Republic of Namibia
Ministry of Health and Social Services

Guidelines for the Management of Drug-resistant Tuberculosis in Namibia
2nd Edition

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PREFACE

Tuberculosis (TB) remains the top killer among infectious diseases globally, responsible for 1.4 million deaths annually. Drug resistance is especially challenging, with an estimated 580,000 incident cases of rifampicin resistance annually. However, only a small minority of those with while drug resistant TB globally access the correct treatment.

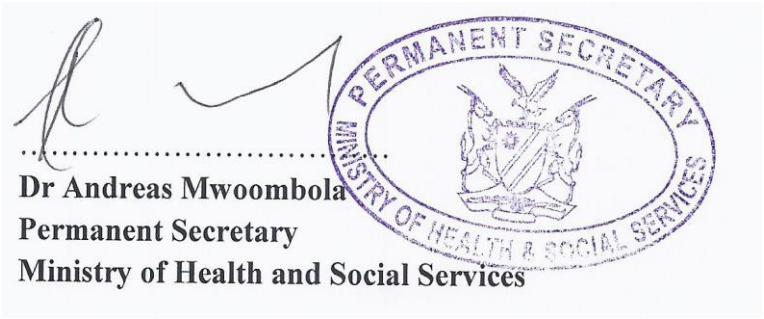
With almost 10,000 cases of TB notified in the country every year, Namibia remains among the World Health Organisation (WHO)'s list of 30 countries with the highest TB burden in the world. The country also has a high prevalence of HIV, with 38% of TB patients in 2016 being HIV-positive. Drug-resistant TB also poses a significant challenge for the country. The 2014/15 anti-TB drug resistance survey revealed that 3.9% of all new bacteriologically confirmed TB cases had multi-drug resistant (MDR) TB, confirming the findings of a similar survey carried out in 2008. This survey also revealed an MDR-TB prevalence of 8.7% among patients who had previously treated for TB.

The National Tuberculosis and Leprosy Programme (NTLP), under Ministry of Health and Social Services (MOHSS), introduced second-line anti-TB medicines in Namibia in the late 1990s for treatment of drug-resistant tuberculosis (DR-TB). The use of these medicines has been described in different editions of the National Guidelines for the Management of Tuberculosis, the latest being the third edition released in 2012.

Since 2007, when the first case of extensively drug-resistant tuberculosis (XDR-TB) was reported, the need for focussed efforts to address DR-TB has become increasingly clearer. These guidelines are based on the latest international recommendations for the diagnosis and management of DR-TB, and are intended for use by clinicians and other health workers involved in the day-to-day management of DR-TB in Namibia. The guidelines should be used alongside the National Guidelines for the Management of Tuberculosis.

This pocket guide is intended for use by all health workers.

The Ministry of Health and Social Services appreciates the efforts of all those who contributed directly or indirectly to the development of these guidelines.



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ABBREVIATIONS

AFB	acid-fast bacilli
AIDS	acquired immune-deficiency syndrome
ART	antiretroviral therapy
Bdq	bedaquiline
CB-DOTS	community-based directly-observed treatment
CBO	community-based organisation
CBTBC	community-based TB care
CCRC	central clinical review council
CPT	cotrimoxazole preventive therapy
Dlm	delamanid
DM	direct (smear) microscopy
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
DTLC	District Tuberculosis and Leprosy Coordinator
ECG	electrocardiogram
FDC	fixed-dose combination
FLD	first line drugs (in the context of anti-TB medicines)
FQ	fluoroquinolone
HIV	human immunodeficiency virus
IPT	isoniazid preventive therapy
KNCV	KNCV Tuberculosis Foundation
LPA	line-probe assay
MDR-TB	multidrug-resistant tuberculosis
MOTT	mycobacteria other than tuberculosis
MoHSS	Ministry of Health and Social Services
MTP	medium-term plan
NAAT	nucleic acid amplification test
NTLP	National Tuberculosis and Leprosy Programme
PDR	poly-drug resistant TB
PTB	pulmonary tuberculosis
SAT	self-administered treatment
SLD	second line drugs (in the context of anti-TB medicines)
SLI	second line injectable
STR	shorter treatment regimen for DR-TB
TB	tuberculosis
TB-IPT	isoniazid preventive therapy
TIPC	Therapeutics Information and Pharmacovigilance Centre
VCT	voluntary counselling and testing (for HIV)
XDR-TB	extensively drug-resistant tuberculosis

1. APPROACH TO A NEWLY DIAGNOSED DR-TB PATIENT

1.1. Overview

Development and spread of drug-resistant tuberculosis (DR-TB) must be prevented at all costs through early detection and effective treatment of both drug-susceptible and drug-resistant TB. Given the unique needs associated with second-line anti-TB treatment, patients with DR-TB should be managed by multidisciplinary teams, with each case discussed by a district and/or regional committee to maximise the chances of successful patient and treatment outcomes. Furthermore, the National TB and Leprosy Programme (NTLP) provides additional support for complicated cases as well as those requiring individualised treatment.

1.2. Definitions

Drug resistant tuberculosis refers to active TB caused by *mycobacterium tuberculosis* bacilli that are resistant to one or more anti-TB medicines.

Four different categories of DR-TB are of clinical significance:

- **Mono-resistance:** resistance to one first line anti-TB medicine.
- **Poly-drug resistance (PDR)**: resistance to more than one first line anti-TB medicine, other than both isoniazid and rifampicin.
- **Multidrug resistance (MDR)**: resistance to isoniazid and rifampicin with or without resistance to other medicines**.**
- **Rifampicin resistance (RR)**: resistance to rifampicin, with or without resistance to other medicines. This category includes MDR, rifampicin monoresistance, rifampicin polyresistance and those with rifampicin resistance detected by molecular methods such as Xpert MTB/RIF.
- **Extensively drug-resistance (XDR)**: resistance to any fluoroquinolone, and at least one of three injectable second-line medicines (capreomycin, kanamycin and amikacin), in addition to MDR.

1.3. Diagnosis of drug-resistant TB

1.3.1. Clinical history

While the detailed approach to the diagnosis of TB is outside the scope of these guidelines, the patient's TB history remains crucial to the interpretation of any DST results suggesting anti-TB drug resistance. *Table 1* outlines factors in the patient's history that are associated with anti-TB drug resistance.

Furthermore, the following risk factors should alert the clinician to the possibility of extensively drug-resistant (XDR) TB:

- Failure of an anti-TB treatment regimen which contains second-line anti-TB medicines particularly an injectable agent, and/or a fluoroquinolone.
- Close contact with an individual with documented XDR-TB or with an individual for whom treatment with a regimen containing second-line medicines is failing or has failed.
- Relapse after treatment for drug-resistant TB.

1.3.2. Clinical Examination

Clinical features of DR-TB are not particularly different from those of drug susceptible TB, but clinicians should be alert to the complications of TB, which may be more common in patients with DR-TB. While DR-TB is by definition a bacteriological diagnosis, a provision for clinical diagnosis of DR-TB can be made *(clinically diagnosed* cases) in some patients where bacteriological confirmation is unlikely. This situation may occur as symptomatic small children, severely immunocompromised adults or those with extra-pulmonary TB who are also close contacts of known patients with DR-TB cases.

1.3.3. Bacteriological Examination

All requests for bacteriological examination for TB must clearly indicate whether they are for diagnosis (in presumptive cases) or for monitoring (following up cases already on treatment) in the spaces provided on the appropriate laboratory form. All diagnostic specimens in Namibia will undergo molecular identification of mycobacterium tuberculosis with Xpert MTB/RIF, which also detects the presence of rifampicin resistance. For those with rifampicin resistance, additional
molecular testing with line probe assay to detect resistance to fluoroquinolone and second line injectables will be performed, in addition to a culture and full conventional drug susceptibility test.

