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REPUBLIC OF SOUTH AFRICA

INTERIM CLINICAL GUIDANCE FOR THE IMPLEMENTATION OF INJECTABLE-FREE REGIMENS FOR RIFAMPICIN-RESISTANT TUBERCULOSIS IN ADULTS, ADOLESCENTS AND CHILDREN

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ABBREVIATIONS & ACRONYMS

ART	Anti-Retroviral Treatment
BDQ	Bedaquiline
CNS	Central Nervous System
CFZ	Clofazimine
DLM	Delamanid
DR-TB	Drug Resistant Tuberculosis
DST	Drug Susceptibility Test
E	Ethambutol
ECG	Electro-cardiogram
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/ $INH_{high\ dose}$	Isoniazid/ Isoniazid high dose
INJ	Injectable agent
IRIS	Immune Reconstitution Inflammatory Syndrome
KM	Kanamycin
LFX	Levofloxacin
LPA	Line Probe Assay
LZD	Linezolid
MO	Medical Officer
MFX	Moxifloxacin
MDR	Multi-Drug Resistant
NCAC	National Clinical Advisory Committee
NDoH	National Department of Health
PCAC	Provincial Clinical Advisory Committee
RIF	Rifampicin
RR	Rifampicin Resistant
SAHPRA	South African Health Products Regulatory Authority
SCR	Shorter course regimen
SLD's	Second Line Tuberculosis drugs
TRD	Terizidone
XDR	Extensively Drug Resistant
WHO	World Health Organization
Z	Pyrazinamide

1. INTRODUCTION

This document provides interim clinical guidance on implementation of the modified short and long treatment regimens for people with Rifampicin Resistant Tuberculosis (RR-TB) in South Africa. National guidelines will be revised in 2019 following publication of the updated WHO policy guidelines on MDR-TB treatment (expected later in 2018).

1.1. DEFINITIONS

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

Different categories:

1.1.1. Mono-resistant TB

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

1.1.2. Poly-drug resistant TB

Resistance to more than one anti-TB drug, other than both Isoniazid and rifampicin

1.1.3. Multidrug-resistant TB (MDR-TB)

Resistance to Isoniazid and rifampicin with or without resistance to other anti-TB drugs

1.1.4. 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.

1.1.5. Extensively drug-resistant TB (XDR-TB)

MDR-TB with resistance to any fluoroquinolone as well as one or more of the three second-line injectable drugs (Capreomycin, kanamycin or amikacin).

1.1.6. Pre XDR-TB

MDR-TB with additional resistance to either a second-line injectable agent or a fluoroquinolone.

1.2. BACKGROUND

Rifampicin-resistant tuberculosis (RR-TB) has been declared a public health crisis by the World Health Organization (WHO). In contrast to the six-month fixed-dose combination treatment regimen offered to people with drug sensitive TB, people diagnosed with RR-TB or multi-drug resistant TB (MDR-TB) are treated with variable combinations of first and second-line anti-tuberculosis drugs, usually for 18 months or more. Numerous studies to investigate shorter, more effective and less toxic treatment regimens are ongoing in an attempt to improve outcomes in children and adults with RR/MDR-TB in South Africa.

The WHO's 2016 DR-TB treatment guidelines include recommendations on the use of a shorter regimen (9-11 months) for patients with RR/MDR-TB under specific conditions[1]. These recommendations were based on studies carried out in multiple countries, including Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Senegal and Swaziland, that showed a high rate of

successful treatment outcomes in selected patients receiving a standardized shorter regimen for <12 months.

South Africa has the 5th highest incidence of RR-TB in the world, with 19,000 cases detected in 2016[2]. Each year, about 65% of diagnosed cases initiate second-line TB treatment, but only 50% of these have successful outcomes. The National Department of Health (NDoH) has been at the forefront of programmatic introduction of new and repurposed drugs for RR-TB since the Bedaquiline Clinical Access Programme (BCAP) began in 2013[3]. As at January 2018, roughly 15,000 patients with RR-TB have received Bedaquiline (BDQ) under programmatic conditions. NDOH provided a policy framework for introduction of new and repurposed drugs which made provision for substitution of the injectable agent with BDQ[4]. This substitution was done for long and short treatment regimens. A retrospective analysis of patients treated in the Western Cape has shown improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in MD-TB patients[5]. Another retrospective analysis of the impact of access to BDQ on RR/MDR-TB and XDR-TB outcomes within South Africa demonstrated its use was associated with an almost 4 times reduction in mortality[6]. Thus, in June 2018 the NDoH took the unprecedented decision to make BDQ routinely available within injectable-free regimens for all patients presenting with RR-TB.

On August 15, 2018 the WHO released a Rapid Communication: *Key changes to treatment of multidrug and rifampicin-resistant tuberculosis* (*MDR/RR-TB)*[7]. This document issues new guidance on treatment based on a meta-analysis of over 12 000 individual patient RR/MDR-TB records. In response to this new recommendation from WHO, this NDoH policy document provides interim guidance on implementation of new injectable-free regimens in South Africa. These will include: a modified short regimen for RR/MDR-TB, a new long regimen for RR/MDR-TB, and an individualized long regimen for RR/MDR-TB with FLQ resistance as well as central nervous system RR/MDR-TB.

Consolidated, updated and more detailed WHO policy guidelines on RR-TB treatment will be provided by end of 2018 and updated national RR/MDR-TB guidance will follow in 2019.

1.3. CURRENT TREATMENT REGIMENS FOR RR/MDR-TB IN SOUTH AFRICA

There are several treatment regimens currently being offered for RR-TB within the National TB Programme across South Africa:

- Most patients with RR/MDR-TB are still receiving the old long regimen made up of **KM – MFX – ETO – TRD – Z** (18-20 months duration).
- Some patients with RR/MDR-TB have started the short (9-11 months) MDR-TB regimen with an injectable agent: (**4-6) KM – MFX – ETO –INH_{hd} – CFZ – Z –E / (5) MFX – CFZ – Z – E**
- Some patients have received BDQ to substitute the injectable agent in cases of toxicity or intolerance, within a short MDR-TB regimen or an old long regimen.
- Patients with pre XDR-TB and XDR-TB currently receive long, individualized regimens containing new and repurposed drugs.

1.4. NEW SHORT AND LONG TREATMENT REGIMENS: OVERVIEW AND DURATION

As of July 2018, injectable-free regimens have been phased in routinely in South Africa. A document titled "Bedaquiline Expansion Plan" was circulated to all provinces[8]. This document made provision for a phased approach between June and July 2018. A short injectable-free treatment regimen may be used for RR/MDR-TB provided specific criteria are met. Adults and children who do not meet inclusion criteria for the short regimen will be offered a long injectable-free treatment regimen. Some patients may initiate treatment with a short regimen but then switch to a long regimen once further diagnostic or other relevant information becomes available. Eligibility criteria for the short and the long regimens are listed under relevant chapters but **Annexure 1** gives an overview of eligibility criteria and various treatment options available for patients with RR-TB.

Recommendations on duration of the short and long treatment regimens are based on WHO guidance on the short course regimen[1] and new data presented in the Lancet on optimal duration for long treatment regimens[9].

1.4.1. Duration of the short injectable-free regimen for RR/MDR-TB

The short injectable-free treatment regimen is given for a total duration of 9-11 months.

The regimen starts with seven drugs: Linezolid (LZD), Isoniazid high dose ($INH_{high\ dose}$), Bedaquiline (BDQ), Levofloxacin (LFX), Clofazimine (CFZ), Pyrazinamide (Z) and Ethambutol (E). Ethionamide is no longer included in the short regimen. Linezolid will only be given for the first 2 months of the intensive phase. Bedaquiline replaces the injectable agent and will be given for 6 months, regardless of the duration of the intensive phase. Levofloxacin replaces Moxifloxacin.

- **Intensive phase is 4 months and may be extended to 6 months** depending on the patient's response to treatment (i.e. smear conversion and clinical response at month 4 of treatment).
- **Continuation phase is 5 months** therefore, the total duration is 9 to 11 months; it is likely that most patients will receive 9 months of treatment in total.

1.4.2. Duration of the long injectable-free regimen for RR/MDR-TB

The long injectable-free treatment regimen is given for a total duration of 18-20 months.

The long regimen will include the core drugs: Linezolid (LZD), Bedaquiline (BDQ), Levofloxacin (LFX), Clofazimine (CFZ) and Terizidone (TRD), based on the new WHO grouping of anti-tuberculosis agents *(see Annexure 6)* [7]. Linezolid will be given throughout the intensive phase. Moxifloxacin may be used in place of Levofloxacin if considered necessary.

- **Intensive phase is 6 months and may be extended to 8 months** depending on the patient's response to treatment (i.e. culture conversion and clinical response at month 4 of treatment).
- **Continuation phase is 12 months** therefore, the total duration is 18 to 20 months; it is likely that most patients will receive 18 months of treatment in total.

1.4.3. Duration of treatment for CNS disease and RR/MDR-TB with fluoroquinolone resistance

Long treatment regimens for FLQ-resistant RR/MDR-TB or central nervous system TB are usually given for a total duration of 18-20 months.

See Sections 5 and 6 for further details.

2. LABORATORY DIAGNOSIS OF RR-TB AND INTERPRETATION OF TEST RESULTS

Choice of treatment regimen and duration of treatment for RR/MDR-TB are guided by results of laboratory-based genotypic & phenotypic drug susceptibility testing (DST) on direct samples and cultured isolates – *see Figure1 and 2*.

First and second-line genotypic testing is done routinely using line probe assays (**1st& 2nd line LPA**) – these tests are carried out on direct samples usually following detection of RR-TB on GXP. These tests are more likely to yield conclusive results on specimens with a high bacillary load (i.e. smear positive samples).

If initial results of 1st and 2nd line LPA done on direct samples are inconclusive or inadequate (e.g. due to a low bacillary load), then these tests will be repeated on the cultured isolate (once positive culture becomes available).

If results of 1st line LPA show INH susceptibility (in the context of Rifampicin resistance), then **phenotypic DST for INH** will be routinely performed on cultured isolate (if available) – this is to confirm susceptibility to INH because the sensitivity of targeted genotypic testing 86% (74–93) meaning that approximately 14% are actually phenotypically resistant[10]. Note that phenotypic INH results will not give information about the INH mutation, only whether or not the isolate is resistant or susceptible to INH.

Phenotypic DST for fluoroquinolones (MFX 0.25 microgram/ml or LFX) will be carried out routinely (reflex test) on all cultured isolates where 2nd line LPA indicates FLQ susceptibility. This is to detect the small proportion of false FLQ susceptible results reported by 2nd line LPA. If the phenotypic DST indicates FLQ resistance after the patient has commenced a short injectable-free regimen, the treatment should be switched to a long regimen for pre-XDR/XDR-TB.

Figure 1.Genotypic and Phenotypic Drug Susceptibility Tests – situations in which they are carried out, and expected results

Type of test		When is this done	Result
Genotypic	1st line LPA	GXP pos/Rif resistant	Susceptibility to Rif & INH, and INH mutation(s)
	2nd line LPA	GXP pos/Rif resistant	Susceptibility to FLQ & INJ
Phenotypic INH		In-lab reflex test when RIF resistant, but susceptible to INH on 1st line LPA	To confirm susceptibility to INH – no mutation
Phenotypic FLQ		In-lab reflex test for all 2ndline LPA results that indicate FLQ **susceptibility**	Susceptibility to LFX/MFX at 0.25 ug/ml
2nd line Phenotypic DST		Reflex test when **resistance** to FLQ and/or INJ is detected on 2nd line LPA	Susceptibility to LZD/ LFX / MFX 0.25 & 1.0 ug/ml *(BDQ and CFZ in 2019)*
		Requested by clinician if 2nd line LPA is susceptible but clinician suspects resistance to 2nd line drugs (e.g. due to previous unsuccessful RR-TB treatment, or XDR contact)	
Individualized Extended Phenotypic DST (from NICD)		Requested by clinician when RR-TB treatment fails, and patient has been previously exposed to 2nd line TB drugs	Susceptibility to multiple 2nd line TB drugs; results will be used to construct a potential salvage regimen

Second-line phenotypic DST detects resistance to LZD, LFX and MFX 0.25 and 1.0 microgram/ml. BDQ and CFZ will be added in 2019. This is a reflex test and will be carried out on cultured isolates once resistance to FLQ and/or INJ (i.e. pre-XDR / XDR-TB) has been detected on 2nd line LPA. It is usually not necessary to send additional specimens (unless requested specifically by lab) and the results should be available after a minimum of 14 days. These second-line phenotypic DST results provide the clinician with a greater repertoire of drug options that MAY be effective in treating pre-XDR and XDR-TB.

Patients with pre-XDR or XDR-TB are not eligible for the short regimen *and should switch to one of the long regimens. Those with FLQ resistant RR/MDR-TB strains (i.e. XDR and pre-XDR FLQ) should receive a long XDR regimen. Those with pre-XDR INJ strains (in the absence of FLQ resistance) may receive the standard long regimen for RR/MDR-TB.*

In cases of RR/MDR-TB where there is a strong possibility of additional resistance to 2nd line agents, e.g. previous unsuccessfully treated RR-TB, or history of close contact with patients with confirmed pre-XDR or XDR-TB, clinicians may **request second-line phenotypic DST** in order to check further susceptibilities to LZD and MFX at 1.0 microgram/ml. ***Contact the lab to request the test on the latest positive cultured specimen and follow up results***.

