health

Department:
Health
REPUBLIC OF SOUTH AFRICA

MANAGEMENT OF RIFAMPICIN-RESISTANT TUBERCULOSIS:

A Clinical Reference Guide

November 2019

TABLE OF CONTENTS

LIST OF TABLES

LIST OF DIAGRAMS

ABBREVIATIONS

aDSM	Active Drug Safety Monitoring and Management
ART	Antiretroviral Treatment
BDQ	Bedaquiline
CNS	Central Nervous System
CFZ	Clofazimine
DLM	Delamanid
DR-TB	Drug Resistant Tuberculosis
DST	Drug Susceptibility Test
EMB	Ethambutol
ECG	Electrocardiogram
EDST	Extended Drug Susceptibility Test
EPTB	Extra-Pulmonary Tuberculosis
EFV	Efavirenz
ETO	Ethionamide
FBC	Full Blood Count
FLQ	Fluoroquinolone
GXP	GeneXpert
HIV	Human Immunodeficiency Virus
HR-TB	Isoniazid resistant tuberculosis
INH / hdINH	Isoniazid/ high-dose Isoniazid
INJ	Injectable agent
IRIS	Immune Reconstitution Inflammatory Syndrome
KM	Kanamycin
LFX	Levofloxacin
LPA	Line Probe Assay

LZD	Linezolid
MIC	Minimum Inhibitory Concentration
MO	Medical Officer
MFX	Moxifloxacin
MDR	Multidrug-Resistant
NCAC	National Clinical Advisory Committee
NDoH	National Department of Health
PCAC	Provincial Clinical Advisory Committee
PHC	Primary Healthcare Clinic/Center
PV	Pharmacovigilance
PVU	Pharmacovigilance Unit
QTc	Corrected QT interval
RIF	Rifampicin
RR	Rifampicin Resistant
SAPHRA	South African Health Products Regulatory Authority
SCR	Shorter Course Regimen
SLDs	Second-Line Tuberculosis Drugs
TRD	Terizidone
XDR	Extensively Drug Resistant
WHO	World Health Organization
PZA	Pyrazinamide

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DEFINITIONS

Drug-resistant tuberculosis (DR-TB) refers to active tuberculosis disease caused by ***Mycobacterium tuberculosis*** bacilli that are resistant to one or more anti-TB drugs.

Different categories:

Mono-resistant TB
Resistance to only one anti-TB drug, without resistance to other drugs

Poly-drug resistant TB
Resistance to more than one anti-TB drug, other than both isoniazid and rifampicin

Multidrug-resistant TB (MDR-TB)
Resistance to isoniazid and rifampicin with or without resistance to other anti-TB drugs

Rifampicin resistant TB (RR-TB)
Resistance to at least rifampicin, with or without resistance to other drugs. This category includes MDR-TB, rifampicin mono-resistant TB, pre-XDR-TB and XDR-TB.

Extensively drug-resistant TB (XDR-TB)
MDR-TB with resistance to any fluoroquinolone as well as one or more of the three second-line injectable drugs (amikacin, kanamycin or capreomycin). Given that South Africa is moving away from the routine use of the injectable agents, this term may have limited clinical relevance. When possible, resistance to individual medications used in the newly recommended regimens should be specified, including resistance to bedaquiline, clofazimine, delamanid and/or linezolid.

Pre-XDR-TB
MDR-TB with additional resistance to either a second-line injectable agent or a fluoroquinolone. Given that South Africa is moving away from the routine use of the injectable agents, this term may have limited clinical relevance and it may be more appropriate to refer instead to fluoroquinolone-resistant RR-TB. However, pre-XDR-TB with injectable resistance is still an exclusion criterion for the shorter regimen. This is because even though the injection is no longer used, resistance to it may be a marker for resistance to other medications in the shorter regimen.

Probable RR-TB

This is a term used to refer to people without bacteriologic confirmation of RR-TB who have symptoms, signs and/or radiology consistent with TB disease and who have been exposed to someone with infectious MDR-TB (>80% concordance between drug susceptibility test [DST] patterns in probable disease and the likely source patient). These individuals should be treated for RR-TB unless they later have bacteriologic confirmation showing rifampicin susceptibility.

Possible RR-TB

This term is used to refer to people with TB disease without bacteriologic confirmation of RR-TB who may be at high risk of having RR-TB and who may merit consideration for treatment while awaiting bacteriologic confirmation (i.e. some persons not responding to first-line therapy even with good adherence). These individuals should receive further work up and may be treated for RR-TB on a case-by-case basis even in the absence of bacteriologic confirmation if no other definitive diagnoses can be demonstrated.

Of note, throughout this document, the term "RR-TB" will be used as a general term to encompass all the forms of RR-TB (including MDR-TB). When a more specific type of RR-TB is being discussed, it will be referred to in more detail (e.g. "rifampicin mono-resistant TB"; "fluoroquinolone-resistant RR-TB").

BRIEF INTRODUCTION

The past five years have seen revolutionary changes in the diagnosis and management of RR-TB, including the use of new and repurposed drugs and novel therapeutic approaches. South Africa has been a global leader in introducing innovation to the field of RR-TB and the work done in the country has had a significant impact on global policy. In 2018, for the first time ever, the World Health Organization (WHO) recommended the use of all-oral regimens for the treatment of RR-TB and issued guidance supporting the use of short-course, all-oral regimens under closely monitored conditions.

In response to these WHO recommendations - as well as a number of new policy documents on diagnosis, patient support, ethics, and infection control - the National Department of Health (NDoH) of South Africa issued updated RR-TB guidelines (Management of Rifampicin Resistant Tuberculosis: 2019 Policy Guidelines). In addition to making new recommendations for the diagnosis, treatment, and prevention of RR-TB in the country, the guidelines also document the scientific and policy rationale underpinning these new recommendations. The guidelines are meant to provide the overarching framework in which all decisions regarding the spectrum of RR-TB management are made.

While the guidelines are meant to serve as the main reference document for RR-TB, there is also a need for an abbreviated set of tools that can be used by front-line clinicians to enhance their clinical care of patients with RR-TB. Thus, the NDoH has developed this clinical reference guide. Within this tool is a series of summary points, flow diagrams, and easy-to-view tables that contain practical information on the clinical management of RR-TB. More detailed information, if needed, can be found in the 2019 national RR-TB guidelines.

SUMMARY TABLE OF MAJOR GUIDELINE CHANGES

Subject Area	Major Policy Changes
Organisation of RR-TB Services	Hospitalisation will be based on the clinical status of the patient and no mandatory minimum hospital stays are required. Nurse-initiated and managed RR-TB treatment (NIMDR) will continue since results show comparable outcomes when compared with physician-initiated care.
Diagnosis	RR-TB diagnosis will be made primarily through the use of the Xpert MTB/RIF Ultra cartridges, with those patients who have ***M. tuberculosis*** with RR-TB having a second sample sent for "DR-TB reflex testing". Smear-negative samples will have first-line LPA done but second-line LPA will only be done on smear positive or culture positive samples. This will affect the turn-around time for results. Phenotypic testing for bedaquiline and clofazimine will be rolled out nationally by the end of 2019.
Treatment	All persons with RR-TB will either be treated with a shorter, all-oral, 9-11 month regimen or with a longer, all-oral 18-20 month regimen. The 9-11 month regimen consists of a "package" of seven medications (bedaquiline, linezolid, clofazimine, levofloxacin, high-dose isoniazid, pyrazinamide and ethambutol), with an intensive phase lasting 4-6 months and a continuation phase lasting 5 months. Children aged 6 years and above and pregnant women can be given the shorter regimen.

Subject Area	Major Policy Changes
Treatment	Persons who do not qualify for the shorter regimen will be given an individualised longer regimen whose composition is based on the presence of fluoroquinolone resistance, the presence of central nervous system disease, drug contra-indications, prior RR-TB drug exposure (including failure of prior RR-TB treatment with or without newer drugs), and the age of the individual (with different recommendations for children under the age of 6 years). All persons who are not responding to therapy will be identified early (i.e. based in part on month 4 culture status) and should be reviewed by the Provincial Clinical Advisory Committee (PCAC) or National Clinical Advisory Committee (NCAC) for a possible rescue regimen. Updated drug dosing recommendations are provided based on pharmacokinetic and safety data in adults and children.
Special Populations	Since children over the age of 6 years and pregnant women can receive bedaquiline, their care is integrated throughout the treatment sections in the policy guidelines. People with HIV should be prioritised for dolutegravir-based ART since bedaquiline cannot be given with efavirenz. A systematic intervention and package of services for people who are using alcohol and/or other substances in provided in the policy guidelines.
Surgical Therapy	The role for greater collaboration with surgical services is emphasised, not just for pulmonary resection but also for the placement of central venous access to administer long-term injectable medications (including the carbapenems).

Subject Area	Major Policy Changes
Monitoring and Management During Treatment, Including for Adverse Events	An updated monitoring chart and standardised symptom screening checklist is included to emphasise screening changes with the new regimens. Detailed monitoring for, and management of toxicity associated with linezolid (anaemia, thrombocytopenia, leucopenia/neutropenia, peripheral neuropathy, optic neuritis) and bedaquiline and clofazimine (QT interval prolongation) is included. Active drug safety monitoring (aDSM) activities and protocols are described in more detail.
Contact Evaluation and Post-Exposure Management	A systematic approach to all persons exposed to RR-TB is described, including disclosure counselling, ruling out active disease, possible treatment of infection/ preventive therapy for high-risk contacts, and long-term follow up.
Management of Drug-Resistant TB that is not RIF-resistant	A systematic approach to the management of isoniazid mono- and poly-resistant TB is described.
Patient Support and Adherence	A more detailed patient support and adherence package is described, including treatment literacy, systematic counselling, screening and management for substance use and mental health concerns, nutritional support, transportation support, and modified Directly Observed Therapy (DOT)/self-administered therapy.
Palliative Care	A more detailed approach to palliative and end-of-life care is described.
Post-Treatment Monitoring	A more detailed approach to following patients after the completion of treatment is provided. Such post-treatment monitoring is essential given that recurrent TB may be more commonly seen with the use of a shorter regimen and that many patients suffer complications as a result of their RR-TB disease or treatment that require ongoing care even after RR-TB treatment is complete.

ORGANISATION OF SERVICES

The majority of RR-TB care and services should be provided in the outpatient setting according to the National decentralisation plan.

Persons with clinical indications for hospitalisation should be admitted for care at the discretion of their providers. The length of hospitalisation should be based on the reason for admission and resolution of the condition(s) that led to hospitalisation.

Nurses should continue to initiate uncomplicated patients on RR-TB treatment, as a 2018 programme review showed that patients treated via NIMDR had comparable outcomes to those initiated on treatment by medical officers. Nurses should receive support from medical officers in the management of complicated patients.

Both the NCAC and the PCACs should continue to be used to provide input on the management of persons with more complicated RR-TB. The PCACs can advise on toxicity management, initial regimen selection in more complicated patients, and end-of-life care. The NCAC's input should be sought on the management of complicated patients (e.g. CNS RR-TB that is fluoroquinolone-resistant), patients in need of rescue regimens, and the care of children with complicated RR-TB who are under the age of 6 years (i.e. who might need bedaquiline or delamanid but who are outside the recommended age ranges). The NCAC should also be informed of pregnant women being treated for RR-TB, although their permission to initiate treatment is not required.

ORGANISATION OF SERVICES: PATIENT FLOW

Primary Health-Care Facilities/General Hospitals

- Identify people with signs and symptoms of TB disease
- Collect specimen for microbiological testing (refer to NHLS diagnostic algorithm)

On receipt of results confirming RR-TB:

- Recall patient and send second specimen for DR-TB reflex
- Counsel patient & explain DR-TB management plan
- Conduct contact evaluation and post-exposure management

Laboratory

- Diagnosis of DR-TB
- Report sent to requesting facility and DR-TB site within 24 hours of confirmation of diagnosis

Patients are either hospitalised or initiated on treatment as outpatients

Before initiating treatment:

- Patient to be registered in a DR-TB register at appropriate facility (usually at a centralised or decentralised unit).
- Counsel the patient and family; obtain consent for DR-TB management; use appropriate DR-TB stationery; conduct psychosocial assessment including history of substance use and mental health screen; refer for further social assessment and support as required.

Patients to start in ambulatory care	Main indications for hospitalisation of patients with RR-TB
• Patient is ambulant, in fair to good general condition (BMI ≥18.0) • Patient is willing and able to attend clinic regularly for clinical review and monitoring, and to receive treatment under directly observed therapy (DOT) with the option of self-administered therapy later in the treatment journey according to locally accepted policies	• Respiratory insufficiency • Haemoglobin <8.0 g/dL • Body Mass Index (BMI) <18 kg/m2 • Central nervous system (CNS) RR-TB disease • Clinically unstable • Unstable social situations that require intensive multi-disciplinary management • Administration of intravenous therapy • Unable to attend primary care facility for treatment (e.g. too weak to ambulate) • Infection control challenges in the patient's home environment • Recurrent treatment interruption where previous outpatient treatment has been unsuccessful • Any condition that in the opinion of the treating clinician would be better managed in the inpatient setting • Patient preference for inpatient care

On discharge from hospital, ask patient about most convenient DR-TB unit or facility for referral for ongoing outpatient management; notify receiving clinic or hospital of the down-referral; arrange transport; complete appropriate documentation (follow up card and DR-TB stationery)

Centralised DR-TB Units	Decentralised DR-TB Units	Satellite MDR-TB Units	Mobile Team

- All DR-TB units are responsible for providing treatment according to local best practices and for monitoring progress of patients throughout their treatment journey
- DR-TB stationery should be maintained at the facility at which the patient is being managed

ROLES OF THE PCACs AND NCAC

Each province has a provincial clinical advisory committee (PCAC), or similar arrangement, through which formal input can be sought on the management of persons with RR-TB. The PCACs can be consulted at any time, and they should provide input on the management of patients in the following situations:

- Initial regimen choice in more complicated patients (i.e. those in whom a choice between the shorter or longer regimens is not clear).
- Toxicity management, especially when consideration of discontinuation of any of the following medications is being considered: linezolid, bedaquiline, levofloxacin / moxifloxacin, clofazimine and/or delamanid.
- End-of-life care.
- INH mono-resistant TB if detected after month 2 of DS-TB treatment.
- CNS RR-TB.
- Initial rescue regimen for persons who are not responding to therapy.
- Discrepant DST results.

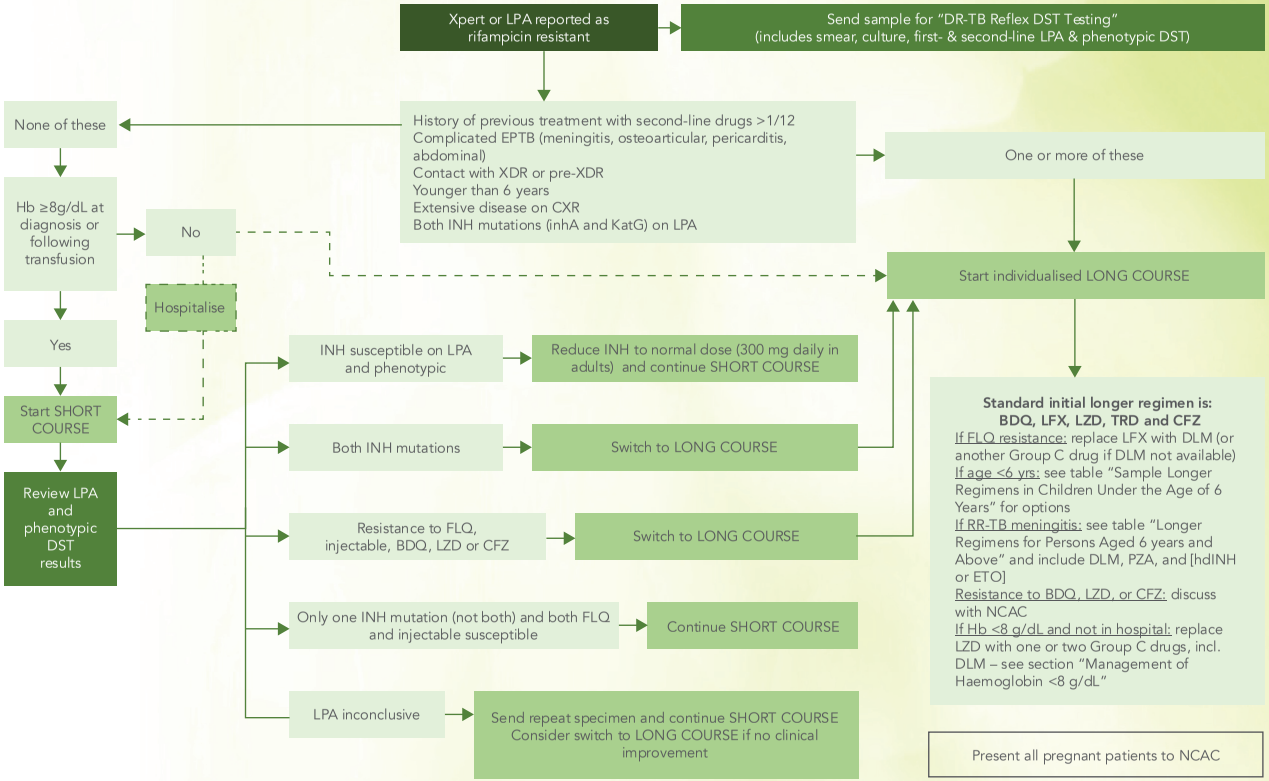
There is also a national clinical advisory committee (NCAC) that can provide formal input on more complicated patients. The NCAC can be consulted at any time and may provide input of the management of patients in the following situations:

- Patients in whom RR-TB treatment has failed.
- Management of children who might need bedaquiline and/or delamanid but who are outside the recommended age groups.
- CNS RR-TB that is fluoroquinolone-resistant.

Note that pregnant women with RR-TB can be initiated on treatment by providers without NCAC approval but these cases should still be presented to the NCAC so that this cohort can be more formally monitored on a national level.

The NCAC contact is: NCAC@WITSHEALTH.CO.ZA

OVERALL FLOW DIAGRAM



LPA = line probe assay; DST = drug susceptibility testing; INH = isoniazid; FLQ = fluoroquinolone; BDQ = bedaquiline; LZD = linezolid; CFZ = clofazimine; LFX = levofloxacin; TRD = terizidone; DLM = delamanid; PZA =

SUMMARY OF DIAGNOSIS

- All persons with signs and symptoms of TB should have a specimen sent for Xpert MTB/RIF Ultra testing.
- Persons who test positive for ***M. tuberculosis*** with rifampin resistance will have a second sample sent to the lab with a request for "DR-TB: reflex DST testing".
- "DR-TB: Reflex DST Testing" includes a sequence of tests starting with smear microscopy: if the smear result is positive then first and second-line LPA will be carried out and the sample will be sent for culture; if the smear result is negative then the 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. Additional phenotypic tests will be done on the culture isolate, based on the results of the first and second-line LPA.
- Clinicians should call the laboratory to discuss any discrepant results, or to determine if additional testing is needed if the patient has a prior history of treatment for RR-TB.
- Ongoing surveillance will determine the need for upfront phenotypic testing of drugs such as bedaquiline, delamanid, linezolid, and/or clofazimine.
- Next generation genome sequencing is a promising technology and may take on a more prominent role in determining drug resistance in the next 5 to 7 years.