Table 1: Factors suggestive of DR-TB in TB patients and people undergoing investigation for TB

RISK FACTORS FOR DR-TB	COMMENTS
Previous treatment for TB	Any previous treatment for TB increases the risk of drug resistance. The risk is much higher among those who have failed treatment than those who have been successfully treated or have completely abandoned treatment. The risk is also higher among those with early relapse (successfully treated less than two years previously)
Poor response to current TB treatment	Failure of sputum smears or cultures to convert at 2-3 months of first line treatment may be due to drug resistance.
Close contact with a case of DR-TB (known or unknown)	While contact with known DR-TB patient is an obvious risk factor, there is often need to explore for close contacts who may have died while on TB treatment, not doing well on TB treatment, have undiagnosed pulmonary symptoms, or have died from undiagnosed pulmonary symptoms.
High risk occupations	Health-care workers and people in congregate settings such as correctional service staff or inmates are at higher risk of exposure to undiagnosed DR-TB.
Unclear or inconsistent TB history	This may indicate prior exposure to non-standard anti-TB treatment or impaired adherence which by themselves increase the risk of DR-TB significantly.
HIV or other causes of immunosuppression	Although HIV alone may not increase the risk of drug resistance significantly, PLHIV who have previously hospitalised or had contact with other TB patients may be at increased risk of DR-TB.
High risk populations	There may be certain population groups such as residents of a certain locality or immigrants in whom outbreaks of DR-TB have been documented or are suspected.

Table 2: Interpreting results of bacteriological examination for TB

TEST	RESULT	SUGGESTED INTERPRETATION
Xpert MTB/RIF	MTB not detected	• TB negative by Xpert MTB/RIF • Active TB is unlikely; re-evaluate patient for risk factors • If extra-pulmonary specimen, disease in a young child or severely immunosuppressed patient, send specimen for mycobacterial culture and phenotypic DST. • Consider additional investigations (X-ray, histology)
	MTB detected; Rifampicin resistance **not** detected	• TB positive with rifampicin sensitivity • This is active TB, to be managed as drug susceptible TB. 'False' positive result is possible if the patient has recently been successfully treated for TB.
	MTB detected; Rifampicin resistance detected	• TB positive with rifampicin resistance • This is active TB; MDR TB is likely (but discordance with conventional DST is not uncommon)
	MTB detected; Rifampicin resistance indeterminate	• TB positive, but rifampicin sensitivity cannot be confirmed on submitted specimen • Repeat test on another specimen from same patient, while treating for presumed drug-susceptible TB
	Error, insufficient specimen, invalid, etc.	• Conclusions cannot be made from submitted specimen, so new specimen should be submitted
Sputum smear	Any Positive	• This is active mycobacterial disease, probably TB • May be interpreted as possible MOTT if Xpert MTB/RIF is negative
	Negative	• May still be active TB, especially if Xpert MTB/RIF and/or culture results are positive • May not be active TB
Mycobacterial culture	No growth after 6 weeks (negative)	• Active TB is highly unlikely if Xpert was also negative • If Xpert or smear were positive in a diagnostic specimen, consider this to be a false negative; patient must be reviewed further
	Mycobacterium Tuberculosis growth	• Culture positive TB • This is active TB; DST results must be followed up
	Mycobacteria other than tuberculosis	• Active TB is unlikely, if Xpert was also negative • If Xpert showed MTB, consider this to be a contamination • MOTT diagnosis requires confirmation with repeat culture or molecular diagnosis on a separate specimen
	Contaminated, lost viability or other invalid	• Conclusions cannot be made from submitted specimen, please re-submit specimen for repeat investigation

1.4. Mycobacterial culture and drug susceptibility testing (C/DST)

Maximum efforts should be made to follow-up or obtain results of culture and DST for patients who are to be started on second-line treatment Occasionally, culture may be negative in cases that are bacteriologically positive by other methods, due to the following factors that can impact negatively on the **culture yield**:

- Poor quality of the sample and/or sample collection procedure
- Delays in specimen transport,
- Inappropriate storage, including during transport,
- Excessively harsh or insufficient decontamination (in the laboratory), and
- Poor quality culture media or incorrect incubation temperature.

Laboratory errors, such as mislabelling or cross-contamination between specimens, may also lead to false-negative or false-positive results.

Due to the high burden of TB in Namibia, the vast majority of mycobacterial isolates are *Mycobacterium tuberculosis*. Results indicating mycobacteria other than tuberculosis (MOTT) should always be interpreted with clinical correlation in mind because MOTT growth in laboratory conditions does not always mean that MOTT is the primary cause of disease. When there is discordance with the clinical picture, isolation of MOTT may be due to contamination or non-pathogenic colonisation.

All cases of rifampicin resistance, including those with MDR –TB and suspected XDR-TB, should also have genotypic and phenotypic DST to the second-line medicines.

Limitations of DST include the following:

- DST is most accurate for rifampicin and isoniazid and less reliable or reproducible for streptomycin, ethambutol and pyrazinamide[1].
- Discordance between phenotypic DST and genotypic DST (usually by Xpert MTB/RIF) to rifampicin may occur, usually due to the higher sensitivity of Xpert MTB/RIF. This must be interpreted carefully.
- DST for second-line anti-TB medicines is much less reliable or reproducible. DST to fluoroquinolones and injectables is relatively reproducible.

Laboratory results should therefore always be interpreted in relation to the patient's history and clinical condition.

[1] DST to pyrazinamide is not routinely available in Namibia

2. TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

2.1. Overview

In general, drug-resistant TB is treated using second line anti-TB medicines, as the standard first line regimens are unlikely to work. Treatment of drug-susceptible forms of TB is covered in the *National Guidelines for the Management of Tuberculosis* and it generally makes use of standardised first line regimens.

2.2. Criteria for starting second line regimens

2.2.1. Patients immediately eligible for second line anti-TB treatment

Patients with the following DST results are immediately eligible for second line anti-TB treatment:

- Confirmed resistance to rifampicin.
- *Confirmed MDR-TB***:** Resistance to at least isoniazid (H) and rifampicin (R)**.**
- Confirmed poly-drug resistant TB:
  - Resistance to isoniazid (H) and ethambutol (E) +/- streptomycin (susceptible to rifampicin).
  - Resistance to rifampicin and ethambutol +/- streptomycin (susceptible to isoniazid).

2.2.2. Other groups of patients eligible for second line medicines

In the absence of bacteriological confirmation, the following are eligible for second line treatment after considering all circumstances around the patient:

- Young children under the age of five years who are diagnosed with active TB, with a close contact, especially a parent or caregiver who has bacteriologically confirmed DR-TB.
- Immunosuppressed patients diagnosed with active TB who are close contacts of known DR-TB patients.
- Relapse, failure or return after loss to follow-up on second-line treatment and smear or culture positive.

2.3. Principles of second-line anti-TB therapy

Table 3 outlines the available medicines for the treatment of DR-TB while *Table 4* summarises the basic principles of second-line anti-TB therapy.