Second-line phenotypic DST must also be requested for patients **NOT RESPONDING CLINICALLY** to treatment after 2 months on the short regimen for RR/MDR-TB or where no reflex results are available at 1 month. ***Contact the lab to request the test on the latest positive cultured specimen and follow up results.*** Review and address adherence challenges and optimize management of co-morbidities.

Repeat 2nd line LPA and **second-line phenotypic DST** must be requested for patients with positive AFB smear results at month 4 of treatment. ***Contact the lab to request the test on the latest positive cultured specimen and follow up results***.

Figure 2: Interpretation of 1st & 2nd line LPA results following commencement of the short regimen based on a diagnosis of Rifampicin-Resistant TB

1st line LPA Result	**Action**
Rif susceptible	continue short RR/MDR-TB regimen, discuss discordance with lab
Rif resistant	continue short RR/MDR-TB regimen, check INH susceptibility result, INH mutation and 2nd line LPA results – amend if required
***inhA* mutation only**	continue short RR/MDR-TB regimen with INH_{hd}
***katG* mutation only**	continue short RR/MDR-TB regimen with INH_{hd}
Both *inhA* & *katG* mutations	switch to long regimen *(patient is no longer eligible for the short regimen)* – follow up 2nd line LPA result as this indicates an increased likelihood of pre-XDR/XDR
Susceptible to INH	continue short RR/MDR-TB regimen with INH_{hd} and wait for INH phenotypic DST result: ○ if confirmed susceptible to INH, reduce INH to normal dose ○ if resistant to INH, continue with INH_{hd}
2nd line LPA Result	**Action**
Susceptible to FQN and INJ	continue with short RR/MDR-TB regimen and give LZD for 2 months. Follow up phenotypic DST for LFX/MFX 0.25 ug/ml
Resistance to INJ susceptible to FLQ	switch to long regimen for RR/MDR-TB *(see Section 4; patient is no longer eligible for the short regimen)*; follow up reflex phenotypic FLQ DST (to check for LFX and MFX 0.25 ug/ml
Resistant to FLQ (with or without resistance to INJ)	switch to long regimen for pre-XDR / XDR-TB *(see section 5)*; follow up reflex second-line phenotypic DST (to check LZD / LFX/MFX 0.25ug/ml and MFX 1.0ug/ml). *(Inclusion of DST for BDQ and CFZ expected in 2019)*

3. THE SHORT (9-11 MONTH) REGIMEN FOR RR/MDR-TB

3.1 ELIGIBILITY CRITERIA FOR THE SHORT REGIMEN

Patients who do not meet the inclusion criteria for the short (9-11 month) regimen should receive a long (18-20 month) treatment regimen for either RR/MDR-TB or pre-XDR / XDR-TB.

3.1.1 Inclusion criteria for the short regimen

Individuals with RR/MDR-TB, *without prior exposure (for more than 1 month) to second-line anti-TB treatment; this includes:*

- ***Rifampicin-resistant (RR) TB:*** *resistance to at least Rifampicin, based on initial GXP result, while awaiting further genotypic 1st and 2nd line LPA results*
- ***Rifampicin mono-resistant TB:*** *resistance to Rifampicin and susceptibility to Isoniazid – reflex phenotypic INH DST will be carried out to confirm INH susceptibility*
- ***Multidrug resistant (MDR) TB:*** *resistance to both Rifampicin and Isoniazid (with either inhA or katG mutation, but not both) and susceptible to FLQ and INJ.*

Uncomplicated RR/MDR Extra-pulmonary TB (EPTB) – *i.e. lymphadenopathy, pleural effusion.*

People living with HIV: *already on ART or due to start (or restart) ART.*

Pregnant women: *with PTB +/- uncomplicated EPTB may receive the short regimen once the case has been reviewed by the National Clinical Advisory Committee (NCAC) – this is for surveillance purposes due to lack of data on use of these regimens in pregnant women.*

Children <12yrs: *younger children with confirmed or presumed RR/MDR-TB are also eligible for a short treatment regimen and should be treated without an injectable agent. Bedaquiline may have to be* ***replaced*** *by an alternative drug until further dosing data becomes available.*

3.1.2 Exclusion criteria for the short regimen

Any previous exposure to second–line treatment for RR-TB *for more than 1 month, regardless of a successful treatment outcome.*

All pre-XDR-TB and XDR-TB

MDR-TB with additional resistance *to Bedaquiline, Clofazimine or Linezolid*

MDR-TB with both katG and inhA mutations

RR/MDR-TB in cases where additional second-line drug resistance is suspected*, despite confirmed susceptibility on 2nd line LPA or phenotypic DST; this includes:*

- *Close contacts of patients with confirmed pre XDR-TB and XDR-TB*
- *Close contacts of patients with MDR-TB with both katG and inhA mutations*
- *Close contacts of patients with second-line TB treatment failure*

Complicated and/or severe forms of extra-pulmonary RR/MDR-TB disease – *e.g. meningitis, osteo-articular, pericardial effusion, abdominal TB – these patients must be treated with a long regimen.*

RR/MDR-TB *with extensive disease e.g. extensive bilateral pulmonary cavitations.*

Any other situation in which the clinician is uncertain of a patient's eligibility *for the short treatment regimen.*

3.2 COMPOSITION OF THE SHORT REGIMEN

The short (9-11 month), injectable-free treatment regimen may be used to treat RR/MDR TB in adults and children of all ages who meet the inclusion criteria as stated above. The regimen initially consists of seven drugs: **LZD – BDQ – LFX – CFZ – $INH_{high\text{-}dose}$ – Z – E,** and specific drugs will be dropped at key time points, depending on the 1st and 2nd line LPA results as they are received.

3.2.1 Drugs included in the short regimen

Linezolid (LZD):

Routinely included within the regimen up front to protect BDQ in the early stages of treatment, particularly in cases of RR-TB where resistance to a FLQ has yet to be detected. South Africa has a high burden of pre-XDR and XDR-TB and inadequate regimens at the start of treatment can drive the acquisition of further drug resistance. LZD will be given for the first 2 months only and will contribute to a robust intensive phase with four core drugs (LZD, BDQ, LFX, CFZ) that are highly likely to be effective against RR/MDR-TB at the beginning of treatment. Most cases of peripheral neuropathy associated with LZD occur after 2 months of exposure; however, myelosuppression tends to occur sooner so there must be close monitoring of FBC including neutrophil count. LZD must be withdrawn in the event of severe haematological adverse effects (Hb< 8 g/dl, neutrophils < 0.75 $x10^9$/L, platelets < 50 $x10^9$/L). Concerns regarding toxicity must be balanced with the efficacy of LZD, and the shorter initial duration aims to minimize harm while maximizing benefits for patients with RR/MDR-TB. Contact the National Advisory Committee for further advice.

High-dose Isoniazid ($INH_{high\text{-}dose}$):
Included in the short regimen for the duration of the intensive phase, regardless of which INH mutation (*inhA* or *katG*) is detected. If smears remain positive (or become positive) by month 4 of treatment with the short regimen, second-line phenotypic DST should be requested on the latest positive culture, and $INH_{high\text{-}dose}$ continued for another 2 months (intensive phase extended to 6 months). Dosage not to exceed 10 mg/kg daily. We shall use the dosage of 10 mg/kg for all patients until we get new information on pediatric usage of isoniazid.

Bedaquiline (BDQ):
Replaces the injectable agent in the short regimen and is given for a minimum duration of 6 months (regardless of duration of intensive phase), unless withdrawn early due to related toxicity or other contraindications. BDQ is superior to the injectable in terms of safety and efficacy in treatment of RR/MDR-TB[7,9]therefore a modified short regimen including BDQ is considered much stronger than the previous injectable-containing short regimen.

Levofloxacin (LFX):
Replaces Moxifloxacin (MFX) in the short regimen to reduce the risk of QT-interval prolongation when used with both BDQ and CFZ. LFX is given for the full duration of the short regimen, i.e. 9-11 months. *Note that if LFX is temporarily unavailable for inclusion in the short, injectable-free regimen then normal dose MFX (400mg) may be used in the interim, with close ECG monitoring, until LFX again becomes available*. Once the course of BDQ is completed, LFX may be switched to MFX for the remainder of treatment, if necessary (e.g. if there is limited availability of LFX in the facility). This switch may be immediate after BDQ is stopped.

Clofazimine:
This drug is a key component of the short regimen and is given for the full duration of the short regimen, i.e. 9-11 months.

Pyrazinamide and **Ethambutol:**
These drugs are included for the full duration of treatment, i.e. 9-11 months. Although it is estimated that 59.1% and 44.1% of MDR-TB isolates in South Africa are also resistant to either Pyrazinamide or Ethambutol respectively; the proportion that are resistant to is lower among rifampicin mono-resistant TB, 13.9% and 11.2% respectively[11], therefore there is still some efficacy benefit in offering both drugs routinely. While Pyrazinamide and Ethambutol are generally well tolerated, these drugs do not have to be replaced if they are withdrawn due to toxicity or intolerance.

3.2.2 Drugs NOT included in the short regimen

Ethionamide (ETO):
ETO is no longer included in the short regimen for RR/MDR-TB. At least 44.7%% of MDR-TB isolates detected in the SA National TB Drug Resistance Survey[11]were found to be ethionamide resistant while the prevalence of the *inhA* mutation was 35% known to confer cross-resistance to ETO. In some provinces, the prevalence of this mutation was >50% and therefore ETO is likely to cause more harm than benefit when offered routinely for treatment of RR/MDR-TB, particularly in view of the limited efficacy of this drug as reported in the recent IPD meta-analysis in the Lancet[9]. In addition, ETO is one of the main contributors to poor adherence to treatment due to the common adverse effect of severe nausea and vomiting, which may also lead to sub-optimal absorption of other TB drugs.

Kanamycin / Amikacin / Capreomycin:
Capreomycin and Kanamycin are no longer recommended in the treatment of RR/MDR-TB due to recent analyses indicating that use of these injectable agents was associated with poor TB treatment outcomes[9]. Both of these agents are also associated with severe adverse events, including reports of

ototoxicity in up to 60% of patients receiving the drug[12]. Amikacin shares a similar toxicity profile; however, it appears to be associated with slightly better treatment outcomes and may be considered the injectable agent of choice in exceptional cases where treatment options are severely limited.

3.3 SHORT REGIMEN FOR ADULTS, ADOLESCENTS, CHILDREN ≥ 12 YEARS (≥30KG)

4-6 months(Intensive Phase):

LZD(2 months only) **–BDQ**(total 6 months)**– LFX – CFZ –INH**$_{\text{high-dose}}$ **–Z – E**

5 months Continuation Phase):

LFX – CFZ – Z – E

3.4 SHORT REGIMEN FOR CHILDREN < 12 YEARS (<30KG)

It has been agreed that children <12yrs with confirmed or presumed RR/MDR-TB should also have access to a short, injectable-free regimen, as discussed in the document entitled: *"Statement on Injectable-Free Regimens for Children under the Age of 12 Years with Rifampicin-Resistant Tuberculosis"*[13]. This position statement was released in July 2018 by the Sentinel Project on Paediatric DR-TB, in collaboration with the Treatment Action Group (TAG) and paediatric TB experts at the Desmond Tutu TB Centre at Stellenbosch University.

Recommended options for replacement of the injectable agent within the short regimen for children <12 years will depend on availability of specific drugs (e.g. DLM) and experience of the treating clinician. If clinicians are uncertain about eligibility or the composition of the short regimen for a child <12 years with RR/MDR-TB, the case can be presented to the NCAC (or provincial expert committees) for advice, or a paediatric DR-TB expert should be consulted for guidance.

Note: children of any age (<12 years) with presumed or confirmed RR-TB meningitis or osteo-articular or disseminated/miliary RR-TB disease require a long regimen, and should be treated under the guidance of a paediatric DR-TB expert.

3.4.1 Children aged 6 – 12 years (or weight 15 – 30kg)

4-6 months (Intensive Phase):

LZD (2 months only) **–DLM*** (total 6 months) **– LFX – CFZ –INH**$_{\text{high-dose}}$ **– Z – E**

5 months (Continuation Phase):

LFX – CFZ – Z – E

***Delamanid** is the preferred replacement for the injectable agent in the short regimen in this age group. DLM is not yet registered by SAHPRA; however, it is available through the Delamanid Clinical Access Programme (DCAP) for children ≥6 years (as per WHO recommendations[14] at DCAP-approved sites. This still requires application to the NCAC for use in each individual case – if approved, DLM is given for a full 6 months. Recommended dosing as follows: > 35kg: 100 mg twice daily; 20-35 kg: 50 mg twice daily; 10-20 kg: 25 mg twice daily.

***PAS** may be used to substitute the injectable agent if DLM is not accessible.

***Amikacin / Bedaquiline** – only use if recommended by an expert or approved by NCAC (or provincial expert committees).