TYPES OF LABORATORY TESTING AND ESTIMATED TURNAROUND TIMES

TYPE OF TEST		WHEN DONE	RESULT
Genotypic	**First-line LPA**	GXP positive and rifampicin resistant	Susceptibility to rifampicin and isoniazid
	Second-line LPA	GXP positive and rifampicin resistant	Susceptibility to fluoroquinolones and injectables
Phenotypic DST for isoniazid		In-lab reflex done when rifampicin resistant and isoniazid susceptible on first line LPA	Confirm susceptibility to isoniazid
Second-line phenotypic DST		In-lab reflex done when susceptible to fluoroquinolones on second-line LPA	Confirm susceptibility to levofloxacin ***or*** moxifloxacin (at 0.25 µg/ml)
		In-lab reflex done when isolate is resistant to fluoroquinolones or injectables on second-line LPA or phenotypic DST, or where both isoniazid mutations are present	Susceptibility to levofloxacin*, linezolid, bedaquiline and clofazimine
Individualised Extended Phenotypic DST (done by the National Institute of Communicable Diseases)		Requested when RR-TB regimen failing, or previous exposure to second-line drugs	Susceptibility to multiple TB drugs, used to construct a rescue regimen

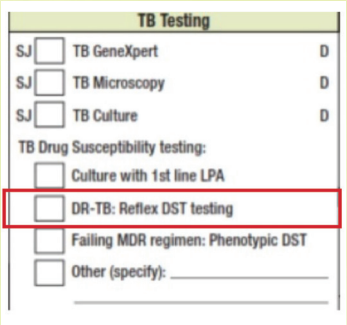
*Where LPA shows fluoroquinolone resistance, no routine phenotypic fluoroquinolone DST will be carried out.

In general, LPA results done directly on sputum should be available within 8-18 days. Cultured specimens should have results within 28 days, and LPA done on cultured isolates will take another 8-18 days after that (so for LPA results on smear-negative, culture-positive samples, results will likely be available within 46 days). Phenotypic DST can take as long as 60 days for results to be available.

LABORATORY REFLEX TESTING WORKFLOW

RIF-R TB on GXP or first-line LPA

Collect second sample for DR-TB Reflex DST Testing (microscopy, culture, first- and second-line LPA, phenotypic DST)



In Lab Reflex

INH susceptible on first-line LPA	FLQ-R / INJ-R / both ***inhA*** and ***katG*** mutation	FLQ-S
Phenotypic DST for: INH	Phenotypic DST for: LFX*, LZD, BDQ, CFZ	Phenotypic DST for: LFX, or MFX 0.25 µg/ml

*Where LPA shows FLQ-resistance, no routine phenotypic FLQ DST will be carried out.

DR-TB = drug resistant tuberculosis;
LPA = line probe assay;
S = susceptible;
INH = isoniazid;
INJ = injectables;
LFX = levofloxacin;
BDQ = bedaquiline;
MFX = moxifloxacin
GXP = GeneXpert;
R = resistant;
RIF = rifampicin;
FLQ = fluoroquinolones;
DST = drug susceptibility testing;
LZD = linezolid;
CFZ = clofazimine;

INTERPRETATION OF LABORATORY TEST RESULTS FOR PERSONS STARTED ON THE SHORTER REGIMEN BASED ON GENEXPERT RIFAMPICIN RESISTANCE

First-line LPA Result	Action
Rifampicin susceptible	Continue shorter RR-TB regimen, discuss any discordance with laboratory.
Rifampicin resistant	Continue shorter RR-TB regimen, modify according to other LPA results.
inhA mutation only	Continue shorter RR-TB regimen, modify according to other LPA results.
katG mutation only	Continue shorter RR-TB regimen, modify according to other LPA results.
Both inhA and katG mutations	Switch to a longer regimen, follow up second-line LPA results and phenotypic DST results.
Isoniazid susceptible	Continue shorter RR-TB regimen, modify according to other LPA results. If phenotypic DST confirms isoniazid susceptible reduce isoniazid to normal dose.
Second-line LPA result	**Action**
Susceptible to fluoro-quinolones	Continue shorter RR-TB regimen with two months of linezolid. Follow up phenotypic DST for levofloxacin, or moxifloxacin (at 0.25 µg/mL).
Resistant to fluoroquinolones	Switch to a longer regimen, follow up phenotypic DST for linezolid, bedaquiline and clofazimine
Susceptible to injectable	Continue shorter RR-TB regimen (if also susceptible to fluoroquinolones).
Resistant to injectable	Switch to a longer regimen, follow up phenotypic DST for levofloxacin, linezolid, bedaquiline and clofazimine.

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REQUESTS FOR EXTENDED DRUG SUSCEPTIBILITY TESTING FOR LONG TERM DR-TB NON-RESPONDERS.

Despite the use of optimized regimens and new drugs for treatment, a select sub-group of patients do not respond. Such patients have limited treatment options and require extended drug susceptibility testing. Testing will include: Linezolid, Bedaquiline, Clofazimine and Rifabutin. The following steps should be followed when making the request.

Identify the **NHLS laboratory number** of the latest positive TB culture

↓

Contact your local NHLS TB laboratory manager or pathologist to electronically refer positive culture to Centre for TB (NICD)

↓

Print result of positive culture; scan, and email Dr Farzana Ismail (farzanai@nicd.ac.za) and Dr Shaheed Vally Omar (shaheedvo@nicd.ac.za), and copy the local NHLS TB lab manager. If scanning of results is not possible, email all relevant patient details (NAME AND SURNAME, DATE OF BIRTH) and lab no. of the latest positive culture.

↓

Title of email should read "Extended susceptibility testing + patient name"

↓

In the content of email, write a shorter clinical summary which includes the patient's drug exposure (drug names and duration)

N.B: Samples will not be processed if the above procedure has not been complied with

LABORATORY TESTING: SPECIAL SITUATIONS

Situation	Recommended Actions
Treatment of a patient where Xpert MTB/RIF Ultra is positive and rifampicin resistant, however second-line LPA results are pending	Asses clinical risk factors and if no exclusion factors start on shorter regimen. If no LPA results within 30 days of sample submission, submit repeat sample for LPA. If no resistance testing results are available, then the patient should continue on the shorter regimen but follow up closely to monitor response both clinically and bacteriologically.
Discrepant results between phenotypic and genotypic tests	Clinician to phone the laboratory to discuss discrepancies. Multiple possibilities for discrepancies exist, including sample mix-up or contamination, "silent" mutations that exist but do not confer resistance; "missed" mutations that are not detected on genotypic testing but do confer resistance; hetero-resistance; infection with multiple strains. In general, treatment should be based on the "most resistant" scenario; consult with PCAC or NCAC.

DIAGNOSIS OF RR-TB IN CHILDREN

Key points to consider in RR-TB diagnosis in children are:

- The diagnosis of TB disease in children is often made on patient history, clinical and radiological grounds with consideration of RR-TB disease based on risk factors for RR- TB, such as recent RR-TB exposure or failure of first-line TB treatment with good adherence. However, children with clinically diagnosed TB may have culture-confirmed RR-TB as well and may even be the index RR-TB case.

- Evaluation should include symptom screening followed by thorough history and clinical examination, and may also include imaging (e.g. chest X-ray, including lateral view) depending on symptoms and suspected site of disease.

- Children should be assessed for growth and nutritional status (weight-for-age, height-for-age and height-for-weight curves, mid-upper arm circumference, signs of malnutrition such as oedema or severe wasting).

- Bacteriological confirmation should always be attempted; at least two good quality specimens should be collected and sent for Xpert MTB/RIF Ultra and mycobacterial culture and DST. Many children will not have bacteriological confirmation due to paucibacillary disease or some forms of extra-pulmonary disease.

- For respiratory samples, children aged 5 years and older can usually expectorate sputum; sputum induction can be used to assist children who struggle to produce samples. Children less than 5 years of age may require gastric aspiration or other form of sputum collection (e.g. induced sputum). Induced sputum and gastric aspirates are relatively simple procedures and should be offered in facilities at primary health care level. These results must be actively followed up – culture and DST may take up to 6 weeks for final results.

- Bacteriological results are frequently negative even if the child has TB disease. Sputum smear results are positive in less than 15% of samples obtained from children, while Xpert MTB/RIF or culture results are positive in about 40% of samples in programmatic settings. It is always worthwhile attempting to obtain samples for confirmation as this greatly improves the accuracy of diagnosis and provision of effective therapy.

- Tests to diagnose EPTB, such as appropriate imaging and collection of specimens (such as fine needle aspirates, biopsies, different bodily fluids and CSF) for bacteriological confirmation and DST, should be performed, where possible. Peripheral lymph node disease is the most common form of EPTB in children, and fine needle aspiration is minimally invasive and has high yield of bacteriological confirmation.

- In children with bacteriologically confirmed pulmonary disease, bacteriological monitoring should be done throughout treatment to assess response to therapy, as for adults.

- Children may be considered to have 'non-severe' disease if they are clinically diagnosed with RR-TB disease with: no bacteriological confirmation, unilateral pulmonary TB disease, non-cavitating TB disease and isolated peripheral lymph node disease.

THE SHORTER REGIMEN FOR RR-TB: SUMMARY POINTS

- People with a diagnosis of RR-TB are eligible to receive the shorter 9-11 month regimen: if they have no prior history of treatment with second-line TB drugs (>1 month); if there is no evidence of resistance to fluoroquinolones, injectable agents, bedaquiline, clofazimine or linezolid; if there is only one INH mutation (***inhA*** or ***katG***) or no mutation causing isoniazid resistance; if they have no close contact with individuals with the above-mentioned characteristics; if there is no evidence of complicated extra-pulmonary RR-TB (i.e. meningitis, pericarditis, osteoarticular, abdominal disease) or extensive, bilateral, cavitary pulmonary RR-TB disease.

- The shorter regimen contains the following medications: bedaquiline, linezolid, clofazimine, levofloxacin, high-dose isoniazid, pyrazinamide and ethambutol, and is usually given for 9 months but may be extended to 11 months.

- The shorter regimen contains a 4-6 month intensive phase consisting of these seven drugs (although linezolid will only be given for two months and bedaquiline will be given for at least six months), depending on the timing of smear conversion.

- The shorter regimen contains a 5-month continuation phase consisting of levofloxacin, clofazimine, pyrazinamide, and ethambutol.

- Bedaquiline may be extended from 6 to 9 months if there is no second-line DST result available, if the patient is slow to smear or culture convert, if there is extensive disease, or there is delayed clinical response.

- Children 6 years and older qualify to receive the shorter regimen if they meet the inclusion criteria listed above.

- Pregnant women qualify to receive the shorter regimen if they meet the inclusion criteria listed above.

- HIV-positive patients with any CD4 count, regardless of ART status, qualify to receive the shorter regimen if they meet the inclusion criteria listed above.

- Pyridoxine should be co-administered with the TB regimen to prevent peripheral neuropathy while receiving isoniazid. Use 50 mg/day for adults and 25 mg/day for children aged 6 to 12 years. Note that pyridoxine has NOT been shown to prevent linezolid-induced neuropathy. Doses of pyridoxine exceeding 100 mg a day can cause or worsen peripheral neuropathy and therefore should never be used.

- If either pyrazinamide or ethambutol needs to be discontinued, no drug substitution is needed. If both drugs need to be discontinued, then drug substitution could include bedaquiline extension or linezolid extension. If other medications need to be stopped, the patient should switch to a longer regimen designed with input from the PCAC or NCAC.

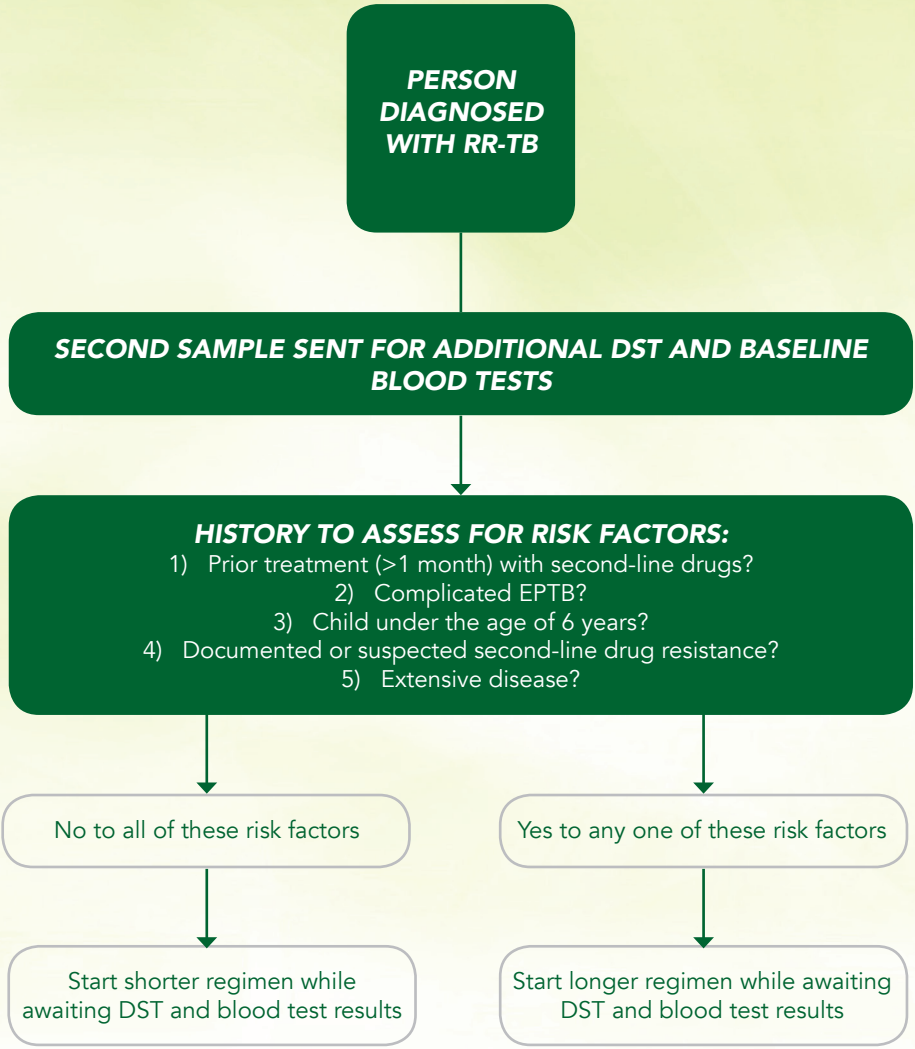
INCLUSION AND EXCLUSION CRITERIA FOR THE SHORTER REGIMEN

Inclusion Criteria	Exclusion Criteria
1) Individuals with RR-TB without 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	1) Any previous exposure (>1 month) to second-line RR-TB treatment regardless of treatment outcome
2) Uncomplicated extra-pulmonary RR-TB, including lymphadenopathy or pleural effusion	2) Persons with RR-TB with resistance to the fluoroquinolones, the injectable agents, or both
	3) Persons with MDR-TB with both ***inhA*** and ***katG*** mutations
	4) RR-TB with additional resistance to bedaquiline, linezolid and/or clofazimine
	5) RR-TB with suspected resistance to second-line drugs, even if susceptibility is demonstrated on DST (i.e. 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)

Inclusion Criteria	Exclusion Criteria
	6) Persons with RR-TB meningitis, pericarditis, abdominal or osteoarticular RR-TB disease
	7) Persons with extensive disease (i.e. bilateral, cavitary disease with significant fibrosis, scarring or cavities in three or more lung zones)
	8) Children under the age of 6 years (since bedaquiline dosing and safety is not yet confirmed in this population)
	9) Any other situation in which the clinician is uncertain of the patient's eligibility for the shorter regimen

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

INITIAL APPROACH TO PATIENTS DIAGNOSED WITH RR-TB



PRINCIPLES OF THE SHORTER TREATMENT REGIMEN IN CHILDREN AGED 6 YEARS AND ABOVE

- The shorter treatment regimen is considered to be a "package" regimen, where the same initial regimen is given to all persons with RR-TB with only minimal modifications allowed.
- Data on the dosing and safety of bedaquiline in children aged 6 years and above has been established and because bedaquiline can be used safely in this group, they qualify for the shorter regimen.
- Data on the dosing and safety of bedaquiline in children under the age of 6 years has not yet been established and thus bedaquiline cannot be routinely used in this population. For this reason, children under the age of 6 years need to receive an individualised regimen whose composition and duration will be based on their clinical status, disease severity, resistance pattern, and site of disease.
- Children with clinically diagnosed RR-TB can receive the shorter regimen based on the DST of their source case (if they do not have a DST of their own) and if they have no other exclusion criteria.
- Children with clinically diagnosed RR-TB will have no smear result to refer to at month 4 of treatment and so will only receive 4 months of high-dose isoniazid on the shorter regimen, unless they are failing to gain weight or improve clinically.
- For children who weigh 30 kg and above, adult dosing of bedaquiline should be used. For those weighing between 16 and 30 kg, use a loading dose of 200 mg once daily for 14 days followed by 100 mg three times a week.
- For children who weigh 16 kg and above, the dose of linezolid should be 10 mg/kg once daily. For children who weigh less than 16 kg, the dose of linezolid should be 15 mg/kg once daily.

SHORTER REGIMEN SUMMARY

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

LZD = linezolid; BDQ = bedaquiline; hdINH = high-dose isoniazid; LFX = levofloxacin; CFZ = clofazimine; PZA = pyrazinamide; EMB = ethambutol.

#The dose of linezolid in children weighing less than 16 kg is 15 mg/kg once daily, and for children weighing 16 kg and above, the dose is 10 mg/kg once daily.

*Bedaquiline should be given at the adult dose of 400 mg once daily for 14 days followed by 200 mg thrice weekly for people whose weight is greater than 30 kg; for those weighing between 16 kg and 30 kg, a dose of 200 mg once daily for 14 days followed by 100 mg thrice weekly should be administered. There are currently no data to support dosing recommendations for bedaquiline for people weighing less than 15 kg.

	2 MONTHS	4 MONTHS	6 MONTHS	9 MONTHS
Linezolid		Give for 2 months even if second-line LPA shows injectable and fluoroquinolone susceptibility		
High-dose isoniazid			Extend for another 2 months if smear positive at month 4*	
Bedaquiline				Continue to 9 months in some patients
Levofloxacin				
Clofazimine				
Pyrazinamide				
Ethambutol				

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

RATIONALE FOR MODIFICATION OF MEDICATIONS IN THE SHORTER REGIMEN

Medication	Included/ Excluded	Rationale
Bedaquiline	Included	Use associated with improved outcomes and reduced mortality.
Linezolid	Included (for two months only)	Use associated with improved outcomes and reduced mortality. Use likely protects against amplification of resistance while awaiting fluoroquinolone susceptibility results. Duration based on minimising toxicity.
Levofloxacin	Included	Use associated with improved outcomes and reduced mortality. Chosen over moxifloxacin because of less QT interval prolongation
Clofazimine	Included	Use associated with improved outcomes. Key component of the shorter regimen. Likely to be responsible for treatment shortening effect.
High-dose isoniazid	Included	Key component of shorter regimen. May still be effective at higher doses (10 mg/kg in adults; 15-20 mg/kg in children) against strains with isoniazid resistance, especially those with ***inhA*** mutations.
Pyrazinamide	Included	Key component of shorter regimen; likely benefits outweigh risks.
Ethambutol	Included	Key component of shorter regimen; likely benefits outweigh risks.
Injectables	Excluded	Only amikacin (i.e. not kanamycin or capreomycin) found to be associated with improved treatment outcomes. Risk of serious adverse events (especially hearing loss and renal failure) outweighs benefits. Should not be used routinely for the treatment of RR-TB.
Ethionamide	Excluded	Associated with worse treatment outcomes in adults. High rate of gastrointestinal intolerance. Not effective if ***inhA*** mutation is present. Could consider this instead of high-dose isoniazid in children with MDR-TB with only ***katG*** mutations (fewer adverse effects compared to adults).

SWITCHING FROM SHORTER REGIMEN TO LONGER REGIMEN

It is important to recognise when a person needs to switch from the shorter regimen to a longer regimen. Input should be sought from the PCAC where needed. A switch to a longer regimen should be strongly considered in the following situations:

- There is genotypic or phenotypic resistance to a fluoroquinolone that was not detected at the beginning of treatment;
- There is a positive culture result at month 4 (delayed culture conversion or reconversion back to positive);
- Bedaquiline, linezolid, levofloxacin or clofazimine is prematurely and permanently discontinued because of toxicity;
- The patient is clinically deteriorating or has not clinically improved.

