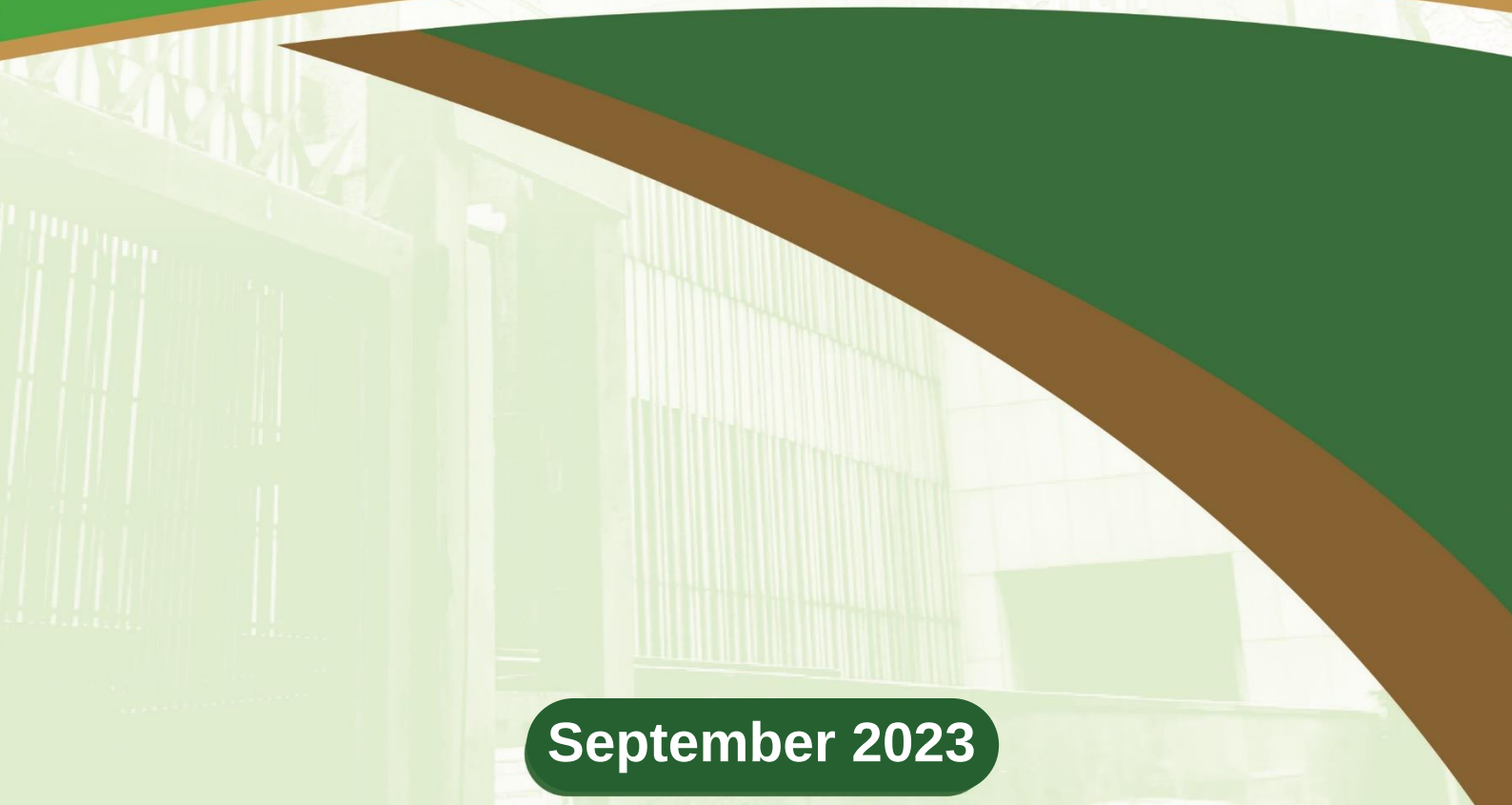
health

Department:
Health
REPUBLIC OF SOUTH AFRICA

CLINICAL MANAGEMENT OF RIFAMPICIN-RESISTANT TUBERCULOSIS

Updated Clinical Reference Guide



September 2023

Abbreviations

aDSM	Active Drug Safety Monitoring and Management
ART	Antiretroviral Treatment
BDQ	Bedaquiline
BPaL	Bedaquiline, Pretomanid and Linezolid
BPaLM	Bedaquiline, Pretomanid, Linezolid and Moxifloxacin
BPaL-L	Bedaquiline, Pretomanid, Linezolid and Levofloxacin
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
LZD	Linezolid
MIC	Minimum Inhibitory Concentration
MO	Medical Officer
MFX	Moxifloxacin
MDR	Multidrug-Resistant
NCAC	National Clinical Advisory Committee
NDoH	National Department of Health
NIMDR	Nurse-Initiated Management of MDR TB
Pa	Pretomanid
PCAC	Provincial Clinical Advisory Committee
PHC	Primary Healthcare Clinic/Centre
PV	Pharmacovigilance
PVU	Pharmacovigilance Unit
QTc	Corrected QT interval
PZA	Pyrazinamide
RIF	Rifampicin
RR	Rifampicin Resistant
SAHPRA	South African Health Products Regulatory Authority
SLDs	Second-Line Tuberculosis Drugs
SMS	Short Message System
STI	Sexually Transmitted Infection
TB-NAAT	TB-Nucleic Acid Amplification Test
TRD	Terizidone
XDR	Extensively Drug-Resistant
WHO	World Health Organization

Foreword

South Africa is a high burden Rifampicin Resistant-Tuberculosis country. Following the Covid-19 pandemic, we have noted that the TB care cascade gaps have increased with fewer patients tested, diagnosed, and successfully treated.

A TB recovery plan was developed to address these gaps. The version 2.0 of the TB recovery plan is aligned with the National Strategic Plan 2023-2028 for HIV, TB & STIs.

This plan aims to find people with undiagnosed TB in communities, link and retain them in care. The recovery plan also prioritizes TB prevention, improvement of TB surveillance systems, advocacy, communication, and social mobilization.

This Updated Clinical Reference Guide is a revision of the Management of RR-TB: A Clinical Reference Guide, published in November 2019. The main changes in the document include introducing the 6-month regimens known as BPaL and BPaL-L regimens, discussion of the new inclusion and exclusion criteria, treatment modalities, treatment follow up and post-treatment follow-up.

It is expected that patients initiated on the existing 9-month and 18-month regimens will continue their treatment regimens until completion. This means that during the years 2023 and 2024, we will have RR-TB patients receiving the 6-month, the 9-month and the 18-month regimens. Therefore, to ensure clinical guidance for all patients on treatment, the existing Clinical Reference Guide of November 2019 will be used concurrently with this updated one for the next 2 years. The shorter 6-month regimen is essential in reducing the loss to follow-up among patients treated with this regimen. Efforts need to be made to identify and initiate eligible patients on this regimen.

The Updated Clinical Reference Guide is based on the latest available evidence and the most recent recommendations from the World Health Organization. It will support the introduction and implementation of BPaL and BPaL-L regimens in South Africa. I urge all provinces to use these guidelines to enhance the clinical management of rifampicin-resistant tuberculosis.

Dr SSS Buthelezi
Director General: Health
Date: 11/08/2023

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1. Introduction

The past five years have seen revolutionary changes in the diagnosis and management of rifampicin-resistant tuberculosis (RR-TB), including the use of new and repurposed drugs and novel therapeutic approaches[1]. 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 [2–6]. In May 2022, the WHO announced that 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid (600 mg), with or without moxifloxacin, may be used programmatically in place of 9-month or longer (≥18 months) regimens, in patients (aged ≥15 years) with multidrug-resistant (MDR)/RR-TB who have not had previous exposure to bedaquiline (BDQ), pretomanid or delamanid (DLM) and linezolid (LZD) (defined as >1 month exposure)[7].

Individuals who had more than 1 month exposure of second line drugs will be started on BPaL-L, resistance to bedaquiline and linezolid must be excluded. Treatment initiation must not be delayed pending results of resistance tests. This regimen may be used without levofloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-extensively-drug-resistant (pre-XDR)-TB). Drug susceptibility testing (DST) to fluoroquinolones must be done, but DST should not delay treatment initiation. The short BPALM regimen showed up to 90% efficacy in clinical trial settings. There is accumulating evidence that this cure rate can be achieved in programmatic settings as well. Levofloxacin will be used in replacement of moxifloxacin in South Africa, although moxifloxacin may be used if levofloxacin is unavailable. LZD is the most toxic drug in the regimen. Healthcare providers must ensure careful monitoring to detect adverse events. Early detection of adverse events can be done at a primary care setting to prevent morbidity and even mortality. Confirmed resistance to any of the components except levofloxacin is a contraindication as is severe extrapulmonary TB.

1.1. Summary table of major guidelines changes

Subject area	Major Policy Changes
Diagnosis	The Line Probe assay will be phased out and the GeneXpert XDR (Xpert MTB/XDR) cartridge will be used to detect fluoroquinolone and INH resistance. This test also detects resistance to ethionamide and the second line injectables (amikacin, kanamycin and capreomycin) in a single test. Phenotypic testing for linezolid and bedaquiline will be rolled out nationally for all patients who have RR-TB. This test can also be done at the clinician's request. Pretomanid testing would be performed at the National TB reference laboratory for all isolates resistant to fluoroquinolones. Definitions of pre-XDR and XDR-TB have been updated in line with the latest WHO guidance.
Treatment	All persons with RR-TB will either be treated with a short, all-oral, 6-month regimen or with a long-individualized regimen. The previously recommended 9–11-month regimen is no longer included in these guidelines. Recommendations for treatment of RR-TB in children < 15 years of age have been updated.