*Note that LZD may be omitted from the short regimen, at the clinician's discretion, in children with non-severe RR/MDR-TB disease (i.e. no bacteriological confirmation, unilateral pulmonary TB disease, non-cavitatory TB disease).**Dose of Linezolid in children 5-15 kg is 15mg/kg once daily and >15kg the dose is 10mg/kg once daily***

3.4.2 Children aged <6 years (or weight <15 kg)

4-6 months (Intensive Phase):

LZD (2 months only)**– PAS* –LFX – CFZ –$INH_{high\text{-}dose}$– Z – E**

5 months (Continuation Phase):

LFX – CFZ – Z – E

*Other potential treatment options in this age group include:

- **Linezolid** – *Note that LZD may be omitted from the short regimen, at the clinician's discretion, in children with non-severe RR/MDR-TB disease (i.e. no bacteriological confirmation, unilateral pulmonary TB disease, non-cavitatory TB disease). If LZD is used, FBC should be carefully monitored.* ***Dose of Linezolid in children 5-15 kg is 15mg/kg once daily and >15kg the dose is 10mg/kg once daily***

- **Delamanid and Bedaquiline** dosing is not currently known in children <3 years and should not yet be used routinely in this age group, except in individual cases and in consultation with a paediatric DR-TB expert and approval from the NCAC. ***This is likely to change in the near future as more data become available from ongoing paediatric PK studies on these drugs.***

3.5 BASIC PRINCIPLES OF TREATMENT WITH THE SHORT REGIMEN

In most cases, the duration of the intensive phase is 4 months, if monthly smear microscopy indicates smear conversion from positive to negative in that period.

Patients whose smears are negative at baseline and remain negative through treatment will only receive 4 months of the intensive phase of treatment.

The intensive phase of treatment should be extended to 6 months if sputum results remain smear positive (or convert to smear positive) at the end of month 4 of treatment.

The change from intensive to continuation phase is indicated by dropping $INH_{high\text{-}dose}$.

Bedaquiline is given for at least 6 months, but in some situations may be extended to 9 months:

- Delayed smear and/or culture conversion (i.e. if INH_{hd} was extended to 6 months)
- No 2nd line LPA or phenotypic DST results available, or LPA 2nd line uninterpretable

- Extensive TB disease as assessed by treating clinician

The continuation phase for patients of all ages will consist of four drugs (LFX, CFZ, Z, E) with a fixed

duration of 5 months. If the intensive phase was not extended beyond 4 months, the continuation phase will also include 2 months of BDQ (to allow for a full 6-month course of BDQ). If the intensive phase was extended to 6 months due to delayed smear conversion, then BDQ can be extended to 9 months, in which case the continuation phase will also include 3 months of BDQ (to allow for an extended 9-month course of BDQ).

Figure 3: Diagrammatic overview of the short regimen, indicating duration of each drug

Initiate regimen: LZD / $INH_{high\text{-}dose}$ /BDQ / LFX / Cfz / Z / E

Dosing recommendations for drugs in the shorter regimen have been simplified across four weight bands to accommodate the formulations available in the country while complying with the international requirements for minimum, maximum and average dose per kg – **see Annexure 2b**.

Aside from BDQ, all drugs are administered daily.

BDQ is administered daily for the first 14 days and then three times weekly thereafter.

TB drugs should be given under strict supervision throughout the treatment period.

Sputum specimens (in cases of PTB) are taken every month for TB smear microscopy and culture.

Refer to **Annexure3** for the monitoring chart and **Annexure 4** for detailed monitoring requirements and regimen modifications at each visit throughout treatment.

4. THE LONG (18-20 MONTH) REGIMEN FOR RR/MDR-TB

4.1 ELIGIBILITY FOR THE LONG REGIMEN

As outlined in previous section, the long regimen may be offered to anyone with RR/MDR-TB who does not meet the inclusion criteria for the short regimen and who does not have RR/MDR-TB with FLQ resistance or RR/MDR-TB meningitis; this includes patients with RR/MDR-TB and:

- Previous exposure to RR-TB treatment for >1 month, regardless of treatment outcome
- Hb<8g/dL, neutrophils <0.75 x10^9/L or platelets <50 x10^9/L at baseline or while exposed to LZD during the first 2 months of the short regimen
- Complicated extra-pulmonary TB (e.g. pericardial or osteoarticular disease), or pulmonary TB with extensive cavitations
- Both *katG* and *inhA* mutations on 1st line LPA (but susceptible to FLQ)
- Close contacts of patients with RR/MDR-TB with both *katG* and *inhA* mutations
- RR/MDR-TB patients with injectable resistance on 2nd line LPA, but sensitive to FLQ (i.e. pre-XDR INJ-resistant TB)

All patients in whom RR/MDR-TB treatment has previously failed, or newly diagnosed patients with RR/MDR-TB who are close contacts of such patients, should be presented to the NCAC (or provincial expert committees) for individualized treatment regimens – **see Annexure 6** for contact details and NCAC application forms.

4.2 LONG REGIMEN FOR ADULTS, ADOLESCENTS, CHILDREN ≥ 12 YEARS (≥30KG)

The long regimen is standardized and has been designed based on the recommended approach and updated classification of anti-TB drugs by the WHO[7] – **see Annexure 7**.

Total duration of the long regimen for RR/MDR-TB in this age group is 18-20 months.

6-8 months (Intensive Phase):
LZD –BDQ– LFX – CFZ – TRD

12 months (Continuation Phase):
LFX – CFZ – TRD

4.3 LONG REGIMEN FOR CHILDREN <12 YEARS (<30KG)

The recommendations for the long regimen for children <12yrs with RR/MDR-TB depends on:

1. **Severity of TB disease** (culture-negative presumed RR/MDR may possibly be treated for shorter duration e.g. 15 months total depending on effective drugs)
2. **Availability/approval of new drugs (DLM and BDQ) for specific age groups**. Once BDQ dose and safety is established in children <12 years of age, this should be routinely included in the

long regimen for children, as for adults. Until such time, DLM is the preferred option and should be used in place of BDQ in children 6-12 years if possible (in settings where DLM is available through DCAP). In all other cases where neither BDQ nor DLM is available for use in children<12 years, PAS should be included in the long regimen for RR/MDR-TB until the newer drugs become available. PAS can be continued for the full duration of treatment, if tolerated (should not be withdrawn at the end of the intensive phase)

3. **Effective drugs in the regimen**. Given the uncertainty of access to new drugs for children <12 years, $INH_{high\text{-}dose}$ or ETO should be included in the long regimen for the full duration of treatment, if tolerated, especially if neither BDQ nor DLM are included. The choice of $INH_{high\text{-}dose}$ or ETO will depend on the INH mutation present. If *inhA* mutation only, use INH 15-20mg/kg/day. If *katG* mutation only, use ETO 15-20mg/kg/day. If both *inhA* and *katG* mutations are present, do not use either drug in the regimen.

6-8 months (Intensive Phase):
LZD – (BDQ or PAS or DLM)– LFX – CFZ – TRD – ($INH_{high\text{-}dose}$ or ETO)

12 months (Continuation Phase):
(PAS if used in IP) – LFX – CFZ – TRD – ($INH_{high\text{-}dose}$ or ETO)

4.4 BASIC PRINCIPLES OF TREATMENT WITH THE LONG REGIMEN

The intensive phase will usually be for 6 months but may be extended to 8 months (thus total treatment duration of 20 months) in the following situations:

- At the clinician's discretion in cases of slow clinical response to treatment (i.e. poor weight gain, ongoing TB symptoms, poor resolution on CXR, delayed smear or culture conversion)
- Bilateral pulmonary disease with extensive cavitations
- Delayed culture conversion (i.e. positive *M. tuberculosis* cultures at month 4)
- Cases where 2nd line LPA results are indeterminate/FLQ susceptibility is not confirmed.

In cases of contra-indication or toxicity to one of the five core drugs in the intensive phase, or if Hb<8g/dL, neutrophils <0.75x10^9/L or platelets <50 x10^9/L at baseline or during treatment while on LZD or a history of psychosis or patient develops psychosis on treatment, refer to the National Clinical Advisory Committee. TRD may be substituted with two category C drugs if there is a history of psychosis or patient develops psychosis on treatment.

LFX can be changed to MFX during the continuation phase once BDQ is completed.

Monitoring of patients on the long regimen should follow the same principles as for the short regimen (**see Annexure 3** for monitoring chart). Key principles are as follows:

- Persons with RR/MDR-TB should be screened for mental health and substance use (**see Annexure 3** for monitoring chart) at baseline and regularly thereafter. In cases where there is any evidence of psychosis or depression – stop TRD. **Refer to NCAC as above**. Previous challenges in adhering to TB treatment or ART should be properly addressed and social

support structures should be identified and offered. All patients should receive RR/MDR-TB counseling.

- FBC including an absolute neutrophil count should be done at baseline, week 2, week 4 and then monthly. If at baseline or during the intensive phase Hb<8g/dL, neutrophils < 0.75 x10^9/L or platelets <50 x10^9/L. LZD should be stopped and refer application should be done to NCAC as above. At every visit the patient should be asked about vision and visual acuity should be done at baseline. LZD should be stopped should toxicity be observed (painful peripheral neuropathy or loss of visual acuity).
- ECGs should be done at baseline and monthly and QtcF should be calculated and recorded: QtcF ≥ 450ms is managed as outlined in **Annexure 8.**Sputum is taken for smear and culture at every visit. Outstanding sputum results should be followed up at every visit, including follow up of baseline second line LPA's and phenotypic FLQ susceptibility results → if FLQ resistance is detected on LPA or phenotypic result change to long regimen for pre-XDR and XDR-TB – *refer to section 5*.

Delayed sputum conversion (beyond month 4) or reconversion of cultures from negative to positive should be addressed promptly. The intensive phase should be extended to 8 months, and appropriate investigations implemented. Ensure the following:

- Assess adherence carefully, screen for substance use and mental illness and enhance support (consider admission)

- Clinician to request extended DST and do full clinical review

- Prepare to present case to the NCAC (or provincial expert committees) for approval for advice, especially if treatment failure (in the context of good adherence to treatment) is suspected.

5. THE LONG REGIMEN FOR FLUOROQUINOLONE (FLQ) RESISTANT TB AND XDR-TB

5.1 INTRODUCTION

A detailed clinical history can help suggest which drugs are likely to be ineffective; therefore, you may need to obtain records from previous health care providers. The probability of acquired drug resistance increases with the duration of drug administration. In particular, evidence of clinical or bacteriological treatment failure during treatment is highly suggestive of drug resistance. If a patient has used a drug for more than a month with persistent positive smears or cultures, that drug should be considered as 'probably resistant', even if DST is reported as susceptible. However, many cases in South Africa of XDR-TB are transmitted. In the case when there is no prior history of TB treatment, the regimen below should be used.

DST results should complement rather than invalidate other sources of data about the likely effectiveness of a specific drug. For example, if a history of prior anti-tuberculosis drug use suggests that a drug is likely to be ineffective due to resistance, this drug should not be relied on as one of the four core drugs in the regimen, even if the strain is susceptible in the laboratory.

Another important pitfall is that due to the delays in confirming the diagnosis, the patient may have already been started on a standard or empiric treatment regimen by the time DST results become available from the laboratory. The possibility of further acquired resistance during this time must be considered. If there is a high probability of acquired resistance to a drug after the specimen for culture and DST was collected, this drug should not be counted as one of the four drugs in the core regimen.

XDR-TB patients have a much-reduced chance for cure and a very high risk of premature death in the absence of the new and repurposed drugs; therefore, management of these cases should be prioritized using the same principles as those for MDR-TB

There is currently no international consensus on the optimum duration of FLQ-resistant TB and XDR-TB treatment therefore the same principles as for RR/MDR-TB treatment apply.

The diagnosis of FLQ-resistant TB and XDR-TB is usually only obtained after that of RR-TB. Patients who are found to have RR-TB are usually started on a standardized regimen consisting the BDQ, LZD, LFX, $INH_{high\text{-}dose}$, CFZ, Z and E. At the time of treatment start, a reflex test is sent to establish resistance to the FLQs. The results of this investigation may only be 14 days to 6 weeks later. Two of the core drugs for the treatment of FLQ-resistant TB, BDQ and LZD thus may have been given without other effective supportive medications.

5.2 PRINCIPLES OF MANAGEMENT OF FLQ-RESISTANT TB

A treatment regimen for a FLQ resistant TB and XDR-TB should be longer, individualized, considering the patient's treatment history, DST results and drug toxicity and intolerance.

The general principles include:

- An intensive phase that include a minimum of 4 drugs that are known or predicted to be effective;

- This is followed by a continuation phase that includes a minimum of 3 drugs that are known or predicted to be effective;

- Drugs that have been used in a previous regimen, on which the patient remained culture positive for 12 months or more, **should not** be included as they are very likely to be resistant even if DST reports susceptibility;
- All patients should have intensive adherence counseling and have challenges to adherence addressed before starting treatment.
- Adherence and adverse effects should be revisited throughout treatment.
- If the patient has been on treatment for RR-TB with either the short or the longer regimen for longer than one month when the diagnosis of FLQ resistance is made, consult the NCAC for a treatment regimen.