Table 3: Grouping of second line anti-TB medicines

Group		Name	Abbreviation
A. Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second line injectables (SLI)		Amikacin Capreomycin Kanamycin (Streptomycin)	Am Cm Km (S)
C. Other core Second line agents		Ethionamide/Prothionamide Cycloserine/Terizidone Linezolid Clofazimine	Eto/Pto Cs/Trd Lzd Cfz
D. Add-on Agents	D1	Pyrazinamide Ethambutol High dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	p-amino salicylic acid Imipenem-cilastatin Meropenem Amoxicillin-clavulanate (Thioacetazone)	PAS Ipm Mpm Amx-Clv (T)

2.4. Selecting the appropriate second line anti-TB regimen

In selecting appropriate treatment for patients with DR-TB three possibilities may be considered:

- Shorter DR-TB treatment regimen (STR) for eligible uncomplicated patients,
- Longer regimen for uncomplicated patients who are ineligible for the STR, or
- Individualised regimens for complicated patients.

2.4.1. The shorter DR-TB treatment regimen

The STR represents a new standardised approach to managing most of uncomplicated cases of DR-TB, with reduced costs, reduced toxicity and potential for improved adherence and overall treatment outcomes. However, there should be careful selection of eligible patients for this 9-11-month regimen.

2.4.1.1. Patients eligible for the STR

- Patients with RR-TB who have not been previously treated with second-line medicines and with low risk of, or with DST results excluding additional resistance

to medicines in STR, particularly the fluoroquinolones and/or second-line injectable.

- Children and HIV infected patients with clinically diagnosed TB who have not been previously treated with SLD and with low risk of additional resistance to fluoroquinolones and/or second-line injectable who have been in close contact with patients with RR-/MDR-TB

2.4.1.2. Patients not eligible for the STR

- Patients with confirmed resistance to second-line injectable or fluoroquinolone by either SL-LPA or phenotypic drug susceptibility testing.
- Patients with suspected resistance to second-line injectable or fluoroquinolone based on contact with an index case or other risk factor.
- Pregnant women.
- Patients already on treatment with a conventional DR-TB treatment regimen for more than a month.
- Patients with high risk of treatment failure, such as severe TB disease (e.g. multiple cavities, extensive parenchymal damage).
- Patients with intolerance to any of the medicines in the STR.
- Patients with extra-pulmonary TB. However, patients with TB pleural effusion and children with TB lymphadenitis may be considered for the STR.

2.4.1.3. Regimen design for the STR

The STR is given as a standardised regimen with little or no room for customisation with substitutions or switches during treatment.

- The intensive phase consists of kanamycin[2], high dose moxifloxacin[3], ethionamide[4], clofazimine, pyrazinamide, ethambutol and high dose isoniazid daily for four months.
- The intensive phase may be extended to a maximum of six months if smear conversion occurs beyond the third month. If a sputum smear conversion is not achieved within four months kanamycin may be given thrice-weekly from the fifth month onwards, but the NTLP must be alerted.
- The continuation phase consists of high dose moxifloxacin, clofazimine, ethambutol and pyrazinamide for a fixed duration of five months;

[2] Amikacin and capreomycin are acceptable alternatives
[3] Gatifloxacin is an acceptable alternative
[4] Prothionamide is an acceptable alternative

- The shorter TB regimen is a standard regimen, so no customisations are allowable except for the ones described herein.
- If the patient remains smear positive and/or is still culture positive at 6 months, the patient will be declared as a *treatment failure*. A *treatment failure* declaration and a switch to an individualised treatment regimen may also be considered earlier in patients with clear lack of response (clinically, smear grading, culture).
- In case of diagnosis of any resistance to fluoroquinolone and/or second-line injectable or adverse effects requiring change of 2 medicines, the patient will be registered as *treatment failure* and an individualised regimen will be designed (not shorter regimen).

The abbreviated notation for the STR is as follows:

4-6Km*-Mfx-Eto-Cfz-Z-H^h-E / 5 Mfx-Cfz-Z-E

(Km=Kanamycin; Mfx=Moxifloxacin; Eto=Ethionamide; Cfz=Clofazimine; Z=Pyrazinamide; H^h= high-dose Isoniazid; E=Ethambutol).

* The 4-6 preceding the Km indicates the variable nature of the intensive phase between 4-6 months depending on smear and/or culture conversion.

Table 4: Basic principles of second-line anti-TB therapy

Basic principle	Comments
1. Management of DR-TB should always involve teamwork	• Decisions by individual practitioners without consultation are discouraged. • All cases of DR-TB should be presented to the responsible district or regional committee. • All individualised regimens for DR-TB must be presented to the NTLP.

2. Use at least 4 medicines certain to be effective.	• Effectiveness of a specific medicine is supported by a number of factors:
	  ○ DST results show susceptibility (for medicines in which there is good laboratory reliability).
	  ○ No prior history of treatment failure with the medicine.
	  ○ No known close contacts with resistance to the medicine.
	  ○ Drug resistance survey documents that resistance is rare in similar patients.
	  ○ The medicine is not commonly used in the area.
	• If at least 4 medicines are not certain to be effective, use 5 – 7 medicines depending on the specific medicines and level of uncertainty.
	• In the case of unclear evidence about the effectiveness of a certain medicine, it can be part of the regimen but it should not be counted as one of the four.

3. Treatment regimen should be based on the history of medicines taken by the patient.	• History of medicine use is often more reliable than a DST in predicting resistance
4. Do not use medicines for which there is high likelihood of cross-resistance.	• Many anti-TB agents exhibit cross-resistance both within and across medicine classes. Knowledge of these relationships is essential in designing regimens for DR-TB.
5. Substitute medicines that are not safe in the patient.	Unsafe use of medicines includes situations where there is • Known severe allergy or unmanageable intolerance, or • High risk of severe adverse medicine effects such as renal failure, deafness, hepatitis, depression and/or psychosis.
6. Include medicines from Groups A to C.	• Regimens should include four core second-line medicines plus pyrazinamide. • If a minimum of four core second-line TB medicines cannot be reached by using agents from Groups A to C alone, medicines from Group D2 (in adults) or, if not possible, medicines from Group D3 are added. Pyrazinamide is added routinely unless there is confirmed resistance from reliable DST, or well-founded reasons to believe that the strain is resistant, or there is risk of significant toxicity. • In all individualised regimens, a medicine from Group D2 (either delamanid or bedaquiline) must be considered, unless contra-indicated.
7. A single new medicine should never be added to a failing regimen.	• This practice tends to amplify resistance

2.4.2. Individualised DR-TB treatment regimen for uncomplicated patients

Most patients continuing treatment for uncomplicated DR-TB before the introduction of the STR will fall into this category. They should continue their regimen as prescribed and monitored as outlined in the guidelines.

Patients with rifampicin resistance who are ineligible for the STR but have no suspected or confirmed resistance to the fluoroquinolone and/or second-line injectable, have not been treated with second-line medicines and have no intolerance may be considered for the conventional regimen.

2.4.2.1. Steps when designing the conventional (longer) treatment regimen for uncomplicated patients

1. Select one medicine from Group A (often levofloxacin),
2. Select one medicine from Group B (kanamycin),
3. Select 1-2 medicines from Group C (often ethionamide and cycloserine; may consider linezolid and/or clofazimine)
4. Add pyrazinamide,
5. Consider high-dose isoniazid and/or ethambutol depending on DST results
6. Add bedaquiline or delamanid if considered safe to do so

A widely-used version of this conventional regimen is shown in Table 5. It should be noted, though, that the version of this regimen without a Group D2 agent is expected to be largely phased out, as experience and availability of D2 medicines increases.