If the patient switches to a longer regimen due to shorter regimen treatment failure, the treatment episode should be registered as "treatment failure" and the patient should be assigned a new treatment episode.

If the patients switches from a shorter to a longer regimen due to detection of second-line drug resistance, then the treatment episode should be continued and the patient switches categories to the longer regimen.

LONGER REGIMENS FOR RR-TB: SUMMARY POINTS

- Persons who do not qualify for the shorter regimen will receive a longer 18-month regimen. The core drugs in the regimen include bedaquiline, linezolid, levofloxacin, clofazimine and terizidone.

- For persons aged 6 years and above who do not meet the shorter regimen inclusion criteria, treatment with the longer regimen will consist of the four to five drugs given for a period of 6 months followed by 12 months of levofloxacin, clofazimine and one additional agent (either linezolid, bedaquiline or terizidone, depending on tolerance).

- Modifications to the regimen will be made if the person has RR-TB with fluoroquinolone resistance or if the person has central nervous system RR-TB disease.

- For persons aged 6 years and above with RR-TB that is resistant to fluoroquinolones, a regimen consisting of bedaquiline, linezolid, clofazimine, terizidone and delamanid should be given for 6 months, followed by a continuation phase of 12 months with three to four drugs including clofazimine, terizidone and one or two additional agents (linezolid, bedaquiline and/or delamanid, depending on tolerance).

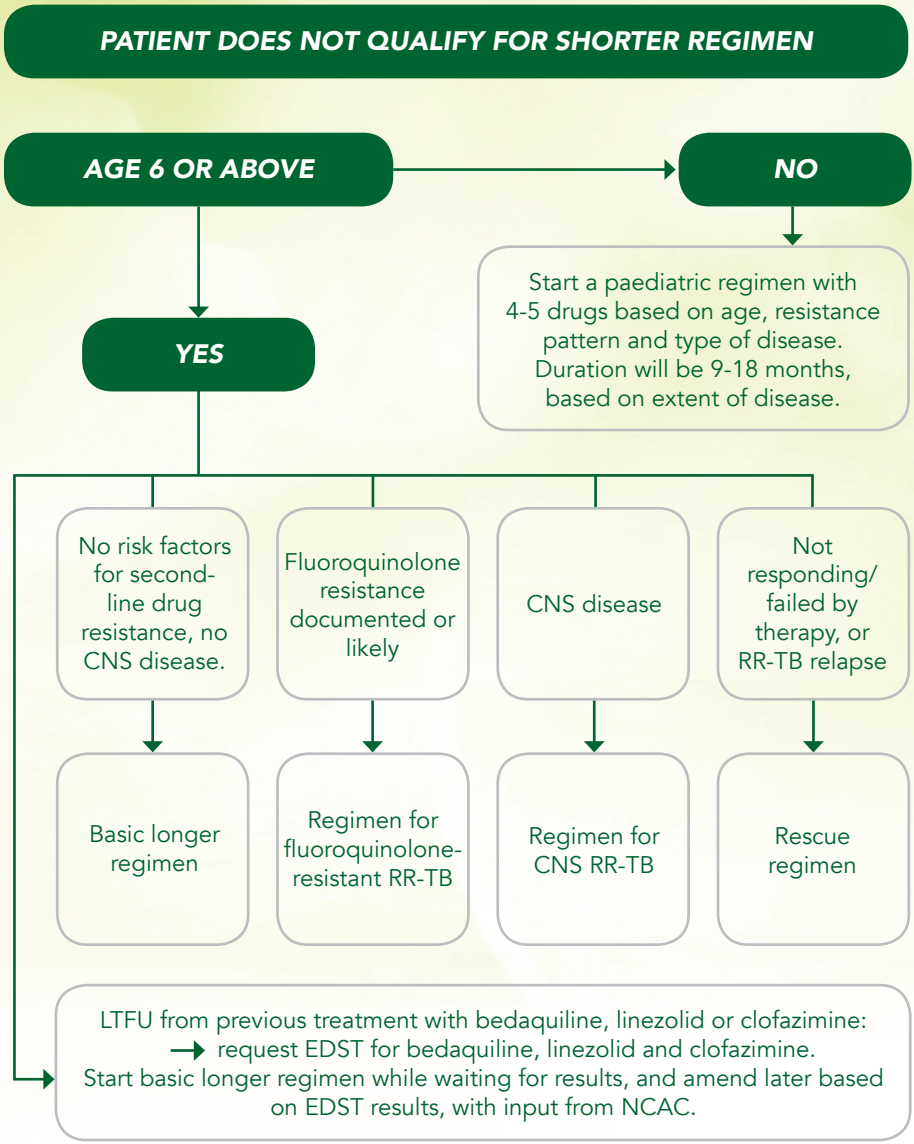
- For persons aged 6 years and above with CNS RR-TB disease, treatment will be 12 months of bedaquiline, linezolid, levofloxacin, (high-dose isoniazid [15 mg/kg] or ethionamide, depending on mutation present), clofazimine, terizidone, pyrazinamide and delamanid. Pyrazinamide and either high-dose isoniazid or ethionamide are included because of their relatively good CNS penetration compared to other drugs. The continuation phase consists of 6 months of levofloxacin, clofazimine, terizidone, pyrazinamide and one additional agent (linezolid, ethionamide or high-dose isoniazid, depending on tolerance.)

- Children under the age of 6 years will receive a regimen consisting of at least four effective drugs, based on the recommended approach by the WHO and prioritising WHO Group A and B drugs where possible. For children aged 3 to 5 years, delamanid should be given instead of bedaquiline, and for children under the age of 3 years, para-aminosalicylic acid should be used until safety and dosing of bedaquiline or delamanid is established in this age group. Duration of treatment will depend on site and severity of disease.

- Pyridoxine should be co-administered with the TB regimen to prevent peripheral neuropathy while receiving isoniazid and/or terizidone. Use 50 mg/day for adults, 25 mg/day for children aged 5 to 12 years, and 12.5 mg/day for children less than 5 years old. Note that pyridoxine has NOT been shown to prevent linezolid-induced neuropathy.

- If, in the 'basic' longer regimen, terizidone is discontinued due to toxicity or intolerance, it is not necessary to substitute with another drug; however, if any of the other drugs have to be discontinued, then substitution is needed. Options could include extension of bedaquiline or linezolid, addition of delamanid, or other group C medication(s).

INITIAL APPROACH TO LONGER REGIMENS



WHO DRUG GROUPINGS AND STEPS TO DESIGNING A LONGER TREATMENT REGIMEN

GROUPS AND STEPS	MEDICINE	COMMENTS
Group A: include all three medicines, where possible	Levofloxacin or moxifloxacin	Include for CNS disease. Omit in fluoroquinolone-resistant RR-TB.
	Bedaquiline	No dosing data currently available in age<6 years.
	Linezolid	Include for CNS disease. Avoid if LZD resistance demonstrated. In patients with Hb <8 g/dL, neutrophils <0.75 x 109/L and/or platelets <50 x 109/L, only consider reintroducing or initiating in hospital under close monitoring; otherwise substitute with other Group C drugs including delamanid.
Group B: add one or both medicines, if possible	Clofazimine	
	Terizidone	Include for CNS disease.
Group C: add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	Only use as a reliably effective drug if susceptibility demonstrated on DST.
	Delamanid	Include for CNS disease. Dosing data not currently available in age <3 years.
	Pyrazinamide	Include for CNS disease. Only use as a reliably effective drug if susceptibility demonstrated on DST.

GROUPS AND STEPS	MEDICINE	COMMENTS
Group C: add to complete the regimen and when medicines from Groups A and B cannot be used	Imipenem-cilastatin, or meropenem, or ertapenem	Adequate CNS penetration. Must be given in combination with amoxicillin/clavulanic acid.
	Amikacin	Only administer in rescue regimens, if there is documented susceptibility, if formal hearing tests can be done, and if the patient consents to its use after the risks and benefits of the drug have been explained.
	Ethionamide	Consider for CNS disease. Should only be given if ***inhA*** mutation is not present.
	para-aminosalicylic acid	

INCLUSION CRITERIA FOR LONGER REGIMENS

All persons with RR-TB who do not qualify for the shorter regimen will receive a longer regimen. There are five possible longer regimens that consist of similar core drugs but are individualised to account for unique clinical situations.

These five possible regimens include:

1. A "basic" longer regimen for persons aged 6 years and above who have RR-TB without additional fluoroquinolone resistance and who do not have complicated clinical disease (i.e. CNS RR-TB), but who still do not meet inclusion criteria for the shorter regimen;

2. A longer regimen for persons aged 6 years and above who have RR-TB that is fluoroquinolone-resistant;

3. A longer regimen for persons aged 6 years and above who have CNS RR-TB disease;

4. An individualised rescue regimen for persons aged 6 years and above who are not responding to treatment, who have been failed by a previous RR-TB treatment regimen (especially one containing bedaquiline, linezolid and/or clofazimine), or who have RR-TB with documented or suspected resistance to bedaquiline, linezolid and/or clofazimine;

5. An individualised regimen for children under the age of 6 years with any form of RR-TB.

LONGER* REGIMENS FOR PERSONS AGED 6 YEARS AND ABOVE

EXAMPLE	INTENSIVE PHASE	CONTINUATION PHASE	COMMENTS
"Basic" longer regimen	6 months of: BDQ–LZD–LFX–CFZ–TRD	12 months of three drugs: LFX–CFZ–TRD (if one of these three drugs are not tolerated, extend either LZD or BDQ instead)	If TRD contra-indicated or not tolerated in intensive phase, then no need to substitute TRD (unless there was previous treatment with second-line drugs, or extensive disease)
Fluoroquinolone-resistant RR-TB longer regimen	6 months of: BDQ–LZD–DLM–CFZ–TRD	12 months of three to four drugs: CFZ–TRD– [LZD, BDQ and/or DLM, depending on tolerance]	Use four drugs in continuation phase if extensive disease, co-morbidities
CNS RR-TB longer regimen	12 months of: BDQ–LZD–DLM-LFX–CFZ–TRD–PZA– [high-dose INH 15 mg/kg, or ETO, depending on INH mutation]	6 months of four to five drugs: LFX– CFZ–TRD–PZA– [LZD or high-dose INH 15 mg/kg or ETO depending on INH mutation]	High-dose INH is higher than usual (15 mg/kg) for CNS disease in adults

*Treatment duration is 18 months but could be extended to 20 months per clinician discretion

LZD = linezolid;
CFZ = clofazimine;
PZA = pyrazinamide;
BDQ = bedaquiline;
TRD = terizidone;
INH = isoniazid;
LFX = levofloxacin;
DLM = delamanid;
ETO = ethionamide

RECOMMENDED DOSING OF DRUGS FOR RR-TB TREATMENT IN PERSONS ≥6 YEARS AND WEIGHING ≥30 KG

For drug dosing in children less than 6 years of age and persons weighing less than 30 kg, refer to paediatric dosing charts.

<table>
<tr><th rowspan="3">Target dose</th><th colspan="4">GROUP A</th><th colspan="2">GROUP B</th></tr>
<tr><th colspan="2">Levofloxacin
(15-20 mg/kg once daily)</th><th colspan="2">Moxifloxacin
(10-15 mg/kg once daily)</th><th>Bedaquiline
(once daily loading dose then thrice weekly dosing)</th><th>Linezolid
(10 mg/kg once daily)</th><th>Terizidone
(15-20 mg/kg once daily for children below 14 years of age and 10–15 mg/kg for individuals >14 years)</th><th>Clofazimine
(2-5 mg/kg once daily)</th></tr>
<tr><th>Formulation</th><th>250 mg dispersible tab</th><th>500 mg tab</th><th colspan="2">400 mg tab</th><th>100 mg tab</th><th>600 mg tab*</th><th>250 mg cap</th><th>100 mg gel caps</th></tr>
<tr><th>Weight bands</th><th></th><th></th><th>Standard dose</th><th>High dose</th><th></th><th></th><th></th><th></th></tr>
<tr><td>30-35 kg</td><td rowspan="2">750 mg (3 tab)</td><td rowspan="2">750 mg (1.5 tab)</td><td rowspan="4">400 mg (1 tab)</td><td>400-600 mg (1-1.5 tab)</td><td rowspan="4">400 mg (4 tab) daily for first 2 weeks, then 200 mg (2 tab) three times a week (M/W/F) for 22 weeks.</td><td rowspan="4">600 mg (1 cap)</td><td>500 mg (2 tab)</td><td rowspan="4">100 mg (1 cap)</td></tr>
<tr><td>36-45 kg</td><td>600 mg (1.5 tab)</td><td rowspan="3">750 mg (3 tab)</td></tr>
<tr><td>46-55 kg</td><td rowspan="2">1000 mg (4 tab)</td><td rowspan="2">1000 mg (2 tab)</td><td>600-800 mg (1.5-2 tab)</td></tr>
<tr><td>>55 kg</td><td>800 mg (2 tab)</td></tr>
</table>

Target dose	GROUP C									
	Isoniazid (Standard: 4-6 mg/kg once daily) (High-dose: 10-15 mg/kg once daily)		**Meropenem*** (20-40 mg/kg IV every 8 hours)	**Amoxicillin-Clavulanate** (every 8 hours)	**Delamanid** (twice daily dosing)	**Ethambutol** (15-25 mg/kg once daily)	**Pyrazinamide** (20-30 mg/kg once daily)	**Amikacin** (15-20 mg/kg once daily)	**PAS (sodium salt or acid)** (200-300 mg/kg once daily or two divided doses)	**Ethionamide** (15-20 mg/kg once daily)
Formulation	**300 mg** tab or **100 mg** tab		**1 g** vial (20ml)	Amoxicillin 500 mg / clavulanic acid **125 mg**	**50 mg** tab	**400 mg** tab	**500 mg** tab	**500 mg** vial (2 ml)	**4 g** sachet	**250 mg** tab
Weight bands	**Standard dose**	**High dose**								
30-35 kg	200 mg (2 x 100 mg tab)	450 mg (1.5 x 300 mg tab)	1 g (20 ml) three times per day IV <u>OR</u> 2 g (40 ml) twice daily IV Clavulanic acid to be administered 30 minutes prior to carbapenem dose	Administer 125 mg clavulanic acid (irrespective of amoxicillin dose) 30 minutes prior to each dose of carbapenem, either three times per day or twice daily	100 mg (2 tab) twice a day	800 mg (2 tab)	1000 mg (2 tab)	625 mg (2.5 ml)	8 g (2 sachet) once daily <u>OR</u> 4 g (1 sachet) twice a day	500 mg (2 tab)
36-45 kg	300 mg (3 x 100 mg tab OR 1 x 300 mg tab)						1500 mg (3 tab)	750 mg (3 ml)		
46-55 kg		600 mg (2 x 300 mg tab)				1200 mg (3 tab)		750–1000 mg (3-4 ml)		750 mg (3 tab)
56-70 kg								1000 mg (4 ml)		
>70 kg							2000 mg (4 tab)			750 mg (3 tab)

*Alternatively, in persons ≥15 years, use imipenem cilastatin 1 g twice daily IV (also with amoxicillin-clavulanate) or ertapenem 2 g once daily IV or IM

RENAL DOSE ADJUSTMENTS FOR ADULTS

Drug dosing for children with renal impairment should be discussed with an experienced clinician.

Drug	Recommended dose and frequency for adults with creatinine clearance <30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Linezolid	No adjustment necessary
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Clofazimine	No adjustment necessary
Terizidone	250 mg once daily ***or*** 500 mg three times per week (not daily)
Delamanid	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Imipenem-cilastatin (given with amoxicillin-clavulanate)	Imipenem: for creatinine clearance 20-40 ml/min dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours Amoxicillin-clavulanate: 250 mg / 125 mg given 30 minutes prior to Imipenem administration
Meropenem (given with amoxicillin-clavulanate)	Meropenem: 1000 mg every 12 hours; for creatinine clearance <10 ml/min dose 1000 mg once daily. Amoxicillin-clavulanate: 250 mg / 125 mg given 30 minutes prior to Meropenem administration

Drug	Recommended dose and frequency for adults with creatinine clearance <30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Ertapenem (given with amoxicillin-clavulanate)	Ertapenem: 500 mg once daily Amoxicillin-clavulanate: 250 mg / 125 mg given 30 minutes prior to Ertapenem administration
Isoniazid	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid	4 g/dose, twice daily maximum dose
Amikacin	Stop amikacin, or if considered essential to treatment administer only with therapeutic drug monitoring
Rifabutin	No adjustment necessary

PRINCIPLES OF LONGER TREATMENT REGIMENS IN CHILDREN UNDER THE AGE OF 6 YEARS

In general, younger children with RR-TB should be managed according to the same principles that guide therapy in older children, adolescents and adults. The following principles are recommended:

- Children under the age of 6 years with any form of RR-TB disease should be treated under the guidance of a clinician with experience in management of paediatric RR-TB.

- Treatment should be based on the DST pattern of the most likely source patient if the child does not have a sample of his or her own with his or her own DST. Following up on all DST results of the source patient is therefore essential.

- Always attempt to treat children with injectable-free regimens, especially very young children and those with non-severe disease. Hearing loss, a frequent severe adverse event caused by injectables, can have a profound impact on language acquisition and ability to learn at school and further development.

- Recommendations on RR-TB treatment regimens for adults also apply to children with severe forms of extra-pulmonary RR-TB (meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease). Treatment of RR-TB meningitis should be guided by the medicines' ability to cross the blood-brain barrier.

- Regimens should consist of at least four drugs to which the organism is likely to be susceptible for the duration of therapy, with possible addition of a fifth drug for the first few months of therapy in cases with severe or multi-bacillary disease. Using more than five drugs adds to the toxicity without necessarily improving treatment efficacy, if Group A and B drugs and/or delamanid are used.

- Regimen construction should be based on the recommended approach by the WHO (as described previously) and should prioritise the WHO Group A and B drugs, as well as delamanid in children aged 3 years and above. Para-aminosalicylic acid is an alternative drug to use in children in instances where the new drugs are not yet available, although its association with worse outcomes in adults should be considered.

- More data on the use of bedaquiline and delamanid in children are expected in the coming years. Currently, the WHO recommends bedaquiline for the treatment of children aged 6 years and above and the use of delamanid for the treatment of children aged 3 years and above. These newer drugs have not been studied extensively in very young children but bedaquiline and delamanid may be considered for treatment of younger children, under the supervision of an expert and with approval for access from the NCAC. In children with fluoroquinolone resistance or in whom there are limited treatment options, extension and combination of bedaquiline and/or delamanid could be considered on a patient-by-patient basis with careful monitoring.

- Although linezolid is a Group A drug with proven effectiveness, its use has frequently been associated with toxicity which is duration dependent. Although use of linezolid throughout treatment is likely to improve efficacy, adverse events may limit use to the first few months. Normal haemoglobin levels vary by age and age-based values should be referred to when assessing linezolid toxicity.

- The duration of therapy in children under the age of 6 years should depend upon the site and severity of disease: children with non-severe disease can be treated for 9 to 15 months while children with severe disease will require 12 to 18 months of therapy depending on their clinical progress. Of note, the 2019 WHO recommendations define severe disease in children less than 15 years as: "…the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)". In children, the occurrence of advanced malnutrition (defined by syndrome or by metrics) or advanced immunosuppression or positive TB bacteriology (Xpert MTB/RIF Ultra, smear, LPA, culture, DST) may also be considered when determining treatment duration.

- There is no specified intensive or continuation phase for these regimens and all drugs should be continued throughout the duration of treatment if possible, unless limited by toxicity or intolerance.