5.3.1 Long regimen for adults, adolescents, children ≥ 12 years (≥30kg) with FLQ-resistant MDR-TB and XDR-TB

6 - 8months (Intensive Phase):

BDQ-LZD* (600mg daily)* **-DLM**** or **PAS** **(4g BD or 8g daily)** **-CFZ -TRD£-Z-INH** high dose or **ETO†**

12months (Continuation Phase):

LZD (600mg daily)* **-CFZ-Z-INH** high dose or **ETO†-TRD£**

* LZD can be reduced to 300mg daily if toxicity occurs

** At some sites DLM is available and can be used. Approval must be sought from the NCAC

† $INH_{high\ dose}$ or ETO use will depend on the INH mutation present. If *inhA* mutation, use INH 10mg/kg/day. If *katG* mutation, use ETO at same dose of RR/ MDR-TB regimen. If both *inhA* and *katG* mutations, do not use either of the drugs.

£ Do not use if previously exposed to this drug in a failing regimen (i.e. sputum culture positive for 12 months or longer).

- Z is included in this regimen as it has a low rate of adverse events; however, clinicians should have a low threshold for drug interruption if adverse events occur.

- If one or more core drugs needs to be omitted or cannot be relied upon as susceptible, then an alternate agent needs to be added to the regimen. This should be **presented to NCAC for review and recommendation.**

5.3.2 Long regimen for children < 12 years (< 30kg) with FLQ-resistant MDR-TB and XDR-TB

6 - 8 months (Intensive Phase):

PAS-(DLM or BDQ once available in age/weight groups **)-LZD-CFZ-TRD-Z-(INH** high dose or **ETO)**

12months (Continuation Phase):

PAS-LZD-CFZ-TRD-Z- (INH high dose or **ETO)†**

†$INH_{high\ dose}$ or ETO usage will depend on the INH mutation present. If *inhA* mutation, use INH 15-20mg/kg/day. If *katG*, use ETO 15-20mg/kg/day. If both *inhA* and *katG* mutations, do not use either of the drugs.

The following cases should be reviewed by the National Clinical Advisory Committee:

- Patient has previously been treated with Linezolid, Bedaquiline, Delamanid or Clofazimine for DR-TB for 1 month or more;
- Patient cannot take Linezolid, Delamanid or Bedaquiline at beginning of treatment or at any period during their treatment;
- Patient previously treated for XDR or pre-XDR TB for 1 month or more;
- Pregnant patients;
- Requests for extension of Bedaquiline or Delamanid treatment beyond the current standard of 6 months must be submitted for review by the National DR TB clinical advisory committee.

6. CLINICAL MANAGEMENT OF RR/MDR-TB CENTRAL NERVOUS SYSTEM (CNS) DISEASE

RR/MDR-TB CNS disease (TB meningitis or tuberculomas) is associated with a high mortality

Clinicians should have a low threshold for performing investigations (e.g. CT brain scan or lumbar puncture) to diagnosed CNS TB disease in people with headache and/or neurologic signs especially in HIV-positive patients and children

As cerebrospinal fluid (CSF) findings can be highly variable with TB meningitis and it can be challenging to differentiate between bacterial and tuberculous meningitis it is recommended to include antibiotic cover (for example ceftriaxone 2 g IV 12 hourly) for 10 days or until bacterial meningitis is ruled out by negative CSF bacterial culture. Cryptococcal meningitis should be ruled out with a CSF CrAG.

Steroids are given with TB medications and are tapered down over 6-8 weeks

Every effort should be made to ascertain TB drug sensitivity results for CNS disease (contact history, sending cerebrospinal fluid for GeneXpert/culture and sensitivity as well as taking TB diagnostic and sensitivity samples from other sites (sputum, lymph node, etc).

Many TB drugs have poor CNS penetration. Thus, the recommended treatment of RR/MDR-TB CNS disease includes the second line drugs with the best CNS-penetration and is for the longer duration of treatment

In patients co-infected with HIV and not on antiretroviral therapy (ART): ART should be initiated 4-6 weeks after TB treatment (to minimize the risk of life-threatening intracranial IRIS). Persons already on ART should continue ART throughout TB treatment.

6.1 RECOMMENDED REGIMEN FOR CNS RR/MDR-TB DISEASE IN ADULTS, ADOLESCENTS AND CHILDREN >12 YEARS (>30KG)

6-8 months (Intensive Phase):

LZD*600mg – BDQ – LFX1000mg – CFZ – TRD – Z – (INHhd 15mg/kg or ETO)

PLUS: Dexamethasone 12 mg IVI 12 hourly (ie. 0.4mg/ kg/ day) for initial stabilization period followed by Prednisone 120mg orally daily. After 1 week gradually taper dose over 6-8 weeks

12 months (Continuation Phase):

LFX1000mg – CFZ – TRD – Z – (INHhd 15mg/kg or ETO)

*If LZD is well tolerated and ongoing close monitoring (for haematological, optic and peripheral neuropathy) is possible, LZD can be extended into the continuation phase.

Where available addition of DLM to the regimen should be considered as good CNS penetration has been demonstrated in rats. Change from intensive phase to continuation phase is based on clinical

response. Repeat CT brain scan may be used to monitor response of tuberculomas to treatment. Residual lesions may be present at end of treatment and do not necessarily represent treatment failure.

All persons with presumed or confirmed FLQ-resistant CNS TB should be presented to NCAC for expert advice (Delamanid should be added; and IV carbapenem may be recommended). RR/MDR-TB treatment as above should be initiated in the interim.

Co-infection with cryptococal meningitis should be ruled out with a CSF CrAG in all HIV infected patients with a CD4+ less than 100.

6.2. RECOMMENDED REGIMEN FOR CHILDREN <12 YEARS (< 30 KG)

- All children with CNS disease should be discussed with an experienced paediaric and/or DR-TB clinician (NCAC may be consulted). For TB meningitis and military TB in children, treatment of both MDR and XDR-TB should include sufficient drugs that penetrate the CSF (LFX, LZD, TRD, Z, ETO and high dose INH).

7. CLINICAL MANAGEMENT OF RR/ MDR-TB and HIV CO-INFECTION

All people living with HIV and RR/ MDR-TB are considered to have advanced HIV and are at high risk of mortality, especially if not on ART[15,16].

7.1 KEY PRINCIPLES OF MANAGEMENT OF HIV AND RR/MDR-TB CO-INFECTION

- The **shorter and longer TB treatment is unchanged in people with HIV although changes to ART may be required.** High pill burden, overlapping drug toxicities, drug-drug interactions, and the risk of immune reconstitution syndrome (IRIS) make patients living with both diseases is complex to manage and monitoring should be *rigorous.*

- **CD4, viral load (VL) is done at baseline and then at 6 months (see Annexure 3) and 1 year (VL is repeated after 2 months if** found unsuppressed). The goal is rapid sustained vital suppression; an unsuppressed viral load required action.

- **RR/MDR-TB ART should be started within two weeks of starting RR/MDR-TB treatment[17] (**in CNS disease, ART is started 4-6 weeks post TB treatment due to the risk of intracranial IRIS[18].

- **Co-trimoxazole prophylaxis reduces mortality and** (unless contraindicated or hypersensitivity) **should be given with TB treatment regardless of CD4 count[17]. Co-trimoxazole** can be used with LZD; regular FBC and neutrophils count monitor for bone marrow suppression.

- **Additional counseling and support** should be provided by the clinical team (TB nurse, doctor and counselors). Key points to address in counseling include increase pill burden, and warning signs of opportunistic infections that require presentation to care.

- **Aggressively diagnose and manage co-morbid opportunistic infections.** In adults with CD4 < 100, reflex cryptococcal antigen (CrAg) test is done before ART initiation; a positive test should be treated with pre-emptive fluconazole treatment; evidence of cryptococcol meningitis (CrAg on cerebrospinal fluid or symptoms of meningitis) requires hospitalized anti-fungal treatment followed by fluconazole ≥ 1 year (discontinue when CD4 > 200 taken 6 months apart). ECG monitoring should be vigilant for QtcF prolongation with concomitant use of BDQ and fluconazole.

Efavirenz (EFV) and BDQ are contraindicated together (EFV lowers the BDQ levels) – EFV should be changed to another antiretroviral agent (see below). LZD and AZT both cause bone marrow suppression; AZT should be changed to TDF (or ABC if renal impairment). Amikacin and TDF can both cause renal impairment and should not be used together.

For persons diagnosed with RR/MDR-TB who have defaulted ART and are currently not on ART- restart on TDF*/TC and LPV/rit (or ATZ/rit) * ABC is used instead of TDF where renal impairment.

For persons on ART, do viral load and CD4 at RR/MDR-TB diagnosis; change ART as per guideline outlined in table below:

Figure4. Guidance for modification of ART regimens during treatment for RR/MDR-TB

Current ART Regimen	Proposed ART regimen	
	VL < 400	**VL** > 400
TDF or ABC/ XTC/ EFV	1. TDF*/ XTC **and** Dolutegravir (if available) Or 2. TDF*/ XTC **and** Lpv/ rit (or ATZ/ rit) † Or 3. TDF*/ FTC/ NVP	TDF*/ XTC **and** LPV/ r (or ATZ/ rit)†
TDF or ABC/ XTC/ NVP	Keep on same ART	Review previous VL and history. If history of treatment interruptions/poor ART adherence or person is clinically unwell/CD4 <50 switch NVP to Lpv/rit (or ATZ/rit).If no change is made address adherence and repeat VL in 2 months – if VL remains > 400change to Lpv/rit (or ATZ/rit)
TDF or ABC or AZT/ XTC and Lpv/ rit (or Dolutegravir)	Change AZT to TDF* Keep rest of regimen unchanged	Review and address reason for increased VL. Refer to guidance on genotyping if VL remains elevated.
XTC = FTC or 3TC		

8. GUIDANCE FOR PERSONS STARTED ON RR/MDR-TB TREATMENT PRIOR TO THIS NEW GUIDANCE DOCUMENT

- At the time of the release of this guidance, patients may be receiving the old long regimen with TRD and/or injectable agent. If patients are receiving Kanamycin, this must be changed to Amikacin with close ongoing audiometry. If Amikacin is not available, then consult the NCAC for advice. For monitoring, adhere to previous guidelines; injectable should be stopped and application made for substitution at earliest sign of ototoxicity.
- In patients who are doing well on a continuation phase with TRD can continue the old long regimen.
- Please apply to NCAC If any clinical or microbiological suspicion of treatment failure.

9. RECORDING AND REPORTING

- Recording and reporting will continue as per norm; stationery has been revised to include the short and long regimens
- Data will be captured on the EDR.web which has been upgraded to distinguish between the short and the long regimens
- The Medical Officers are responsible for assigning DR-TB outcomes once a patient has completed treatment. Treatment outcomes are given according to updated WHO DR-TB treatment outcome *(**see Annexure 9** for short regimen and **Annexure 10** for long regimen)*
- Serious adverse events should be reported to the NDOH Pharmacovigilance Centre for Public Health Programmes (NPC) – ***see Annexure 11*** *for report form*. Guidance on grading of adverse events is given in **Annexure 12**.

10. FREQUENTLY ASKED QUESTIONS ON THE NEW RR/MDR-TB REGIMENS IN SOUTH AFRICA

10.1 TREATMENT INITIATION AND INDICATIONS FOR THE NEW SHORT, LONG AND INDIVIDUALIZED REGIMENS (INCLUDING FOR ADULTS, CHILDREN AND PREGNANT LADIES)

What anti-tuberculosis medications are in the new short regimen for RR/MDR-TB?

LZD (2 months) * - INH high-dose (4 – 6 months) † – BDQ (6 months)* – LFX (9-11 months) – CFZ (9-11 months) – Z (9-11 months) – E (9-11 months). Inclusion and exclusions criteria for the short regimen are outlined in section 3.2

† Length determined by smear and clinical response

*BDQ can be extended to 9 months under specific circumstances please refer to short regimen section

What anti-tuberculosis medications are in the new long regimen for RR/MDR-TB and when is this regimen used?

The new long regimen is: LZD – BDQ – LFX – CFZ –TRD. If there is a contra-indication to one of these medications (for example, LZD is contraindicated if Hb < 8 g/dl, neutrophils < 0.75 x10^9/L, platelets < 50 x10^9/L) - please contact NCAC for advice on which medication to use for substitution. Please refer to section 4.2 for inclusions and exclusions for long regimen. Patients with RR/MDR-TB with extensive cavitations, complicated extra-pulmonary TB (ie. abdominal, osteo-articular or pericardial disease), prior exposure to RR/MDR-TB drugs for > 1 month, or patients with RR/MDR-TB with injectable resistance (but FLQ sensitivity) are treated with the long regimen. RR/MDR-TB with FLQ resistance should be treated with an individualized long regimen for FLQ resistant TB refer to section 5. Patients with central nervous system TB should be treated with an individualized regimen for CNS disease refer to section 6. Contact NCAC for patients with RR/MDR-TB failure (or relapse with prior exposure to any of CFZ/BDQ or LZD) for advice on individualized treatment regimens.

My patient has a GeneXpert which shows rifampicin resistance; LPA results are pending. Which treatment do I start him/her on?