Table 5: Suggested individualised regimen for uncomplicated patients

Initial Phase		Continuation Phase	
Medicines	Minimum duration in months	Medicines	Minimum duration in months
Kanamycin Ethionamide Levofloxacin Cycloserine, and Pyrazinamide +/- Ethambutol subject to susceptibility + High dose pyridoxine	8 months *and* lasting at least 4 months after culture conversion	Ethionamide Levofloxacin, and Cycloserine +/- Ethambutol +/- Pyrazinamide + High dose pyridoxine	12 months

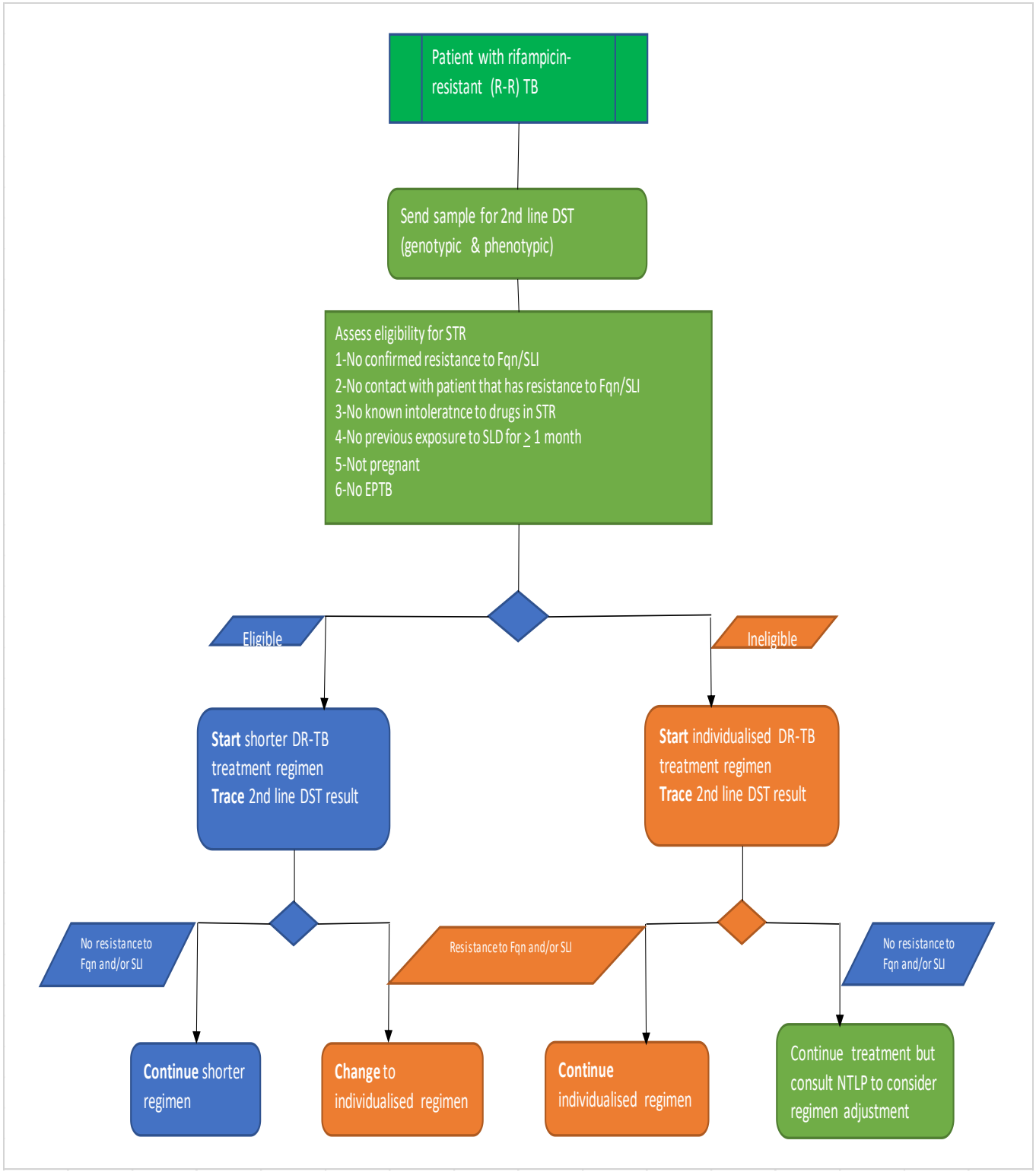

Figure 1 (above): Selecting patients for the STR

2.4.3. Individualised DR-TB treatment regimen for complicated patients

Complicated patients will include patients with rifampicin resistance in whom the STR and the individualised regimen for uncomplicated patients cannot be used. These include all those with intolerance or resistance to injectable and/or fluoroquinolone (confirmed or suspected) as well as those who have been treated with SLDs before.

These patients should only be treated with regimens approved by the NTLP, preferably based on a proposed regimen by the regional teams taking into account the treatment history and DST patterns (including from second line LPA). The regimen design should include the following aspects:

1. Select either bedaquiline or delamanid.
2. Select one medicine from Group A (often moxifloxacin or high-dose levofloxacin),
3. Select one medicine from Group B which has not been used previously or to which there is susceptibility,
4. Select medicines from Group C (preferably those that have not been used before),
5. Add pyrazinamide (but do not count as one of the effective medicines),
6. If 4-5 *effective* medicines are not in the regimen yet, select from group D3 (only one of imipenem and meropenem can be selected). Where options are severely limited, a combination of bedaquiline *and* delamanid may be considered under special approval.

2.5. Treating other forms of drug resistance

2.5.1. Regimens for poly-drug resistant TB

Care should be taken to evaluate the medical history for possible resistance which may have developed, but may not be apparent from the laboratory results. As such, treatment for poly-drug resistant TB should never rely solely on DST results.

2.5.1.1. Poly-drug resistance with resistance to rifampicin (susceptible to isoniazid)

These patients should be treated with the same regimens as for MDR-TB, with isoniazid at a high dose included. The majority of these patients will be eligible for the STR.

2.5.1.2. Poly-drug resistance with susceptibility to rifampicin

Caution should be taken when interpreting these DST results, as many patients with DST results suggesting poly-drug resistance actually have MDR-TB. One therefore

needs to also look at the treatment history. When in doubt, treat as MDR-TB and consult the NTLP. The regimen for confirmed PDR-TB will include rifampicin as follows:

- Initial phase: At least Rifampicin, kanamycin, levofloxacin, ethionamide and pyrazinamide for at least 4-6 months and 2 consecutive negative cultures.
- Continuation phase: Rifampicin, levofloxacin and ethionamide for at least 6 months.

2.5.2. Regimens for mono-resistant TB

2.5.2.1. Rifampicin monoresistance

These patients should be treated with the same regimens as for MDR-TB, with isoniazid at a high dose included. The majority of these patients will be eligible for the STR.

2.5.2.2. Isoniazid monoresistance

If this is discovered while the patient is already on treatment, the standard first-line treatment regimen may be continued, but a new sample should be sent for DST. If susceptibility to a high concentration of isoniazid is confirmed, then high dose isoniazid may be used in the standard first-line regimen and the continuation phase may have to be modified appropriately. There is need for closer monitoring of these patients.

2.5.3. Regimens for extensively drug-resistant (XDR) TB

XDR-TB and MDR-TB with additional resistance to fluoroquinolones and/or second line injectables present a significant clinical challenge. Principles of regimen design remain as outlined for MDR-TB, with most patients being eligible for the individualised DR-TB treatment regimen for complicated patients. Treatment options are severely limited, and there should be adequate consultation before commencing treatment.

2.6. Dosing of medicines for treatment of DR-TB

Table 6 summarises the dosages of second line anti-TB medicines in adults.

2.6.1.1. Dose escalation (dose ramping)

Most medicines can be started at full dose. The dose of ethionamide, cycloserine and PAS can however be increased over a 2-week period in situations where side effects are likely to occur.