Short (6-month) RR-TB regimen	The 6-month BPaL-L regimen, comprising bedaquiline, pretomanid, linezolid (600 mg) and levofloxacin, will be used programmatically in place of 9-month or longer (≥18 months) regimens, in non-pregnant patients (aged ≥15 years) with MDR/RR-TB and Pre XDR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure). Individuals who had more than 1 month exposure of second line drugs will be started on BPaL-L, but resistance to bedaquiline and linezolid must be excluded. Treatment initiation must not be delayed pending results of resistance tests. This regimen may be used without levofloxacin (BPaL) in the case of documented resistance to fluoroquinolones. Drug susceptibility testing (DST) to fluoroquinolones should be done using the GeneXpert XDR cartridge but this should not delay treatment initiation. All persons who are not responding to therapy will be identified early (i.e. based in part on month 3 culture status) and should be reviewed by the Provincial Clinical Advisory Committee (PCAC) or National Clinical Advisory Committee (NCAC) for a possible rescue regimen.
Individualized long regimen	This is to be offered to persons with documented resistance to pretomanid and/or BDQ and/or LZD. Prior exposure to pretomanid, linezolid and bedaquiline for more than a month is not an indication for a long-individualized regimen. Extended DST will be done on request by clinicians only to support individualized long regimen. The composition of the regimen will depend on the drug resistance pattern, prior drug exposure and toxicity. The long-individualized regimen can be offered to persons with RR-TB that have a high risk of resistance to BDQ and/or LZD. Please contact the NCAC for advice on the composition of the regimen.

1.2. Definitions

Microbiologically confirmed: when a biological specimen is positive by smear microscopy, culture, or a rapid diagnostic test for *Mycobacterium tuberculosis (M. tuberculosis)* recommended by the World Health Organization (WHO). This is also referred to as bacteriologically confirmed.

Clinically diagnosed: when a person who does not fulfil the criteria for bacteriological confirmation has been diagnosed with TB by a medical practitioner who has decided to give the person a full course of RR-TB treatment.

New case: a person with TB disease who has never been treated for TB or has only previously ever taken TB drugs for less than 1 month.

Drug-resistant tuberculosis (DR-TB) refers to tuberculosis disease caused by *Mycobacterium tuberculosis* bacilli that are resistant to one or more anti-TB drugs. Case definitions[6,8,9] and outcome definitions have recently been revised[9].

1.3. Categories of resistant tuberculosis

- **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.
- **Pre-Extensively drug-resistant** TB (Pre XDR-TB): TB disease caused by strain of *Mycobacterium tuberculosis* (M. tuberculosis) complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to fluoroquinolones.
- **Extensively drug-resistant TB (XDR-TB):** TB disease caused by a strain of *Mycobacterium tuberculosis (M. tuberculosis)* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one additional Group A drug either BDQ or LZD.
- **Extensive (or advanced) pulmonary TB disease**: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, **severe disease** is defined by presence of cavities, parenchymal involvement of more or equal to one full lobe, miliary pattern, or mediastinal lymphadenopathy with airway compression on chest radiography.
- **Severe extrapulmonary TB:** meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease. In children aged below 15 years, severe EPTB is any extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes) or simple pleural effusion.

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, pre-XDR-TB, XDR-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”).

1.4. Organisation of services

Most of the RR-TB care and services should be provided in the outpatient setting according to the National decentralization plan which aligned with our policy framework on decentralized and deinstitutionalized management of multidrug-resistant tuberculosis[10]. Children do not need to be treated by central sites and can be managed closer to home where there are health care staff comfortable with the care of children.

Persons with clinical indications for hospitalization should be admitted for care at the discretion of their healthcare providers. The length of hospitalization should be based on the reason for admission and resolution of the condition(s) that led to hospitalization. It is not necessary to wait for smear or culture conversion prior to discharge from hospital.

Nurses who have been trained to prescribe second-line TB treatment should continue to initiate uncomplicated patients on RR-TB treatment, as a 2018 programme review showed that patients treated via Nurse Initiated management of MDR-TB (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. central nervous system (CNS), XDR-TB), patients in need of rescue regimens, and the care of children with severe RR-TB. The NCAC should also be informed of pregnant women being treated for RR-TB, although permission to initiate treatment is not required. A TB pregnancy registry will be developed to record and monitor outcomes of patients treated for RR-TB during pregnancy.

1.5. Patient Flow (Adapted from the policy framework on MDR-TB treatment)[10]

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)
- Advise patient that results will follow by SMS and he/she needs to act accordingly

On receipt of results confirming RR-TB:

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

Laboratory

- Diagnosis of RR-TB
- Report sent to requesting facility and SMS to patient 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 RR-TB register at appropriate facility (usually at a centralised or decentralised unit); this includes children who are clinically diagnosed and do not have microbiological confirmation of RR-TB
- Counsel the patient and family; obtain consent for RR-TB management; use appropriate DR-TB stationery; conduct psychosocial assessment including history of substance use and mental health screen; refer for NSP if necessary; 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 ≥18.5) • Patient is willing and able to attend clinic regularly for clinical review and monitoring, and to receive treatment under directly observed therapy (DOT) at facility or in the family 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/m^2 • 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 RR-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 RR-TB units are responsible for providing treatment according to local best practices and for monitoring progress of patients throughout their treatment journey
- RR-TB stationery should be maintained at the facility at which the patient is being managed

1.6. Roles of the PCACs and NCAC

Each province should have a provincial clinical advisory committee (PCAC), or similar arrangement, through which formal input can be sought on the management of persons with RR-TB[11]. The PCACs can be consulted at any time, and they should provide input on the management of patients in the following situations:

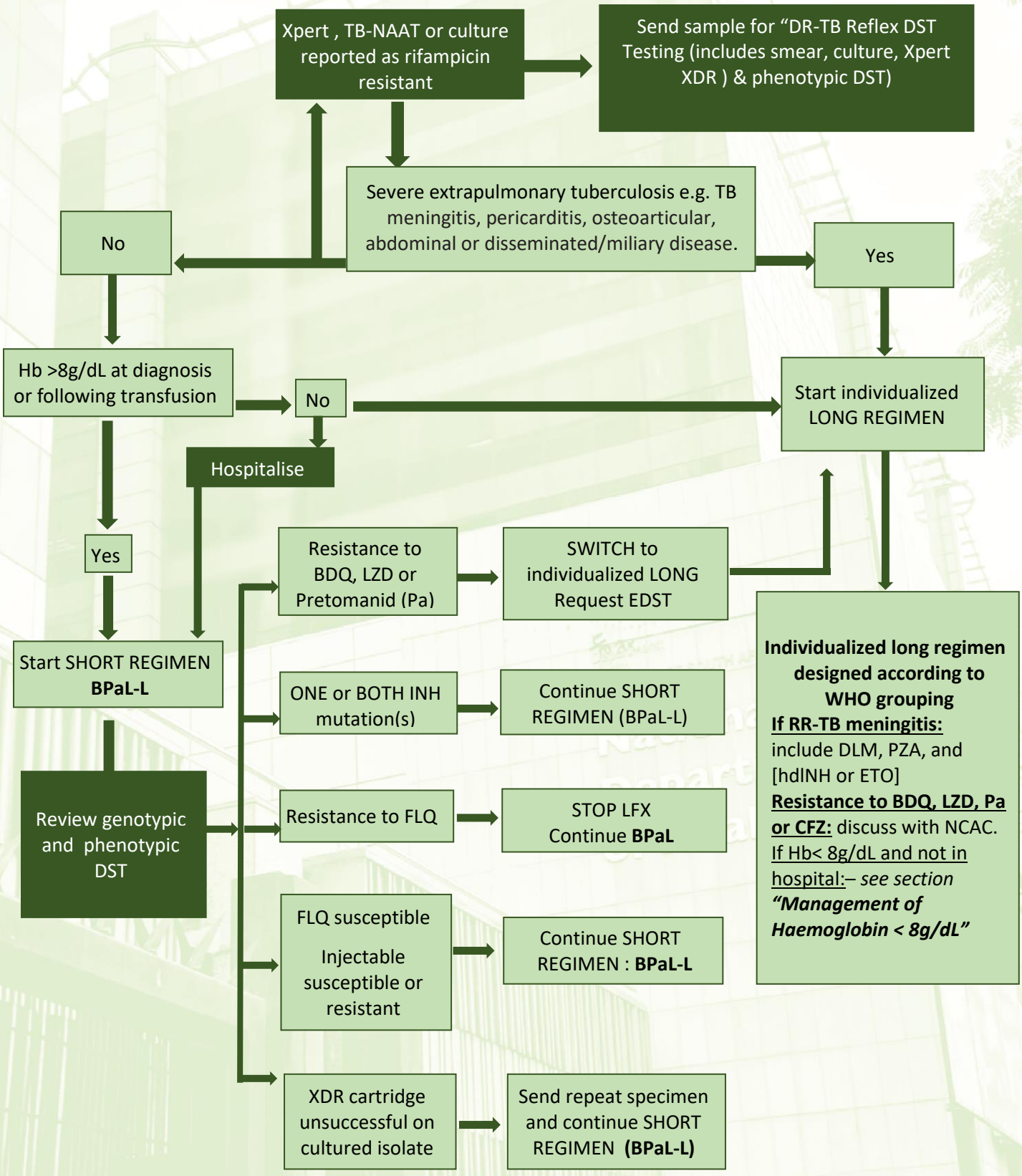
- Initial regimen choice in more complicated patients (i.e. those in whom a choice between the short and long regimens is not clear).
- Failed XDR-TB
- Treatment regimen design for children, especially if being managed in primary care
- Toxicity management, especially when consideration of discontinuation 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 and subsequent rescue regimen for persons who are not responding to therapy.
- Discordant 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 with complicated RR-TB.
- CNS RR-TB that is fluoroquinolone-resistant.

RR-TB during pregnancy – 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[11]

1.7. Overall Flow Diagram for people ≥ 15 years of age



2. Diagnosis of RR-TB

2.1. Key points

- All persons with signs and symptoms of TB should have a specimen sent for Genotypic testing (e.g. Xpert MTB/RIF Ultra testing) [12].
- Persons who test positive for M. tuberculosis with rifampicin resistance will have DR-TB reflex testing that includes TB microscopy, TB culture, genotypic, second line testing for fluoroquinolones (Xpert XDR cartridge) and phenotypic testing for bedaquiline and linezolid.
- Clinicians should call the laboratory to discuss any discordant results.
- Resistance testing for delamanid and pretomanid should be requested in all patients with > 1 month exposure prior (in addition to bedaquiline and linezolid) when these tests become available.