If the patient meets the inclusion criteria and there are no exclusions to the short regimen – please refer to section 3.1 (for e.g. prior exposure to second line TB drugs for > 1-month, complicated extra pulmonary TB, close contact with pre/XDR-TB, Hb < 8 g/dl, neutrophils < 0.75 x10^9/L, platelets < 50 x10^9/L) then start treatment with the new short regimen – LZD – BDQ – LFX – CFZ – $INH_{high\text{-}dose}$ – Z – E. At every subsequent visit, check 1st and 2nd line LPA results, as well as phenotypic FLQ drug susceptibility results if available and reassess regimen. If INJ resistance is detected (but TB is FLQ sensitive) change regimen to the long regimen. If FLQ resistance is detected the regimen will need to be changed to an individualized long regimen. **Please consult NCAC if FLQ resistance is detected after > 1 month after initiation with the short regimen**.

Can children be treated with the injectable free short regimen?

Children <12yrs with confirmed or presumed RR/MDR-TB should also have access to a short, injectable-free regimen. Recommended options for replacement of the injectable agent within the new short regimen depend on availability of specific drugs (e.g. DLM) and experience of the

treating clinician. If clinicians are uncertain about eligibility or the composition of the short regimen for a child <12 years with RR/MDR-TB, the case should be presented to the NCAC (or provincial expert committees) for advice, or a paediatric DR-TB expert should be consulted for guidance.

Currently (until BDQ dosing for children becomes available) – depending on the age of the child and the availability of DLM - the treatment is LZD* $_{(2\ months\ only)}$ – DLM or PAS $_{(total\ 6\ months)}$ – LFX – CFZ – $INH_{high\text{-}dose}$ – Z – E**.** Please refer to section 3.4.

** LZD may be omitted from the short regimen, at the clinician's discretion, in children with non-severe RR/MDR-TB disease (i.e. no bacteriological confirmation, unilateral pulmonary TB disease, non-cavitatory TB disease).*

My patient has MDR-TB and a HB < 8 g/dL. Is he/she eligible for the shorter regimen?
No; please contact the NCAC for advice and guidance on treatment regimen (in most cases two category C drugs will be used to substitute for LZD).

My patient has a positive GeneXpert and has had previous MDR-TB many years ago with a successful treatment outcome – which treatment do I initiate?
Previous exposure to second line anti-tuberculosis drugs for > 1 month is an exclusion to the new short regimen, regardless of previous treatment outcomes. The patient should be initiated on the new long regimen.

My patient has RR/MDR-TB meningitis which treatment do I start?
An individualized long regimen which includes drugs with good central nervous system penetration should be initiated: Z – CFZ – BDQ – TRD – LFX– LZD - ETO or $INH_{high\text{-}dose}$ (depending on mutation). If available consider adding Delamanid to the regimen. If FLQ resistance is detected, or the patient has had prior MDR-TB, start treatment and present to NCAC for expert opinion (may require inclusion of a carbapenem in the regimen).

My patient has extra pulmonary TB are they eligible for the new short regimen?
Patients with simple extra pulmonary TB (ie. lymph node TB or pleural effusion) – and no other exclusions to the short course are eligible for the new short regimen. Patients with complicated TB (including pericardial, osteo-articular, abdominal or urogenital TB) should be started on the long regimen.

My patient has MDR-TB with both a Kat G and inhA mutation (and no FLQ or INJ mutation on second line LPA) what treatment should I initiate?
Presence of both mutations is an exclusion criteria for the new short regimen. Initiate the long regimen LZD– BDQ – LFX – CFZ –TZD (unless there is a contra indication to one of those drugs). If Hb < 8 g/dl, neutrophils < 0.75 $x10^9$/L, platelets < 50 $x10^9$/L, LZD is contraindicated - please contact NCAC for advice on which anti-TB medication to use to replace LZD.

Can pregnant women receive the new short regimen?
Yes. The case should be submitted to NCAC for approval.

When do I include Ethionamide (ETO) in the treatment of newly diagnosed patients with RR/MDRTB?

ETO is no longer a core component of the new short or longer regimen, however it is recommended for use where the TB strain is thought to have susceptibility to ETO (ie. no Kat G mutation or ETO sensitivity confirmed on phenotypic drug sensitivity tests) in the following scenarios: 1) Long regimen for children < 12 (children experience less adverse events from ETO than adults do). 2) Central nervous system (CNS) TB (ETO has good CNS penetration) 3) Individualized long regimen for FLQ resistant TB 4) Individualized long salvage regimens for RR/MDR-TB failure (under RR/MDR-TB expert recommendation) 5) As recommended by drug advisory committee/DRTB expert as a category C drug to substitute for LZD in the long regimen (eg. Hb < 8 g/dl, neutrophils < 0.75 $x10^9$/L, platelets < 50 $x10^9$/L)

Note patients who are on the old short or long regimen may continue on ETO (unless contra-indication develops or ETO resistance is demonstrated on drug susceptibility tests).

My patient has started the old short course regimen prior to this guidance, are they eligible for the new short course?

At the time of the release of this guidance, patients may be receiving the old short regimen with an injectable agent or the old long regimen with TRD and/or injectable agent. If patients are receiving Kanamycin, this must be changed to Amikacin with close ongoing audiometry. If Amikacin is not available, then consult NCAC for advice. For monitoring, adhere to previous guidelines; injectable should be stopped and application made for substitution at earliest sign of ototoxicity.

Patients are doing well on a continuation phase of the old long regimen can continue on the same treatment.

Please apply to NCAC If any clinical or microbiological suspicion of treatment failure.

10.2 DURATION OF TREATMENT

How is the treatment length of high dose INH, CFZ, LFX, E and Z decided within the new short regimen?

At month 4 of treatment smears and clinical condition or the patient is reviewed. If smear is positive (or there is poor clinical progress) – request repeat LPA and phenotypic extended drug sensitivities from the lab. Extend high dose INH ,and present the case to NCAC for input (between months 4 – 6 a decision should be made taking into account the clinical picture, CXR, microbiology and history if the short regimen can be continued (with extension of high dose INH to 6 months, BDQ to 9 months and E-Z-LFX-Cfz to 11 months) OR if treatment is failing and a new regimen should be initiated).

Within the new short regimen what are the indications to extend BDQ to 9 months?

Extensions should be applied for through NCAC. Indications may include delayed smear/culture conversion or clinical response, or if second line LPA results are inconclusive or unavailable.

What is the treatment duration for the new long regimen for RR/MDR-TB?
The intensive phase is 6 – 8 months, with a continuation phase of 12 months: total treatment duration is 18 – 20 months.

10.3 LINEZOLID MONITORING

My patient is on LZD what monitoring is needed?
Full blood count (FBC) with a neutrophil count should be done at baseline, week 2, week 4 and then monthly. If Haemoglobin (Hb) < 8 g/dL, neutrophils <0.75 $x10^9$/L or platelets <50 $x10^9$/L at baseline or during treatment with LZD: stop LZD and consult NCAC or MDR-TB expert for advice. Depending on the individual circumstances - treatment regimen may need to be changed (for example: new short course regimen may need to be changed to long regimen), 2 category C drugs may need to be used to replace LZD, or patient may need to be transfused and LZD re-challenged at a lower dose.

Monitor for peripheral neuropathy and optic toxicity at every visit. If toxicity develops – stop LZD and consult NCAC/DRTB expert for advice.

10.4 RELATED TO MANAGEMENT OF RR-TB AND HIV COINFECTION

Which RR/MDR-TB treatment and ART do I start in my patient who has been <u>newly</u> diagnosed with both HIV and RR-TB/MDR-TB ?
Start RR/MDR-TB treatment as per guidance (inclusion and exclusion criteria for new short and long regimen are the same for people with and without HIV). Antiretroviral therapy (ART) should be started as soon as patient is tolerating TB treatment (ideally within 2 weeks; in patients with central nervous system TB disease or cryptococcal meningitis ART should be started 4 – 6 weeks after initiation of TB/cryptococcal treatment).

The following ART should be initiated:
<u>First choice (if available):</u> TDF*/XTC/DTG

<u>If this is not available use:</u> TDF*/XTC/LPV/r (or ATV/r if available)
OR
TDF*/XTC/NVP (only an option if CD4 is < 250 (female) and CD4 < 350 (male)

My patient is on TDF/3TC/EFV and has been diagnosed with RR-TB. What ARV's should I change to?

BDQ and EFV are contraindicated together; EFV should be changed to DTG or LPV/r (or ATV/r) or NVP as per table below.

Table 3. Guidance for modification of ART regimen when BDQ-containing RR -TB treatment is initiated

Current ART Regimen	**Proposed ART regimen**	
	VL < 400	**VL** > 400
TDF (or ABC)/ XTC/ EFV	1. TDF*/ XTC **and** Dolutegravir (if available) Or 2. TDF*/ XTC **and** Lpv/ rit (or ATV/r) † Or 3. TDF*/ FTC/ NVP	TDF*/ XTC **and** LPV/ r (or ATV/ r)
TDF (or ABC)/ XTC/ NVP	Keep on same ART	Review previous VL and history. If history of treatment interruptions/poor ART adherence or person is clinically unwell/CD4 <50 switch NVP to Lpv/rit (or ATZ/rit). If NVP is continued – address reasons for unsuppressed viral load and repeat VL in 2 months – if VL remains > 400 change to LPV/r (or ATV/r)
TDF (or ABC or AZT)/ XTC and LPV/rit (or DTG)	Change AZT to TDF* Keep rest of regimen unchanged	Review and address reason for increased VL. Refer to guidance on genotyping if VL remains elevated.
DTG = Dolutegravir; TDF = Tenofovir; XTC = Emtricitabine (FTC) or Lamivudine (3TC); ATV/r = Atazanavir/ritonavir; LPV/r = Lopinavir/ritonavir; NVP = Nevirapene; EFV = Efavirenz; VL = viral load; AZT = Zidovudine; ABC = Abacavir		

My patient is newly diagnosed with RR-TB and is virally suppressed on second line ART (AZT/3TC/LPV/r). Can I give a RR-TB regimen which includes LZD with AZT or do I need to make change to the ART regimen?

LZD should not be co-administered with AZT. Change ART to TDF/3TC/LPV/r(or ATV/r). NRTI's maintain antiviral activity (even in the presence NRTI-resistance mutations) and thus this regimen can adequately maintain viral suppression[19].

My patient is newly diagnosed with RR-TB, and defaulted ART which ART should I start?

Do VL if > 400 initiate TDF (ABC if renal impairment)/XTC/LPV/r (or ATV/r). ART should be initiated once patient is tolerating TB medications ideally within 2 weeks (ART should be initiated at 4 – 6 weeks post treatment initiation in patients with intracranial TB or cryptoccocal meningitis).

10.5 Related to management of FLQ-resistant TB

My patient is on the new short regimen and the LPA second line has come back FLQ resistant TB 2 weeks after treatment initiation, what do I do?
Change to long individualized treatment for FLQ resistant TB (refer to section 5). At DCAP sites, cases should be presented to NCAC for approval of a regimen which including delamanid (DLM).

My patient started on the short regimen 2 months ago. Now the phenotypic drug susceptibility test for FLQ indicates resistance. What should I do?
Contact NCAC for advice on which drugs to include in a long-individualized regimen.

10.6 Treatment for patients with rifampicin-susceptible, isoniazid-resistant tuberculosis

In patients who are rifampicin-susceptible, isoniazid-resistant tuberculosis the use of 2HRZE/4HR regimen is more likely to fail than in isoniazid-susceptible TB patients[1,20]. An addition of Levofloxacin is recommended after rifampicin-resistance and fluoroquinolone-resistance have been excluded with rapid molecular test.

The regimen is: HRZE plus Levofloxacin for 6 months[21]. Ideally, HR-TB treatment is only started after isoniazid resistance and susceptibility to fluoroquinolone have been reliably confirmed[21].

Extending the duration of treatment beyond 6 months may be necessary when HR-TB is detected in the course of first-line TB treatment or in patients with extensive disease[21].