2.6.1.2. Dosing frequency

Most anti-TB medicines, including all those in the STR, should be given once a day as the high peaks attained in once-a-day dosing are more efficacious. Once-a-day dosing is preferred for other second-line medicines depending on patient tolerance. However, ethionamide, cycloserine and PAS may be given in split doses during the day to reduce adverse effects. If DOT cannot be assured for twice daily dosing, it is preferable to give these medicines once daily.

Table 6: Dosing of second line oral medicines in adults

Medicine	DAILY DOSE	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400-800mg/day	400 mg	600 mg	600mg	800mg	800 mg
Ethionamide	500–750 mg/day	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day	500 mg	500 mg	500 mg	750 mg	750 mg
p-amino salicylic acid	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Delamanid	100 mg twice daily (total daily dose = 200 mg)					
Clofazimine	100 mg daily	100mg	100mg	100mg	100mg	100mg
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanic-acid 7/1	80 mg/kg/day in 2-3 divided doses[5]	1750 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanic-acid 8/1	80 mg/kg/day in 2-3 divided doses5	2000 mg	3000 mg	3000 mg	3000 mg	3000 mg
High-dose isoniazid	10mg/kg, maximum 600mg/day	300mg	400mg	500mg	600 mg	600mg
Imipenem/cilastatin	1000mg imipenem/1000 mg cilastatin twice daily					
Meropenem	1000mg three times daily (alternative dosing is 2000 mg twice daily)					

Table 7: Dosing of second line injectable in adults

MEDICINES	DAILY DOSE	30–33 kg	34–40 kg	41–45 kg	46–50 kg	51–70 kg	>70 kg
Kanamycin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Amikacin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Capreomycin	15–20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg	1000 mg

2.7. Extrapulmonary DR-TB

In general, extrapulmonary DR-TB is treated with the same strategy and length of time as pulmonary DR-TB. However, experience with the use of shorter treatment regimens for patients with extrapulmonary disease is limited, hence the recommendation to use

[5] If combined with meropenem, dosage must be at the same frequency as meropenem

individualised (longer) regimens. Adjuvant therapy with corticosteroids may be considered when the TB affects the central nervous system, pericardium, eye, larynx or if it causes severe bilateral pleural effusion.

2.8. Role of surgery

Patients with MDR TB and *all* of the following should be considered for surgical intervention:

- Patients who remain smear positive, while on fully monitored treatment for more than six months, *and*
- Have resistance to a large number of medicines, *and*
- Have localised pulmonary disease.

The most common operative procedure in patients with pulmonary DR-TB is resection surgery. Generally, at least two months of therapy should be given prior to resection surgery to decrease the bacterial load in the surrounding lung tissue. Even with successful resection, an additional 12-24 months of chemotherapy should still be given. Patients who are eligible for surgery in this way are generally not eligible for the shorter treatment regimen.

2.9. Adjuvant therapy

- Vitamin B6 (pyridoxine) should be given to all patients receiving cycloserine to minimise neurological side effects. The standard dose is 50mg of pyridoxine for every 250mg of cycloserine. Pyridoxine (preventive 25mg-100mg/day; treatment up to 200mg/day) may also be given to counter neuropathic effects of isoniazid, ethionamide or linezolid.
- Multivitamin tablets may be given to patients, particularly where there are concerns of nutritional inadequacies, but care should be taken as mineral-containing multivitamins can interfere with the absorption of fluoroquinolones.
- Gastric protection with an H2 antagonist (e.g. ranitidine) or proton pump inhibitor (e.g. omeprazole) may be given to patients receiving both ethionamide and PAS.
- Corticosteroids (Prednisolone 1 mg/kg and gradually decreasing to 10 mg per week when a long course is indicated) may be used in the following conditions:
  - Central nervous system involvement,
  - Pericarditis,

- Severe immune reconstitution syndrome,
- Severe bilateral pleural effusion,
- Tuberculosis of the eye,
- Tuberculosis of the larynx.

3. TREATMENT OF DR-TB IN SPECIAL CONDITIONS AND SITUATIONS

3.1. Children

- In general, childhood DR-TB is managed the same way as in adults, with the exception that it is often difficult to obtain sputum samples in younger children. Majority of bacteriological results in young children will be negative, even if disease is present.
- Children are often infected by adults; therefore, the source case must always be identified. It is often justifiable to treat children empirically for DR-TB based only on clinical presentation and a known close contact with DR-TB. Such patients on treatment without bacteriological confirmation may be termed *Clinically Diagnosed cases* of DR-TB.
- Monthly monitoring of body weight is especially important in paediatric cases, with adjustment of doses as children gain weight.
- Gastric aspirate samples can be used for both diagnostic and monitoring purposes.
- All medicines, including the fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible.
- In children who are not culture-positive initially, treatment failure may be difficult to assess. Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement.
- Weight loss or, more commonly, failure to gain weight adequately, is often one of the first (or only) signs of treatment failure.

3.2. Pregnancy

- Most pregnant patients should be started on treatment as soon as the diagnosis is made. However, since most teratogenic effects occur in the first trimester, and if the patient wishes, treatment may be delayed until the second trimester for very stable patients with minimal disease.
- Treatment regimen must contain 3-4 oral second-line anti-TB effective medicines plus pyrazinamide. The regimen should be reinforced with an injectable agent and other medicines as needed immediately postpartum.

- Despite limited data on safety and long-term use of fluoroquinolones, Cs, PAS and Amx/Clv in pregnancy, they are considered the medicines of choice for DR-TB treatment during pregnancy.
- Aminoglycosides can be particularly toxic to the developing foetal ear and so can, to a lesser extent, capreomycin. Cm is the injectable medicine of choice if an injectable agent cannot be avoided because of an immediate life-threatening situation resulting from DR-TB.
- Ethionamide may be avoided as it can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.
- There may not be a clear transition between the intensive phase and continuation phase, and the injectable agent can be given for three to six months postpartum even in the middle of treatment, depending on bacteriological response.

Table 8: Dosage of second line medicines in children

Medicine name	Daily paediatric dose in mg/kg (max dose in mg)
Bedaquiline [6]	400mg daily for 2 weeks, then 200mg 3 times a week
Delamanid	20 – 34kg 50mg twice daily, for 24 weeks >35kg 100mg twice daily, for 24 weeks
Fluoroquinolones	
Levofloxacin	15 – 20 (1000)
Moxifloxacin	7.5 – 10 (800)
Second-Line Injectable	
Kanamycin	15 – 20 (1000)
Amikacin	15 – 20 (1000)
Capreomycin	15 – 20 (1000)
Other core second-line agents	
Ethionamide/protionamide	15 – 20 (1000) 2x daily
Cycloserine/terizidone	10 – 20 (1000) 1x/2x daily
Linezolid	10mg/kg/dose twice daily for children < 10; 300mg daily for children ≥ 10 years of age (600)
Clofazimine	2 – 3 (200)
Add on agents	
Pyrazinamide	30 – 40
Ethambutol	15 – 25
Isoniazid	7 – 15
PAS	200 – 300
Amoxicillin – clavulanate	80 (4000 amoxicillin and 500 clavulanate)
Meropenem	20 – 40 (6000)

[6] There is no recommendation for general use of bedaquiline in children under the age of 12, but there is limited experience with adolescents for whom it may be used if options are severely limited.

