrophils <0.75 or platelets <50

Key: HH: Isoniazid / LZD: Linezolid / LFX: Levofloxacin/ CFZ: Clofazamine PZA: Pyrazinamide/ BDQ: Bedaquiline /EMB: Ethambutol/ TRD: Terizidone / DLM: Delamanid NCAC: National Clinical Advisory Committee

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DRUG CHOICES & DURATION OF THE SHORT REGIMEN

4-6 months (Intensive phase)

$$LZD_{(2m)} + BDQ_{(6m)} + HH(4\text{-}6m) + LFX + CFZ + PZA + EMB$$

5 Months (continuation phase)

$$LFX + CFZ + PZA + EMB$$

- Give BDQ for full 6 months. May switch LFX to Moxifloxacin when BDQ completed.
  - BDQ >30kg: 400mg 14/7 then 200mg M/W/F for 22 weeks
  - 16-30kg: 200mg 14/7 then 100mg M/W/F for 22 weeks
- BDQ can be extended to 9 months if extensive disease, or late conversion or 2nd line uninterpretable / not available or delayed clinical response
- LZD for 2 months: Do FBC 2w, 4w and then monthly on LZD; LZD Dose: < 16kg: 15mg/day & > 16kg: 10mg/day.
- High Dose INH for 4 months: If smear negative by end month four and good clinical response: Stop INH.
  - IF still smear positive at 4m: can extend INH to 6m
- If PZA or EMB not tolerated: can be withdrawn without being replaced. IF both discontinued – consider BDQ or LZD extension
- Give Pyridoxine 50mg/ day to adults (not >100mg/d) and 25mg/d children age 5-12

	2 M	4 M	6 M	9 M
Linezolid		Give LZD for 2m		
HDINH			Extend 2m if smear pos at 4m	
Bedaquiline				Can extend to 9m*
LFX & CFZ &PZA& EMB				

The Basic Long RRTB Regimen: FLQ Sensitive (18-20m)
Adults, Adolescents and children ≥6 yrs & ≥ 16kg

WHO CAN BE INITIATED ON THE BASIC LONG REGIMEN

- Possible resistance to other 2nd line drugs
  - RR / MDRTB with prior exposure to 2nd line anti-TB agents >1 month
- MDRTB with dual mutation (Kat G and inhA mutation) or RR / MDRTB who had close contact with MDR Dual mutation
- PREXDR with INJ resistance but sensitive to FLQ
- Complicated disease
  - RR / MDRTB Complicated / Severe EPTB (pericardial or osteoarticular disease / Abdominal TB)
  - RR / MDRTB Extensive lung disease e.g. bilateral severe cavitation
- RR / MDRTB If clinician unsure if the patient meets the criteria for short regimen
- Hb<8g/dl or neutrophils <75 or platelets <50 at baseline or while on LZD in first 2 months of short regimen.

WHO MAY NOT BE INITIATED ON THE BASIC LONG REGIMEN

- Any patient with FLQ resistance or close contact with FLQ resistance (present to NCAC)
- Patients who need a rescue regimen
- TB meningitis (see separate regimen)
- Children < 6 years old

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DRUG CHOICES & DURATION OF THE BASIC LONG REGIMEN

6 months (Intensive phase)

$BDQ_{(6m)}$ +LZD + LFX + CFZ + TRD

12 Months (continuation phase)

LFX + CFZ + TRD

- Positive culture at month 4, clinical worsening or poor weight gain: Send eDST and do Xray. Counsel and consider rescue regimen
- Treatment duration of 18m could be extended to 20m per clinician discretion.
- LTFU from previous short regimen /previous exposure to 2nd line drugs with BDQ, LZD or CFZ:
  - Start basic longer regimen with at least five drugs
  - Do a DRTB reflex test and request eDST
  - Amend later based on eDST results with input from NCAC.

ADVERSE EVENTS AND SUBSTITUTIONS

Always discuss substitutions with NCAC

- LZD: Do FBC at baseline, 2w, 4w and monthly.
  - If HB <8g/dl / neutrophils <0.75 / platelets <50: see guide on LZD and anaemia management
- If TZD contraindicated or not tolerated in intensive phase – no need to substitute for another drug.
- If TZD not tolerated in continuation phase extend either LZD or BDQ (need 3 active drugs in continuation phase.)
- If any of the other drugs have to be discontinued: substitute with extension of BDQ or LZD, addition of Delamanid or other group C medications.

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RRTB FLQ resistant Long Regimen
Adults, adolescents and children ≥6yrs & ≥16kg

WHO IS ELIGBLE FOR THE FLQ-RESISTANT LONG REG

- FLQ resistant TB
  - XDRTB
  - PreXDR with FLQ resistance

WHO MAY NOT BE INITIATED ON THE FLQ-RES LONG REG

- Patients on either longer or shorter regimen who have a positive culture at month 4 – consider a rescue regimen
- Patents who have failed on a previous RRTB regimen – especially if they contained BDQ, LZD and /or CFZ
- Patients with suspected resistance to BDQ / LZD / CFZ or confirmed resistance to any of those three.