- There is a long-standing practice in the care of children with RR-TB to "add drugs just in case they may be effective". However, unless susceptibility can be proven, adding drugs such as pyrazinamide and ethambutol is of little benefit to the majority of children and should be avoided. Drug susceptibility testing for pyrazinamide and ethambutol is not routinely available in South Africa (and therefore the efficacy of these drugs is unknown in most cases).

- High-dose isoniazid was not considered in the WHO grouping of drugs, although there are emerging data to suggest this drug has a role to play in the treatment of RR-TB. It could be considered in children in which an effective regimen cannot otherwise be composed. However, using more than five drugs adds to both the pill burden and toxicity of the regimen without necessarily improving treatment efficacy, particularly if Group A and B drugs and/or delamanid are used.

- Adherence support for the child and the caregivers is essential to ensure optimal outcomes in children. Because preparation and administration of the medications used to treat RR-TB can be complicated, intensive support should be provided to the family throughout treatment.

- Child-friendly formulations of the medications should be used whenever possible. If these are not available, then extemporaneous preparations will be needed. Preferably these can be prepared daily by cutting or crushing the tablets, and mixing with water, pap, or milk. This should be done in consultation with a pharmacy specialist.

- Monitoring and management of adverse events is essential, particularly for children receiving linezolid.

SAMPLE LONGER REGIMENS IN CHILDREN UNDER THE AGE OF 6 YEARS

Drug dosing for children with renal impairment should be discussed with an experienced clinician.

DRUG SUSCEPTIBILITY PATTERN	AGE GROUP	SUGGESTED REGIMEN
RR-TB that is NOT fluoroquinolone resistant or central nervous system disease	3-6 years	LFX–LZD–CFZ– TRD–[DLM or PAS]
	0-3 years	LFX–LZD–CFZ–TRD – [PAS or ETO/high-dose INH]
RR-TB that is resistant to fluoroquinolones	3-6 years	LZD–CFZ–TRD–DLM–[PAS or ETO]
	0-3 years	LZD–CFZ–TRD–DLM* –[PAS and/or ETO/high-dose INH]
RR-TB central nervous system disease	<6 years	LFX–LZD–TRD–DLM* – [ETO/high-dose INH]–[PZA]

*Benefit of delamanid use likely outweighs risks in these populations and should be strongly considered for use.

LZD = linezolid;
TRD = terizidone;
INH = isoniazid;
LFX = levofloxacin;
DLM = delamanid;
ETO = ethionamide;
CFZ = clofazimine;
PZA = pyrazinamide;
PAS = para-aminosalicylic acid

WEIGHT-BASED DOSING RECOMMENDATIONS FOR CHILDREN <6 YEARS AND PERSONS WEIGHING <30KG

Target dose	Group A			
	Levofloxacin (15-20 mg/kg once daily)		**Moxifloxacin** (10-15 mg/kg once daily)	**Bedaquiline** (once daily loading dose then thrice weekly dosing)
Formulation **Weight**	**100 mg dispersible tab**	**250 mg tab* (scored)**	**400 mg tab**	**100 mg tab****
<3 kg	Consult with experienced clinician			
3-3.9 kg	60 mg (Dissolve 1 tab in 10 ml of water. Administer 6 ml. Discard rest)	62.5 mg (Break 1 tab in half. Crush and mix in 10 ml water. Administer 5 ml. Discard rest)	Consult with experienced clinician for children <5 kg	Consult with experienced clinician for children <15 kg Dose-finding studies are ongoing for children aged <6 years and <15 kg – consult specialist or NCAC for dosing advice if bedaquiline is approved for a young child on an individual basis.
4-4.9 kg	80 mg (Dissolve 1 tab in 10 ml of water. Administer 8 ml. Discard rest)	75 mg (Break 1 tab in half. Crush and mix in 10 ml water. Administer 6 ml. Discard rest)		
5-6.9 kg	100 mg (Dissolve 1 tab in small amount of water)	125 mg (Break 1 tab in half. Crush and mix in small amount of water).	80 mg (Crush and mix 1 tab in 10 ml of water. Administer 2 ml. Discard rest).	
7-9.9 kg	150 mg (Dissolve 1.5 tab in small amount of water)	150 mg (Crush and mix 1 tab in 10 ml water, administer 6 ml, discard rest).	120 mg (Crush and mix 1 tab in 10 ml of water. Administer 3 ml. Discard rest).	
10-15.9 kg	200-300 mg (Dissolve 2-3 tab in small amount of water)	250-375 mg (Crush and mix 1-1.5 tab in small amount of water)	200 mg (Break 1 tab in half. Crush and mix in small amount of water).	(For child ≥15 kg, dose as below)
16-23.9 kg	300-400 mg (Dissolve 3-4 tab in small amount of water)	375-500 mg (Crush and mix 1.5-2 tab in small amount of water)	200- 300 mg (Crush and mix 0.5-0.75 tab in small amount of water)	2 tab (200 mg) daily for first 2 weeks, then 1 tab (100 mg) 3 times a week (M/W/F) for 22 weeks.
24-30 kg	500 mg (Dissolve 5 tab in small amount of water)	500 mg (Swallow 2 tabs whole, or crush and mix in small amount of water)	400 mg (Swallow 1 tab whole, or crush and mix in small amount of water)	
>30 kg	(Refer to adult dosing table)		(Refer to adult dosing table)	4 tab (400 mg) daily for first 2 weeks, then 2 tab (200 mg) 3 times a week (M/W/F) for 22 weeks.

*These film-coated scored tablets can be broken in half but cannot easily be broken further with accurate dosing. It takes about 15 minutes to dissolve fully in water with stirring. Or the tablets can be crushed and added to food or water to enable easy administration. ***Note that levofloxacin is the preferred fluoroquinolone in children; moxifloxacin will only very rarely be used as it may be indicated in a very small group of patients with RR-TB and demonstrated resistance to levofloxacin and susceptibility to moxifloxacin, but these patients are likely to be managed under specialist care.***

Target dose	Group A		Group B	
	Linezolid (10-12 mg/kg once daily for ≥16kg 15 mg/kg once daily for <16 kg)		**Terizidone** (15-20 mg/kg once daily)	**Clofazimine** (2-5 mg/kg once daily)
Formulation **Weight**	**20 mg/ml suspension**	**600 mg tab**	**250 mg cap**	**100 mg tablet or gel caps#**
<3 kg	Consult with experienced clinician			
3-3.9 kg	Consult with experienced clinician for children <4 kg		Consult with experienced clinician for children <5 kg	Consult with experienced clinician for children <5 kg
4-4.9 kg	70 mg (3.5 ml)	60 mg (Crush 1 tab and mix in 10 ml water. Administer 1 ml. Discard rest)		
5-6.9 kg	80 mg (4 ml)	90 mg (Crush 1 tab and mix in 10 ml water. Administer 1.5 ml. Discard rest)	100-125 mg (Mix contents of 1 cap into 10 ml of water. Administer 4-5 ml. Discard rest)	100 mg three times a week (1 cap M/W/F)
7-9.9 kg	120 mg (6 ml)	120 mg (Crush 1 tab and mix in 10 ml water. Administer 2 ml. Discard rest)	125-175 mg (Mix contents of 1 cap into 10 ml of water. Administer 5-7 ml. Discard rest)	
10-15.9 kg	160-200 mg (8-10 ml)	150-180 mg (Crush 1 tab and mix in 10 ml water. Administer 2.5-3.5 ml. Discard rest)	175-250 mg (Mix contents of 1 cap into 10 ml of water. Administer 7-10 ml. Discard rest)	
16-23.9 kg	160-220 mg (8-11 ml)	180-210 mg (Crush 1 tab and mix in 10 ml water. Administer 3-3.5 ml. Discard rest)	250-500 mg (Mix contents of 1-2 caps in small amount of water)	100 mg alternate days (1 cap alt days)
24-30 kg		300 mg (Break 1 tab in half and swallow, or crush and mix in small amount of water)	500 mg (Swallow 2 caps whole, or mix contents in small amount of water)	100 mg daily (1 cap daily)
>30 kg	(Refer to adult dosing table)		(Refer to adult dosing table)	(Refer to adult dosing table)

Dose-finding studies are ongoing for children weighing <15 kg and aged<6 years – consult specialist or NCAC for dosing advice if bedaquiline is approved for a child on an individual basis. ***Note: bedaquiline tablets can be crushed and administered with a small quantity of water if the child has difficulty swallowing tablets.*

#Clofazimine gel capsules cannot be easily crushed, dissolved or opened and so reduced dosing frequency is recommended as it is not easy to give daily doses of less than 100mg.

Target dose	Group C				
	Isoniazid (Standard: 10-15 mg/kg/day) (High-dose: 15-20 mg/kg/day)		**Meropenem** (20-40 mg/kg IV every 8 hours)	**Amoxicillin-Clavulanate** (every 8 hours)	**Delamanid** (twice daily dosing)
Available formulation	**100 mg tab and 300 mg tab (if >20 kg)**		**1 g vial (20ml)**	**250 mg / 62.5 mg in 5 ml suspension**	**50 mg tab**
Weight (kg)	**Standard**	**High-dose**			
<3 kg	Consult with experienced clinician				
3-3.9 kg	50 mg (Crush and mix 100 mg tab in 10 ml water, give 0.5 ml, discard rest).	50 mg (Crush and mix 100 mg tab in 10 ml water, give 0.5 ml, discard rest).	Consult with experienced clinician	Consult with experienced clinician	Consult with experienced clinician for children <16 kg Dose-finding studies are ongoing for children aged <3 years – consult specialist or NCAC for dosing advice if delamanid is approved for a young child on an individual basis.
4-4.9 kg					
5-6.9 kg	75 mg (Crush and mix 100 mg tab in 10 ml water, give 0.75 ml, discard rest).	100 mg (Crush and mix 100 mg tab in small amount of water).	100 mg (2 ml)	Clavulanate 25 mg (2 ml)	
7-9.9 kg	100 mg (Crush and mix 100 mg tab in small amount of water).	150 mg (Crush and mix 1.5 x 100 mg tab in small amount of water).	200 mg (4 ml)	Clavulanate 37.5 mg (3 ml)	
10-15.9 kg	150 mg (Crush and mix 1.5 x 100 mg tab in small amount of water).	200 mg (Crush and mix 2 x 100 mg tab in small amount of water).	300 mg (6 ml)	Clavulanate 62.5 mg (5 ml)	
16-23.9 kg	200 mg (Crush and mix 2 x 100 mg tab in small amount of water).	300 mg (Crush and mix 3 x 100 mg tab or 1 x 300 mg tab in water)	400-450 mg (8-9 ml)	Clavulanate 100 mg (8 ml)	25 mg (0.5 tab) twice daily
24-30 kg	300 mg (Crush and mix 3 x 100 mg tab or 1 x 300 mg tab in water)	400-450 mg (Crush and mix 1.5 x 300 mg tab in water)	550 mg (11 ml)	Clavulanate 125 mg (10 ml)	50 mg (1 tab) twice daily
>30 kg	(Refer to adult dosing table)		(Refer to adult dosing table)	(Refer to adult dosing table)	50 mg twice daily until 35 kg (then refer to adult dosing table)

Target dose	Group C						
	Ethambutol (15-25 mg/kg once daily)		**Pyrazinamide** (30-40 mg/kg once daily)		**Amikacin** (15-20 mg/kg once daily)	**PAS (sodium salt or acid)** (200-300 mg/kg once daily or two divided doses)	**Ethionamide** (15-20 mg/kg once daily)
Available formulation	**100 mg dispersible tablet**	**400 mg tab**	**150 mg dispersible tablet**	**500 mg tab (scored)**	**500 mg vial (2 ml)**	**4 g sachet**	**250 mg tab**
Weight (kg)							
<3 kg	Consult with experienced clinician						
3-3.9 kg	80 mg (Dissolve 1 tab in 10 ml water, administer 8 ml. discard rest)	80 mg (Crush and mix 1 tab in 10 ml water, give 2 ml, discard rest)	Consult with experienced clinician	Consult with experienced clinician	Consult with experienced clinician	Consult with experienced clinician	Consult with experienced clinician
4-4.9 kg							
5-6.9 kg	100 mg (Dissolve 1 tab in small amount of water)	120 mg (Crush and mix 1 tab in 10 ml water, administer 3 ml, discard rest)	150 mg (Dissolve 1 tab in small amount of water)	250 mg (Break tablet in half, crush and mix with small amount of water).	100 mg (0.4 ml)	1.5 g once daily OR 750 mg twice a day	125 mg (Break 1 tab in half. Crush and mix in small amount of water).
7-9.9 kg	200 mg (Dissolve 2 tab in small amount of water)	200 mg (Crush and mix 1 tab in 10 ml water, administer 5 ml, discard rest)	300 mg (Dissolve 2 tab in small amount of water)		150 mg (0.6 ml)	2 g once daily OR 1 g twice a day	
10-15.9 kg	300 mg (Dissolve 3 tab in small amount of water)	280 mg (Crush and mix 1 tab in 10 ml water, administer 7 ml, discard rest)	450 mg (Dissolve 3 tab in small amount of water)	500 mg (Crush and mix 1 tab in small amount of water)	(200-250 mg) 0.8-1 ml	2-4 g once daily OR 1-2 g twice a day	250 mg (Crush and mix 1 tab in small amount of water)
16-23.9 kg	400 mg (Dissolve 4 tab in small amount of water)	400 mg (Crush mix 1 tab in small amount of water)	750 mg (Dissolve 5 tab in small amount of water)	750 mg (Crush and mix 1.5 tab in small amount of water)	300-375 mg (1.2-1.5 ml)	4-6 g once daily OR 2-3 g twice a day	375 mg (Crush and mix 1.5 tabs in small amount of water)
24-30 kg	-	600 mg (Crush mix 1.5 tab in small amount of water)	-	1000 mg (Crush and mix 2 tab in small amount of water)	500mg (2 ml)	6-8 g once daily OR 3-4 g twice a day	500 mg (Crush and mix 2 tabs in small amount of water)
>30 kg	(Refer to adult dosing table)		(Refer to adult dosing table)		(Refer to adult dosing table)	(Refer to adult dosing table)	(Refer to adult dosing table)

RESCUE REGIMENS: SUMMARY

- Patients on either the longer or shorter regimen who have a positive culture at month 4 are likely to be failed by treatment and possibly need a rescue regimen.
- Persons with RR-TB with suspected or confirmed resistance to bedaquiline, linezolid and/or clofazimine need an individualised regimen based on extended drug susceptibility test results and with input from NCAC.
- All persons in need of a rescue regimen should have specimens sent for extended drug susceptibility testing.
- Rescue regimens should be designed with input from the NCAC: Group C drugs will be needed to compose an effective regimen.
- Surgical consultation should be obtained as well.
- Ensuring adequate patient support is an essential part of care.

APPROACH TO DESIGNING RESCUE REGIMENS OR REGIMENS FOR PATIENTS WITH RR-TB AND SUSPECTED OR CONFIRMED RESISTANCE TO LINEZOLID, CLOFAZIMINE AND/OR BEDAQUILINE

All persons in need of a rescue regimen will need to have a sample sent for extended DST. While awaiting the results of that DST, an empiric rescue treatment regimen will be needed. Input should be sought from the NCAC.

The following principles should be used to design a rescue regimen:

- Delamanid should be used if there is no history of previous exposure.
- A carbapenem should be used if there is no history of previous exposure. Imipenem is the most widely available carbapenem, but both meropenem and ertapenem have been used to treat RR-TB. Carbapanems must be given with clavulanic acid, and the only way to give clavulanic acid is in combination with amoxicillin. Thus amoxicillin-clavulanate should be administered (as per dosing tables) 30 minutes prior to the infusion or injection. Long-term IV access is usually needed to administer the carbapenems, although ertapenem can be given intramuscularly.
- Ethionamide should be used if there is a ***katG*** mutation (in the absence of ***inhA***).
- Para-aminosalicylic acid should be used.
- Amikacin may be used if there is documented susceptibility to the medication and if formal hearing assessments can be done throughout treatment. Patients should be extensively counselled about the risk of amikacin use, including loss of hearing, and should give at least verbal informed consent to receive the medication.
- Groups A and B drugs should be added to the empiric regimen while awaiting DST results, based on an assessment of the risks and benefits of each individual drug. High-dose moxifloxacin (800 mg daily) could be considered with careful monitoring.
- Surgical consultation should be considered.
- Direct observation of therapy must be provided in a patient-centered manner for all persons on rescue regimens

- Identify and address any contributing factors to treatment failure (e.g. poorly controlled diabetes, challenges with treatment adherence, high viral load on ART, substance use).

SPECIAL CONSIDERATIONS FOR PERSONS ON LONGER REGIMENS

Situation	Possible Actions
Persons not responding to treatment	Careful assessment in any persons with a positive culture at month 4, clinical worsening or poor weight gain. Review adherence, screen for any contributing factors that could relate to non-adherence (substance use, mental health, socio-economic factors), and ensure adherence support in place. Send extended DST and perform chest X-ray. Consider rescue regimen.
Persons who are lost to follow up (LTFU) during treatment then return to care	"Welcome back" counselling and additional adherence support. Thorough assessment on reasons for LTFU (e.g. substance use, mental health, undisclosed adverse events, socio-economic factors). Send sputum for reflex testing and request extended DST. Regimen selection to consider patient's clinical status, extent of disease, comorbidities, bacteriologic status at time of LTFU (i.e. smear and culture status), length of therapy received, and length of time between LTFU and return to care. In patients who have a microbiological/radiological and clinical picture confirming TB disease, an empiric long treatment regimen may be started while awaiting extended DST results, with input from PCAC/NCAC as needed.
Persons who have a history of previous second-line drug treatment	Send sputum for 'DR-TB reflex testing' and request extended phenotypic DST. Start on a longer regimen including at least five drugs. Contact NCAC for advice if extended DST shows resistance to bedaquiline, linezolid or clofazimine.
Bedaquiline interruptions	If interruption of less than 30 days, then bedaquiline can be re-started at the three times a week dosing. If 30 days or more have been missed, then bedaquiline needs to be reloaded. In such cases, 400 mg once daily for 7 days should be given followed by 200 mg three times a week (or, if the patient weighs between 16 and 30 kg, reload with 200 mg daily for 7 days then 100 mg three times a week).

RR-TB IN PREGNANCY AND BREASTFEEDING

- In the majority of cases, RR-TB is diagnosed some time after women have fallen pregnant, and it is known that women are at increased risk of being diagnosed with TB disease during pregnancy. However, in some cases women fall pregnant after starting RR-TB treatment – a situation that is entirely avoidable. Exposure to second-line TB medications may pose a considerable risk to the developing foetus, particularly during the first trimester, and the efficacy of RR-TB treatment for the mother may be reduced due to the physiological changes in pregnancy. These risks and effects have not been well described due to the exclusion of pregnant women from TB clinical trials and the paucity of routinely collected data related to RR-TB diagnosis, treatment and outcomes during pregnancy and post-partum. ***Therefore, all non-pregnant women of child bearing potential should be appropriately counselled throughout RR-TB treatment and offered family planning as part of routine RR-TB care.***

- Pregnant women with RR-TB qualify for the shorter treatment regimen and should receive this regimen if they meet all of the inclusion criteria.

- Pregnant women who do not meet criteria to receive the shorter regimen should receive a longer regimen based on the same principles used in regimen designed for non-pregnant patients.

- Bedaquiline is currently considered one of the safer drugs to use in pregnant women based on animal studies, and there is growing experience with safe use of bedaquiline in pregnancy.

- Linezolid, levofloxacin, moxifloxacin, clofazimine, terizidone and delamanid are all considered to be possibly unsafe in pregnant women based on animal studies, but these medications should not be denied to pregnant women with RR-TB given their association with improved treatment outcomes.

- **Amikacin should not be used in pregnancy given the associated foetal ear toxicity.**

- Ethionamide should only be used if there are no other treatment options since it has been potentially associated with neural tube defects and can exacerbate pregnancy-associated nausea and vomiting.