2.2. Types of laboratory testing and estimated turnaround times

TYPE OF TEST		WHEN DONE	Estimated TAT*	RESULT
Primary diagnosis: Mtb and first-line		Diagnostic investigation using WHO recommended molecular diagnostics	48 hours	Mtb detected and susceptibility to rifampicin and isoniazid or rifampicin only (test dependent)
Genotypic	**XDR cartridge**	Mtb detected and rifampicin resistant	48 hours	Susceptibility to isoniazid, ethionamide, second line injectables and fluoroquinolones.
Phenotypic DST for isoniazid (will not be done routinely)		In-lab reflex done when rifampicin resistant and isoniazid susceptible.		Confirm susceptibility to isoniazid if INH will be added to the treatment regimen.
Second-line phenotypic DST		In-lab reflex done when resistant to rifampicin.		Confirm susceptibility to linezolid and bedaquiline
		If resistant to FLQ or BDQ or LZD laboratories will send samples to NTBRL for pretomanid testing.		Susceptibility to pretomanid.
Individualized Extended Phenotypic DST (done by the National Institute of Communicable Diseases)		Requested when RR-TB regimen failing, resistant to BDQ or LZD or previous exposure to second-line drugs		Susceptibility to multiple TB drugs, used to construct a rescue regimen

*TAT, Turn around time

2.3. Laboratory reflex testing workflow

NATIONAL HEALTH LABORATORY SERVICE

DR-TB Reflex Algorithm

*unsuccessful = indeterminate on instrument report and only for a specific drug (INH or FLQ) that has an indeterminate result. Please note that BDQ, LZD and Pa should be done in parallel.

**Pa - all FLQ-R isolates should be referred to the National TB Reference Laboratory (CTB/NICD/NHLS, Johannesburg) for Pretomanid testing

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Division of the National Health Laboratory Service

2.4. Interpretation of laboratory test results

Patients started on the short regimen based on genotypic (e.g. GeneXpert) rifampicin resistance

Genotypic Results INH, ETH, SLID and FLQ and phenotypic BDQ, LZD and Pa	Action
INH resistant (any combination of inhA and/or katG mutation) or katG	Continue short RR-TB regimen (BPaL-L), modify according to other genotypic and phenotypic susceptibility results.
INH susceptible	Continue short RR-TB regimen (BPaL-L), modify according to other genotypic and or phenotypic results.
Susceptible to fluoroquinolones	Continue BPaL-L
Resistant to fluoroquinolones	Continue BPaL and stop levofloxacin
Susceptible or Resistant to injectable	Continue BPaL-L
Resistant to ethionamide	Continue BPaL-L

Short RR-TB regimen = BPaL-L

2.5. Extended DST request

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Centre for Tuberculosis
National TB Reference Laboratory
WHO TB Supranational Reference Laboratory Network
1 Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 885 5317 or +27 (11) 885 5323
Extended Drug Susceptibility Specialized Reference Laboratory Testing

REQUESTS FOR EXTENDED DRUG SUSCEPTIBILITY TESTING FOR CLIENTS NOT RESPONDING TO THEIR DR-TB REGIMEN

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 panel of anti-TB drugs e.g. Linezolid, Bedaquiline, Pretomanid amongst others. The following steps should be followed when making the request.

Identify the **NHLS laboratory number** of the latest sample that is culture positive for TB

↓

Contact your local NHLS TB laboratory manager to electronically refer positive culture to the National TB Reference laboratory at the Centre for Tuberculosis (NICD/NHLS)

↓

Print result of positive culture; scan, and email Dr Farzana Ismail (farzanai@nicd.ac.za) & 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 drug susceptibility testing (EDST) + patient name"

↓

In the content of email, write a short 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

Chairperson: Prof Eric Buch Acting CEO: Dr Karmani Chetty
Physical Address: 1 Modderfontein Road, Sandringham, Johannesburg, South Africa Postal Address: Private Bag X4, Sandringham, 2131, South Africa
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Practice number: 5200296

2.6. Laboratory testing: Special situations

Situation	Recommended Actions
Treatment of a patient where Genotypic testing (e.g. Xpert MTB/RIF Ultra) is positive and rifampicin resistant, however GeneXpert XDR results are pending	Assess clinical risk factors and if no exclusion factors start on a short regimen. If no *GeneXpert XDR* results within 30 days of sample submission, submit repeat sample for DR-TB reflex testing. If no resistance testing results are available, then the patient should continue the short regimen but follow up closely to monitor response both clinically and microbiologically.
Discordant results between phenotypic and genotypic tests	Clinician to phone the laboratory to discuss discordant results. In general, treatment should be based on the "most resistant" scenario; consult with PCAC or NCAC.

2.7. Key points to consider in RR-TB diagnosis in children

- 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 also have Xpert MTB/RIF or culture-confirmed RR-TB and may even be the index RR-TB case.
- Microbiological confirmation should always be attempted; at least two good-quality specimens should be collected and sent separately for Xpert MTB/RIF Ultra and mycobacterial culture and DST. Many children will not have microbiological 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 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 the primary healthcare level. Stool specimens can be sent for Xpert MTB/RIF Ultra, but not for culture – it is less sensitive than gastric aspirate or induced sputum but gives the opportunity to confirm TB and RIF DST. These results must be actively followed up – culture and DST may take up to 6 weeks for final results.
- Tests to diagnose EPTB, such as appropriate imaging and collection of specimens (such as fine needle aspirates, biopsies, different bodily fluids and CSF) for microbiological 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 microbiological confirmation.
- In children with microbiologically confirmed pulmonary disease, microbiological monitoring (with culture) 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 < 1 lobe, non-cavitating TB disease, mediastinal lymphadenopathy with no airway compression or simple pleural effusion on chest radiography; or isolated peripheral lymph node disease.

3. Management of RR-TB in children under 15 years of age

3.1. Introductory remarks

In March 2022, the World Health Organization (WHO) issued updated guidelines for management of tuberculosis in children and young adolescents, which recommend that delamanid and bedaquiline can be used in all age groups, along with updated dosing guidance for all TB drugs[13]. Therefore, previous age restrictions on use of these medications in children are no longer relevant.

The WHO-recommended 6-month regimens, BPaL and BPaLM, only apply to non-pregnant persons aged 15 years and older, as pretomanid safety has not been established during pregnancy or in children. However, most children with RR-TB do not require a long 18-month treatment regimen to achieve cure of the disease.

Based on the results of the SHINE trial, which focused on treatment shortening for drug-susceptible (DS)-TB in children with non-severe disease[14], the WHO now recommends a total duration of only 4 months of treatment in children with smear negative, non-severe DS-TB. A similar approach to shorter treatment has been adopted by clinicians experienced in the management of paediatric RR-TB, and children with non-severe RR-TB disease can be successfully treated with a shorter duration of treatment than is usually recommended for adults. However, close monitoring for recurrent disease, for at least 12 months following completion of treatment, is considered essential for these children.

Local availability of paediatric formulations of TB drugs also determine which regimens are feasible in South Africa, particularly among young children for whom the adult drug formulations are typically poorly tolerated and difficult to administer. Wherever possible, paediatric formulations should be considered for young children and infants or for those who struggle to swallow adult formulation tablets. Pediatric formulations including delamanid 25 mg dispersible tablet, levofloxacin 100 mg dispersible tablet, bedaquiline 20 mg dispersible tablet, clofazimine 50 mg dispersible tablet are available at selected sites in Eastern Cape and Kwazulu-Natal through a donation programme. These will be scaled up in near future. There are new concerns regarding the sustainability of the supply of terizidone (TRD), which is often still used in paediatric RR-TB regimens.

Therefore, it is important to emphasize the general principles of RR-TB treatment and regimen design in this age group, as there is no standardized treatment regimen for all children under 15 years of age. Composition and duration of treatment regimens may vary between individual children and is based on resistance profile of the organism as well as site and severity of the RR-TB disease.

The following recommendations for treatment of RR-TB in children under 15 years of age follows the approach outlined in the Sentinel Guide for Management of MDR-TB in Children [15], considering available programmatic paediatric data, extrapolated efficacy data from adult clinical trials, expert paediatric opinion and the latest WHO recommendations.

3.2. Principles of RR-TB treatment in children under 15 years of age

The general approach to paediatric RR-TB regimen design is the same for children of all ages (0-14 years). The following principles of treatment are recommended:

- In designing treatment regimens for children, the following factors must be considered:
  - RR-TB regimen composition is based on the current WHO drug grouping **(see Section 2.7).** The regimen should include at least 4 drugs considered to be effective, with possible addition of a 5th drug if needed (severe disease, site of infection, or only ≤ 1 group A drug in regimen). Priority must be given to WHO Group A & B drugs and delamanid; using more than five of these drugs in cases of MDR/pre-XDR-TB may add to the toxicity profile of the regimen without necessarily improving treatment efficacy.
  - All-oral regimens must be prioritised (except for rescue regimens where options are limited, and injectable agents are available and likely to be effective).
  - Disease severity, i.e., severe versus non-severe disease (based on definitions from the SHINE trial and the WHO 2022 definition for children < 15 years, see Table 3.21 below) – children with severe disease may require five drugs in their regimen initially.
  - Site of disease – children with more extensive disease (particularly CNS, miliary, bone or pericardial disease) are likely to require five drugs in their regimen. Treatment of RR-TB meningitis should be guided by the medicines' ability to cross the blood-brain barrier.
  - Drug resistance profile – treatment should be based on the DST pattern of the *M. tuberculosis* strain from the most likely source case if the child does not have an *M. tuberculosis* isolate of his/her own with DST results. Following up on all DST results for samples from the child and the source patient is therefore essential (with special consideration for checking resistance to the fluoroquinolones, BDQ, CFZ, and LZD)
  - Toxicity and tolerability of drugs, and feasibility of adverse effect monitoring – specific medicines, e.g. LZD, may not be a feasible option for some children in view of the considerable risk of toxicity and stringent monitoring requirements (e.g., frequent blood draws to check full blood count (FBC) and differential white cell count) which may be challenging for some children and their families.
  - Availability of paediatric formulations – some medicines (e.g., 100 mg CFZ capsules) cannot be easily administered to young children and may have to be substituted with other effective medicines.
- Drug dosing is based on the child's weight (and age in infants), in accordance with the 2022 WHO RR-TB treatment guidelines [13] – see Annexure 1 for drug dosing in children weighing under 30 kg and for those weighing over 30 kg. Doses of drugs must be modified as children gain or lose weight over the weight band thresholds.
- Child-friendly formulations of TB medications should be used whenever possible, if acceptable to the child and caregiver. If paediatric formulations are not available, then extemporaneous preparations may be required. These can be prepared daily by cutting or crushing the tablets, and mixing with water, pap, yoghurt or milk. This should be done in consultation with a pharmacist or a pharmacist's assistant.
- Persons at primary healthcare facilities dispensing the TB medicines to the

child/caregiver for administration at home should carefully check the doses of each medicine and that the correct formulation is used, especially if there is more than formulation for a specific medicine (e.g., a 100mg dispersible levofloxacin tablet is different in mg strength from the 250 mg adult levofloxacin formulation).