3.3. Breastfeeding

- Institute full course of anti-TB treatment even in breastfeeding mothers.
- Where feasible, alternative infant feeding options may be provided (especially if the mother is considered highly infectious and/or there are significant concerns about unknown effects of second line anti-TB medicines in breast milk on the baby).
- It should be noted, however, that *breast milk is often the best and sometimes the only feasible feeding option for most infants*. Any arrangement to care for the baby must consider the dangers of unsafe replacement feeding practices.
- If the mother is sputum smear-positive, family members may be approached to assist with the care of the infant until she becomes sputum smear-negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should be offered a surgical mask until she becomes sputum smear-negative.
- In addition, bonding of the infant with the mother or a designated guardian should be promoted to provide adequate psycho-emotional stimulation.

3.4. Contraception

Although there is no contraindication to the use of oral contraceptives with the non-rifampicin containing regimens, all female DR-TB patients of child-bearing age should be offered injectable contraception or intra-uterine contraceptive device (if available) to avoid the risk of falling pregnant while on treatment. The use of condoms should generally be recommended.

3.5. Diabetes mellitus

- Diabetic patients with DR-TB should be managed in consultation with a specialist or experienced physician due to the dysglycaemic effects of some medications such as ethionamide and fluoroquinolones. It is desirable that the diabetes be under control at DR-TB treatment initiation and throughout DR-TB treatment.
- Diabetics have an increased likelihood of baseline renal dysfunction and risk of nephrotoxicity.
- Monitoring of renal function and electrolytes must be more frequent than in non-diabetic patients (at least weekly while on the injectable).
- Weekly or more frequent monitoring of blood glucose is warranted.

3.6. Renal insufficiency

Care should be taken in the administration of second-line anti-TB medicines in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to *Table 9*. The formula to calculate the estimated creatinine clearance rate (CrCI) is as follows:

$$\textbf{\textit{Estimated Creatinine clearance}} = \frac{(\mathbf{140} - \textbf{\textit{Age}})\ \textbf{\textit{x}}\ (\textbf{\textit{body weight in kg}})\ \textbf{\textit{x}}\ \mathbf{1.23}}{\textbf{\textit{serum creatinine}}, \mu\textbf{\textit{mol/l}}}$$

In female patients, the above is multiplied by 0.85. Normal values are *97 to 137ml/min for males* and *88 to 128ml/min for females*

3.7. Liver disorders

- Patients with a history of liver disease can receive the usual DR-TB chemotherapy regimens provided there is no clinical evidence of severe chronic liver disease; recent history of acute hepatitis or excessive alcohol consumption. However, closer monitoring of liver function is warranted.
- In general, patients with chronic liver disease should not receive pyrazinamide. All other medicines can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the medicines responsible may have to be stopped.
- Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-TB treatment. In this case, it is possible to defer anti-TB treatment until the acute hepatitis has been resolved. When it is necessary to treat DR-TB during the acute hepatitis, the combination of four non-hepatotoxic medicines is the safest option.

Table 9: Adjustment of commonly used anti-TB medicine dosages in patients with renal insufficiency

Medicine	Change in dosage?	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving haemodialysis
Isoniazid	No change	No change	300 mg once daily
Rifampicin	No change	No change	600 mg once daily
Pyrazinamide	No change	Yes	25–35 mg/kg per dose *3 times per week*
Ethambutol	No change	Yes	15–25 mg/kg per dose *3 times per week*
Levofloxacin	No change	Yes	750–1000 mg per dose *3 times per week*
Moxifloxacin	No change	No change	400mg once daily
Clofazimine	No change	No change	100mg once daily
Cycloserine	Yes	Yes	250 mg once daily or 500mg *3 times per week*
Ethionamide	No change	No change	250–500 mg per dose *daily*
PAS	No change	No change	4 g/dose, twice daily
Streptomycin	Yes	Yes	12–15 mg/kg per dose *2-3 times per week*
Capreomycin	Yes	Yes	12–15 mg/kg per dose *2-3 times per week*
Kanamycin/Amikacin	Yes	Yes	12–15 mg/kg per dose *2-3 times per week*
Linezolid	No change	No change	600mg once daily
Delamanid	No change	No change	Not enough evidence – use with caution
Bedaquiline	No change	No change	Not enough evidence – use with caution
Amoxicillin/clavulanate	Yes	Yes	1000mg once to twice daily
Meropenem	Yes	Yes	500mg twice to thrice daily

3.8. Seizure disorders

- Cycloserine should be avoided in patients with poorly controlled seizure disorders. However, in cases where cycloserine is a crucial component of the treatment regimen, it can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. The risks and benefits of using cycloserine should be discussed with the patient and the decision whether to use cycloserine made together with the patient.
- Caution must also be exercised when giving isoniazid as it may trigger seizures.
- The use of isoniazid and rifampicin may interfere with some commonly used anti-seizure medications. Interactions should be checked before their use.
- Seizures that present for the first time during anti-TB therapy are likely to be the result of an adverse effect of one of the anti-TB medicines, particularly cycloserine or isoniazid.

3.9. Psychiatric disorders

- Patients with a history of overt psychiatric illness should be evaluated by a psychiatrist at some point, preferably early during treatment for DR-TB and at any point if symptoms re-appear. Any psychiatric illness identified should be fully addressed.
- There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often related to the chronicity of the condition and socioeconomic stress factors associated with the disease.
- Medical treatment, individual counselling and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication. Group therapy provides a supportive environment for DR-TB patients and should be provided for all patients, including those without psychiatric conditions. Every facility that treats patients with DR-TB is encouraged to conduct regular support group sessions for these patients.
- Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of cycloserine may outweigh the risk. Close monitoring is recommended if it is used in patients with psychiatric disorders.
- All facilities treating DR-TB should have an organised system for psychiatric emergencies (e.g. psychosis, suicidal tendencies, etc.).

3.10. Substance dependence

- Patients with substance dependence disorders, including alcohol dependence, should be offered treatment for their addiction. Consultation with social workers, psychiatrists and/or the drug rehabilitation centres is encouraged to formulate the treatment plan.
- Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication to anti-TB treatment.
- If DR-TB treatment is repeatedly interrupted because of the patient's dependence to alcohol or psychoactive substances, TB treatment may be suspended until measures to ensure adherence have been established.
- Good DOT facilitates patient contact with and support from health-care providers, which often improves treatment outcomes even in patients with substance dependence.

- Cycloserine will have a higher incidence of adverse effects in patients who are dependent on alcohol or other substances, and predisposes to seizures. However, if cycloserine is considered important to the regimen, it should be used and the patient closely observed for adverse effects, which should then be adequately treated.

4. ORGANISATION OF TREATMENT

4.1. Initiating treatment

Once a diagnosis of rifampicin resistant TB has been made, the local DR-TB team/committee should meet and assess the eligibility to the STR. The team will document the decision and propose treatment. Meanwhile the patient should be prepared as set out in *Figure 2*. Preferably, the treatment decision should be informed by the results of the second line LPA on second-line injectable and fluoroquinolone resistance.

4.2. Hospital admission

While it is preferable to hospitalise patients starting treatment for DR-TB to perform baseline tests, stabilise them and prepare for the long-term treatment support; hospitalisation should not be viewed as mandatory; the priority should be on ensuring delivery of a well supervised effective treatment regimen to the patient.

4.3. Discharging from the hospital

Hospitalised patients with DR-TB may only be discharged from the hospital to continue treatment on an ambulatory basis if the following criteria have been met:

1. The treating doctor, DTLC, social worker and nurse in charge must all agree that the patient can be discharged.
2. The DTLC must have arranged for assured continuation of DOT after discharge.
3. The DOT provider should have met the patient.
4. The medical team should have met the family or relatives to discuss DOT options as well as TBIC.
5. The social worker should certify that the home environment facilitates adherence to treatment.
6. The environmental health practitioner or nurse must assess the patient's residence.
7. Documentation to the receiving health district or facility must be completed.