- Breastfeeding should be encouraged in most women, and the medications used to treat RR-TB are not a contraindication to breastfeeding. However, appropriate infection control measures must be followed.

- The health of the foetus, neonate and infant is likely to be optimised if their mother is healthy, thus, most interventions that are likely to improve the health and well-being of pregnant and breastfeeding women would be in the best interests of their babies.

- Note that pregnant women with RR-TB can be initiated on treatment by providers without NCAC approval but these cases should still be presented to the NCAC so that this cohort can be more formally monitored and data collected on a national level.

SUMMARY PRINCIPLES ON HIV AND RR-TB CO-INFECTION

- The shorter and longer regimens should be given to people with HIV based on the DST of the infecting TB strain and other risk factors, and HIV status alone does not mandate any changes in the regimen composition.
- Persons with HIV may need to change their ART regimen since bedaquline cannot be given with efavirenz. ART options include dolutegravir, nevirapine, or lopinavir/ritonavir (or atazanavir/ritonavir) depending on the viral load. Zidovudine also causes toxicity to the bone marrow and should be substituted with another nucleoside reverse transcriptase inhibitor (NRTI) in persons who are on linezolid.
- All persons newly diagnosed with RR-TB who are HIV-positive should have a CD4 count and viral load tested at the time of RR-TB treatment initiation and after 6 months. A repeat viral load can be tested at 2 months if the baseline viral load is detectable.
- For persons not yet on ART, HIV treatment should be initiated within 2 to 8 weeks after starting RR-TB therapy if patient is tolerating RR-TB treatment and are clinically stable. In patients with CD <50 cells/mm3 ART should be started within 2 weeks. In patients with RR-TB meningitis, initiate ART 4 to 6 weeks after starting RR-TB medication if patient is tolerating RR-TB treatment and are clinically stable. This is due to the risk of intracranial immune reconstitution inflammatory syndrome (IRIS).
- Co-trimoxazole therapy should also be provided regardless of CD4 count.
- Identification and management of other co-morbid opportunistic infections is required for persons with RR-TB and HIV.
- Additional counselling support will be needed to help people with RR-TB and HIV successfully adhere to their treatment.

ANTIRETROVIRAL THERAPY IN HIV-INFECTED PERSONS WITH RR-TB

All people co-infected with RR-TB and HIV should receive antiretroviral therapy (ART) to improve chances of RR-TB treatment success. The ART choices in patients with RR-TB outlined in this section take into consideration the following factors:

- Efavirenz induces hepatic metabolism of bedaquiline and therefore decreases bedaquiline exposure; concomitant use of efavirenz and bedaquiline is contra-indicated.

- Zidovudine and linezolid should not be used together as both drugs can cause bone marrow suppression.

- Dolutegravir can be used concurrently with bedaquiline, linezolid and other currently recommended second-line RR-TB medications and should be used in first-line ART regimens for all patients ≥20 kg newly initiating ART. The fixed dose combination of tenofovir–lamivudine–dolutegravir can be used in patients ≥10 years of age and weighing ≥35 kg, provided that tenofovir is not contra-indicated and adequate renal function is ensured by checking eGFR/creatinine (as outlined in the table).

- Dolutegravir may also be used in second-line ART regimens. However, until further evidence becomes available, it is currently recommended that, in second-line ART regimens, dolutegravir should be used with at least one fully effective nucleoside reverse transcriptase inhibitor. In most cases, this would be zidovudine, because tenofovir or abacavir are likely to be compromised if there is a history of ART interruption and/or unsuppressed viral load on first-line ART.

    - In comparison, boosted protease inhibitors have been shown to be effective in achieving sustained virological suppression when used in conjunction with nucleoside reverse transcriptase inhibitors even if both nucleoside reverse transcriptase inhibitors are compromised by resistance. For this reason, protease inhibitors can be used in second-line ART regimens with tenofovir–emtricitabine (or abacavir–lamivudine) in cases where zidovudine is contra-indicated e.g. during treatment with linezolid (see below).

- Dolutegravir may cause a small increase in the risk of neural tube defects in the developing foetus. Women of child bearing potential who are started on dolutegravir and RR-TB treatment should be carefully counselled about the possible teratogenic effects of both dolutegravir and RR-TB therapy; this risk is limited to the first trimester of pregnancy. Dolutegravir is currently considered safe if started after the first trimester of pregnancy; any woman who is planning to fall pregnant or who may be in early pregnancy should be offered alternative ART therapy. All women of child bearing potential should be offered effective contraception.

- Dolutegravir can be used in children and adolescents weighing ≥20kg but the fixed-dose combination of tenofovir–lamivudine–dolutegravir can only be prescribed for those ≥10 years of age and weighing ≥35 kg. Children who weigh between 20 and 35 kg may receive dolutegravir in combination with abacavir–lamivudine, or zidovudine–lamivudine if not also receiving linezolid. Children weighing <20 kg should receive a lopinavir/ritonavir-based regimen while on bedaquiline.

ASSESSMENT OF RENAL FUNCTION PRIOR TO STARTING TENOFOVIR

Tenofovir is contra-indicated in patients with inadequate renal function, which can be assessed by checking eGFR/creatinine, as detailed in the table below.

Tenofovir is contra-indicated and should not be used in ART regimens for any patients <10 years of age or weighing <35 kg.

[Table adapted from page 7 of the national 2019 ART Clinical Guidance]

Age/pregnancy status	What must be measured?	Acceptable level for TDF use	***Counahan Barratt formula*** eGFR (mL/min/1.73 m^2) $= \frac{(height\ [cm] \times 40)}{(creatinine\ [\mu mol/L])}$
≥10 and <16 years of age	eGFR using Counahan Barratt formula	>80 mL/min/ 1.73 m^2	
Adults and adolescents ≥16 years	eGFR using MDRD equation*	>50 mL/min/ 1.73 m^2	
Pregnant women	Absolute creatinine level	<85 µmol/L	

*Modification of Diet in Renal Disease Study (MDRD) equation:
GFR (mL/min/1.73 m^2) = 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African)

MANAGEMENT OF ANTIRETROVIRAL THERAPY IN PERSONS WITH RR-TB

Management of ART is based on three potential scenarios for HIV-infected patients with RR-TB: a) initiation of ART after starting RR-TB treatment in ART-naïve patients; b) re-starting ART during RR-TB treatment in patients who previously interrupted ART; c) modifications to ART regimens in patients on ART when RR-TB treatment is initiated.

a) Initiation of ART after starting RR-TB treatment in ART-naïve patients

Timing of ART initiation:

- Initiate ART within 2 to 8 weeks of starting RR-TB treatment (patients with a CD4 less than 50 should initiate ART within 2 weeks).

- If RR-TB meningitis or cryptococcal meningitis, initiate ART 4 to 6 weeks after starting RR-TB medication (or antifungal medication in the case of cryptococcal meningitis), due to risk of intracranial immune reconstitution inflammatory syndrome (IRIS).

Choice of ART regimen:

- Initiate tenofovir–lamivudine–dolutegravir (TLD) as first-line ART if ≥10 years of age and weight ≥35 kg, provided that, before starting tenofovir, adequate renal function is ensured by checking eGFR/creatinine. Use abacavir if tenofovir is contra-indicated.

- ***Every effort should be made to obtain and use dolutegravir*** as this is the preferred first-line ART option and is considered in the best interests of the patient. However, if dolutegravir is not available, then the following ART options may be considered:

    - » If the patient is female with a CD4 <250 or male with CD4 <400, initiate ART with tenofovir–emtricitabine–nevirapine. A lead-in dose of nevirapine (200 mg daily for first two weeks followed by 200 mg bd) is required. Use abacavir if tenofovir is contra-indicated.

    - » If the patient is female with a CD4 ≥250 or male with CD4 ≥400, initiate ART with tenofovir–emtricitabine–lopinavir/ritonavir. Use atazanavir/ritonavir if the patient complains of gastrointestinal side effects to lopinavir/ritonavir. Use abacavir if tenofovir is contra-indicated.

- For children who weigh between 20 and 35 kg, use abacavir–lamivudine–dolutegravir. If dolutegravir is not available, and for any child who weighs <20 kg, use abacavir–lamivudine–lopinavir/ritonavir.

b) Re-starting ART during RR-TB treatment in patients who previously interrupted ART

- If previously on first-line ART with tenofovir–emtricitabine–efavirenz, initiate a second-line protease inhibitor-based regimen, such as ***tenofovir–emtricitabine–lopinavir/ritonavir***. Address reasons for ART treatment interruption. Repeat viral load after six months.

    - The national ART guidelines recommend that the same ART regimen should be restarted in patients who previously interrupted first-line ART. However, for patients with RR-TB, efavirenz cannot be used with bedaquiline. In addition, tenofovir (and therefore abacavir) may have been compromised, and so dolutegravir would be unprotected if started or reintroduced with tenofovir (or abacavir). Zidovudine would still be an effective option to use with dolutegravir, but zidovudine should not be used with linezolid due to overlapping toxicities. Therefore, a protease inhibitor-based regimen with tenofovir or abacavir may be used (as explained above) for the duration of linezolid, which will usually be no longer than 2 months if the patient is on the shorter RR-TB regimen. After linezolid is completed or withdrawn, the ART regimen can be switched to ***zidovudine–lamivudine–dolutegravir*** once the haemoglobin is >10 g/dL. This ART regimen has no drug-drug interactions with bedaquiline and no further changes are required once bedaquiline is completed.

- If previously on first-line ART with tenofovir–lamivudine–dolutegravir, restart the same regimen. Use abacavir if tenofovir is contra-indicated.

- If previously on second-line ART with a protease inhibitor, urgently address reasons for ART treatment interruption and restart the same regimen as before. If previously on second-line ART containing zidovudine, use tenofovir–emtricitabine–lopinavir/ritonavir while the patient is also taking linezolid. Use abacavir if tenofovir is contra-indicated. If the patient complains of gastrointestinal side effects with lopinavir/ritonavir, consider switching to atazanavir/ritonavir. Repeat viral load after three months.

- For children <10 years of age and <35 kg (discuss with experienced clinician if necessary):

    - » If previously on first-line efavirenz-based regimen, start a lopinavir/ritonavir-based regimen and use stavudine if zidovudine contra-indicated (i.e. concomitant use of linezolid). Consider using atazanavir/ritonavir if lopinavir/ritonavir is not tolerated for children ≥ 6 years of age and ≥ 15 kg. Counsel on adherence.

    - » If previously on second-line ART with a protease inhibitor, urgently address reasons for ART treatment interruption, restart a lopinavir/ritonavir based regimen and use stavudine if zidovudine contra-indicated (i.e. concomitant use of linezolid). Consider using atazanavir/ritonavir if lopinavir/ritonavir not tolerated. Counsel on adherence. Repeat viral load after three months and refer to guidance on genotyping if viral load remains unsuppressed.

c) Modifications to ART regimens in patients on ART when RR-TB treatment is initiated

Review the patient's viral load (treatment initiation should not be delayed while awaiting viral load results; most recent viral load can be used for initial management decisions while awaiting repeat viral load result from baseline [at RR-TB treatment initiation]); see also tables below.

- If viral load suppressed (<50 cells/mL) on first-line ART regimen, switch to tenofovir–lamivudine–dolutegravir, provided adequate renal function is ensured by checking eGFR/creatinine.

- If viral load suppressed (<50 cells/mL) on second-line ART regimen with a protease inhibitor, continue same ART regimen but avoid zidovudine and use tenofovir or abacavir instead; this can be switched back to zidovudine once linezolid is completed and haemoglobin is >10 g/dL.

- If viral load unsuppressed (≥1,000 cells/mL) on first-line ART, switch to a protease inhibitor-based second-line regimen and address adherence. While using linezolid, use tenofovir–emtricitabine (or abacavir–lamivudine if tenofovir contra-indicated) along with a protease inhibitor. Once linezolid is completed and haemoglobin is >10 g/dL, ART regimen can be switched to zidovudine–lamivudine–dolutegravir.

- If viral load unsuppressed (≥1,000 cells/mL) on second-line ART, continue second-line ART regimen and address adherence. While using linezolid, use tenofovir–emtricitabine (or abacavir–lamivudine if tenofovir contra-indicated) instead of zidovudine. Refer to guidance on genotyping if viral load remains unsuppressed.

- If viral load is between 50 and 1,000 on any ART regimen, discuss individual ART plan with NCAC or other clinicians with appropriate ART and RR-TB experience.

Children <10 years of age or weighing <35 kg, and on ART at the time of RR-TB treatment, should be counselled along with their parents / caregivers regarding any possible changes to ART regimens. All children in whom first- or second-line protease inhibitor-based regimens appear to be failing should receive a thorough assessment of the cause of an elevated viral load, as per page 16 of the ***2019 ART Clinical Guidance.*** As for older children, adolescents and adults with persistently raised viral load, interventions should be implemented to re-suppress the viral load, including enhanced adherence support as outlined in the ***Adherence Guideline on HIV, TB and NCDs.*** HIV resistance testing should only be considered as recommended in the 2019 ART Clinical Guidance.

If managing clinicians are unsure or in doubt about any aspect of viral load management or switching ART medications, discuss with the NCAC or an experienced clinician/paediatrician, or contact the National HIV & TB Health Care Worker Hotline on 0800 212 506.

ART MODIFICATIONS FOR HIV-INFECTED PERSONS AGED ≥ 10 YEARS AND WEIGHING ≥ 35 KG AND ON ART WHEN RR-TB TREATMENT IS INITIATED

ART REGIMEN AT RR-TB DIAGNOSIS	PROPOSED ART REGIMEN*	
	VL <50 cells/mL	**VL ≥1,000 cells/mL****
TDF–FTC–EFV	TDF–3TC–DTG (combination known as TLD) ***If DTG not available:*** 1. TDF–FTC–LPV/r# 2. TDF–FTC–NVP (only in women with CD4 nadir <250 and men with CD4 nadir <400)	TDF–FTC–LPV/r# Once linezolid is completed and Hb >10 g/dL, could be changed to AZT–3TC–DTG
ABC–3TC–EFV	ABC–3TC–DTG ***If DTG not available:*** 1. ABC–3TC–LPV/r# 2. ABC–3TC–NVP (only in women with CD4 nadir <250 and men with CD4 nadir <400)	ABC–3TC–LPV/r# Once linezolid is completed and Hb >10 g/dL, could be changed to AZT–3TC–DTG
TDF–3TC–DTG	TDF–3TC–DTG	
TDF–FTC–LPV/r	TDF–FTC–LPV/r#	
ABC–3TC–LPV/r	ABC–3TC–LPV/r#	
AZT–3TC–LPV/r	TDF–FTC–LPV/r# ***(ABC can be used if TDF contra-indicated; once linezolid is completed and Hb >10 g/dL, regimen can be changed back to AZT–3TC–LPV/r)***	

*Consult NCAC or other expert for individual ART plan if viral load between 50-1,000.
**In line with updated national HIV guidance, adherence support should be reviewed, viral load should be repeated in 3 months; persistently raised viral load with good adherence should trigger assessment for potential genotyping.
#Consider ATV/r if patient complains of pill burden or gastrointestinal side effects with LPV/r.

VL = viral load; TDF = tenofovir disoproxyl fumarate; FTC = emtricitabine; 3TC = lamivudine; ABC = abacavir; EFV = efavirenz; DTG = dolutegravir; LPV/r = lopinavir/ritonavir; ATV/r = atazanavir/ritonavir; NVP = nevirapine; AZT = zidovudine

ART REGIMEN MODIFICATIONS FOR HIV-INFECTED CHILDREN <10 YEARS OR WEIGHING <35 KG AND ON ART AT RR-TB TREATMENT INITIATION

ART REGIMEN AT RR-TB DIAGNOSIS	PROPOSED ART REGIMEN*	
	VL <50 cells/mL	VL ≥1,000 cells/mL**
Children 20-35 kg ABC–3TC–EFV	ABC–3TC–DTG ***If DTG not available:*** ABC–3TC–LPV/r#	D4T–3TC–LPV/r# Once linezolid is completed and Hb in normal range for age, could be changed to: AZT–3TC–DTG
Children 20-35 kg ABC–3TC–LPV/r (first-line)	ABC–3TC–DTG ***If DTG not available:*** Continue ABC–3TC–LPV/r#	Continue ABC–3TC–LPV/r# Once linezolid is completed and Hb in normal range for age, could be changed to: AZT–3TC–DTG
Children 20-35 kg AZT–3TC–LPV/r (second-line)	D4T–3TC–LPV/r# Once linezolid completed and Hb in normal range for age, regimen can be changed back to: AZT–3TC–LPV/r#	
Children 20-35 kg ABC–3TC–DTG	Continue ABC–3TC–DTG	
Children <20 kg ABC–3TC–EFV	ABC–3TC–LPV/r#	D4T–3TC–LPV/r# Once linezolid is completed and Hb in normal range for age, switch D4T to AZT
Children <20 kg ABC–3TC–LPV/r (first-line)	Continue ABC–3TC–LPV/r#	
Children <20 kg AZT–3TC–LPV/r (second-line)	D4T–3TC–LPV/r# Once linezolid completed and Hb in normal range for age, regimen can be changed back to: AZT–3TC–LPV/r#	

*Consult experienced paediatrician for individual ART plan if viral load between 50-1,000.
**In line with updated national HIV guidance, adherence support should be reviewed, viral load should be repeated in 3 months; persistently raised viral load with good adherence should trigger assessment for potential genotyping.
#Consider ATV/r in children ≥6 years of age and ≥15 kg if LPV/r not tolerated.
VL = viral load; 3TC = lamivudine; ABC = abacavir; EFV = efavirenz; DTG = dolutegravir; LPV/r = lopinavir/ritonavir; ATV/r = atazanavir/ritonavir; AZT = zidovudine; D4T = stavudine

OVERLAPPING TOXICITIES BETWEEN ART AND RR-TB TREATMENT

Potential Toxicity	ART	RR-TB Medication	Comments
Anaemia	Zidovudine	Linezolid	Co-administration is not recommended
Lactic acidosis	Stavudine	Linezolid	Avoid use of stavudine unless ART options severely limited (e.g. in younger children)
Leucopaenia/ neutropaenia	Zidovudine	Linezolid	Co-administration is not recommended
Peripheral neuropathy	Didanosine, stavudine	Isoniazid, linezolid, terizidone	Avoid use of didanosine and stavudine if possible (may be required for younger children with limited ART options). If on isoniazid or terizidone, give pyridoxine daily to prevent neuropathy (50 mg for adults, 25 mg for children 5 to 12 years, 12.5 mg for those <5 years old). Pyridoxine does not prevent linezolid-induced neuropathy.
Psychosis	Efavirenz	Terizidone, isoniazid	While theoretically the concomitant use of these medications could increase risk of psychosis, these classes of drugs have a long history of being used together safely.
Renal toxicity	Terizidone	Amikacin	Avoid use of amikacin
Thrombocytopaenia	Zidovudine	Linezolid	Co-administration is not recommended

MANAGEMENT OF RR-TB AND OTHER CO-MORBIDITIES

Co-Morbid Condition	Management Strategies
Diabetes mellitus	Excellent glucose control (may need insulin). Close monitoring of blood glucose and HbA1C. Close monitoring for adverse events that may be more common (i.e. peripheral neuropathy, renal failure). Enhanced adherence support. Do not exceed a dose of 500 mg twice daily when using metformin with dolutegravir.
Hepatitis B	Close monitoring of liver function. Should initiate therapy with tenofovir and lamivudine/ emtricitabine
Hepatitis C	Close monitoring of liver function. Limited data on drug-drug interactions with directly acting agents (but data suggest there are no significant drug-drug interactions). Delay treatment for hepatitis C until RR-TB treatment is complete, unless patient has unstable liver disease or develops worsening liver function during RR-TB treatment.
Substance use	Routine and non-judgmental screening with WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). Refer to Annex in full guidance document. Brief counselling intervention with motivational interviewing. Should initiate RR-TB treatment even if there is not complete sobriety. Enhanced adherence support. Harm reduction counseling. Referral to substance use treatment center.