- 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.
- Very young children (under the age of 5 years) with any form of RR-TB disease should be treated under the guidance of a clinician with experience in the management of paediatric RR-TB. This also applies for children with XDR-TB (i.e., MDR plus resistance to fluoroquinolone and resistance to bedaquiline and/or linezolid), as individualized longer regimens and in-patient management may be necessary.
- Treatment duration in children is usually based on site and severity of disease (see Table 3.21 below), as well as extent of drug resistance. Good outcomes have been reported among adults following treatment with 3 or 4 drugs for 6 months (BPaL and BPaLM). Results from the SHINE trial [14] indicate that children with non-severe DS-TB disease can be successfully treated with a shorter (4-month) duration with effective drugs. Therefore, children with non-severe RR-TB disease are also likely to be successfully treated with shorter (6-month) regimens containing at least 4 effective drugs; those with more severe disease are likely to require longer treatment for 9 or 12 months (see Figure 3.1). Clinicians may also extend treatment for individuals in cases of slow or inadequate clinical, radiological and/or microbiological treatment response. There is no specified intensive or continuation phase for paediatric RR-TB regimens and most drugs should be continued throughout treatment, if possible, unless limited by toxicity or intolerance. Bedaquiline and delamanid are mostly used for 6 months only but can be extended to 9 months in consultation with an expert/specialist. Linezolid is often only tolerated for up to 2 months; however, some children may benefit from linezolid for the full duration of treatment if tolerated.

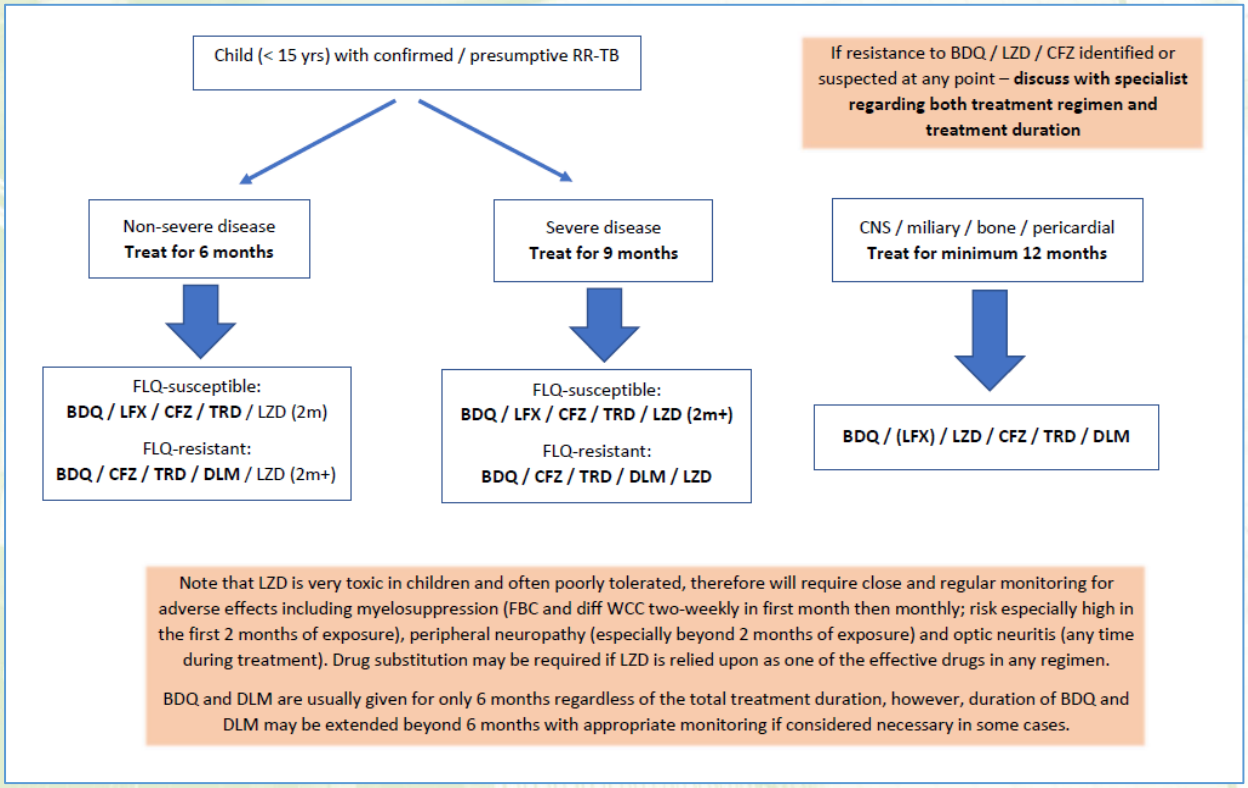
Table 3.2.1: Severe versus non-severe disease in children < 15 years

Severe TB disease in children < 15 years	Non-severe TB disease in children < 15 years
• CXR: bilateral disease (consolidation, infiltrates), or presence of cavities. • Mediastinal lymph nodes causing airways compression. • Extrapulmonary forms of disease other than peripheral LNs or simple pleural effusion.	• Peripheral lymphadenopathy. • CXR: unilateral disease (consolidation, infiltrates in < 1 lobe in total) without cavities. • Small/simple pleural effusions. • Mediastinal lymph nodes without airways compression.

3.3. Approach to treatment of RR-TB in children under 15 years of age

Figure 3.1 summarizes the approach to treatment of RR-TB in children < 15 years of age. The proposed drug combinations in this figure are examples for common scenarios, but the regimens have to be individualized based on the factors discussed in Section 3.2.

Figure 3.1: Approach to treatment of RR-TB in children < 15 years



- DLM may be used in replacement of terizidone.
- Ethionamide to replace TRD in the long regimen.

3.4. Sample individualized regimens for children under the age of 15 years

Table 3.4.1 below provides some examples of individualized regimens that would be appropriate in various situations based on drug susceptibility test pattern and site / severity of disease. Clinicians with limited experience in the management of paediatric RR-TB are advised to discuss cases with more experienced clinicians. All cases of RR-TB with confirmed or presumed resistance to BDQ / LZD / CFZ should be referred to a paediatric DR-TB expert or paediatric infectious diseases' expert or to the PCAC/NCAC for guidance on optimal treatment.

Table 3.4.1: Examples of individualized regimens for children < 15 years

DRUG SUSCEPTIBILITY PATTERN	SEVERITY OF DISEASE	SUGGESTED REGIMEN AND DURATION	COMMENTS
RR-TB that is NOT fluoroquinolone-resistant and NOT central nervous system disease, osteoarticular or spinal TB	Non-severe	BDQ – LFX – CFZ – (TRD or DLM) for 6 months; and +/- LZD for first 2 months*	If INH susceptible on pDST, hdINH may be considered instead of DLM or TRD#
	Severe	BDQ – LFX – LZD** – CFZ – (TRD or DLM) for 9 months	If LZD withdrawn in first 2 months, consult with expert and potentially replace LZD with another effective drug (DLM, TRD, PAS, hdINH or ETO)
RR-TB that is resistant to fluoroquinolones	Non-severe	BDQ – LZD** – CFZ – TRD – DLM for 6 months	
	Severe	BDQ – LZD** – CFZ – TRD – DLM for 9 months	Use PAS if TRD is unavailable. If LZD is withdrawn in first 2 months, consult with expert and replace LZD with another effective drug (PAS, hdINH or ETO)
RR-TB central nervous system disease or spinal TB	Severe	BDQ – [LFX] – LZD** – CFZ – TRD – DLM for 12-18 months	Use LFX if strain is susceptible. Consider carbapenems or ETO / hdINH in CNS and miliary disease
RR-TB with confirmed or probable resistance to BDQ / CFZ / LZD	Severe	Individualized rescue regimen required	Refer and/or obtain expert guidance

* Use LZD for up to 2 months if tolerated and feasible to monitor – if not tolerated for first 2 months, no need to substitute provided the child can tolerate 4 other effective drugs

** Use LZD for as long as tolerated and feasible – consider the preferences of caregivers and ability of staff to adequately monitor for LZD adverse effects in children, particularly bone marrow suppression (Hb < 8 g/dL,

neutrophils < 0.75 x 10^9/L and/or platelets <50 x 10^9/L) which may require frequent blood draws, and the ability to monitor for peripheral neuropathy/optic neuritis.

[#] TRD has been shown to reduce plasma concentrations of INH; concomitant use of these drugs should be avoided where possible

BDQ = bedaquiline; LZD = linezolid; LFX = levofloxacin; CFZ = clofazimine; TRD = terizidone; DLM = delamanid; hdINH = high dose isoniazid; ETO = ethionamide; PAS = para-aminosalicylic acid

3.5. ART regimen modification for children aged one month to <10 years, and >3 to <30 kg, living with HIV and on ART at RR-TB treatment initiation

Refer to annexure 2: 2023 ART guidelines of the National Department of Health [16].