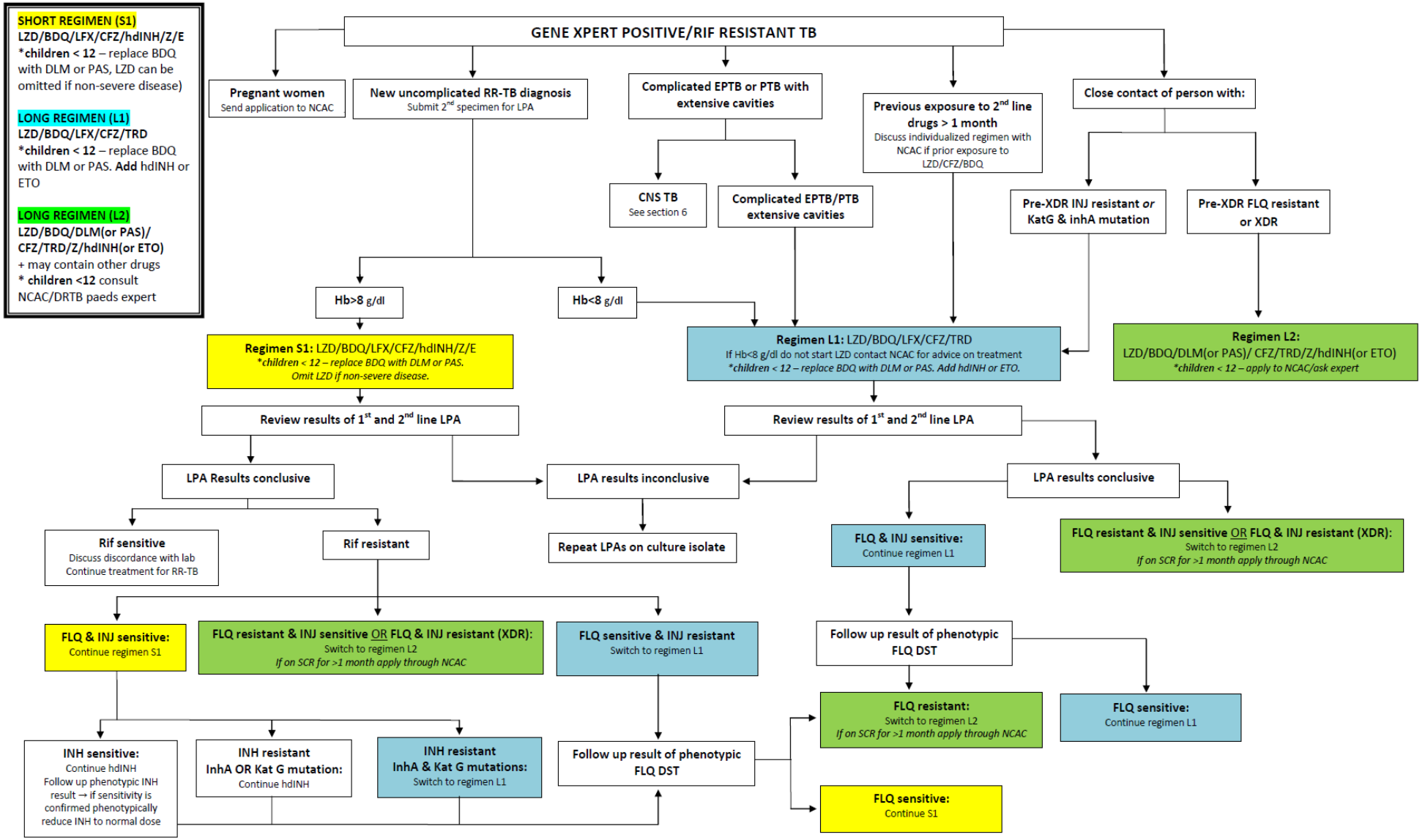
Follow up of these patients should be done using monthly TB smear and culture although this group of patients do not belong to the EDR Web. We shall keep this group on ETR.net

PHC facilities diagnosing these patients need to source Levofloxacin from their nearest district hospitals.

REFERENCES

1. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis 2016 update. World Health Organization; 2016.
2. World Health Organization. Global Tuberculosis Report. Geneva: 2017.
3. Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting : an interim cohort analysis. Int J Tuberc Lung Dis 2015;19:979–85. doi:10.5588/ijtld.14.0944.
4. Directorate Drug-Resistant TB TB & HIV. Introduction of new drugs, drug regimens and management for drug-resistant TB in South Africa : Policy framework. 1.1. Pretoria: National Department of Health; 2015.
5. Zhao Y et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug-resistant tuberculosis: a retrospective cohort study. Clinical Infectious Diseases, ciy 727, https://doi.org/10.1093/cid/ciy727. Published 24 August 2018.
6. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a

retrospective cohort study. Lancet Respir Med 2018;2600:1–8. doi:10.1016/S2213-2600(18)30235-2.
7. World Health Organization. Rapid communication: key changes to treatment of multidrug and rifampicin-resistant tuberculosis (MDR/RR-TB). World Health Organization; August 2018.
8. Directorate Drug-Resistant TB TB & HIV. Bedaquiline Expansion Plan. June 2018.
9. The Collaborative Group for the Meta-analysis of Individual Patient Data in MDR-TB treatment 2017; Nafees Ahmad, Shama D Ahuja et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821-34.
10. Matteo Zignol, Andrea M. Cabibbe, Anna S. Dean, Daniela Cirillo, Christopher Gilpin, Rumina Hasan, Sven Hoffner, Nazir Ismail, Leen Rigouts, Stefan Niemann, Karin Weyer, Natavan Alikhanova, Cecilia Ama, Sönke Andres, Anna Barbova, Angeli Borbe-Reyes, Andries Dreyer, Michèle Driesen, Zahra Hasan, Alamdar Hussain, Alexander Jurilio, Mostafa Kamal, Faisal M. Khanzada, Thomas A. Kohl, Mikael Mansjö, Paolo Miotto, Shaheed V. Omar, Ivita Sela, Mehriban Seyfaddinova, Girts Skenders, Alena Skrahina, Sabira Tahseen, Philippe Glaziou, Mario C. Raviglione. Genetic sequencing for surveillance of drug resistance in tuberculosis in highly endemic countries: a multi-country population-based study. *Lancet Infect Dis*. 2018 Mar 21. pii: S1473-3099(18)30073-2. doi: 10.1016/S1473-3099(18)30073-2
11. Ismail N, Mvusi L et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis 2018. Published online April 20, 2018.
12. Seddon J A, Godfrey-Faussett P, Jacobs K, et al. Hearing loss in patients on treatment for drug-resistant tuberculosis. Eur Respir J 2012; 40: 1277–1286.
13. Sentinal Project. Statement on Injectable Free Regimens for Children under the Age of 12 Years with Rifampicin-Resistant Tuberculosis. Available at http://sentinel-project.org/wp-content/uploads/2018/07/Recommendations-for-Injectible-Free-Regimens-in-Children-with-Rif-Resistant-TB.pdf.
14. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: Interim policy guidance 2016 http://www.who.int/tb/publications/Delamanid_interim_policy/en/
15. Gandhi NR, Andrews JR, Brust JC, Montreuil R, Weissman D, Heo M, Moll AP, Friedland GH, Shah NS. Risk factors for mortality among MDR-and XDR-TB patients in a high HIV prevalence setting. The International Journal of Tuberculosis and Lung Disease. 2012 Jan 1;16(1):90-7.
16. Schnippel K, Firnhaber C, Ndjeka N, Conradie F, Page-Shipp L, Berhanu R, et al. Persistently high early mortality despite rapid diagnostics for drug-resistant tuberculosis cases in South Africa. Int J Tuberc Lung Dis. 2017;21(10):1106-11.
17. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017.
18. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in Human immunodeficiency virus (HIV)-associated tuberculous meningitis. Clin Infect Dis. 2011;52:1374–1383. https://doi.org/10.1093/cid/cir230
19. Paton NI, Kityo C, Hoppe A, Reid A, Kambugu A, Lugemwa A, van Oosterhout JJ, Kiconco M, Siika A, Mwebaze R, Abwola M. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. New England Journal of Medicine. 2014 Jul 17;371(3):234-47.
20. WHO treatment guidelines for isoniazid-resistant tuberculosis. 2017 Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. Geneva, World Health Organization
21. Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis. Version 1st November 2017.


SHORT REGIMEN (S1)
LZD/BDQ/LFX/CFZ/hdINH/Z/E
*children < 12 – replace BDQ with DLM or PAS, LZD can be omitted if non-severe disease)
LONG REGIMEN (L1)
LZD/BDQ/LFX/CFZ/TRD
*children < 12 – replace BDQ with DLM or PAS. Add hdINH or ETO
LONG REGIMEN (L2)
LZD/BDQ/DLM(or PAS)/ CFZ/TRD/Z/hdINH(or ETO)
+ may contain other drugs
* children <12 consult NCAC/DRTB paeds expert
GENE XPERT POSITIVE/RIF RESISTANT TB
Pregnant women
Send application to NCAC
New uncomplicated RR-TB diagnosis
Submit 2nd specimen for LPA
Complicated EPTB or PTB with extensive cavities
Previous exposure to 2nd line drugs > 1 month
Discuss individualized regimen with NCAC if prior exposure to LZD/CFZ/BDQ
Close contact of person with:
CNS TB
See section 6
Complicated EPTB/PTB extensive cavities
Pre-XDR INJ resistant or KatG & inhA mutation
Pre-XDR FLQ resistant or XDR
Hb>8 g/dl
Hb<8 g/dl
Regimen S1: LZD/BDQ/LFX/CFZ/hdINH/Z/E
*children < 12 – replace BDQ with DLM or PAS.
Omit LZD if non-severe disease.
Regimen L1: LZD/BDQ/LFX/CFZ/TRD
If Hb<8 g/dl do not start LZD contact NCAC for advice on treatment
*children < 12 – replace BDQ with DLM or PAS. Add hdINH or ETO.
Regimen L2:
LZD/BDQ/DLM(or PAS)/ CFZ/TRD/Z/hdINH(or ETO)
*children < 12 – apply to NCAC/ask expert
Review results of 1st and 2nd line LPA
Review results of 1st and 2nd line LPA
LPA Results conclusive
LPA results inconclusive
LPA results conclusive
Rif sensitive
Discuss discordance with lab
Continue treatment for RR-TB
Rif resistant
Repeat LPAs on culture isolate
FLQ & INJ sensitive:
Continue regimen L1
FLQ resistant & INJ sensitive OR FLQ & INJ resistant (XDR):
Switch to regimen L2
If on SCR for >1 month apply through NCAC
FLQ & INJ sensitive:
Continue regimen S1
FLQ resistant & INJ sensitive OR FLQ & INJ resistant (XDR):
Switch to regimen L2
If on SCR for >1 month apply through NCAC
FLQ sensitive & INJ resistant
Switch to regimen L1
Follow up result of phenotypic FLQ DST
INH sensitive:
Continue hdINH
Follow up phenotypic INH result → if sensitivity is confirmed phenotypically reduce INH to normal dose
INH resistant
InhA OR Kat G mutation:
Continue hdINH
INH resistant
InhA & Kat G mutations:
Switch to regimen L1
Follow up result of phenotypic FLQ DST
FLQ resistant:
Switch to regimen L2
If on SCR for >1 month apply through NCAC
FLQ sensitive:
Continue regimen L1
FLQ sensitive:
Continue S1

ANNEXURE 2a – weight-banded dosing chart for adults, adolescents and children>12 years

Updated: September 2017

DRUG DOSING CHART FOR ADULT DRUG RESISTANT TB PATIENTS

Drug	*Average Daily Dose	Weight Class			
		<33 Kg	33-50 Kg	51-70 Kg	>70Kg
Kanamycin (Km) (1 g vial)	15-20 mg/kg daily	By wt.	500-750 mg	1000 mg	1000 mg
*Kanamycin (Km) (1 g vial) TIW dosing	25 mg/kg three times per week (Mon/Wed/Fri)	By wt.	By wt	By wt	By wt (Maximum 2g)
Levofloxacin (Lfx) (250 mg/500mg)	15-20 mg/kg daily	By wt.	750 mg	1000 mg	1000 mg
Clofazamine (100mg)		100mg			
Pyrazinamide (Z) (500 mg)	30-40 mg/kg daily	By wt.	1000-1750 mg	1750-2000 mg	2000-2500mg
Ethambutol (E) (400 mg)	15-20 mg/kg daily	By wt.	800-1000mg	800-1200mg	1200 mg
High dose INH (100, 300 mg)	15 mg/kg daily	By wt.	By wt.	By wt.	By wt. (Maximum 900mg)
Ethionamide (Eto) (250 mg)	15-20 mg/kg daily	By wt.	500 mg	750 mg	750mg
Isoniazid (H) (100, 300 mg)	5 mg/kg daily	By wt.	300 mg		
**Moxifloxacin (Mfx) (400 mg)		400 mg	400 mg	800 mg (shorter regimen)** 400mg (longer regimens)	800 mg (shorter regimen)** 400mg (longer regimens)
Terizidone (Trd) (250 mg)	15-20 mg/kg daily	By wt.	750 mg		
PAS (4 g sachets)		4g daily	8g daily or 4g twice daily		
Bedaquiline (Bdq) (100mg)	400mg once daily for 2 weeks followed by 200mg three times per week (Monday/Wednesday/Friday) for 22 weeks				
Linezolid (600mg)	Reduce to 300 mg if severe ADRs	300 mg	600 mg		
Delamanid (Dlm)	100 mg twice daily for 24 wks	-	100 mg twice daily		
†Rifabutin		300 mg	300 – 450 mg		

* Kanamycin may be dosed **Three Times per Week (TIW)** for months 5-6 of the Shorter DR-TB regimen and for the full duration of the intensive phase in longer individualised DR-TB regimens including pre-XDR/XDR TB regimens.