Co-Morbid Condition	Management Strategies
Substance use	Pharmacotherapy-assisted treatment (i.e. naltrexone or acamprosate for alcohol use), opioid substitution therapy (methadone, suboxone) should be considered where appropriate.
People who are incarcerated	Should have access to all medications and therapeutic innovations. Enhanced counselling and adherence support, especially around time of release from prison or movement within the prison system.
Mobile populations	Access to therapy regardless of country of origin. Prioritise use of shorter regimen when possible. Enhanced adherence support.
Renal failure	Use renal dosing for medications that are renally cleared. Avoid use of injectables
Cigarette smoking	Screen for active smoking at each visit. Counselling to reduce or stop cigarette smoking. Consider pharmacotherapy or nicotine replacement therapy.

SUMMARY PRINCIPLES FOR MONITORING AND MANAGEMENT OF ADVERSE EVENTS

- All persons with RR-TB need baseline assessments and monthly monitoring during treatment. This includes assessments for substance use and mental health.
- Persons on either regimen need monthly samples sent for smear and culture for therapeutic decision making.
- Increased attention needs to be given for monitoring for linezolid toxicity (full blood count with differential, visual acuity testing, screening for peripheral neuropathy) and for QT interval prolongation (ECG at 2 weeks then monthly thereafter) in addition to previous monitoring.
- Management of adverse events is essential for improving chances of treatment success, and medications to treat adverse events should be provided free of charge.
- Recording adverse events and their management in clinical records is crucial, as is the reporting of serious, severe, or unexpected adverse events.
- Specific guidance for managing anaemia, QT interval prolongation, peripheral neuropathy and hepatotoxicity are included in the guidelines.
- Young children may need tailored monitoring since the ability to rely on symptom screening in this population is limited.

SUMMARY MONITORING TABLE

Monitoring parameters at baseline and beyond		Longer regimen: intensive phase							Longer regimen: continuation phase											
		Shorter regimen: intensive phase				Shorter regimen: continuation phase														
Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18-20	
Counselling	X	Sessions 1-3			X	Additional counselling as required throughout treatment														
Substance use and mental health screen	X	WHO ASSIST and mental health screen			X	Review substance use and mental health status at every visit throughout treatment														
Evaluation by Clinician	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess for TB symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X	Monthly if aged <6 years																		
BMI, and NSP (if BMI <18.5)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review family planning	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Sample for smear, culture	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
LPA first line	X				X (if culture still positive)	X (if reconversion to positive culture after initial culture conversion)														
LPA second line	X				X (if culture still positive)	X (if reconversion to positive culture after initial culture conversion)														
Phenotypic INH susceptibility	In-lab reflex if first-line LPA shows INH susceptible																			
Phenotypic FLQ susceptibility	In-lab reflex if second-line LPA shows FLQ susceptible	X (if culture positive at month 4 or reconversion to positive after initial conversion)																		
Phenotypic extended DST	In-lab reflex if second- line LPA shows FLQ resistant	X (if culture positive at month 4 or reconversion to positive after initial conversion)																		

Monitoring parameters at baseline and beyond		Longer regimen: intensive phase									Longer regimen: continuation phase								
		Shorter regimen: intensive phase				Shorter regimen: continuation phase													
Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18-20
Chest X-ray	X						X												
HIV testing	X			X (repeat test after 3 months if previously negative)									X (repeat test if previously negative)						
CD4 count	X						X						X						
Viral load	X	If not suppressed, repeat earlier per national guidance					X						X						X
FBC and neutrophil count on LZD	X	Wks 2 and 4	X	Repeat monthly, or more often as required, while on linezolid															
Finger prick blood glucose	X	As required throughout treatment																	
Creatinine	X	Repeat monthly if on injectable agent, otherwise repeat as required if baseline creatinine was abnormal, or if person is clinically unwell through treatment																	
K+ and Mg2+	X	Repeat monthly if on injectable agent, otherwise repeat as required if vomiting or diarrhoea or if QTcF prolonged, or if person is clinically unwell through treatment																	
TSH – only if on PAS or ETO	X			X	Repeat every 3 months while on PAS or ETO, or as required if QTcF is prolonged														
ALT	X	Repeat if vomiting, right upper quadrant pain, jaundice, or if person is unwell or any evidence of liver injury																	
Audiometry	X			X	Only mandatory at selected facilities, but service is available for any patient in need														
ECG	X	X	X	X	X	X	X			X			X			X			X
Visual acuity and PNP while on LZD	X	X	X	Assess VA using Snellen chart; repeat monthly, or more often as required, while on linezolid															

List of facilities that will continue doing audiometry as from 01/01/2020 include: Nkqubela Hospital and Jose Pearson Hospital (Eastern Cape); Dr JS Moroka Hospital and Pelonomi Hospital (Free State); Sizwe Hospital (Gauteng); King Dinuzulu Hospital (KZN); Modimolle MDR-TB Hospital (Limpopo); Witbank TB Hospital (Mpumalanga); West End Hospital and Harry Surtie Hospital (Northern Cape); Tshepong Hospital (North West) and Brooklyn Chest Hospital (Western Cape).

ADVERSE EVENT SCREENING QUESTIONNAIRE

This checklist should be completed at each follow up visit for anyone receiving RR-TB treatment, regardless of the regimen. Any "yes" answers should be followed up for more details.

Ask the patient: "Since your last visit, have you experienced any of the following symptoms?"

1. Headache	YES ☐	NO ☐
2. Vision changes	YES ☐	NO ☐
3. Depression/sadness	YES ☐	NO ☐
4. Anxiety/worries	YES ☐	NO ☐
5. Rashes or sores	YES ☐	NO ☐
6. Chest pain	YES ☐	NO ☐
7. Coughing blood	YES ☐	NO ☐
8. Difficulty breathing	YES ☐	NO ☐
9. New cough	YES ☐	NO ☐
10. Nausea/vomiting	YES ☐	NO ☐
11. Diarrhoea	YES ☐	NO ☐
12. Abdominal pain	YES ☐	NO ☐
13. Fainting	YES ☐	NO ☐
14. Joint pain/swelling	YES ☐	NO ☐
15. Burning/tingling hands/feet	YES ☐	NO ☐
16. Fatigue/tiredness	YES ☐	NO ☐
17. Easy bruising/bleeding	YES ☐	NO ☐
18. Changes in hearing	YES ☐	NO ☐

19. Other (specify): _____

SUMMARY TABLE ON IDENTIFICATION AND MANAGEMENT OF KEY ADVERSE EVENTS

TYPE OF ADVERSE EVENT	LIKELY CULPRIT TB DRUGS	IDENTIFICATION	MANAGEMENT
Anaemia	Linezolid	Monthly monitoring of FBC and neutrophils is essential for persons on linezolid	At baseline: if moderate to severe anaemia (Hb <8 g/dL), initiate medical work up and treat underlying conditions. Only consider initiating linezolid while Hb <8 g/dL if patient is under close monitoring in hospital with option for transfusion. If close monitoring and/or hospitalisation is not possible, avoid linezolid and start a longer regimen. If linezolid is started in hospital and Hb does not improve and stabilise above 8 g/dL, switch to a longer individualised regimen in which linezolid is replaced by Group C agents including delamanid. During treatment: if baseline Hb was >8 g/dL and patient initiated a shorter course regimen with linezolid but then Hb drops to <8 g/dL ⟶ investigate for other causes and, depending on the duration of linezolid and the severity of the drop in Hb, either: hospitalise with close monitoring for linezolid reintroduction, switch to longer regimen with substitution of linezolid, or continue the shorter regimen without linezolid (discuss with PCAC/NCAC or experienced clinician for last option).
Arthritis/ arthralgia	Pyrazinamide, fluoroquino-lones	Clinically defined	Non-steroidal anti-inflammatory drugs, physical therapy, massage, topical therapy, consider substitution or withdrawal of pyrazinamide if no improvement.

TYPE OF ADVERSE EVENT	LIKELY CULPRIT TB DRUGS	IDENTIFICATION	MANAGEMENT
Depression or anxiety	Terizidone, high-dose isoniazid	Clinically defined	Counselling, antidepressants, referral to psychiatric support, assess for suicidal/homicidal ideation, consider substitution of terizidone or high-dose isoniazid. AVOID USE OF TRICYCLIC ANTIDEPRESSANTS as these can prolong the QT interval.
Diarrhoea	Para-aminosalicylic acid	Increased stool frequency >3 times per day, primarily liquid.	Assess for other causes, rehydrate, assess electrolytes, consider drug substitution for para-aminosalicylic acid.
Electrolyte disturbances (hypokalaemia and hypo-magnesaemia)	Amikacin, kanamycin, capreomycin	Regular blood tests (potassium and magnesium)	If potassium is low (<3.5 mEq/L), replace with oral potassium and consider replacing magnesium as well if levels are low. If potassium <2.5 mEq/L then hospitalise and replace IV.
Hearing problems	Amikacin, kanamycin, capreomycin	Identified through audiometry or problems in communication	Stop the injectable agent if any hearing symptoms or if hearing loss >30 dB at multiple frequencies. Consider substituting with an alternative drug such as delamanid. Injectable agents should not be used if hearing loss cannot be formally monitored by audiometry.
Hepatotoxicity	Pyrazinamide, ethionamide, bedaquiline, clofazimine, delamanid, para-aminosalicylic acid, fluoro-quinolones, rifabutin	Nausea and vomiting with RUQ pain and tender liver or visible jaundice	Stop all drugs if ALT > 5 times the upper limit of normal (ULN) or if > 3 times the ULN and patient has symptoms of drug-induced liver injury. Wait for liver function to return to normal or at least <3 times ULN.

TYPE OF ADVERSE EVENT	LIKELY CULPRIT TB DRUGS	IDENTIFICATION	MANAGEMENT
Hepatotoxicity	Pyrazinamide, ethionamide, bedaquiline, clofazimine, delamanid, para-aminosalicylic acid, fluoro-quinolones, rifabutin	Nausea and vomiting with RUQ pain and tender liver or visible jaundice	RR-TB drugs should be reintroduced sequentially, every 5 to 7 days, with monitoring of liver function before introducing the next drug. The least hepatotoxic drugs should be added first: linezolid, delamanid and fluoroquinolone can be given altogether to provide a backbone regimen. Then introduce potentially hepatotoxic drugs (clofazimine, bedaquiline, ethionamide, isoniazid) one by one every 5 to 7 days while monitoring liver function tests to identify the responsible drug. Pyrazinamide should not be reintroduced.
Ichthyosis / dry skin	Clofazimine	Clinical findings	Give emollient creams. Monitor for skin and soft tissue infection if scratching
Leucopaenia/ neutropaenia	Linezolid	Monthly monitoring of FBC and neutrophils is essential for persons on linezolid	If moderate to severe (<1,000 cells/L), initiate medical work up, treat underlying conditions, hold linezolid until leucopaenia resolves, consider switch to longer regimen with linezolid substitution if withheld for >2 weeks.
Nausea and vomiting	Ethionamide, para-aminosalicylic acid	Clinically defined	This common adverse event may lead to non-adherence so intense management is necessary. Consider anti-emetic therapy.

TYPE OF ADVERSE EVENT	LIKELY CULPRIT TB DRUGS	IDENTIFICATION	MANAGEMENT
Nausea and vomiting	Ethionamide, para-aminosalicylic acid	Clinically defined	Consider separating the dosing of ethionamide and para-aminosalicylic acid from the other drugs by administering in the evening. Consider reducing the dose of ethionamide and building up to full dose over 2 weeks. With new onset nausea and vomiting, consider hepatotoxicity, hepatitis, pancreatitis, or increased intracranial pressure.
Peripheral neuropathy	Isoniazid, linezolid, terizidone	Clinically defined	Prevent neuropathy in patients taking isoniazid and/or terizidone by giving pyridoxine daily (50 mg for adults, 25 mg for children aged 5 to 12 years and 12.5 mg for children <5 years old) while using isoniazid or terizidone. Pyridoxine does not prevent linezolid-induced neuropathy. If clinically evident neuropathy that interferes with patient's daily activities, stop terizidone, isoniazid and/or linezolid and substitute with another effective agent (such as delamanid). Consider the use of pregabalin or gabapentin to treat pain. AVOID USE OF TRICYCLIC ANTIDEPRESSANTS as these can prolong the QT interval. Can be challenging to monitor in young children, thus a shorter course of linezolid could be considered in young children.

TYPE OF ADVERSE EVENT	LIKELY CULPRIT TB DRUGS	IDENTIFICATION	MANAGEMENT
Psychosis	Terizidone, high-dose isoniazid, fluoro-quinolones	Clinically defined	Referral to psychiatric support, assess for suicidal/ homicidal ideation, consider substitution of terizidone or high-dose isoniazid. Haloperidol and risperidone can both cause QT prolongation, so increase frequency of ECG monitoring in patients receiving these medications.
QT interval prolongation	Bedaquiline, clofazimine, delamanid, moxifloxacin	Prolonged QTc interval >450ms on routine ECG monitoring at week 2, week 4 then monthly for the first 6 months of treatment, with calculation of the QTc interval using the Fridericia formula	Assess if person is taking other QT interval prolonging drugs. Assess for cardiac symptoms – chest pain, palpitations, dyspnoea, syncope. If symptomatic, consider admission for cardiology evaluation. If asymptomatic, and QTc interval >470 msec but <500 msec repeat ECG at rest, check TSH, correct electrolytes, and monitor weekly until stable. If QTc interval >500 msec, repeat ECG, check and correct electrolytes, check TSH, assess for other causes of QT interval prolongation, withhold other non-essential QT-prolonging medications.
Rash (severe), Stevens-Johnson Syndrome (SJS)	Any drug, but some drugs are more likely to cause rash, such as pyrazinamide	Severe rash, peeling skin, mucous membranes involvement, patient unwell	Stop all drugs. Symptomatic management until clinical condition has improved. Re-introduce drugs only after consultation with the NCAC or other RR-TB expert.

TYPE OF ADVERSE EVENT	LIKELY CULPRIT TB DRUGS	IDENTIFICATION	MANAGEMENT
Renal impairment	Amikacin, kanamycin, capreomycin	Regular blood tests, symptoms of high potassium	If creatinine rises >1.3 times the upper limit of normal (ULN) or potassium is elevated, stop injectable, substitute with alternative drug.
Seizures	Terizidone, high-dose isoniazid, fluoroquino-lones	Clinically defined	Head CT, rule out other causes, antiseizure medications, consider substitution of terizidone or high-dose isoniazid.
Skin hyper-pigmentation	Clofazimine	Clinically defined	Counselling and support; plans for managing inadvertent disclosure.
Thrombocyto-paenia	Linezolid	Monthly monitoring of FBC is essential for persons on linezolid	If moderate to severe (<50 x 10^9/L), initiate medical work up, treat underlying conditions, hold linezolid until thrombocytopaenia improves, consider switch to longer regimen with linezolid substitution if withheld for >2 weeks.
Thyroid dysfunction	Ethionamide, para-aminosalicylic acid	Regular blood test (TSH), clinical hypothyroidism or goitre	Exclude other causes (e.g. lithium, amiodarone, previous radioiodine therapy, pregnancy-associated thyroid dysfunction, and Hashimoto's disease). Consider thyroxine supplementation if clinical hypothyroidism, or raised TSH and decreased FT4. If raised TSH and normal FT4 repeat both in 1 month. If TSH >10 IU/mL, start thyroxine at 50 mcg daily and repeat TSH in one month. Monitor TSH every month and increase the dose by 25 mcg until TSH normalises (TSH <5 mIU/L).

TYPE OF ADVERSE EVENT	LIKELY CULPRIT TB DRUGS	IDENTIFICATION	MANAGEMENT
Thyroid dysfunction	Ethionamide, para-aminosalicylic acid	Regular blood test (TSH), clinical hypothyroidism or goitre	Thyroid dysfunction resolves upon discontinuation of the causative agent, but hormone replacement must continue at least 2 to 3 months after completed RR-TB treatment.
Visual problems	Ethambutol, linezolid	Regular testing of visual acuity with Snellen chart or age appropriate measure, including papillary responses and "fixate and follow" response in children <2 years of age and symbol charts in children ages 3 to 5 years	Withhold ethambutol and/or linezolid and refer the patient to ophthalmologist for further evaluation and management. Do not reintroduce without discussing with NCAC (or other RR-TB expert) and preferably with ophthalmologist. If the patient has RR-TB with extensive disease or further drug resistance, and optic toxicity due to linezolid is ruled out by an ophthalmologist, reintroduction of linezolid may be considered with careful monitoring.

MANAGEMENT OF HAEMOGLOBIN <8.0 G/DL

Anaemia can be a common finding in people living with RR-TB, especially those who are co-infected with HIV. There are multiple potential causes of anaemia, including TB itself, other infections, medications, malignancy, pregnancy, bleeding and/or malnutrition, including iron deficiency, folate deficiency and vitamin B12 deficiency. Persons with anaemia merit a careful workup and close management, as persons with RR-TB and anaemia have been shown to have worse treatment outcomes than those without anaemia.

Linezolid is recommended for all persons with RR-TB as its use has been associated with improved outcomes and decreased mortality. One common side effect of the drug, however, is bone marrow suppression manifesting as anaemia, thrombocytopaenia, and/or leucopaenia/neutropaenia. The most common presentation of persons with linezolid-induced bone marrow suppression is anaemia. For this reason, anaemia with a haemoglobin of <8 g/dL in persons taking (or about to start) linezolid merits careful work-up and correction. Note: the other haematological abnormalities may occasionally occur in isolation, without anaemia, and any patient with neutrophils $<0.75 \times 10^9$/L or platelets $<50 \times 10^9$/L also require further investigation, temporary discontinuation of linezolid and closer monitoring.

Given the importance of linezolid in the treatment of RR-TB, all attempts should be made to correct underlying baseline anaemia so the medication can be used. For persons with RR-TB and a haemoglobin of <8 g/dL, linezolid should be at least temporarily withheld and the following actions are recommended:

- Hospitalisation of any persons due to start (or reintroduce) linezolid while their haemoglobin is <8 g/dL – for management of anaemia (with blood transfusion if indicated) and close clinical monitoring; linezolid should not be initiated (or reintroduced) in very severe anaemia, or if the haemoglobin continues to drop or does not improve and stabilise following transfusion;
- Review of full blood count, differential and other investigations to determine possible aetiology of anaemia;
- Review of other medications that could possibly be associated with anaemia;
- Test for pregnancy in women;
- Assessment for other infections, including parasites and viral pathogens (i.e. parvovirus);

- Transfusion with packed red blood cells should be considered while in hospital;

- It is important to note that, since TB is a common cause of anaemia, treatment with an effective regimen including linezolid may sometimes cause the haemoglobin to improve. For this reason, all efforts should be made to initiate or reintroduce linezolid with close clinical monitoring and to identify and treat other causes of a low haemoglobin.

Approach to a patient with a haemoglobin of <8 g/dL prior to the start of RR-TB treatment

Persons who have a baseline haemoglobin <8 g/dL and are otherwise eligible to start RR-TB treatment with the shorter regimen have two options:

1. Start the shorter regimen including linezolid ***but only if patient is admitted to hospital or other inpatient facility*** for close clinical monitoring, for assessment of aetiology of anaemia, and appropriate management which may include blood transfusion. If the haemoglobin continues to drop then linezolid should be discontinued and the patient should switch to a longer regimen – linezolid to be substituted with one or two Group C drugs, including delamanid. ***Note that initiating treatment with lower doses of linezolid should be avoided due to concerns of sub-optimal efficacy.***

2. Avoid linezolid altogether and start a longer regimen in which linezolid is substituted with one or two Group C drugs, including delamanid. In these cases, hospitalisation is not required if the patient is clinically stable and not symptomatic of anaemia, and there are no other indications for hospitalisation. The aetiology of anaemia should still be assessed as an outpatient, although haemoglobin may improve with RR-TB treatment. Linezolid reintroduction may be considered on a case-by-case basis if haemoglobin increases to above 10 g/dL – discuss with an experienced clinician or NCAC.