3.6. Weight-based dosing recommendations for children and adolescents aged <15 years and weighing <30 kg –

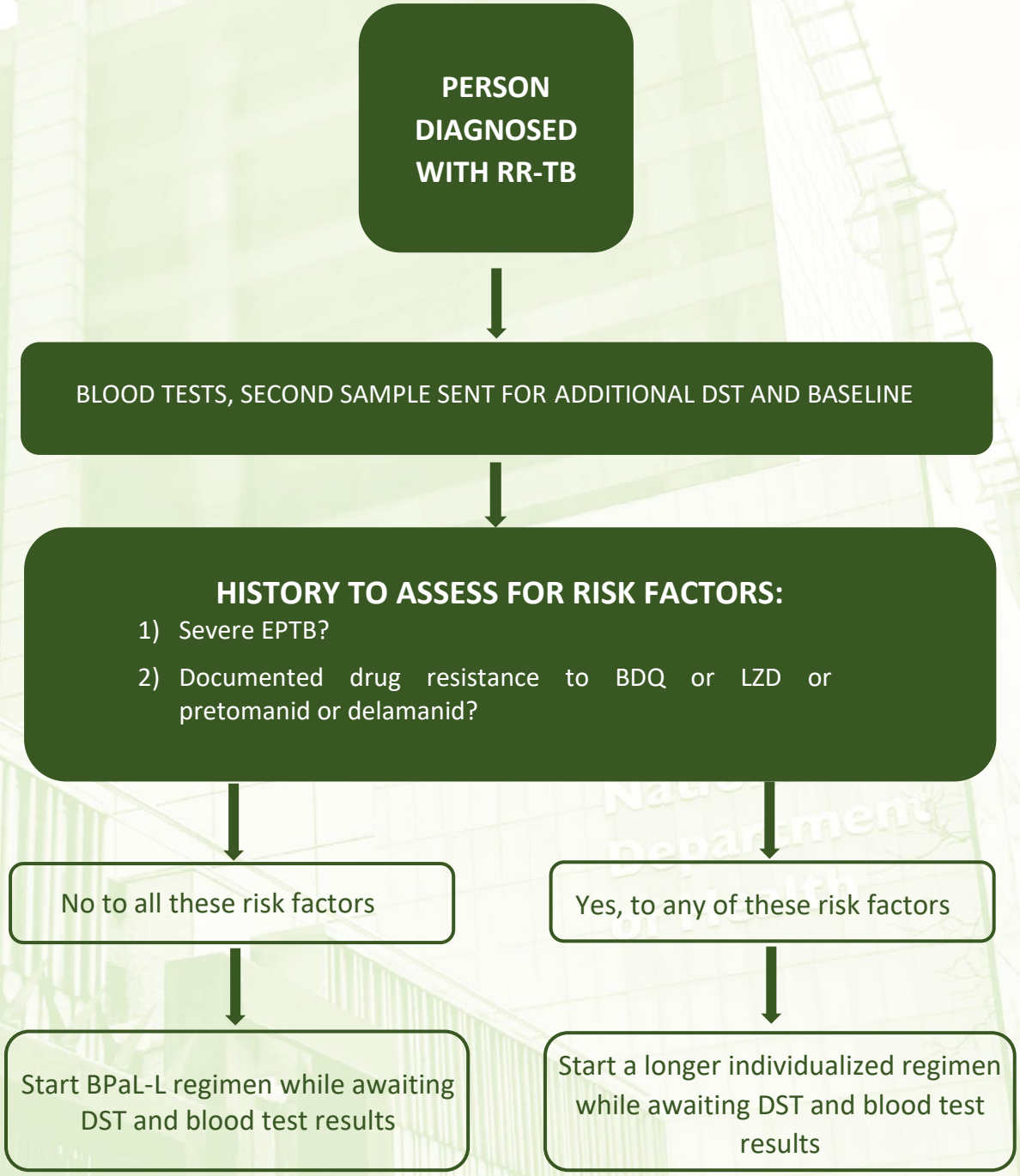
See below in annexure 1: Weight-based dosing of medicines used in multidrug-resistant TB regimens, adults and children[a] (World Health Organisation 2022 operational handbook) [17].

4. Management of RR-TB in children above 15 years of age and non-pregnant adults

4.1. Key points regarding the Short Regimen for RR-TB (BPaL-L)

- Most People with a diagnosis of RR-TB will be eligible to receive the short BPaL-L.
- The short regimen contains the following medication bedaquiline, pretomanid and linezolid with or without additional levofloxacin for 6 months. This can be extended to 9 months at the clinician's discretion.
- If fluoroquinolone resistance is detected, BPaL can be used without levofloxacin or moxifloxacin for 6 months.
- Prior use of bedaquiline, delamanid or pretomanid and linezolid (>1 month) is not a contraindication for BPaL-L. However, resistance to these agents must be excluded. If found to be resistant to bedaquiline, linezolid, delamanid or pretomanid the client is no longer eligible for BPaL-L regimen.
- Severe extra-pulmonary RR-TB meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease may not be treated with BPaL-L.
- Linezolid dose is 600 mg/daily. This should be given for at least 8 weeks. In the case of toxicity or intolerability the dose can be interrupted (while other medicines in the regimen are continued) for a total of a maximum of 8 weeks throughout the treatment course.
- There is no specified intensive or continuation phase for these regimens and all drugs should be continued throughout treatment, if possible, unless limited by toxicity or intolerance.
- HIV-positive patients with any CD4 count, regardless of ART status, qualify to receive the short RR-TB regimen if they meet the inclusion criteria listed above.
- Pyridoxine does not need to be prescribed in patients receiving BPaL-L.

4.2. Initial approach to patients diagnosed with RR-TB



4.3. Inclusion and exclusion criteria for Short RR-TB Regimen

The short RR-TB regimen in this chapter refers to the 6-month BPaL-L and BPaL regimens[18]. It does not refer to the 9-month regimen currently used per the 2019 Clinical Reference Guide.

	Inclusion Criteria	Exclusion Criteria
Resistance patterns	• Individuals with: RR-TB: resistance, based on initial genotypic result, while awaiting further susceptibility results	• Documented resistance to Bedaquiline or Linezolid. • RR-TB with additional resistance to pretomanid or delamanid • XDR-TB (resistance to the fluroquinolones and/ resistance to bedaquiline or linezolid)
Clinical criteria	• Non-severe extra-pulmonary RR-TB, including lymphadenopathy or pleural effusion. • Persons with extensive pulmonary disease (i.e. bilateral, cavitary disease with significant fibrosis, scarring or cavities in three or more lung zones) should have their treatment extended to 9 months.	• Persons with severe extra-pulmonary RR-TB meningitis, pericarditis, osteoarticular, abdominal or disseminated/miliary disease
Specific populations		• Children under the age of 15 years (since pretomanid safety is not yet confirmed in this population) • Pregnant women (since pretomanid safety is not yet confirmed in this population)

Patients with extensive disease can have their regimen extended to 9 months at the discretion of the clinician.

4.4. Switching from BPaL-L to Long Individualized Regimen

It is important to recognize when a person needs to switch from the short RR-TB regimen to a longer regimen. Input should be sought from the PCAC or NCAC where needed.

A switch to a long individual regimen should be strongly considered in these situations:

- Resistance to Bedaquiline, pretomanid, clofazimine, delamanid or linezolid is detected.
- There is a positive culture result at month 4 (delayed culture conversion or reconversion back to positive). Resistance to bedaquiline, pretomanid, clofazimine, delamanid or linezolid must be excluded.
- Bedaquiline, linezolid or pretomanid is prematurely and permanently discontinued because of toxicity.
- Delamanid testing is currently not being routinely done, the NTBRL is planning on starting to test for pretomanid. Clofazimine will also not be routinely tested, it will only be tested as part of EDST. Delamanid resistance testing should be requested if history of > 1 month exposure as resistance is contraindication to BPaL-L regimen and would then require an individualized regimen.
- The patient is clinically deteriorating or has not clinically improved. Other causes must be excluded in a culture negative patient.
- Extended DST is required.

If the patient switches to a longer regimen due to short RR-TB regiment treatment failure, the treatment episode should be registered as “treatment failure” and the patient should be assigned a new treatment episode.

4.5. Longer Individualized Regimens for RR-TB: Summary Points

- Persons who do not qualify for the short RR-TB regimen will receive a long individualized 18-month regimen.
- The commonest reason for a long regimen is bedaquiline resistance.
- Resistance to pretomanid, delamanid and linezolid are also an indication that the patient needs to be in the longer regimen.
- For persons aged 15 years and above who do not meet the short regimen inclusion criteria, treatment with the long regimen will consist of an individualized regimen given for a period of 18 months.
- Pyridoxine 50 mg should be prescribed for patients receiving a regimen containing TRD or hdINH.
- For persons aged 15 years and above without CNS RR-TB disease, a regimen of consisting of as many category A drugs that are still considered to be susceptible, with terizidone and clofazimine. In addition, select category C based on likely efficacy – consider an individual’s prior drug exposure, toxicity history and documented resistance.
- Treatment of CNS disease should consist of drugs with adequate CNS penetration to which the client’s isolate is likely to be susceptible.
- The regimen should be designed using the WHO drug grouping approach.
- Children under the age of 15 years should be treated as per Section 3.

4.6. WHO Drug Groupings

Steps to designing a Long-Individualized Treatment Regimen[19,20].

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	Include if no resistance.
	Linezolid	Include for all including CNS disease, unless contraindication or resistance. In patients with Hb <8 g/dL, neutrophils <0.75 x 10^9/L and/or platelets <50 x 10^9/L, only consider reintroducing or initiating in hospital under close monitoring.
Group B: Add one or both medicines, if possible	Clofazimine	Possible cross resistance to bedaquiline.
	Terizidone	Include for CNS disease.
Group C: Add to complete the regimen and when medicines from Group A and B cannot be used	Ethambutol	Only use as a reliably effective drug if susceptibility demonstrated on DST.
	Delamanid	Include for CNS disease.
	Pyrazinamide	Include for CNS disease. Only use as a reliably effective drug if susceptibility demonstrated on DST.
	Imipenem-cilastatin, or meropenem, or ertapenem	Adequate CNS penetration. Must be given in combination with amoxicillin/clavulanic acid.
	Amikacin	Administer if not enough other drug options to compose an effective regimen. Only administer 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. Therapeutic drug monitoring must be done.
	Ethionamide	Consider for CNS disease. Should only be given if *inhA* mutation is not present.
	Para-aminosalicylic acid	Use in rescue regimens.

An individualized long regimen should be offered for persons aged 15 years and above who are not responding to treatment, who have been failed by a previous RR-TB treatment regimen (especially one containing bedaquiline, pretomanid, delamanid, linezolid and/or clofazimine), or who have RR-TB with documented or suspected resistance to bedaquiline/clofazimine, linezolid and pretomanid/delamanid.

4.7. Recommended dosing of drugs for RR-TB treatment in persons weighing ≥30 kg

See Annex 1 of the document

5. Bedaquiline interruptions [21]

Duration of interruption	Instructions for reloading
< 2 weeks	No reloading needed
2-4 weeks	3 days 400mg* bedaquiline daily
1 – 12 months	7 days 400mg* bedaquiline daily
> 12 months	14 days 400mg* bedaquiline daily
If the patient weighs between 16 and 30 kg, reload with 200 mg daily [21].	