4.4. Ambulatory treatment

Ambulatory treatment refers to treatment that is provided on an outpatient basis. It is generally the preferred method of treatment delivery; there is widespread evidence of superior or comparable treatment outcomes when compared to hospitalisation-based models of care. The decision on a management model should be on an individualised basis. For patients being initiated on DR-TB treatment using the ambulatory care model

it is mandatory that all necessary logistics are put in place to ensure daily administration of the injectable.

The following ambulatory treatment options are considered:

- **Ambulatory throughout treatment**: Initiate treatment on an ambulatory basis with no hospitalisation unless there is a drastic change in circumstances.
- **Ambulatory after stabilisation**: Hospitalise to initiate treatment, then discharge to ambulatory care once clinical condition has stabilised, and major symptoms have been controlled.
- **Ambulatory after sputum conversion**: Hospitalise until no longer infectious, as determined by smear and/or culture conversion.
- **Ambulatory in continuation phase**: Hospitalise for the whole duration of the initial/injectable phase.
- **No ambulatory treatment**: Hospitalise throughout the duration of treatment, unless a change in circumstances warrants ambulatory treatment.

Based on the above-mentioned models, the duration of hospital stay may range from a few days to several months. Patients and their families must be informed of this in advance, particularly on the potential for prolonged hospital stay depending on the circumstances. A social worker should be available to help the patients and their families deal with the psychosocial consequences of prolonged hospitalisation and treatment. DR-TB touches on all aspects of the patient's life, hence the need for these patients to be managed by a multidisciplinary team.

Error! Reference source not found.*2* and *figure 3* summarise the approaches to the management of DR-TB in Namibia. Local standard operating procedures can be developed based on this summary.

4.5. Use of multi-disciplinary teams

Facilities managing DR-TB should have a committee responsible for planning and overseeing the management of these patients. These teams should include, among others, the following:

- The district tuberculosis and leprosy coordinator (DTLC),
- At least two medical officers (preferably including a senior medical officer),
- Pharmacist or pharmacy assistant,
- Nurse-in-charge of the TB ward,
- Social worker,

- DOT worker (field supervisor, coordinator or training officer),
- Clinical mentor, where available,
- Rehabilitation professional (physiotherapist, occupational therapist or medical rehabilitation worker),
- Other clinical and management staff depending on need and availability,

PRE-TREATMENT ASSESSMENT

1. Go through the Regimen Eligibility checklist to determine the most appropriate regimen.
2. Discuss implications of treatment with the patient and family, and sign the DR-TB treatment consent form.
3. Conduct a full clinical assessment and record the weight and height.
4. Collect baseline sputum for direct microscopy, and culture and DST
5. Perform HIV counselling and testing if HIV status is unknown.
6. Collect blood for FBC, U&E, LFT, TSH, CD4 count (if HIV+ and not on ART) or HIV viral load (if on ART >3 months); and urine for pregnancy test (women).
7. Perform baseline Chest X-ray examination.
8. Perform baseline ECG and measure the QTc interval.
9. Conduct social assessment to address potential psychosocial barriers to treatment (e.g. care of children, rent, occupation, etc).
10. Perform baseline audiometry.
11. Ensure adequate documentation (DR-TB register; DR-TB patient booklet; electronic tools).
12. Screen (and document) all close contacts for symptoms. Where appropriate, follow up with sputum Xpert MTB/RIF, culture/DST, chest X-ray, and/or other relevant investigations. Children under 5 years will require special attention.
13. Consult the NTLP where necessary.

INTENSIVE PHASE OF TREATMENT

1. The patient must be on at least 5 anti-TB medicines, including an injectable and fluoroquinolone.
2. Daily DOT by a health care worker is mandatory.
3. Perform and document weekly side effects screening.
4. Collect monthly sputum for DM and culture, and document results.
5. Collect blood for monthly U&E and document serum potassium and estimated creatinine clearance rate. In patients at risk of renal impairment, this should be performed weekly.
6. Perform monthly audiometry and document the audiogram.
7. Perform monthly ECG monitoring and document QT interval.
8. Repeat Chest X-ray at 4 months then at 9 month for those on STR and every 6 months for those on individualised regimen.
9. Arrange for regular reviews by the social worker.
10. Arrange for regular reviews by the rehabilitation professional (occupational therapist, physiotherapist, medical rehabilitation worker).

Figure 2 (above): Management of DR-TB patients during the intensive phase

PREREQUISITES FOR CHANGING FROM INTENSIVE PHASE TO CONTINUATION PHASE

1. The patient should have completed at least
    - 4-6 months of the intensive phase if on the STR
    - 6 months or more of intensive phase if on the individualised regimen.
2. The patient should have completed at least 2 months of intensive phase treatment after **culture conversion**. This may be waivered in cases of EPTB or in whom it is not possible to obtain monthly sputum for cultures.
3. The patient should have clinically improved

CONTINUATION PHASE OF TREATMENT

1. Duration of continuation phase is
    - At least 5 months if on STR
    - At least 12 months if on individualised regimen
2. The patient must be on *at least* 3 anti-TB medicines
3. Patient swallows medicine daily under direct observation by a designated and accountable DOT supporter
4. Weekly supplies of medicines are provided to the DOT supporter by the health facility nurse
5. The patient is reviewed monthly by the TB focal nurse, and is assessed for side effects and sputum samples are collected for DM
6. Sputum samples for collected for culture are collected every month and the patient is reviewed by the doctor

DISCHARGING THE PATIENT FROM TREATMENT

1. The local DR TB committee including the doctor and the DTLC must agree on the outcome
2. The following final treatment outcome classifications may be assigned: *Cured*, *Treatment completed*, *Lost to follow-up*, *Failed*, *Died* (NB: Please note that '*transferred-out*' should not be routinely assigned as a final outcome)
3. All documentation (including electronic forms) should be updated accordingly
4. Arrangements should be made to follow up the patient 3-monthly for one year, with symptom screening as well as sputum DM and culture.

Figure 3 (above): Management of DR-TB patients during the continuation phase

PRE-REQUISITES FOR AMBULATORY TREATMENT OR DISCHARGING THE PATIENT FROM HOSPITAL

1. The treating doctor, DTLC, social worker, nurse in charge and a community TB care supervisor must all agree that the patient can be managed from their usual place of residence.
2. The DTLC and the CBTBC supervisor must have arranged for assured continuation of DOT after discharge.
3. The DOT provider should have met the patient and his/her family.
4. The medical team should have met the family or relatives to discuss DOT options as well as TBIC.
5. The social worker should certify that the home environment facilitates adherence to treatment.
6. The environmental health practitioner, IC nurse or DOT provider must assess the patient's residence.
7. Documentation to the receiving health district or facility must be completed.
8. As a minimum, the treating team should ensure that the patient has a clear understanding of the following:
    - ✓ How often the medicines are to be taken,
    - ✓ How often the DOT supporter collects medicine from the health facility,
    - ✓ When and where the next appointment,
    - ✓ When and why the next sputum sample is needed,
    - ✓ What to do if there is a problem,
    - ✓ How to prevent transmission at home and in the community, and
    - ✓ How long the treatment is expected to last.

Figure 4 (above): Pre-requisites for ambulatory treatment

5. TREATMENT MONITORING

5.1. Pre-treatment screening and evaluation

Pre-treatment evaluation offers the best opportunity to prepare the patient for DR-TB treatment. More intensive monitoring is indicated in patients with pre-existing conditions (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others).