Approach to a patient who started the shorter regimen and whose haemoglobin drops to <8 g/dL

If a patient has started the shorter regimen with linezolid and their haemoglobin drops to <8 g/dL (from a higher level at baseline), linezolid should be withheld and a medical workup performed to assess the aetiology of the anaemia.

Cases may be discussed with PCAC/NCAC or RR-TB expert for advice but there are three potential management options, depending on the duration of linezolid received and the cause and severity of the drop in haemoglobin:

1. Re-challenge linezolid at full dose within the shorter regimen ***but only if patient is admitted to hospital or other inpatient facility*** for close clinical monitoring, for assessment of aetiology of anaemia, and appropriate management which may include blood transfusion. If the haemoglobin continues to drop then linezolid should be discontinued and the patient should switch to a longer regimen – linezolid to be substituted with one or two Group C drugs, including delamanid. ***Note that re-challenging with lower doses of linezolid should be avoided due to concerns of sub-optimal efficacy.***

2. Switch to a longer regimen ***without*** linezolid (substitute with one or two Group C drugs, including delamanid) – this option may be necessary if: linezolid has to be withheld very soon after starting treatment and cannot be reintroduced; there is no phenotypic confirmation of second-line drug susceptibility; and/or the patient cannot be hospitalised for medical workup and re-challenge of linezolid.

3. In some select cases it may be possible to continue the shorter regimen without linezolid, taking into account extent of disease, isoniazid resistance pattern and mutations, phenotypic confirmation of second-line drug susceptibility pattern, duration of linezolid received, history or evidence of close contact with persons with pre-XDR or XDR-TB strains. This option should only be considered under the guidance of an experienced RR-TB clinician or in consultation with PCAC/NCAC.

Approach to a patient on the longer regimen whose haemoglobin is <8 g/dL (either at baseline or after having received linezolid)

The decision to start (or re-challenge/continue) linezolid within a longer regimen for a patient with haemoglobin <8 g/dL will be made on a case-by-case basis, taking into consideration the duration of RR-TB therapy to date (if applicable), degree of TB drug resistance, extent of disease, patient clinical evolution and clinical severity of anaemia. Cases may be discussed with PCAC/NCAC or RR-TB expert for advice but potential management options include:

1. Start the longer regimen with linezolid (or continue/re-challenge linezolid) at full dose ***but only if and when the patient is admitted to hospital or other inpatient facility*** for close clinical monitoring, review of FBC and differential for assessment of aetiology of anaemia, and appropriate management (which may include blood transfusion) or discontinuation of linezolid in cases of worsening anaemia (preferably under supervision of a clinician with experience in managing RR-TB);

2. Avoid linezolid altogether and continue the longer regimen ***without*** linezolid and substitute with delamanid or other Group C drugs. In these cases, hospitalisation is not required if the patient is clinically stable and not symptomatic of anaemia; aetiology of anaemia should still be assessed as an outpatient, although haemoglobin may improve with RR-TB treatment.

There are concerns that linezolid dose reduction (e.g. from 600 mg to 300 mg) could be associated with decreased efficacy and may result in development of linezolid resistance (particularly if the remaining regimen is relatively weak), thus linezolid should only be re-challenged at the full dose, unless advised otherwise by an experienced clinician.

MANAGEMENT OF PATIENTS WITH QT INTERVAL PROLONGATION

Many of the drugs in the newly recommended treatment regimens - including clofazimine, bedaquiline, delamanid and moxifloxacin - can cause prolongation of the QT interval. Although not an adverse event in and of itself, a prolonged QT interval can be a risk factor for a fatal cardiac arrhythmia. Fortunately, experience has shown that while these medications can prolong the QT interval to varying degrees, their use is associated with improved outcomes in people living with RR-TB. Thus, while it is prudent to continue to routinely monitor the QT interval, providers need not fear the use of these medications.

There are multiple factors that can cause QT interval prolongation including time of day, gender, nutritional status, electrolyte abnormalities, hypothyroidism, and other non-TB medications. If a patient is found to have a prolonged QT interval on routine ECG monitoring, all these possibilities should be assessed prior to discontinuing drugs required for RR-TB treatment. Be aware of co-administration of other medications that can lead to QT interval prolongation, including haloperidol and tricyclic antidepressants - these may have to be avoided or continued (with closer ECG monitoring) as per clinician discretion.

Any patient who has QT interval prolongation (QTc greater than 450 ms) and symptoms consistent with a possible cardiac arrhythmia should be hospitalised. Cardiac symptoms may include syncope, fainting, chest pain, palpitations, dizziness and loss of consciousness. A medical assessment should be performed and any medications that can prolong the QT interval should be withheld until the cause of the symptoms is assessed.

In asymptomatic persons who are found to have QT interval prolongation on routine ECG monitoring, the following approach should be used:

- If the corrected QT interval (using Fridericia's formula; QTcF) is greater than 450 ms but less than 470 ms, then routine monitoring should be continued.

- If the QTcF is greater than 470 ms but less than 500 ms, then the ECG should be repeated at rest on the same day and, if still prolonged but asymptomatic, the patient should be monitored weekly until stable; check TSH and correct electrolytes; review history of administration of other (non-TB) medications that can lead to QT interval prolongation.

- If the QTc is greater than 500 ms, then repeat ECG at rest, check and correct electrolytes, check TSH, assess for other causes, and withhold all QT-prolonging drugs (including the TB drugs moxifloxacin, delamanid, clofazimine and bedaquiline). These drugs may be re-challenged sequentially once QTcF improves to less than 500 ms – monitor ECGs closely during re-challenge. It is recommended to discuss these cases with other experienced RR-TB clinicians and/or a cardiologist. Note: in patients with complete bundle-branch block demonstrated on ECG, it is preferable to use the JT rather than the QT interval (consult a clinician with experience in cardiology/ECGs).

Fridericia's formula for the QT interval corrected for heart rate (QTcF) is the QT interval measured in milliseconds divided by the cubed root of the preceding R-R interval in seconds:

$$QTcF = \frac{QT}{\sqrt[3]{(RR)}}$$

MANAGEMENT OF PATIENTS WITH PERIPHERAL NEUROPATHY

Peripheral neuropathy can have a devastating effect on the life of a person being treated for RR-TB. Early identification and management can avoid permanent consequences of this disabling adverse event. For this reason all persons on treatment with isoniazid or linezolid should be formally screened at each clinic visit for signs and symptoms of peripheral neuropathy.

While many patients may complain about leg or join pain, peripheral neuropathy usually presents with sensory findings (i.e. numbness, tingling, burning sensations) in the soles of the feet or the palms. At advanced stages, there may be may be loss of motor control and weakness and patients may describe clumsiness or tripping.

In addition to asking about symptoms, all patients should be examined for signs of peripheral neuropathy at each clinic visit. This includes testing of peripheral reflexes (i.e. ankles, wrists, knees) and sensory testing with a monofilament.

In persons found to have peripheral neuropathy, isoniazid, terizidone and/or linezolid are often the culprits. All persons on isoniazid or terizidone should receive pyridoxine (vitamin B6) to prevent peripheral neuropathy. Use pyridoxine doses of 50 mg daily for adults, 25 mg daily in children 5 to 12 years old and 12.5 mg daily in children under the age of 5 years. Doses of pyridoxine exceeding 100 mg a day can cause or worsen peripheral neuropathy and therefore should never be used. Note that pyridoxine has NOT been shown to prevent linezolid-induced neuropathy and therefore should NOT be given to persons taking linezolid if they are not also taking isoniazid or terizidone.

Other common causes of peripheral neuropathy include alcohol use, other medications (e.g. stavudine) or diabetes mellitus, and these causes should be assessed as well in any patient found to have peripheral neuropathy.

Where available pregabalin may be used to decrease the pain related to peripheral neuropathy (pregabalin does not prolong the QT interval whereas amitriptyline does). If the peripheral neuropathy is severe (causes pain or inhibits activities of daily life) and other causes have been ruled out, the patient's isoniazid, terizidone and linezolid should be discontinued. Cases may be presented to NCAC for further advice if required.

MANAGEMENT OF PATIENTS WITH HEPATOTOXICITY

Many medications used in the treatment of RR-TB can cause liver toxicity. This is also true of the medications used to treat common comorbidities, most notably HIV. Transient elevations in ALT can be seen throughout RR-TB treatment and are usually self-limiting. In some cases, more serious liver problems can occur and early identification and management is essential to prevent fulminant hepatic failure.

Persons on RR-TB treatment should have an ALT done at baseline, with a repeat ALT if vomiting, RUQ pain, jaundice, or any evidence of liver injury. Patients with signs of liver failure require hospitalisation. If they develop symptoms that could be consistent with hepatitis (i.e. persistent vomiting, ascites, jaundice, abdominal pain) and the ALT is greater than 3 times the upper limit of normal, then they should have their RR-TB drugs held until the symptoms resolve and re-introduced in the manner described below. If the ALT is found to be greater than 5 times the upper limit of normal regardless of the presence of symptoms, all RR-TB drugs should be held until the ALT normalises and reintroduced in the manner described below. All persons should also undergo medical assessment and work up for other possible causes of hepatitis, including viral hepatitis, alcohol use, traditional medicine use, or other medical conditions.

Re-introduction of RR-TB drugs should be sequential, every 5 to 7 days with monitoring of liver function before introducing the next drug. The least hepatotoxic drugs should be added first: linezolid – delamanid – fluoroquinolone can be given altogether to provide a backbone regimen. Then introduce the potentially hepatotoxic drugs sequentially, with one drug added every 5 to 7 days in the following order: clofazimine, bedaquiline, ethionamide, isoniazid. Monitor liver function tests after addition of each one to identify the drug that is likely to have been responsible for the liver injury. Pyrazinamide should never be re-introduced. Only essential RR-TB drugs should be re-introduced.

DRUG SUBSTITUTION OR EXTENSION FOR TOXICITY MANAGEMENT

Regimen	Discontinued drug	Possible substitutions	Comments
Shorter regimen	Pyrazinamide, ethambutol, or high-dose isoniazid	Bedaquiline extension	
	Bedaquiline, linezolid, clofazimine, and/or fluoroquinolone	Switch to longer regimen	
Longer regimen	Bedaquiline	Extend linezolid; add other Group C drugs, including delamanid	Ensure there are at least three effective drugs in the continuation phase
	Linezolid	Extend bedaquiline; add other Group C drugs, including delamanid	Ensure there are at least three effective drugs in the continuation phase
	Levofloxacin	Extend bedaquiline; add other Group C drugs, including delamanid	Ensure there are at least three effective drugs in the continuation phase
	Clofazimine	Extend bedaquiline; add other Group C drugs, including delamanid	Ensure there are at least three effective drugs in the continuation phase
	Terizidone	No substitution needed in 'basic' longer regimen, unless severe or extensive disease; could consider extending bedaquiline if needed	Ensure there are at least three effective drugs in the continuation phase

SUMMARY ACTIVITIES FOR ACTIVE DRUG SAFETY MONITORING

Active drug safety monitoring (aDSM) consists of the following 3 core activities:

1. Patients targeted for aDSM should receive active and systematic clinical and laboratory assessment during RR-TB treatment to detect drug toxicity and adverse events.

2. All adverse events detected should be managed in a timely fashion in order to deliver the best possible patient care.

3. All severe (Grade 3 and above) adverse events and ***serious*** adverse events (SAEs) should be systematically collected in patient files and entered on EDR.web - these data will be reported to the national pharmacovigilance centre (NPC). The NPC collects this type of data from the entire country and uses it to characterise the types of adverse events seen most commonly, assess the safety of the RR-TB treatment and inform future policy on the use of these medicines.

In order for standardised data to be collected from a wide range of providers, scales have been developed to determine the severity of common adverse events. These scales tend to use a rating system from 1 to 4, with 1 being a mild side effect, 2 being a moderate side effect, 3 being a severe side effect, and 4 being considered a life-threatening side effect. See below for an example of a rating scale. With laboratory values, rating severity is often easier since discrete cut-off values can be used.

The term ***serious*** when applied to an adverse event in aDSM denotes a very specific category of side effect and it is different from a ***severe*** adverse event. A ***serious*** adverse event (SAE) is defined as an adverse event that results in any of the following:

- Hospitalisation or prolongation of hospitalisation to manage the adverse event;
- Permanent disability;
- Congenital abnormality;
- Death or life-threatening experience.

Providers must document adverse events when they occur, and they should attempt to rate them using the severity scale below. An attempt should be made to determine causality where possible. This may be straightforward if the side effect is known to be associated with a particular medication (e.g. thrombocytopenia due to linezolid). In a multidrug regimen, it can be difficult to determine which drug is causing which side effect. Physicians, however, should follow best management practices and the evolution of the event over time could lead to a more precise causality assessment.

SEVERITY RATING SCALE FOR ADVERSE EVENTS

Mild (Grade 1)	Symptoms cause no or minimal interference with usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)
Moderate (Grade 2)	Symptoms cause greater than minimal interference with usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)
Severe (Grade 3)	Symptoms cause inability to perform usual, age appropriate, social and functional activities (e.g. going to work, shopping, cooking, using transport, hobbies)
Potentially life- threatening (Grade 4)	Symptoms cause inability to perform basic, age-appropriate, self-care functions (e.g. bathing, dressing, toileting, continence, feeding, movement); OR Medical or operative intervention required to prevent permanent impairment, persistent disability, or death
Death (Grade 5)	Death, regardless of cause or relationship to TB medications

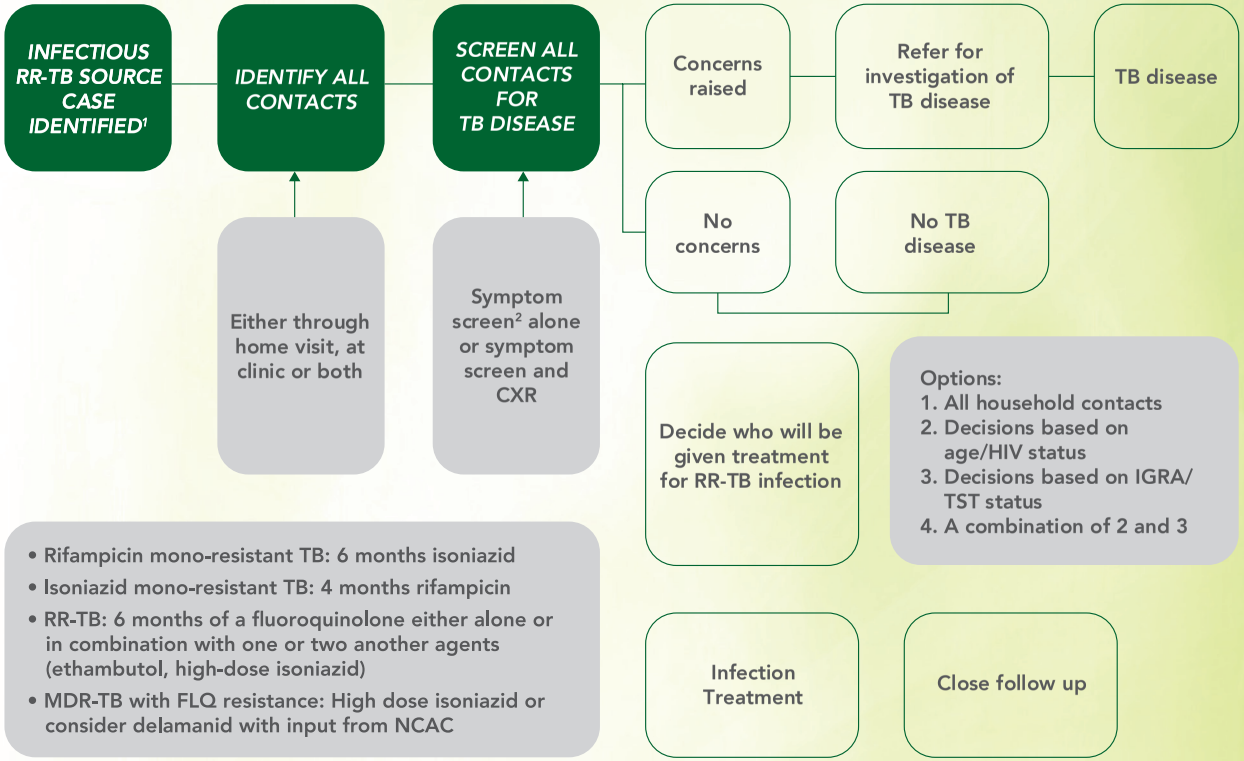
CONTACT EVALUATION AND POST-EXPOSURE MANAGEMENT: SUMMARY

- All persons exposed to RR-TB in the household or other high-risk setting should be urgently seen to rule out active RR-TB disease, including symptom screening and chest X-ray, with specimen sampling if any evidence of clinical TB disease.
- All persons with exposure to RR-TB who have signs and symptoms of TB should be investigated for TB disease. If TB treatment is deemed appropriate then treat based on the resistance pattern of the source patient while awaiting their own DST results.
- Persons who have no signs and symptoms of TB after exposure have two management options: close clinical monitoring and assessment to rule out active disease that may develop after the initial post-exposure assessment or administration of RR-TB "preventive" therapy for selected high-risk contacts.
- If monitoring is the option selected, persons should be counselled about signs and symptoms that should prompt an assessment for TB; contacts should be followed up at least every 6 months (children should be followed up more frequently, every 2 or 3 months) for a period of 2 years after the initial exposure.
- If the preventive therapy option is selected, then a fluoroquinolone-based, multidrug regimen is preferred (either levofloxacin and high-dose isoniazid or levofloxacin, high-dose isoniazid and ethambutol). Discussion of such cases with a clinician experienced in managing RR-TB may be helpful.
- If the person is exposed to fluoroquinolone-resistant RR-TB, then high-dose isoniazid could be given. Note that delamanid could be considered as a potential option in very select cases and in discussion with the NCAC.
- All persons given preventive therapy should be closely monitored for the development of adverse events or active disease.

DEFINITIONS USED IN CONTACT EVALUATION AND POST- EXPOSURE MANAGEMENT

Epidemiological terms	RR-TB index case	The first confirmed RR-TB case identified during an investigation.
	RR-TB contact	A person exposed to an infectious RR-TB index case
Clinical States	TB exposure	A situation where a person has been exposed to TB disease, often through close and prolonged contact.
	TB infection	A condition where a person has a positive immunological test for TB infection (TST, IGRA), in the absence of symptoms and physical signs of disease (both acute and chronic) in the absence of a test result for TB infection, preventative treatment may still be given to high risk contacts based on exposure history and risk factors.
	TB disease	Clinical, radiological, or microbiological pathology consistent with TB.

OVERALL APPROACH TO RR-TB POST-EXPOSURE MANAGEMENT*



*Note: lack of IGRA/TST results should not be a barrier to treatment of infection.

MANAGEMENT STEPS FOR CONTACT EVALUATION AND POST- EXPOSURE MANAGEMENT

Post-exposure management for RR-TB should be offered to all individuals exposed to the disease. The four steps that should be followed include:

Step	Details
Disclosure counseling	This should be offered to the source patient as a routine part of contact tracing. Should follow best practices established for HIV. Should be done by a trained or experienced health care worker or counsellor and include: a review of reasons to disclose RR-TB status; a role playing or practice disclosure session; identification of a trusted person to disclose to first; selection for site of disclosure (clinic, home); identification of possible consequences of disclosure; development of an action plan following disclosure.
Evaluation to rule out RR-TB disease	Symptom screening, history, weight, physical examination for everyone. Chest X-ray (AP/PA and lateral) for high risk contacts (e.g. children under 5 years, persons HIV co-infected, health care workers or others based on clinician's decision). Sputum (or other specimen) sampling for Xpert MTB/RIF for high risk contacts with evidence of clinical TB disease. Consider use of TST or IGRA if available, but these tests may be falsely positive or falsely negative and should not delay initiation of treatment or preventive therapy.
Consideration of preventive therapy (treatment of infection) for high-risk contacts	Risk determined by source-case factors (e.g. smear-positive), environmental factors (e.g. close and repeated contacts) and host factors (age, HIV status, other immunocompromising conditions). A history of liver disease or other drug contraindication to preventative therapy drug options should be ruled out prior to treatment. Children of any age with HIV and those HIV-uninfected under the age of 5 years should be offered preventive therapy.