PRINCIPLES

- Treatment regimens should be individualised considering the history and pDST result

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DRUG CHOICES & DURATION OF THE FLQ-RESISTANT LONG REGIMEN

6 months (Intensive phase)

BDQ +LZD + DLM + CFZ + TRD

12 Months (continuation phase) : 3-4 drugs

CFZ + TZD + (Choose one or two: LZD / BDQ / DLM)

- Use 4 drugs in continuation phase if extensive disease or co-morbid disease.
- Omit Fluroquinolones
- Treatment duration is 18 months but could be extended to 20 months per clinician discretion
- LZD: This is a key drug
  - If HB <8g/dl / neutrophils <0.75 / platelets <50: Admit patient and see guide on LZD and anaemia management.

Discuss with NCAC when:

- Resistance suspected or detected resistance to core drugs
- Previous Rx >1m with LZD, BDQ, DLM or CFZ
- Core drugs contraindicated or not tolerated
- Previously treated for XDR / PreXDR for >1month
- Pregnant patients
- Diagnosed of FLQ resistance >1month on short regimen

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RRTB Rescue Long Regimen
Adults, adolescents and children ≥6yrs & ≥ 16kg

WHEN TO CONSIDER A RESCUE REGIMEN

- Any patient with a positive culture at month 4: likely to have failed and may need a rescue regimen.
- Patents who have failed on a previous RRTB regimen – especially if it contained BDQ, LZD and /or CFZ
- Patients with suspected resistance to BDQ / LZD / CFZ or confirmed resistance to any of those three.
- Consider in any RRTB Relapse: especially if treated with BDR, LZD and or CFZ

PRINCIPLES

- All persons in need of a rescue regimen should have specimens sent for eDST (extended DST). Start the rescue regimen whist awaiting results. Add Group A&B drugs based on risks and benefits of each drug.
- Design regimen with input from NCAS – Group C drugs will be needed.
- Use DLM if no history of previous exposure and add Carbapenem or Meropenem (add Amox/Clav 30 minutes prior to infusion)
- Use ETO if Kate G mutation present (in absence of InhA mutation) and add PAS
- Consider Amikacin if document susceptibility and access to hearing assessments.
- Consider High dose Moxifloxacin with careful monitoring
- Surgical consultation should be considered
- DOT in a patients centred manner

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DRUG CHOICES & DURATION OF THE RESCUE REGIMEN

EXAMPLE of Rescue Long regimen whilst waiting for eDST

BDQ +LZD + DLM + PAS+ CFZ + TRD +

+ ETO (if Kat G only mutation)

- BDQ can be extended to 9 months if extensive disease, late conversion..
- The Intensive phase is 6-8 months depending on culture conversion and clinical response
- LZD is a key drug. IF not tolerated discuss with NCAC
- PAS at 4g bd or 8g od. PAS has to be taken with acidic food such as amazi / Morvite
- Have a low threshold to stop PZA of adverse events. NO need to replace

HOW TO APPLY FOR AN EDST

Write a summary of patient history and include following

- NHLS Barcode and date of latest positive culture
- Name of patient, DOB, short clinical summary
- History of exposure to 2nd line drugs and culture results

Send via email to your local NHLS TB manager as well as Dr Farzana Ismail (farzanai@nicd.ac.za) with eDST and patient name in subject line.

The local lab will the requested culture sample to NICD for testing – it may take 6-8 weeks.

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RRTB CNS Long regimen

Adults, Adolescents and children ≥6yrs ≥ 16kg

WHEN TO USE THE CNS LONG REGIMEN

- Patients with confirmed or highly probable TBM

PRINCIPLES

- High mortality - seek specialist advice,
- Low threshold to investigate (CT or LP).
- Every effort to be made to send CSF for GeneXPert / culture and DST
- Rule out Cryptococcal meningitis with a CSF CrAG
- ART is initiated after 4-6 weeks.
- Use drugs with good CSF Penetration (LFX / LZD / TZD / Z / ETO / HDINH)
- Discuss all children <12 years (<30kg) with an expert
- Repeat CTs may be used to monitor tuberculomas. Residual lesions may be present at end of treatment and do not necessarily represent treatment failure

DRUG CHOICES & DURATION OF THE CNS LONG REGIMEN

12 months (Intensive phase)
BDQ + LZD + DLM + LFX + CFZ + TRD + PZA
+ (HH Or ETO*)
6 Months (continuation phase) of 4-5 drugs
LFX + CFZ + TRD + PZA + (LZD or ETO or HH*)