6. Rescue (XDR-TB) regimens

6.1. Introductory remarks

Clients with RR-TB and suspected or confirmed resistance to linezolid, clofazimine, bedaquiline and pretomanid/delamanid need to be given a rescue regimen. All persons requiring treatment with a rescue regimen should have a specimen or sample sent for EDST. 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[11]:

- Delamanid should be used if there is no history of previous exposure to it or to pretomanid.
- 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. Carbapenems must be given with clavulanic acid; 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 may be used if there is a katG mutation (in the absence of inhA).
- Para-aminosalicylic acid may 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. Therapeutic drug monitoring should be employed with use of amikacin.
- 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.
- 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).

6.2. Special considerations for persons on long regimens

Situation	Possible Actions
Persons not responding to treatment	• Careful assessment in any persons with a positive culture at month 3, 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. • Confirm BDQ and LZD sensitivity. • Send extended DST request and perform chest X-ray. • Offer long individualized 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 treatment with BDQ, Pa, LZD	• Send sputum for 'DR-TB reflex testing' and request extended phenotypic DST. • Start on a long regimen including at least five drugs. • Contact NCAC for advice

7. Renal dose adjustments for adults

Drug dosing for children with renal impairment should be discussed with experienced clinicians. The table below refers to adults.

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)
Pretomanid	No dosage adjustment is required
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
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 Imipenem
Ertapenem (given with amoxicillin-clavulanate)	• Ertapenem: 500 mg once daily • Amoxicillin-clavulanate: 250 mg / 125 mg given 30 minutes prior to Imipenem
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

8. RR-TB in pregnancy and breastfeeding

- All non-pregnant women of childbearing potential should be appropriately counselled throughout RR-TB treatment and offered family planning as part of routine RR-TB care.
- Healthcare providers can initiate RR-TB treatment for pregnant patients without NCAC approval. A pregnancy registry will be developed so that this cohort can be more formally monitored and data collected nationally.
- Pregnant women with RR-TB do not qualify for the short BPaL-L regimen because the safety of pretomanid has not been established in pregnancy. Based on the experience from the BEAT Tuberculosis study [22] pregnant patients with RR-TB may benefit from a 6-month treatment regimen containing Group A and B drugs with delamanid. That is bedaquiline, delamanid, linezolid and levofloxacin.
- Pregnant women on treatment will be closely monitored. Regular reports will be shared with the National Essential Medicines List Committee and all stakeholders. A pregnancy registry will also be put in place in due course.
- Bedaquiline is currently considered one of the safer drugs to use in pregnant women based on animal studies, and there is growing experience with the safe use of bedaquiline in pregnancy.
- There are limited data on the use of linezolid, levofloxacin, moxifloxacin, clofazimine, terizidone and delamanid during pregnancy, but emerging data from cohort studies (including from South Africa) indicate that many of these medications may be used safely with appropriate monitoring and guidance. Several studies are underway to assess pharmacokinetics and safety of second-line TB medications during pregnancy and breastfeeding.
- 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 fetus, neonate and infant is likely to be optimized 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.

9. Management of RR-TB among people living with HIV

The content of this chapter is aligned with the National 2023 ART Clinical Guideline [16].

9.1. Key Principles

- The short and longer DR-TB regimens may both be offered to people with HIV, and HIV status alone does not mandate any changes in the DR-TB regimen composition.
- To improve the chances of RR-TB treatment success, all people co-infected with RR-TB and HIV should receive antiretroviral therapy (ART) to suppress their viral load (VL).

9.2. Considerations RR-TB/HIV co-infected clients

- Treating RR-TB and HIV simultaneously can:
  - Negatively affect serum drug levels due to drug-drug interactions
  - Negatively affect adherence, due to increased pill burden
  - Potentiate side effects due to overlapping toxicities, e.g., hepatic toxicity
- Selected ART regimens should therefore be optimized to avoid drug-drug interactions, minimize toxicities and reduce pill burden.
- DTG in combination with tenofovir (TDF) and lamivudine (3TC), in the fixed-dose combination known as TLD, is the optimized regimen of choice, provided the client has normal renal function.
  - Dolutegravir can be used concurrently with all currently recommended RR-TB medications.
  - TLD is well tolerated and minimizes the additional pill burden due to ART (TLD is one tablet once a day).
  - ABC, 3TC and DTG (ALD) can be used in children < 10 years of age or weighing < 30 kg. Paediatric DTG 10 mg dispersible tablets are available for children weighing < 20 kg.
  - For a client with an eGFR of < 50, TDF can be replaced with abacavir (ABC).
- Recommendations for routine VL, creatinine and eGFR, and CD4 count monitoring of clients on ART are still applicable, in addition to the routine monitoring investigations for the management of their RR-TB diagnosis.
- Co-trimoxazole therapy should be provided regardless of CD4 count, as TB is a WHO Stage 3 condition.
- 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.
- Clinicians should provide integrated TB and ART management at clinical consultation visits. Failure to combine care leads to increased visits and significantly increases the risk of disengagement.

9.3. Antiretroviral Therapy in HIV-infected persons with RR-TB

Initiating (or re-initiating) ART after starting RR-TB treatment

- For ART naïve clients and clients re-initiating ART after previously interrupting ART, TLD should be initiated within 2 to 8 weeks after starting RR-TB therapy. In patients with CD4 <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 due to the risk of intracranial immune reconstitution inflammatory syndrome (IRIS).

Clients who are already on ART when RR-TB is diagnosed

- Clients who are already on ART when RR-TB is diagnosed should have a CD4 count and viral load test at the time of RR-TB treatment initiation. Any VL > 50 c/mL should receive a thorough 'ABCDE' assessment, have interventions implemented, and have a repeat VL in 3 months' time (see The VL monitoring and management algorithm on page 21 of the 2023 ART Clinical Guideline).
- Clients who have not yet been transitioned to TLD should be evaluated and transitioned as a matter of urgency:
- Clients on the following regimens qualify for a same-day switch to TLD (regardless of VL result*):
    - TEE
    - AZT, 3TC, DTG
    - Any protease inhibitor (PI) containing regimen if the client has a VL of < 1000 c/mL
    - Any PI-containing regimen if the client has been on the regimen for less than 2 years
    - Any PI-containing regimen on which the client is less than 80% adherent

*Note: While the VL does not influence the decision to switch to TLD on the same day, the VL result in the last 12 months should still be checked. If the VL in the last 12 months was not suppressed, continue to switch same day, but do an ABCDE assessment and provide enhanced adherence counselling (EAC) if needed, as per the VL Monitoring and Management algorithm on page 21 of the 2023 ART Clinical Guideline. If the VL was not done in the last 12 months, do it at this visit, but do not wait for the result to switch.

- Clients on a PI-containing regimen who have two or more consecutive VLs ≥ 1000 c/mL taken two or more years after starting the PI regimen, and who are adherent to their regimen, may require a resistance test before switching to TLD.

Please refer to the 2023 ART Clinical Guidelines for further guidance.
https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

9.4. Earlier antiretroviral agents that are no longer recommended in standard care

- Although PIs increase bedaquiline exposure via enzyme inhibition, this does not appear to increase toxicity. PI based regimens are compatible with RR-TB treatment. But note that the dose of rifabutin needs to be reduced with PIs. However, in the 2023 ART guideline, all clients on a PI regimen should be transitioned to a DTG-containing regimen. PIs will only be used in an ART regimen if DTG has been shown to be inactive based on a resistance test.
- Efavirenz induces hepatic metabolism of bedaquiline and decreases bedaquiline exposure; therefore, concomitant use of efavirenz and bedaquiline is contra-indicated. Efavirenz is no longer a preferred first-line antiretroviral agent, and all clients on TEE should be switched to TLD.
- Zidovudine and linezolid should not be used concurrently, as both drugs can cause bone marrow suppression. Zidovudine is no longer part of standard first and second-line regimens.

9.5. Assessment of renal function before starting tenofovir

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

Tenofovir should not be used for any patients <10 years of age or weighing <30 kg.

Age/pregnancy status	What must be measured?	Acceptable level for TDF use	**Counahan Barratt formula** eGFR (mL/min/1.73 m^2) $= \frac{height\ [cm] x\ 40}{creatinine\ [\mu mol/L]}$
≥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	

Table adapted from page 8 of the national 2023 ART Clinical Guidance[20]

* The MDRD formula is automatically calculated by the laboratory for those 18 years and older, using a modified version of this formula to estimate eGFR. For assistance in manually calculating the eGFR for adolescents between 16 and 18 years of age, please contact one of the "Helplines" on page 23. Alternatively, use the calculator provided at https://www.mdcalc.com/mdrd-gfr-equation, or one of numerous smartphone applications available for this purpose. Ensure that the website/application uses the correct unit of measurement (i.e., µmol/L) for the creatinine level.

10. Management of RR-TB and other co-morbidities

- This section has been included in this clinical guidance because it is essential. However, there is no update here. The information is based on existing clinical reference Guide[11].

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). • 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 counselling. • Referral to substance use treatment center. • Pharmacotherapy-assisted treatment (i.e. naltrexone or acamprosate for alcohol use), opioid substitution therapy (methadone, suboxone) should be considered where appropriate and available.
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 province or country of origin. • Prioritize 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.

11.Monitoring patients on RR-TB treatment

11.1. Monitoring Schedule for a patient on a BPaL-L/BPaL 6 month regimen

An example of the schedule of baseline, routine, and post-treatment monitoring examinations for the BPaL-L/BPaL regimen.

Examination	Baseline	2 Weeks	Monthly	End of Treatment	6 & 12 Months Post Treatment
Clinical evaluation					
Clinical assessment					
Psychosocial assessment[b]					
Weight/BMI					
Performance status					
Peripheral neuropathy screening					
Visual acuity and colour discrimination screening					
Assessment and follow-up of adverse events					
Outcome consultation					
Bacteriological evaluations					
Sputum smear					
Sputum culture					
Sputum DST[c]				**If smear or culture positive**	
Other samples (smear/ culture/DST)				**If no documented response to treatment**	
Radiology, ECG and laboratory evaluations					
Chest X-ray					
ECG					
Full blood count					
Liver function tests (AST, ALT and bilirubin)					
Serum electrolytes					
Urea, creatinine					
Pregnancy test					
HIV/HBV/HCV tests					
BSL/HbA1c					

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BPaL: bedaquiline, pretomanid and linezolid; BPaL-L:

bedaquiline, pretomanid, linezolid and levofloxacin; BSL: blood sugar level; DST: drug susceptibility testing; ECG: electrocardiography; HbA1c: glycosylated haemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TB: tuberculosis; WHO: World Health Organization.