**If the higher dose of 800mg moxifloxacin not tolerated, reduce dose to 400mg

†Reduce dose to 150mg if using together with a protease inhibitor. The concomitant use of Rifabutin and Bedaquiline is contraindicated

ANNEXURE 2b – weight-banded dosing chart for children <12 years

Drug name	Daily paediatric dose in mg/kg (maximum dose in mg)
Amoxicillin-Clavulanate	80 mg/kg (4000 mg amoxicillin and 500 mg Clavulanate): only to be given with Meropenem
Clofazimine	2 – 3 mg/kg
Delamanid	50 mg twice daily for 20 to 34 kg, for 6 months 100 mg twice daily for > 35 kg, for 6 months
Ethambutol	15 – 25 mg/kg
Ethionamide	15 – 20 mg/kg (1000 mg) twice a day
Isoniazid	15 – 20 mg/kg
Levofloxacin	15 – 20 mg/kg (1000 mg)
Linezolid	10 mg/kg/dose twice daily
Meropenem	20 – 40 mg/kg (6000 mg)
Moxifloxacin	7.5 – 10 mg/kg (800 mg)
PAS	200 – 300 mg/kg
Pyrazinamide	30 – 40 mg/kg
Terizidone	10 -20 mg/kg (1000 mg) twice a day

ANNEXURE 3 – monitoring chart for short and long regimens

	Base-line	Longer Regimen: Intensive Phase						Longer Regimen: Continuation phase											
		Shorter Regimen: Intensive phase				Shorter regimen: Continuation phase													
Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18-20
DRTB counseling sessions	X	Sessions 1 - 3			X														
Screen for substance use and asses mental health*	X				X														
Evaluation by PHC doctor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse drug reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assesses for TB symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																		
BMI and NSP if BMI< 18.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review contraception	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X																		
Smear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Culture	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DST 1st line(LPA)	X				X(If still culture positive)			X (if reconversion to positive cultures after initial culture conversion)											
DST 2nd line (LPA)	X				X (if still culture positive)			X (if reconversion to positive cultures after initial culture conversion)											
Phenotypic extended DST	X if LPA second line resistance (reflex)				X if culture positive at month 4 or reconversion to positive after initial culture conversion														
Phenotypic FLQ sensitivity	Reflex if second line LPA is FLQ susceptible																		
Chest X-ray	X						X												
HIV testing	X			X(if previous test-ve)									X (if previous test -ve)						
CD4 count	X						X						X						
Viral load	X						X						X						X
FBC and neutrophil count if on Lzd†	X	Week 2 and 4	X	X	X	X	X	X	X	X									
Finger prick blood glucose	X																		
Creatinine	X	Do monthly if on injectable agent. Otherwise repeat if baseline Cr was abnormal, or if person is clinically unwell																	
K and Mg	X	Do monthly if on injectable agent. Otherwise repeat if vomiting, diarrhea, if QtcF is prolonged or when patient is clinically unwell																	
TSHif on PAS or ETHIO or if QtcF is prolonged	X			X															
ALT	X	Repeat if vomiting, RUQ pain, jaundice, patient is unwell or any evidence of liver injury																	
Audiometry*	X			X	Monthly if on injectable. If any changes in audiometry should be referred for Audio management & care (stop injectable)														
ECG**	X	X	X	X	X	X	X			X			X			X			X
Ask about vision & do Snellens monthly while on Lzd	X	X	X	X	X	X	X												

ANNEXURE 4 – Detailed monitoring requirements

- * ask if person has ever smoked or used drugs/alcohol in their life. If yes → do ***CAGE-AID or other screen***. ***Ask:*** 1. Have you felt you should cut down on your drinking or using drugs? 2. Have people annoyed you by criticizing your drinking or drug use? 3. Have you felt bad or guilty about your drinking or drug use? Have you ever had a drink or used drugs first think in the morning to steady your nerves or get rid of a hangover (eye opener***?). If answered YES to > 1 CAGE-AID question*** **OR if smoking** further screen with WHO ASSIST (http://www.who.int/substance_abuse/activities/assist_v3_english.pdf), and provide a brief counselling and education intervention. Patients that score *high risk* on WHO ASSIST may need referral to treatment.
- † FBC and differential count (neutrophil count) before starting Lzd, and then at 2 and 4 weeks and then monthly while on LZD at baseline, week2 and week
- *Audiometry: should be done at baseline and month 3 for all patients even if not on an injectable. If receiving an injectable audiometry should be done MONTHY.
- **ECG: do at baseline ECG and repeat monthly if on Bedaquiline can reduce to 3 monthly if on Clofazimine without BDQ. Management of QTC >450 ms is outlined in Annexure 7

ANNEXURE 5 – short regimen modifications throughout treatment

Review visit	Key Actions
Baseline	• Review all available sputum results, baseline blood results (FBC with neutrophil count, HIV test, viral load, CD4 count, Cr, Mg, K, ALT results • Do pregnancy test and ECG and review both results → discuss contraception • Review inclusion and exclusions criteria for short course regimen and decide if patient is eligible for short course • If eligible, HB >8g/dL, baseline ECG* does not indicate QTcF prolongation → start regimen and adjust ART as needed • Do baseline visual acuity see Annexure 12 for Snellens chart • Send for baseline hearing tests • Screen for smoking and drugs/alcohol use† → do brief intervention and refer for treatment as needed • Screen for mental health‡ • Identify support structures for patient; initiate RR/MDR-TB counselling
2 weeks	• Review LPA results if conclusive and amend regimen if indicated • Repeat FBC and neutrophil count • Review baseline hearing tests results
4 weeks	• Review LPA results if not previously available and amend regimen if indicated • Review FBC result: if Hb<8g/dL, neutrophils <0.75 x10^9/L or platelets <50 x10^9/L, drop Lzd and switch to longer regimen. • repeat FBC and neutrophil count • Repeat and review ECG* for QtcF prolongation
8 weeks	• Check initial sputum smear and culture result - if 1st& 2nd line LPAs were initially uninterruptable, check results of repeat LPAs done on culture isolate should be available. • If LPA FLQ results were susceptible – review phenotypic FLQ susceptibility. If resistance change to individualized long regimen. • Review FBC and neutrophil count and repeat. • Stop Lzd • Repeat and review ECG* for QtcF prolongation
Sputum should be taken and results reviewed every month. **ECG's should be done and reviewed monthly until BDQ completed.** **Adherence, change in substance use, and mental health should be assessed regularly.**	
4 months	• Review all smear & culture results. ○ If smear conversion (from positive to negative) has occurred, or if smears have remained negative since treatment start, stop INHhd – this is the switch to continuation phase ○ If no smear conversion has occurred at this stage, continue all treatment for another 2 months (i.e. continue intensive phase) If smears are positive at 4 months this is a risk for treatment failure. Request extended DST, reassess clinical condition and prepare to present to NCAC for input • Repeat and review ECG * for QtcF prolongation
6 months	• Review all monthly smear and culture results • Consider eligibility for extension of BDQ to 9 months- refer section 3.5

	• If latest available smears **and** cultures are negative, stop BDQ and not eligible for BDQ extension, stop BDQ. • Stop INH_{hd} • If necessary, Lfx may be switched to Mfx when BDQ has been stopped • Repeat VL if person is on ART • If on EFV-based 1st line ART with viral suppression at baseline, may revert to this regimen if latest VL suppressed.
9 months	• Review all monthly smear and culture results • Stop treatment if there was no delay in smear conversion (at Month 4) and patient is clinically well and meets criteria for cure or treatment completion • If intensive phase was extended to 6 months and BDQ extended to 9 months, then stop BDQ (if applicable) and continue Z / E / Lfx / Cfz for another 2 months • Repeat and review ECG * for QtcF prolongation
11 months (for patients who had their intensive phase extended)	• Review all monthly smear and culture results • Stop treatment if patient is clinically well and meets criteria for cure or treatment completion • If there are any concerns, present case to PCAC / NCAC • Repeat and review ECG * for QtcF prolongation
6 months & 12 months post-completion of treatment	• Monitor for signs & symptoms of relapse- assess clinically, do CXR and send sputum for smear & culture. • Repeat and review ECG * for QtcF prolongation

m management of QtcF prolongation is outline in Annexure 7.

† ask if person has ever used drugs/alcohol in their life. If yes → do ***CAGE-AID or other screen***. ***Ask:*** 1. Have you felt you should cut down on your drinking or using drugs? 2. Have people annoyed you by criticizing your drinking or drug use? 3. Have you felt bad or guilty about your drinking or drug use? Have you ever had a drink or used drugs first think in the morning to steady your nerves or get rid of a hangover (eye opener***?). If answered YES to > 1 CAGE-AID question*** further screen with WHO ASSIST (http://www.who.int/substance_abuse/activities/assist_v3_english.pdf), and provide a brief counselling and education intervention. Patients that score *high risk* on WHO ASSIST may need referral to treatment.

‡ Ask about symptoms of depression or anxiety and manage accordingly.

ANNEXURE 6 – NCAC application details and criteria

To apply to the National Clinical Advisory Committee please send an email to:

ncac@witshealth.co.za

Date of presentation:	**Clinical Site:**	**For treatment as inpatient or outpatient?**
File or Hospital number:	**Date of Birth / Age:**	**Gender:**

Reason for submission for individualised regimen: (includes PTB and EPTB, regardless of HIV/ART status)

Cases for PROVINCIAL review		Cases for NATIONAL review	
	Pre-XDR TB (RIF, INH, plus resistance to either an injectable or a fluoroquinolone		Unable to construct a regimen with at least two of the following four drugs: a) fluoroquinolone, b) an injectable, c) linezolid, d) bedaquiline
	XDR TB (RIF, INH, injectable and fluoroquinolone		Under 18 years of age
	RR TB for drug substitution		Any stage of pregnancy
	MDR with both*inhA* and *KatG* mutations		Exposure to standard XDR regimen >3 months before submission for individualised regimen
	MDR failure (failure to convert at 6-8 months or confirmed reconversion at any point)		XDR failure (failure to convert at 6-8 months or confirmed reconversion at any point)

Other (describe):

Past Medical History (other than HIV and TB)

Details of cardiac abnormalities or other chronic diseases (include details of current medications and dosages, as well as monitoring parameters to assess level of control):

HIV STATUS	POSITIVE NEGATIVE UNKNOWN **Date tested:**		
ART DETAILS		Never received ART before	
		Previously on ART (but not now) **Regimen:**	
		Currently on ART; **Regimen: Duration (years):**	
Latest monitoring results:	**CD4:**	**VL:**	**HepB:**

	Date:	Date:	Date:
Further relevant details:			
TB History			
Previous TB episodes and treatment history (include dates and details of TB drugs received, any episodes of treatment interruption, and eventual treatment outcome):			
Current treatment episode and disease progression (include dates and details of TB drugs received and related toxicities or adverse events):			
Clinical Findings			
Describe site of disease and relevant findings on examination and further investigations:			

Weight: **Height:**	**Pregnant / Not pregnant:** **Date tested:** **Weeks gestation:** **EDD:**	**ECG date:** **QTcF:** **Other findings:**

Sputum Monitoring Chart:

Sample date	Lab #	GXP RIF	AFB Smear	Culture	LPA Rif	LPA INH	inh A	KatG	Am	Cm	Ofx	Mfx	Other

Blood Monitoring Chart:

Date	Na^+	K^+	Creat	GFR	Mg^{2+}	Ca^{2+}	WCC	Hb	Plts	ALT	TSH

Proposed Tailored Drug Regimen: (WEIGHT:)			
Drug	**Dose**	**Route**	**Frequency**

Other relevant information	
Responsible Medical Officer: (Name and signature)	**Date:**

ANNEXURE 7 – updated WHO grouping of TB medications

GROUP	MEDICINE	Abbreviations
Group A: **Include all three medicines (Unless they cannot be used)n**	Levofloxacin **OR** Moxiflozaixn	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: **Add both medicines (Unless they cannot be used)**	Clofazimine	CFz
	Cycloserine **OR** Terizidone	Cs
Group C: **Add to complete the regimen when medicines from Group A and TB cannot be used**	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin **OR** Meropenem	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)	Am (S)
	Ethionamide **OR** Prothionamide	Eto Pto
	p- aminosalicylic acid	PAZ

ANNEXURE 8 – ECG monitoring and management of QTc prolongation

QTcF on ECG at baseline	Action
<450 ms = normal	Start BDQ/ and repeat ECG after 2 weeks **(not eligible for BDQ if baseline QTcF>450ms-consult PCAC)**
QTcF on follow-up ECG done at 2 weeks then monthly	**Action**
<450 ms = normal	Cont BDQ with routine QTcF monitoring
450-469 ms or increase in interval <30 msec = mild prolongation	Cont BDQ with routine QTcF monitoring
470-499 ms or increase in interval 30-50 msec = moderate prolongation	If no clinical cardiac symptoms (chest pain, palpitations, dizziness and syncope) then continue BDQ and repeat ECG after **1 week** **If clinical cardiac symptoms then withhold BDQ and other QT-prolonging drugs and repeat ECG within 1 week**
>500 ms Or increase in interval ≥50 msec = severe prolongation	Stop BDQ, LFX & CFZ. Exclude other causes of QT prolongation (drugs, electrolyte disturbances, hypothyroidism) and manage appropriately. Repeat ECG after 48 hours. If QTcF decreasing, monitor **weekly.** When QTcF**<470ms, restart, LFX, CFZ & BDQ sequentially**, with QTcF monitoring in between.

	Consult an expert if QTcF remains elevated >470ms at 2 weeks.