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- Use high dose LFX (1000mg in adults)
- *Use HH at 15mg/kg/day if inhA/mutation present.
- Use ETO if Kat G mutation present. Use neither in dual mutation
- PAS and either HH or ETO is included because of relatively good CNS penetration
- In continuation phase choose between LZD, ETO or HH depending on INH mutation and tolerance.
- All patients on INH or TZD must be on Pyridoxine: 50mg/day in adults; 25mg/ day age 5-12 years. Pyridoxine does not prevent LZD induced PN.
- Treatment duration is 18 months but could be extended to 20 months per clinician discretion

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DRTB DOSING CHART Persons >30kg

Drug	Tablet size	*Average daily dose	Weight Class				
			30-35kg	36-45kg	46-55	56-70kg	>70kg
Bedaquiline	100mg		400mg 2 weeks then 200mg M/W/F for 22 weeks				
Linezolid	600mg	10mg/kg/day	600	600	600	600	600
Levofloxacin	250mg/500mg	15-20mg/kg/day	750	750	1000	1000	1000
Clofazamine	100mg gel cap	2-5mg/kg/day	100				
PZA	500mg	30-40mg/kg/day	1000	1000	1500	1500	2000
Ethambutol	400mg	15-20mg/kg/day	800	800	1200	1200	1200
High Dose INH	100, 300mg	10-15mg/kg/day	450	450	600	600	600
Low Dose INH	100mg /300mg	4-6mg/kg/day	200	300	300	300	300
Terizidone	250mg	15-20mg/day	500	750			
Delamanid	50mg tab	100mg bd	100mgbd				
PAS	4g satched	200-300mg/kg/d	8g	8g	8g	8g	8g
Ethionamide	250mg	15-20mg/kg/day	500	500	750	750	750
Moxifloxacin	400mg	10mg/kg/day	400	400	400	400	400
Moxifloxacin High	400mg	15mg/kg/day	400-600	600	600-800	800	800
Mereponem	1g vial (20ml)	20-40mg/kg Ivi TDS	2g (40ml) bd. Clavulinic acid 30min prior to use				
Amoxicillin - Clavulanate	500mg/125mg	30 min before each Meropenem dose	Administer 125mg clavulinic acid 30min prior to each dose of carbapenem				
Rifabutin	300mg			300-450mg			
Amicacin	500mg vial (2ml)	15-25mg/day	625mg	750mg	750mg	1000mg	1000mg

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DOSING chart Children <30kg Nov 2019

Drug	Tablet size	*Average daily dose	Weight Class							
			3-3.9kg	4-4.9kg	5-6.9kg	7-9.9kg	10-15.9kg	16-23.9	24-30kg	>30kg
BDQ	100mg							200mg 2w then 100mg M/W/F for 22w		adult
LZD	600mg tab	10mg - 12/kg >16yrs / 15mg/kg <16 yrs		60mg	90mg	120mg	150-180	180-210	300	adult
LZD	20mg/ml	10mg - 12/kg >16yrs / 15mg/kg <16 yrs		70mg	80mg	120mg	160-200	160-220		
LVX	250mg scored	15-20mg/kg/day	62,5	75	125	150	250-375	375-500	500	adult
LVX	100mg disp tab	15-20mg/kg/day	60	80	100	150	200-300	300-400	500	adult
CFZ	100mg gel cap	2-5mg/kg/day			100mg M/W/F			100mg alt days	100mg	adult
PZA	500mg	30-40mg/kg/day			250	250	500	750	1000	adult
PZA	150mg disp tab	30-40mg/kg/day			150	300	450	750		
EMB	400mg	15-25mg/kg/day	80	80	120	200	280	400	600	adult
EMB	100mg disp tab	15-25mg/kg/day	80	100	200	300	400			
HHINH	100, 300mg	15-20mg/kg/day	50	50	100	150	200	300	400-450	adult
INH	100mg /300mg	10-15mg/kg/day	50	50	75	100	150	200	200	adult
TZD	250mg caps	15-20mg/day			100-125	125-175	175-250	250-500	500	adult
DLM	50mg tab	100mg bd						25mgbd	50mgbd	50mg bd till 35kg
PAS	4g satched	200-300mg/kg/d			1.5g	2g	2-4g	4-6g	6-8g	
ETO	250mg	15-20mg/kg/day			125	125	250	375	500	adult
MOX High	400mg	10mg -15mg/kg/day			80mg	120mg	200mg	200-300	400	adult
MER	1g vial (20ml)	20-40mg/kg IVI q8h			100mg	200mg	300mg	400-450	550	adult
AM/Clv	250/62.5mg per 5ml susp	30 min before each Meropenem dose			25mg	37.5mg	62.5mg	100mg	125mg	adult
AM Inj	500mg vial (2ml)	15-25mg/day			100	150	200-250	300-375	500	adult

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