[a] Vital signs, TB symptom screen, pain, nausea, appetite and nutrition, diarrhoea and candidiasis. Clinical assessment should focus on monitoring the response to treatment and addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.

[b] Food security, housing, mental state and substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible, as per country-specific questionnaires.

[c] Ideally, the patient should at baseline have a WHO-recommended rapid molecular test (for rifampicin and fluoroquinolone resistance). Other investigations, if available, include culture-based second-line DST, next-generation sequencing and DST for the BPaL-L component drugs.

11.2. Principles for monitoring and management of adverse events

- All persons with RR-TB need baseline assessments and monthly monitoring during treatment. This includes assessment 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 to 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 reporting 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.

11.3. Safety Monitoring:

Haematological

Anaemia in TB patients is common. It is often due to TB itself, a normocytic normochromic anemia. Treating the TB treats the anaemia. There may be other contributing factors including nutritional deficiencies, blood loss from hemoptysis or other sources and HIV co-infection. TB patients are vulnerable to drops in Hb and may decompensate. The greatest safety concern is anaemia due to myelosuppression, caused by LZD. This can be life threatening. Most cases of anaemia occur in the first 2 months of therapy.

Prior to starting treatment: Ideally a full blood count with a differential white cell count and platelets needs to be done prior to starting treatment. However, from a practical point of view, healthcare providers can use a point-of-care test. If the Hb is above 8 g/dl, then BPaL-L can be started. If the Hb is below 8 g/dl, the treatment may need to be delayed until the anaemia is corrected patients with severe anaemia and RR TB should be admitted to hospital. If possible and acceptable, a transfusion of packed cells should be considered.

There is no evidence for using Bdq, Pa with Lfx or Mfx and introducing LZD later. As the patient's bacillary load is high at this time, an inadequate regimen may result in amplification of resistance. If LZD may not be started, the PCAC or NCAC must be involved in the regimen design.

For the weeks 2 to 8: full blood count with a differential white cell count and platelets needs to be done every second week. However, from a practical point of view, a point of care Hb can be used. Again, if the Hb drops below 8g/l, the patient should be admitted for close follow up. If possible and acceptable, a transfusion of packed cells can be considered. A treatment interruption should occur if the patient is symptomatic.

For weeks 2, 4 and then weeks 8, 12, 16, 20 and 24: full blood count with a differential white cell count and platelets needs to be done every four weeks. However, from a practical point of view, a point of care Hb can be used. If the Hb drops below 8g/l, LZD can be stopped provided there has been a clinical response. This would include a reduction of symptoms, increase in weight, reduction in smear positivity, and if it has performed, culture conversion. LZD must be used for at least 2 months.

Peripheral neuropathy.

This adverse event tends to occur later in treatment, with a peak time of onset around 16 weeks [23]. The patients' experience of it is subjective.

Grade 3 peripheral neuropathy by the DAIDS tables is one that causes severe symptoms. This grade is applied if there is an inability to perform usual social and functional activities without intervention or if hospitalization is indicated. It is dependent on the individuals usual social and functional activities. This is too late. The key to detection and management of this condition is patient and healthcare provider education and counselling. As with most adverse events, pre-treatment counselling needs to include the common symptoms to watch out for: pins and needles, pain, and numbness. The BPNS is a useful and more objective guide to any worsening.

The severity of the TB, clinical response and mycobacterial response need to be considered. LZD remains a key drug in the regimen even in RR/MDR TB, withdrawal too early may compromise the efficacy of the regimen. Consult DR-TB experienced clinician/NCAC to assist if unsure if to continue or stop LZD.

Table 10.3.2.1 Management of peripheral neuropathy.

	RR/MDR TB BPaL L	Pre-XDR TB B Pa L
Weeks 1 to 8	Consider reduction of dose or change to an individualized longer regimen without LZD	Change to an individualized longer regimen without LZD
Week 8 to 16	Reduce the dose of LZD Consider permanent discontinuation if culture conversion has occurred	Reduce the dose of LZD Consider permanent discontinuation if culture conversion has occurred
Weeks 16+	Permanent discontinuation of LZD if culture conversion has occurred. Continue with Bedaquiline, Pretomanid and Levofloxacin.	Permanent discontinuation of LZD if culture conversion has occurred Continue with BPa.

Consider/manage contributing factors to peripheral neuropathy where possible (diabetes, chronic alcohol abuse). Treat pain adequately (use of pregabalin for example).

Optic neuritis

This is an uncommon adverse event but if left can cause permanent disability. Optic neuritis is usually bilateral.

It is important to establish a baseline for all patients about to start the regimen. An ophthalmological history should be taken. Prior visual problems including trauma, near-or shorted-sightedness, infections and cataracts should be recorded. Poor visual acuity prior to treatment is not a reason to withhold LZD. A full slit lamp examination is not necessary. Visual acuity should be measured using a Snellen test. It should be noted if the patients wear spectacles, and the Snellens should be done with them on. The tumbling E may also be used instead of Snellens chart. The visual acuity for each eye should be recorded as -/6 (20) R and -/6 (20) L. It is important that visual acuity be checked at every visit when the patient is on LZD. At each visit, the patient should be asked if there are any changes in visual acuity. If there is more than a two line drop in visual acuity, this requires action. If possible, the patient should be referred for (ophthalmology) assessment with a full examination of the optic nerve. If this cannot be done, then LZD should be permanently discontinued.

11.4. 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?"

ADVERSE EVENTS SYMPTOMS			GRADING/DETAILS
1. Headache	YES	NO	
2. Anaemia	YES	NO	
3. Vision changes	YES	NO	
4. Depression/sadness	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. QTcF Prolongation	YES	NO	
20. Renal Failure/ Nephrotoxicity	YES	NO	
21. Hepatotoxicity/ Jaundice	YES	NO	
22. Lactic Acidosis	YES	NO	
23. Other (specify): ___			

11.5. Active Drug Safety Monitoring activities

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 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 EDRWeb - 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 characterize 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.
4. All adverse events that lead to interruption of a drug or the entire treatment regimen must be recorded in the folder and in the EDRWeb regardless of grading.
5. Sentinel sites need to record all adverse events (Grade 1 to 5) in both the patient's folders and the EDRWeb.

For standardized 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 5, with 1 being a mild side effect, 2 being a moderate side effect, 3 being a severe side effect, 4 being considered a life-threatening and 5 leading to death, side effect. Rating severity is often easier with laboratory values since discrete cut-off values can be used. See below for an example of a rating scale.

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:

- Hospitalization or prolongation of hospitalization to manage the adverse event;
- Permanent disability;
- Congenital abnormality;
- Life-threatening experience;
- Death.

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 event's evolution over time could lead to a more precise causality assessment.

11.6. Severity rating scale for adverse events

Severity	Impact of symptoms
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

12.Treatment outcomes definitions

Treatment outcome applicable to short and long regimens are defined in the table below[9].

Treatment Outcome	Definition

Cured	• A pulmonary patient with bacteriologically confirmed DR-TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response and no evidence of failure (clinical deterioration).
	• Bacteriological response refers to bacteriological conversion with no reversion.
	  ○ Bacteriological conversion describes a situation where at least two consecutive cultures taken on different occasions at least 7 days apart, are negative.
	  ○ Bacteriological reversion describes a situation where at least two consecutive cultures taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.
	  ○ That is at least 3 negative TB cultures during the entire duration of treatment.
	TB smear microscopy and cultures must be taken at the beginning of treatment(baseline), 2 weeks later, 4 weeks later and monthly thereafter.

Treatment completed	• A patient who has TB culture converted. • Has two negative TB cultures during treatment. • Who completed treatment as recommended by the national policy • No evidence of clinical deterioration.
Treatment success	• The sum of treatment cured and completed.
Loss to Follow Up	A patient who has interrupted their treatment for: • ≥ 2 consecutive months • Any reason without medical approval

Treatment Failure	• A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy (change of 2 or more drugs).
	• Reasons for change of treatment include:
	  ○ no clinical response and/or no bacteriological response.
	  ○ adverse drug reactions.
	  ○ or evidence of additional drug resistance to medicines in the regimen.
	When someone is started on a shorter regimen and later it is picked up on the baseline sample that they had a condition that qualified them to be on the longer regimen, the patient may not be captured as a failure. They should be de-registered from the shorter regimen and registered in the new group.

Moved	• 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. • The treatment outcome is reported by the facility where the patient is newly registered
Transferred Out	• Referred from one facility to another reporting and recording facility in another district, province or country to continue treatment. • The treatment outcome is reported by the facility where the patient is newly registered
Died	A 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

13. Post-treatment follow up

All patients who successfully complete treatment need to be evaluated twice, 6 and 12 months post-treatment. During these visits a physical examination must be conducted; and a sputum must be collected for TB microscopy and TB culture. Laboratory results must be documented in the patient folder and the electronic treatment register.

Individuals may develop various conditions during treatment for RR-TB that require ongoing treatment and follow up. These conditions may be due to 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[11]. Although most patients will be managed through PHC following completion of RR-TB treatment, some patients with post-TB lung disease may benefit from functional respiratory assessment (e.g. lung function tests, CT imaging) and long term follow up by pulmonology services in tertiary centres.

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 (core 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.