ANNEXURE 9 – RR-TB treatment outcomes for the short regimen

Treatment outcome	DEFINITION
Cured	1. A patient who has TB culture converted. 2. Received treatment for a total duration of 9 months or more 3. Has at least 3 consecutive negative TB cultures during continuation phase (at least 30 days apart) 4. No evidence of clinical deterioration
Treatment completed (success)	1. A patient who has TB culture converted 2. Received treatment for a total duration of 9 months or more 3. Has less than 3 consecutive negative TB cultures during continuation phase (at least 30 days apart) 4. No evidence of clinical deterioration
Loss to follow up (previously known as defaulter)	1. A patient with treatment interrupted - >= 2 consecutive months - Any reason without medical approval
Treatment failure	1. A patient who failed to culture convert by month 6 2. In the initial 6 months of treatment - >= 2 of 5 cultures are positive - Clinical condition deteriorating 3. Treatment stopped on clinical grounds 4. More than 2 new drugs added because of poor clinical response 5. Was discussed at the Provincial Review Committee and the decision to terminate any further DR-TB treatment taken
Moved	1. Referred from one facility to another facility within the same district to continue treatment. This is not an outcome, but serves to match patient moving within the district to prevent double counting 2. The treatment outcome is reported by the facility where the patient is newly registered
Transferred Out	1. Referred from one facility to another reporting and recording facility in another district, province or country to continue treatment 2. The treatment outcome is reported by the facility where the patients is newly registered
Died	A patient who died 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.

ANNEXURE 10 – RR-TB treatment outcomes for the long regimen

Treatment Outcome	Definition
Cured	1. A patient who has TB culture converted. 2. Received treatment for at least 12 months after TB culture conversion 3. Has at least 3 consecutive negative TB cultures during continuation phase 4. Total duration of treatment not to be less than 18 months 5. No evidence of clinical deterioration
Treatment completed (success)	1. A patient who has TB culture converted. 2. Received treatment for at least 12 months after TB culture conversion 3. Has less than 3 consecutive negative TB cultures during continuation phase 4. Total duration of treatment not to be less than 18 months 5. No evidence of clinical deterioration
Loss to Follow Up	1. A patient with treatment interrupted - >= 2 consecutive months - Any reason without medical approval
Treatment Failure	1. A patient who failed to culture convert by month 6 2. In the final 12 months of treatment - >= 2 of 5 cultures are positive - Clinical condition deteriorating 3. Treatment stopped on clinical grounds 4. More than 2 new drugs added because of poor clinical response 5. Was discussed at the Provincial Review Committee and the decision to terminate any further DR-TB treatment taken
Moved	1. Referred from one facility to another facility within the same district to continue treatment. This is not an outcome, but serves to match patient moving within the district to prevent double counting 2. The treatment outcome is reported by the facility where the patient is newly registered
Transferred Out	1. Referred from one facility to another reporting and recording facility in another district, province or country to continue treatment 2. The treatment outcome is reported by the facility where the patients is newly registered
Died	Patient who dies for any reason during treatment
Still on treatment	Still on treatment after prescribed period
Not Evaluated	A category IV patient recorded in the register and did not receive any of the above outcomes

ANNEXURE 11 – Pharmacovigilance reporting form

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

NDoH Pharmacovigilance Centre for Public Health Programmes (NPC)
Adverse Drug Reaction (ADR) / Product Quality Problem Report Form
This report will be shared with the Medicines Control Council (MCC), 012 395 9133

Reporting Health Care Facility/Practice					
Tel: 012 395 9506 (NPC)	Facility/Practice				
Fax: 086 241 2473	District		Tel		
Email: npc@health.gov.za	Province		Fax		

Patient Details							
Patient Initials		File/Reference Number		Date of Birth/Age			
Sex	□M □F □Unk	Race		Weight (kg)		Height (cm)		Pregnant?	□N □Y
Allergies				Estimated Gestational Age at time of reaction			

Suspect Medicine(s) **[Medicines suspected to have caused the ADR]**

Trade Name [Generic Name if Trade Name is unknown]	Name of Manufacturer	Route	Dose (mg) and Interval	Date Started	Date Stopped	Reason for use	Batch Number / Expiry Date

All other Medicines Patient was taking at time of reaction **[Including over-the-counter and herbal products]**

Trade Name [Generic Name if Trade Name is unknown]	Name of Manufacturer	Route	Dose (mg) and Interval	Date Started	Date Stopped	Reason for use	Batch Number / Expiry Date

Adverse Drug Reaction/Product Quality Problem			
Date and time of onset of reaction		Date reaction resolved/duration	

Please describe Adverse Reaction/Product Quality Problem: (kindly add as much clinical information as possible)

Intervention **[tick all that apply]**	**Patient Outcomes** **[tick all that apply]**
□ No intervention	□ Patient recovered □ Patient recovering
□ Intervention unknown	□ Patient not recovering □ Outcome unknown
□ Patient counselled/non-medical treatment	□ Patient died; Date of death:_____
□ Discontinued Suspect Drug; **Replaced with**:_____	□ Impairment/Disability □ Congenital Anomaly
□ Decreased Suspect Drug Dosage; **New Dose**:_____	□ Patient hospitalised or hospitalisation prolonged
□ Treated ADR with:_____	□ Life threatening □ Other:_____
□ Referred to hospital; **Hospital Name**_____	□ ADR reappeared after restarting suspect drug/similar drug (rechallenge)?: □ N □ Y □ Not done □ Unknown
□ Other Intervention (e.g. dialysis): _____	

Laboratory Results

Lab Test	Test Result	Test Date	Lab Test	Test Result	Test Date

Co-morbidities/Other Medical Condition(s) **[tick all that apply]**

□ Hypertension □ Diabetes □ Asthma □ Tuberculosis □ HIV/AIDS □ Other:

Reported by

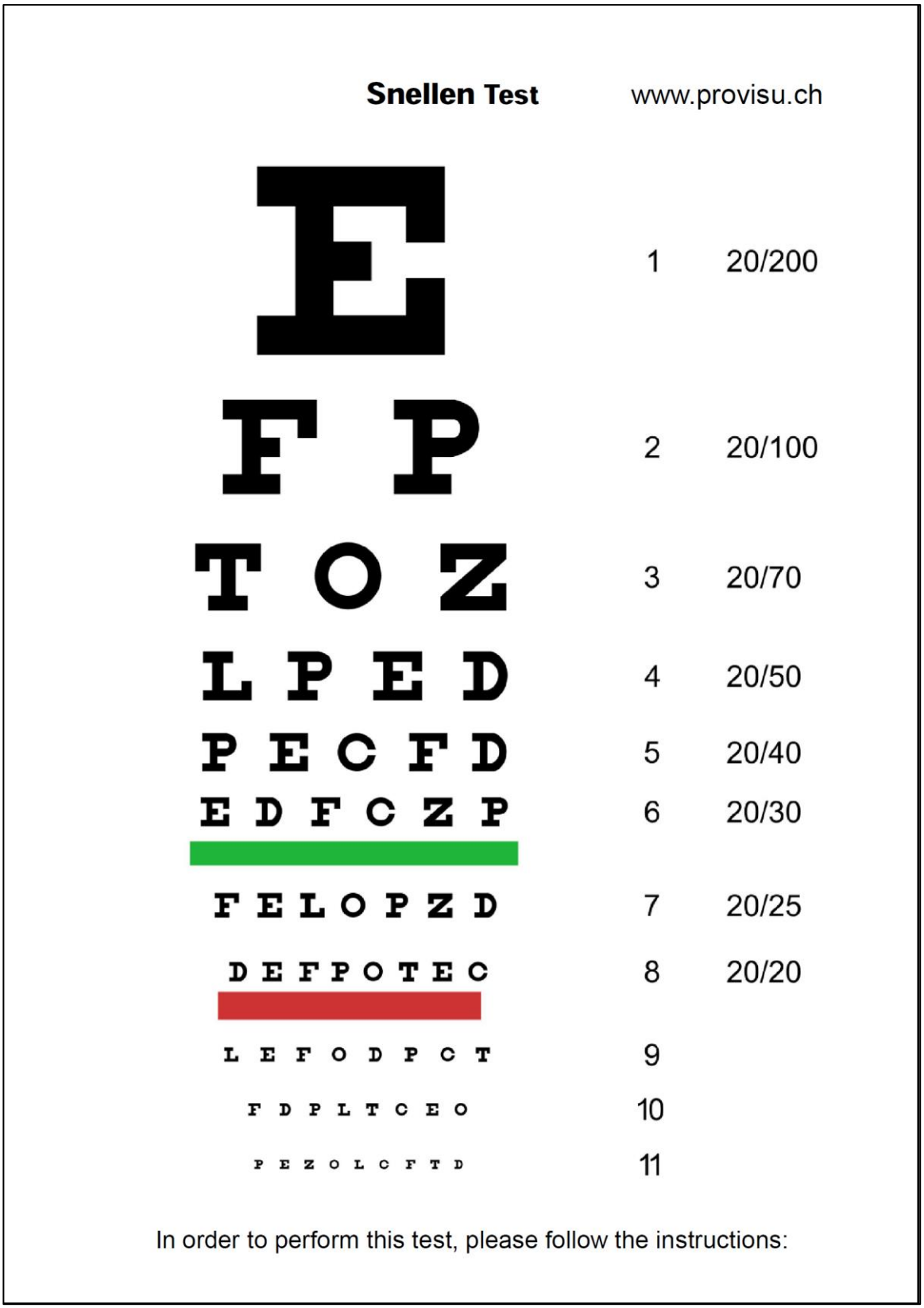
Name		E-mail	
Designation	□ Nurse □ Pharmacist □ Doctor □ Other:	Date Reported	
Telephone	Signature	**VERSION 33.0 June 2016**	

THIS ADR REPORT IS NOT A CONFIRMATION THAT THE REPORTER OR THE SUSPECT MEDICINE(S) CAUSED THE ADR

ANNEXURE 12 – Guidance on grading adverse events

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

ANNEXURE 13 – Snellen chart for assessing visual acuity



www.provisu.ch

Snellen Test

1. Print the test page in A4 standard format. Place yourself 2.8 meters (or 9 feet) away from the chart. If the test page is in another format, or if you wish to perform the test facing the screen, you will have to calculate the distance at which you must stand facing it, using the following formula: measure the height of the letter E (first line, 20/200) in millimeters. Then, divide the value of this measurement by 88. Finally, multiply it by 6. The result shows the distance at which you must be placed, in meters.
   E.g. (42/88) x 6 = 2.8 m

2. Test your visual acuity with correction (contact lenses or glasses).

3. Test one eye at a time. Start with the right eye, covering the left one without pressing on it. Then, examine the left eye by doing the opposite. If you are using correction glasses, you can cover the eye with a sheet of paper.

4. Read the letters from the largest to the smallest.

5. To make the examination easier and faster, another person can help you by showing the letters you must read among the lines of letters.

6. If you can read the letters of the 8th line, your sight is optimal (visual acuity 20/20).

7. If your visual acuity is less than 20/20 or if you have doubts about your sight, visit your ophthalmologist.

NOTE: take the results as a recommendation. The results do not indicate a diagnosis whatsoever. Performing the test does not mean you should skip regular visits to your eye doctor, because you could easily miss signs that only a trained eye care practitioner would find.

ANNEXURE 14: CONSENT FORM

CONSENT FORM FOR PATIENTS WITH DRUG RESISTANT TB (DR -TB)

UNDERTAKING BY PATIENT

I …….. (Name patient) of (residential physical address)

……

My date of birth is……../……../…… (Day/Month/Year)

Understand the nature of my disease and treatment as explained by the Medical Doctor/ Clinical Nurse Practitioner/Clinical Associate, hereby give an undertaking that

1. I have been informed that the duration of my treatment may be shorter (9 to 11 months) or longer (18 to 20 months) depending on what type of Drug Resistant TB I have. There will be a number of different medicines that I will have to take.
2. I will take the medicines that are prescribed to me and follow the instructions given to improve my health and protect that of others
3. I will tell the Medical Doctor/ Clinical Nurse Practitioner/Clinical Associate of any difficulties or problems in following treatment, or if I do not understand how to take my treatment.
4. I agree to be hospitalised (as needed) for the time to be determined by my Medical Doctor/ Clinical Nurse Practitioner/Clinical Associate if hospitalisation necessary to for me to get my medicines and to be followed up.
5. I have been told that my treatment regimen may contain clofazimine, a medicine which is not yet registered in South Africa but has been found to be very effective in treating my condition
6. I will provide the sputum specimens required to check if I am improving or not at least every month.
7. I will provide the blood specimens required to check for any potential side effects caused by the medicines
8. I will undergo electrocardiographic (ECG) to check my heart and audiometric tests(to check my hearing) needed to monitor any possible side effects
9. I will cover my mouth and nose when I cough at all times to prevent spreading the infection to others
10. I will show consideration and respect for the rights of other patients and health-care providers during my stay in the hospital

Name ……..Signature Patient: ……

Date: ……

UNDERTAKING BY HEALTH CARE WORKER (MEDICAL DOCTOR/CLINICAL NURSE PRACTITIONER/CLINICAL ASSOCIATE)

I, ……..... (Name of Medical Doctor/ Clinical Nurse Practitioner/Clinical Associate) at……

health care facility)

Undertake to:

1. Explain fully to you the nature of your disease and explain the treatment plan to you (including any side effects you might experience).
2. Provide you with regular clinical progress reports whilst on treatment
3. Ensure confidentiality of your medical condition at all times
4. Address your complaints or concerns to the best of my ability
5. Address any socio-economic problems you may encounter whilst in hospital as far as reasonably possible

Name: …….. Signature: ……..

Designation…….

Date: ……..

Witness: …….. Date: ……..

Witness ……. Date: ……..