Step	Details
Consideration of preventive therapy (treatment of infection) for high-risk contacts	Other high-risk contacts could be offered preventive therapy on a case-by-case basis (e.g. children over the age of 5 years, persons HIV co-infected, health care workers). Treatment regimens usually include a fluoroquinolone and one other drug (usually high-dose isoniazid, ethambutol or both) and lasts for 6 months after last exposure. High-dose isoniazid (or delamanid) could be used for people exposed to fluoroquinolone-resistant RR-TB.
Close follow up to rule out incident RR-TB disease	Every 6 months (more frequently for children <5 years old) for at least 12 to 24 months

RIFAMPICIN RESISTANT TB PATIENTS HOUSEHOLD CONTACTS

Inclusion criteria

All household contacts of Rifampicin Resistant TB (RR-TB) patients, (including those with Multi-drug Resistant TB – MDR-TB – and Extensively Drug Resistant TB – XDR-TB - irrespective of HIV status and age, but with no TB disease or symptoms and signs of TB

Exclusion criteria

- Confirmed DS-TB or RR-TB (MDR-TB and XDR-TB) disease;
- Presence of symptoms and signs of TB;
- Active liver disease (acute or chronic);
- Presence of symptoms and signs of severe peripheral neuropathy;
- History of adverse reaction to any of the drugs used for TPT;
- Excessive use of alcohol defined as:

- For men: More than 4 standard drinks on any day or 14 per week
- For women: More than 3 standard drinks on any day or 7 per week

Box 1: Standard measure of alcoholic drinks

The equivalent of one standard drink is calculated based on the percentage of alcohol in the drink:

- **Beer/wine coolers:** Beer and wine coolers are typically 5% alcohol. A standard drink is 360mls.
- **Malt liquor:** Malt liquor is approximately 7% alcohol, and a standard drink is 240- 270mls.
- **Cider:** Cider is about 6% alcohol, and a standard drink is about 300mls.
- **Wine:** Table wine is 12% alcohol, making a standard drink 150mls of wine. Fortified wines, such as sherry or port, are stronger, and a standard drink is 90 – 120mls.
- **Spirits and liqueur:** Spirits typically contain 40% alcohol, while liqueur typically contains less alcohol. A standard drink of whiskey, gin, vodka, or brandy is 45mls, while a standard drink of liqueur, cordial or aperitif is 60 – 90mls. A shot is typically filled to about 45mls, which is the equivalent of a standard drink.

Management of contacts of patients with RR-TB

Symptom screening

- All adults and adolescents who are household contacts of a person with RR-TB, irrespective of HIV status, should be screened for TB symptoms and signs and if found to be asymptomatic, assessed for eligibility for TPT.
- Preventive treatment should be individualised after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the resistance pattern of the source case and potential adverse events.
- Those at high-risk to be treated (children, PLWHIV and individuals receiving immunosuppressive therapy).
- Drugs selected according to the drug susceptibility profile of the source case.

Treatment options

There are two main management options for persons exposed to RR-TB infection (who have no signs and symptoms of TB):

Treatment option 1 (for contacts exposed to a patient with fluoroquinolone - FLQ-susceptible RR-TB)

» A fluoroquinolone-based regimen (ideally Levofloxacin - LFX) given alone or in combination with other medicines that are likely to be efficacious, and possibly including:

» Ethambutol - EMB if susceptibility is documented in the index case (although high rates of EMB resistance may make this less effective) and/or;

» High-dose-INH (shown to be potentially effective in people exposed to RR-TB with INH resistance);

» Three-drug regimen of EMB, high-dose INH and LFX for 6 months (based on consultations with Local experts available on ncac@witshealth.ac.za);

» Single drug regimen of INH (normal or high dose) for 6 months – for exposure to rifampicin mono-resistant TB, where susceptibility to INH is confirmed; this could also be an option for contacts exposed to patients diagnosed with RR-TB based on a positive Xpert MTB/RIF or Ultra that is Rif-resistant but LPA negative/ inconclusive and/or culture negative;

» Single drug regimen of high-dose INH (15 – 20 mg/kg) for 6 months for children below 15 years and 10 – 15 mg/kg in adults – for exposure to MDR-TB with ***inhA*** mutation only;

» LFX for 6 months – for exposure to MDR-TB with kat G mutation only and documented quinolone susceptibility.

Treatment option 2 (for contacts who are exposed to an index patient with fluoroquinolone-resistant MDR-TB)

» High-dose INH - Single drug regimen of high-dose INH 10 – 15 mg/kg in adults and 15 - 20 mg/kg/daily in children for 6 months;

Monitoring option

- Persons should be educated and counselled about the risk of developing TB disease, TB signs and symptoms and the importance of reporting to health facilities for an assessment for TB once these develop
- Contacts should be screened for TB every 3 months for the first 12 months and every 6 months up to 24 months after initial exposure. Children may require monthly follow up for the first 6 to 9 months and then 3 monthly until 24 months.

MEDICINES TO BE CONSIDERED FOR TREATMENT OF RR-TB INFECTION

RESISTANT TYPE EXPOSURE	DRUGS/ MEDICINES	PATIENT TYPE/ WEIGHT BAND	DOSAGE	FREQUENCY	DURATION
Fluoroquinolone susceptible RR	LFX	Adult	15 – 20 mg/kg [maximum = 1.5 g]	Once, daily	6 months
		Child	15 – 20 mg/kg [maximum = 1.5 g]	Once, daily	6 months
	High-dose INH*	Adult	10 – 15 mg/kg	Once, daily	6 months
		Child	15 – 20 mg/kg	Once, daily	6 months
	Ethambutol	Adult	15 – 25 mg/kg	Once, daily	6 months
		Child	15 – 25 mg/kg	Once, daily	6 months
Fluoroquinolone resistant RR	High-dose INH*	Adult	10 – 15 mg/kg	Once, daily	6 months
		Child	15 – 20 mg/kg	Once, daily	6 months
	Delamanid**	Adult	3 – 4 mg/kg [maximum = 200 mg]	Twice, daily	6 months
		7 – 23 kg	25 mg [maximum = 200 mg]	Twice, daily	6 months
		24 – 24 kg	50 mg [maximum = 200 mg]	Twice, daily	6 months
		≥ 35 kg	100mg [maximum= 200 mg]	Twice, daily	6 months
Mono-resistant to Rifampicin	INH* normal dose	Adult	4 – 6 mg/kg**	Once, daily	6 months
		Child	5 – 10 mg/kg	Once, daily	6 months
MDR-TB with kat G mutation	LFX	Adult	15 – 20 mg/kg [maximum = 1.5 g]	Once, daily	6 months
		Child	15 – 20 mg/kg [maximum = 1.5 g]	Once, daily	6 months
MDR-TB with inh A mutation	LFX	Adult	15 – 20 mg/kg [maximum = 1.5 g]	Once, daily	6 months
		Child	15 – 20 mg/kg [maximum = 1.5 g]	Once, daily	6 months
	High-dose INH*	Adult	10 – 15 mg/kg	Once, daily	6 months
		Child	15 – 20 mg/kg	Once, daily	6 months

* Given with Pyridoxine (vitamin B6): 25 – 50 mg per day
** Dosing in younger children (i.e. less than 3 years of age) still being established

CONTACT CATEGORISATION AND TREATMENT OUTCOMES FOR TB PREVENTIVE THERAPY

» Contacts offered treatment for LTBI may be categorised either as new or previously treated

» The only treatment outcome possibilities are completed, lost to follow up, stopped or died as described in the table below.

Contact Categories and Treatment Outcomes for TB Preventative Therapy

CATEGORY DEFINITION	
New	A contact who has never had treatment for TB infection (IPT or other) or who took treatment for less than 4 weeks.
Previously treated	A contact who has taken treatment for TB infection (IPT or other) for 4 weeks or more in the past and either completed or stopped for whatever reason (adverse events, developed TB, lost to follow up)
TREATMENT OUTCOMES	
Treatment completed	A contact who has taken treatment and completed treatment within the prescribed period.
Lost to follow up	A contact whose treatment was interrupted for two consecutive months or more during the treatment period.
Treatment stopped	A contact whose treatment was stopped during the treatment period, as a result of serious adverse events or development of TB disease.
Died	A contact who dies for any reason during the course of TB treatment

DRUG-RESISTANT TB THAT IS NOT RIFAMPICIN-RESISTANT: SUMMARY

- In South Africa, Xpert MTB/RIF testing using the Ultra cartridge provides information on the present or absence of ***M. tuberculosis*** and the presence or absence of rifampicin resistance. Information about the presence or absence of resistance to other medications is not provided by this test.

- Genotypic or phenotypic testing for isoniazid may be requested in persons who, in the absence of rifampicin resistance, are not responding to first-line TB treatment, who have not had a successful treatment outcome after a full course of first-line TB treatment, and in those who are contacts of such individuals. Note that susceptibility testing for ethambutol and pyrazinamide is not routinely provided in South Africa.

- For persons found to have isoniazid-resistant TB that is not also rifampicin resistant, clinicians should review all available test results to ensure that rifampicin resistance has not been missed on any previous samples.

- There are some populations where detection of rifampicin resistance may pose a challenge, including those who have TB with a 491 mutation in the rpoB gene – this mutation is not detected by routine testing methods.

- If isoniazid resistance is detected, there is a possibility that there is also resistance to pyrazinamide and ethambutol.

- Care must be taken not to add a single drug to a failing regimen for isoniazid mono-resistant TB, as this can lead to worse clinical outcomes and amplification of resistance.

- Extending the duration of treatment beyond six months may be necessary when isoniazid resistance (in the absence of rifampicin resistance) is detected during the course of first-line TB treatment (as opposed to before starting treatment), or in patients with extensive disease.

- Progress should be monitored with monthly samples for TB smear and culture however, recording and reporting of isoniazid mono-resistant TB cases should be done through ETR.net (and not through EDR.web as for rifampicin-resistant cases).

- Hetero-resistance refers to the presence of ***M. tuberculosis*** strains with different resistance patterns. This could be due to infection with one strain where resistance has developed in some sub-populations, or due to infection with multiple strains with different resistance patterns.

MANAGEMENT OF DRUG-RESISTANT TB THAT IS NOT RIFAMPICIN-RESISTANT

Recommendations for management of isoniazid mono-resistant TB (in the absence of rifampicin resistance):

- If isoniazid resistance is detected within 28 days of starting first-line TB treatment, then the patient should switch to a regimen containing high-dose isoniazid (10 mg / kg / day), rifampicin, pyrazinamide, ethambutol and levofloxacin, given daily along with pyridoxine (50 mg / day) for 6 months. This regimen can be given as a Rifafour combination tablet plus additional isoniazid, levofloxacin and pyridoxine as loose tablets.

- If isoniazid resistance is detected after 28 days of starting first-line TB treatment, then there is a high risk of amplification of rifampicin resistance. An Xpert MTB/RIF Ultra test should be repeated to rapidly assess for rifampicin resistance.

- If ***M. tuberculosis*** is detected and no rifampicin resistance is detected, then the patient should switch to a regimen containing high-dose isoniazid (10 mg / kg / day), rifampicin, pyrazinamide, ethambutol and levofloxacin, given daily along with pyridoxine (50 mg / day) for 6 months. This regimen can be given as a Rifafour combination tablet plus additional isoniazid, levofloxacin and pyridoxine as loose tablets.

- If the Xpert MTB/RIF Ultra test is negative for ***M. tuberculosis***, or if there is a possibility or suspicion that rifampicin resistance was missed by Xpert testing, then phenotypic testing for rifampicin should be requested. While awaiting phenotypic DST results, regimen options should be discussed with an experienced clinician. This may include continuing first-line TB therapy with increased doses of isoniazid (10 mg / kg / day) and rifampicin (up to 20 mg / kg / day), or initiating an empiric RR-TB treatment regimen, depending on the clinical status and risk factors of the individual patient.

Recommendations for management of hetero-resistant TB:

- If hetero-resistance is suspected or confirmed, treatment should be based on the strain with the highest level of resistance.

- If one of the strains is shown to be susceptible to rifampicin on drug susceptibility testing, then rifabutin may be included in the second-line TB treatment regimen.

SUMMARY OF PATIENT SUPPORT STRATEGIES

- All persons being treated for RR-TB should be supported to successfully complete treatment, and this is as essential as the medications given.
- Pre-treatment counselling should focus on treatment literacy, participatory decision making, and identifying barriers to adherence so an individualised plan can be made.
- Counselling should be a routine part of treatment throughout the administration RR-TB therapy.
- Screening for mental health and substance use disorders using validated tools (e.g. WHO ASSIST tool for substance use) should take place at baseline and at month 4, with monthly review of mental health and substance use during treatment. Patients with a positive screen should be assessed in more depth with counselling, medication and/or group therapy offered as indicated.
- Lack of transportation to medical appointments is a major challenge and a mechanism to provide free transport must be part of RR-TB treatment.
- All persons on treatment for RR-TB qualify for and should receive a disability grant; this should be applied for as soon as possible after starting RR-TB treatment.
- Persons on treatment for RR-TB often require nutritional support, and resources for providing nutritional supplementation should be identified and used to eliminate food insecurity among people with RR-TB.
- Some patients may not need Directly Observed Therapy (DOT) and consideration of self-administered therapy could be considered following best practices established in the country.

TREATMENT OUTCOME DEFINITIONS FOR THE SHORTER REGIMEN

Treatment Outcome	Definition
Cured	1. A patient who has TB culture converted. 2. Received treatment for a total duration of 9 months or more. 3. Has at least three consecutive negative TB cultures during continuation phase (at least 30 days apart). 4. No evidence of clinical deterioration
Treatment completed (success)	1. A patient who has TB culture converted. 2. Received treatment for a total duration of 9 months or more. 3. Has less than three consecutive negative TB cultures during continuation phase (at least 30 days apart). 4. No evidence of clinical deterioration
Loss to Follow Up	A patient with treatment interrupted for: - ≥2 consecutive months - Any reason without medical approval
Treatment Failure	1. A patient whose TB culture results in the first 4 months of treatment failed to convert to negative by month 6. 2. Two or more cultures in the continuation phase are positive and clinical condition deteriorating 3. Treatment stopped on clinical grounds 4. More than two new drugs added to regimen due to poor clinical response 5. Case discussed by a Provincial Review Committee and decision taken to terminate RR-TB treatment
Moved	1. Referred from one facility to another facility within the same district to continue treatment. This is not an outcome, but serves to match patient moving within the district in order to prevent double counting Received treatment for a total duration of 9 months or more. 2. The treatment outcome is reported by the facility where the patient is newly registered

Treatment Outcome	Definition
Transferred Out	1. Referred from one facility to another reporting and recording facility in another district, province or country to continue treatment. 2. The treatment outcome is reported by the facility where the patient is newly registered
Died	Patient who dies for any reason during treatment
Still on treatment	Still on treatment after prescribed period
Not Evaluated	A patient recorded in the register and who does not have the necessary recorded data to enable classification of any outcome

TREATMENT OUTCOME DEFINITIONS FOR LONGER REGIMENS

Treatment Outcome	Definition
Cured	1. A patient who has TB culture converted. 2. Has at least three consecutive negative TB cultures during continuation phase (at least 30 days apart). 3. Total duration of treatment not to be less than 18 months. 4. No evidence of clinical deterioration.
Treatment completed (success)	1. A patient who has TB culture converted. 2. Has less than three consecutive negative TB cultures during continuation phase (at least 30 days apart). 3. Total duration of treatment not to be less than 18 months. 4. No evidence of clinical deterioration.
Loss to Follow Up	A patient with treatment interrupted for: - ≥2 consecutive months - Any reason without medical approval
Treatment Failure	1. A patient whose TB culture results in the first 4 months of treatment failed to convert to negative by month 6. 2. In the final 12 months of treatment: - ≥2 of 5 cultures are positive - clinical condition deteriorating 3. Treatment stopped on clinical grounds 4. More than two new drugs added to regimen due to poor clinical response 5. Case discussed by a Provincial Review Committee and decision taken to terminate RR-TB treatment
Moved	1. Referred from one facility to another facility within the same district to continue treatment. This is not an outcome, but serves to match patient moving within the district in order to prevent double counting. 2. The treatment outcome is reported by the facility where the patient is newly registered

Treatment Outcome	Definition
Transferred Out	1. Referred from one facility to another reporting and recording facility in another district, province or country to continue treatment. 2. The treatment outcome is reported by the facility where the patient is newly registered
Died	Patient who dies for any reason during treatment
Still on treatment	Still on treatment after prescribed period
Not Evaluated	A patient recorded in the register and who does not have the necessary recorded data to enable classification of any outcome

SUMMARY POINTS ON PALLIATIVE AND END-OF-LIFE CARE

Palliative care refers to care aimed at relieving suffering and should be part of the treatment for all persons with RR-TB.

Examples of palliative care during treatment could include the use of inhaled medications to relieve breathlessness, supplemental oxygen, physical therapy for any mobility limitations, and counselling for psychosocial distress.

Persons with RR-TB may suffer long-term consequences that affect their health even after they complete RR-TB treatment (e.g. loss of hearing, peripheral neuropathy, pulmonary insufficiency). Care should be provided for such conditions even after completion of RR-TB treatment.

Some patients will not be cured by RR-TB therapy, although this number is decreasing with the use of the newer drugs. Discontinuation of therapy and end-of-life care initiation should take place following consultation with the PCAC, provincial multidisciplinary teams and after all therapeutic options have been considered.

Such decisions should also consider the values and beliefs of the person with RR-TB, the clinical status of the person with RR-TB, and the locations where end-of-life care can be administered.

SUMMARY POINTS ON POST-TREATMENT FOLLOW UP

Persons may develop conditions during treatment for RR-TB that require ongoing treatment and follow up. These conditions may be due the impact of RR-TB on the lungs (including fibrosis, scarring, and reactive airway disease) or due to side effects of RR-TB treatment (e.g. hearing loss). People with RR-TB should be followed for these conditions even after completion of RR-TB therapy. The table below summarizes some of the more common chronic conditions that affect people with RR-TB and management options.

Condition	Management following completion of RR-TB treatment
Reactive airway disease	Inhaled beta-2-agonists and inhaled corticosteroids. Management in PHC.
Chronic bronchitis	Inhaled beta-2-agonists and inhaled corticosteroids; antibiotics as needed for flare ups. Management in PHC.
Pulmonary insufficiency	Oxygen therapy
Hearing loss	Hearing aids, cochlear implants. Management in audiology, rehabilitation medicine.
Peripheral neuropathy	Physical therapy, sturdy shoes. Management in PHC, rehabilitation medicine.
Depression/anxiety	Counselling, antidepressants, anxiolytics. Management in PHC, with access to psychiatry services
Right heart failure (cor pulmonale)	Tailored therapy with diuretics, inotropes, afterload reduction. Management in PHC, with access to cardiology services.
Chronic haemoptysis	Volume repletion, consideration of surgical intervention. Management in PHC, with access to surgical services.
Super-infections (e.g. aspergilloma, nocardia)	Targeted antimicrobial therapy, consideration of surgical intervention. Management in PHC, with access to infectious diseases specialists and surgical services.

The World Health Organization and the USAID provided consultants
that helped with development of these guidelines.