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Annexure 1:

Weight-based dosing of medicines used in multidrug-resistant TB regimens, adults and children[a]

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Levofloxacin (Lfx)	**100 mg dt (10 mg/mL)**	5 mL (0.5 dt)	1	1.5	2	3	–	–					
	250 mg tab (25 mg/mL)	2 mL[b]	5 mL (0.5 tab)[b]		1	1.5	2	3		4			
	500 mg tab	–					1	1.5		2			
	750 mg tab	–						1		1.5			
Moxifloxacin (Mfx)	**100 mg dt (10 mg/mL)**	4 mL	8 mL	1.5	2	3	4	4		–			
	400 mg tab (40 mg/mL) Standard dose	1 mL[b]	2 mL[b]	3 mL[b]	5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	1					
	400 mg tab high dose[c]	–		–	–	–		1 or 1.5	1.5	1.5 or 2	2		

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Bedaquiline (Bdq)	**20 mg dt**	0 to <3 months: 1.5 od (2 weeks); then 0.5 od M/W/F (22 weeks) ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks		0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥6 months: 4 od for 2 weeks; then 2 od M/W/F	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F	10 od for 2 weeks; then 5 od M/W/F		20 od for 2 weeks; then 10 od M/W/F		–			
	100 mg tab (10 mg/mL)[d]	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F[b] ≥ 3 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b]		0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F[b] 3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b] ≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F[b]	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b] ≥ 6 months: 12 mL od for 2 weeks; then 6 mL od M/W/F[b]	2 od for 2 weeks; then 1 od M/W/F		4 od for 2 weeks; then 2 od M/W/F					
	100 mg tab (10 mg/mL)	–								200 mg daily (od) for 8 weeks; then 100 mg dose daily (od)			Dosing scheme is for BPaL-L/BPaL regimen (>14 years).

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Linezolid (LZD)	**20 mg /mL susp**	2 mL	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	–			
	150 mg dt (15 mg/mL)	2.5 mL	5 mL (0.5 dt)	1		2[e]		2	3	–			
	600 mg tab (60 mg/mL)	–	1.25 mL[b]	2.5 mL[b]		5 mL (0.5 tab)[b, e]		5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	1		

Group B medicines	Formulation	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Clofazimine (Cfz)	**50 mg cap or tab**[f]	1 M/F	1 M/W/F		1		2	2					For children <24 kg, the use of the 50 mg tab is preferred.
	100 mg cap or tab[f]	–	1 M/F		1 M/W/F		1	1					
Cycloserine or **terizidone** (Cs/Tz)	**125 mg mini cap (Cs) (12.5 mg/mL)**	2 mL[b, g]	4 mL[b]	1	2	3	4	4		–			
	250 mg cap (25 mg/mL)	1 mL[b, g]	2 mL[b]	5 mL[b]	1	2	2	2		3			

Group C medicines	Formulation	3–<5 kg[a]	5–<7 kg[a]	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Ethambutol (E or EMB)	100 mg dt (10 mg/mL)	5 mL (0.5 dt)	1	2	3	4	–	–					–
	400 mg tab (40 mg/mL)	1.5 mL[b]	3 mL[b]	4 mL[b]	6 mL	1	1.5	2		3		4	
Delamanid (Dlm)	25 mg dt	1 od	<3 months: 1 od ≥3 months: 1 bd		1 bd	2 morning 1 evening		2 bd		–			
	50 mg tab[h] (5 mg/mL)	5 mL (0.5 tab) od[b]	<3 months: 5 mL (0.5 tab) od[b] ≥3 months: 5 mL (0.5 tab) bd[b]		5 mL (0.5 tab) bd[b]	10 mL (1 tab) morning 5 mL (0.5 tab) evening		1 bd		2 bd			

Group C medicines	Formulation	3–<5 kg[a]	5–<7 kg[a]	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Pyrazinamide (Z or PZA)	150 mg dt (15 mg/mL)	5 mL (0.5 dt)	1	2	3	5	–	–					–
	400 mg tab (40 mg/mL)	2.5 mL[b]	5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	2	2.5	3	4			5	
	500 mg tab (50 mg/mL)	2 mL[b]	5 mL (5 mL)[b]		1	1.5	2	2.5	3			4	
Imipenem–cilastatin (Ipm/**Cln**)	500 mg + 500 mg powder for injection, vial (10 mL)	Not used in patients aged <15 years (use meropenem)						2 vials (1 g + 1 g) bd					Only to be used with clavulanic acid.
Meropenem (Mpm)	1 g powder for injection, vial (20 mL)	1 mL tid	2 mL tid	4 mL tid	6 mL tid	9 mL tid	11 mL tid	1 vial tid or 2 vials bd					Only to be used with clavulanic acid.
Amikacin (Am)	500 mg/2 mL solution for injection, ampoule	–[i]								3–4 mL	4 mL	4 mL	Recommended only in adults aged >18 years.
Streptomycin (Sm)	1 g powder for injection, vial	–[i]								Calculate according to the dilution used			Recommended only in adults aged >18 years.
Ethionamide or Prothionamide (Eto/Pto)	125 mg dt (Eto) (12.5 mg/mL)	3 mL[b]	7 mL[b]	1	2	3	4	4		–			Although once daily dose advised, two divided doses can be also given to improve tolerance.
	250 mg tab (25 mg/mL)	–	3 mL[b]	5 mL (0.5 tab)[b]	1	2		2		3		4	
P-aminosalicylic acid (PAS)	PAS sodium salt (equivalent to 4 g PAS acid) sachet	0.3 g bd	0.75 g bd	1 g bd	2 g bd	3 g bd	3.5 g bd	4 g bd				4–6 g bd	Usually given in divided doses.

Other medicines	Formulation	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Isoniazid[j] (INH or H) **(high dose)**	50 mg/5 mL soln	5 mL	9 mL	15 mL	20 mL	–	–	–					Pyridoxine is always given with high-dose isoniazid in children (1–2 mg/kg) and in people at risk of side- effects (e.g. those with HIV or malnutrition). In infants, pyridoxine may be given as part of a multi-vitamin syrup.
	100 mg dt or tab (10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	4	4	4.5	–			
	300 mg tab	–				1	1.5	1.5		2			
Clavulanic acid[j] **(as amoxicillin/ clavulanate)** (Amx/clav)	62.5 mg clavulanic acid as amoxicillin/ clavulanate (250/62.5 mg), powder for oral solution, 5 mL	1.5 mL tid	2 mL tid	3 mL tid	5 mL tid	8 mL tid	10 mL tid	10 mL bd or tid		–			Only available in combination with amoxicillin. To be given with each dose of imipenem/cilastatin (bd) or meropenem (tid).
	125 mg clavulanic acid as amoxicillin/ clavulanate (500/125 mg) tab	–					1 tid	1 bd or tid					
Pretomanid (Pa)	200 mg tab	–						1					Currently only used as part of the BPaL-L/ BPaL regimens.

bd: two times a day; BPaL: bedaquiline, pretomanid and linezolid; BPaL-L: bedaquiline, pretomanid, linezolid and levofloxacin; cap: capsule; DR-TB: drug-resistant TB; dt: dispersible tablet; g: gram; GDG: Guideline Development Group; HIV: human immunodeficiency virus; kg: kilogram; MDR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; mg: milligram; mL: millilitre; M/F: Monday and Friday, M/W/F: Monday, Wednesday and Friday; od: once daily; soln: solution; susp: suspension; tab: tablet; TB: tuberculosis; tid: three times a day; WHO: World Health Organization.

[a] Dosing guidance is based on currently available data and may be revised once additional data are available. Dosages were established by the GDGs for the WHO guidelines on DR-TB treatment (2018 and 2020 updates), the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and the expert consultation on dosing convened by WHO in October 2021, following the GDG meeting on child and adolescent TB in June 2021.

Doses for children and young adolescents weighing <46 kg were revised according to Annex 6 of the 2022 WHO operational handbook on tuberculosis – Module 5: Management of tuberculosis in children and adolescents (153), which was informed by an expert consultation on dosing convened by WHO in October 2021 (154). They are based on the most recent reviews and best practices in the treatment of (paediatric) MDR/RR-TB. For certain medicines the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling and maturation (155). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. The guidance for the 3–<5 kg weight band and for bedaquiline and delamanid is based on currently available data and may be revised when new data become available.

[b] Dissolving of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide. This avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred).

[c] The higher dose may be used except when there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has low-level drug resistance.

[d] Bedaquiline adult tablets (100 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole. Vigorous stirring/shaking is needed prior to administering the 100 mg tablet crushed and suspended in water.

[e] When using the 600 mg tab and the 150 mg dt to dose children weighing 16 to <24 kg, the dose in mg/kg will exceed 10–12 mg/kg and clinicians may opt to administer 1.5 dt or 4 mL of the 600 mg tab dispersed in 10 mL water.

[f] Clofazimine tablets are technically not dispersible but they do slowly (this takes approximately 5 minutes) dissolve in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred prior to administration. The 100 mg soft gel capsule is difficult to swallow for young children and therefore countries are strongly encouraged to make the 50 mg tablet formulation available.

[g] In children weighing 3 to <7 kg doses are lower than previously recommended. This is because of relatively high exposures associated with risk of neuropsychiatric adverse events, which is especially concerning when co-administering cycloserine with delamanid.

[h] Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.

[i] Amikacin and streptomycin may be used in adults aged 18 years or more, in situations where an effective regimen cannot otherwise be designed using oral agents, when susceptibility is demonstrated and when adequate measures are in place to monitor for adverse events. Given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school, the use of injectable agents in children should be exceptional and limited to salvage therapy, and the treatment needs to be provided under strict monitoring to ensure early detection of ototoxicity. If used, the weight-based daily dose for amikacin is 15–20 mg/kg and for streptomycin it is 20–40 mg/kg for children aged 2 years and older. To determine the dosing for infants and children aged below 2 years, a paediatric DR-TB expert should be consulted and a lower mg/kg dose used to compensate for immature clearance. Co-administration with lidocaine is advised to reduce pain at the injection site (156).

[j] These medicines are only recommended as a companion agent (amoxicillin/clavulanic acid) or are not included in Groups A, B and C, because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (isoniazid).

Specific comments on dosing children with medicines used in second-line MDR-TB regimens:

- For dosing of premature and low birth weight infants weighing <3 kg, advice should be sought from a paediatric DR-TB expert.
- For dosing of infants weighing 3 to <5 kg, a paediatric DR-TB expert should be consulted whenever possible.
- The use of child-friendly, dispersible tablets in infants and young children is preferred over manipulating adult tablets or administering or manipulating capsules. Where applicable, the dosing provided is based on dissolving the dispersible formulation in 10 mL of water and administering the number of mL (aliquots). The number of mL in the table reflects the dose to provide. The dissolved solution should be used immediately and the remainder of the 10 mL should be discarded.
- For some weight bands, dosing is indicated with both child-friendly, dispersible formulations and adult formulations. If adult formulations are used, the table provides the dose using aliquots in mL and tablet fractions where applicable (if the fraction is 0.5 or more). Aliquots refer to the volume to administer after crushing and dissolving the tablet in 10 mL of water.