Table 10: Examination at baseline and monitoring during the intensive phase (IP) of the STR

Month in the intensive phase	0	IP1	IP2	IP3	IP4	IP5	IP6
Body weight	X	X	X	X	X	X	X
Sputum smear	X	X	X	X	X	X	X
Sputum culture	X	X	X	X	X	X	X
Sputum DST[7] (1st & second line)	X						
LFT	X	X		X			
U&E	X	X	X	X	X	X	X
FBC	X			X			
Serum glucose	X						
TSH	X			X			
Audiogram	X	X	X	X	X	X	X
Visual test	X						
HIV	X						
Pregnancy test	X						
ECG	X	X	X	X	X	X	X
CXR	X				X		

Table 11: Monitoring during the continuation phase (CP) of the STR

Month in the continuation phase	CP1	CP2	CP3	CP4	CP5
Body weight	X	X	X	X	X
Sputum smear	X	X	X	X	X
Sputum culture	X	X	X	X	X
LFT	X			X	
Audiogram	X	X	X		
ECG	X				

[7] DST includes both conventional DST and 2nd line LPA, which should have been performed during diagnosis

5.2. Monitoring progress of treatment

- *Monitoring symptom and signs*: Patients should be asked about symptoms at every encounter if possible, and screened for side effects. For children, height and weight should be measured regularly to ensure that they are growing normally. The recurrence of TB symptoms after sputum conversion, for example, may be the first sign of treatment failure.
- *Laboratory monitoring*: Sputum smear and culture examination must be performed **monthly throughout the entire treatment duration**.
    - Culture conversion is not equivalent to cure. A certain proportion of patients may initially convert and later revert to positive sputum cultures.
    - It is usually not necessary to repeat DST regularly during treatment. For patients who *persistently* remain smear and culture-positive during treatment or who are suspected of having treatment failure, DST to second line medicines should be repeated.
    - In addition to pointing to treatment failure, persistently positive sputum smears may indicate colonisation of damaged lungs by mycobacteria other than TB. This may be confirmed by mycobacterial culture results.
- *Radiological monitoring:* For both the shorter and longer treatment regimens baseline chest radiographs should be performed, and repeated at six months (four months for the STR) and whenever clinically indicated. In some patients being considered for surgery, a thoracic CT scan is justifiable.

5.3. Monitoring for adverse effects during treatment

5.3.1. Symptom monitoring

Patients should be routinely screened for adverse effects at least weekly during the intensive phase, and monthly during the continuation phase.

DOT providers should be trained to screen patients regularly for symptoms of common adverse effects: rash, gastrointestinal symptoms (nausea, vomiting, and diarrhoea), psychiatric symptoms (psychosis, depression, anxiety, and suicidal ideation), jaundice, ototoxicity, peripheral neuropathy and symptoms of electrolyte wasting (muscle cramping, palpitations). DOT providers should also be trained in simple adverse effect management and when to refer patients to a nurse or doctor.

5.3.2. Biochemical monitoring

Blood should be collected for monthly monitoring of electrolytes and renal function. It should be noted that second-line injectables may generally cause serum electrolyte imbalances, particularly electrolyte wasting. Patients may present with hypokalaemia and occasionally hypocalcaemia and hypomagnesemia. If not corrected, hypokalaemia can cause fatal cardiac arrhythmia, in addition to general fatigue and muscle weakness. Second-line injectables may also cause nephrotoxicity, manifesting as a lowering of the creatinine clearance rate. The team should note that serum creatinine alone may not be sensitive enough to detect worsening renal compromise; the creatinine clearance or glomerular filtration rate should be periodically calculated and charted. Liver function and serum uric acid may be monitored every three months, particularly because of the potential pyrazinamide toxicity.

5.3.3. Audiometry

Audiometric examination should be performed at baseline and at least monthly while the patient is receiving the second-line injectable. In addition to physical examination of the ears with an otoscope, an audiogram is charted for each audiometric measurement, denoting the hearing intensity threshold (in decibels-dB, shown on the vertical axis) for each ear at various frequencies (in Hertz-Hz, shown on the horizontal axis). The threshold on the right ear is usually plotted as an O whereas that for the left ear is plotted as an X. Normal hearing threshold ranges from *0dB* to *26dB* hearing level.

Table 12: Interpreting the threshold hearing levels on an audiogram

Threshold level (read per frequency per ear)	Classification
0-25 dB	Normal hearing
26-40 dB	Mild hearing loss
41-70 dB	Moderate hearing loss
71-90 dB	Severe hearing loss
>90 dB	Profound hearing loss

It is helpful to read more than one audiogram for each patient to determine the trend. The typical pattern of hearing loss caused by second-line injectables is sensorineural, affecting high-frequency perception first, and manifesting as a drop in the hearing threshold intensity at the higher frequencies compared to previous audiograms. This drop may be detected with regular audiometry before the patient notices it, and should be addressed early before the patient suffers significant disability.

Ototoxicity is present when there is

a) 20dB decrease at any one frequency,

b) 10dB decrease at any two adjacent frequencies, or

c) Loss of response at three consecutive test frequencies where responses were previously obtained.

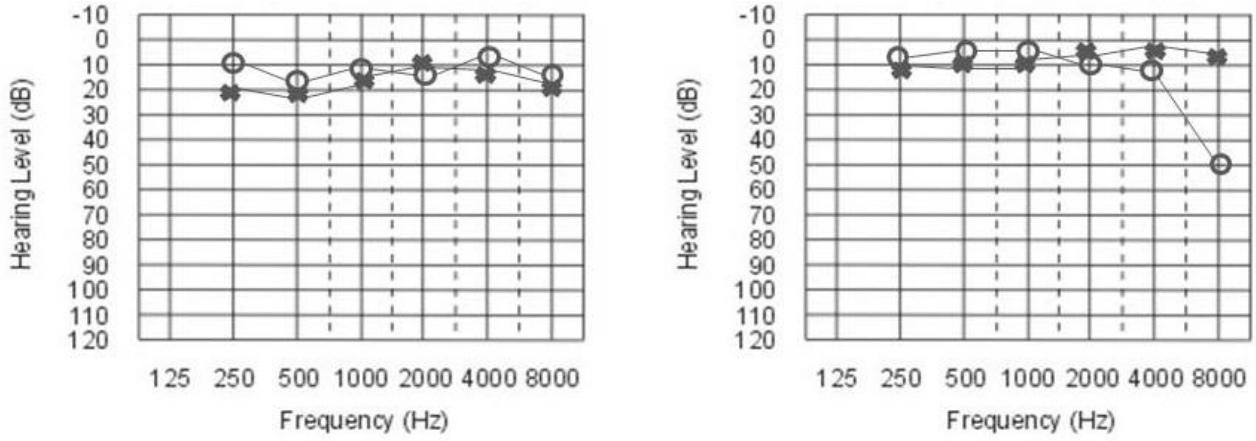

Figure 5: Example of an audiogram showing a 35dB decrease in hearing threshold on the right ear at 8000Hz (right) from a normal baseline (left)

5.3.4. Electrocardiography

Clofazimine, moxifloxacin, bedaquiline and delamanid are potentially cardiotoxic, with toxicity manifesting as prolongation of the QT interval. Baseline and monthly ECGs with a standard 12-lead ECG machine are required to monitor the QT interval. It is desirable to obtain a corrected QT interval (QTc) using the Fredericia method (QTcF). The primary reading should be performed on Lead II, Lead V5 or Lead V6, by medical officers familiar with interpreting ECG waves.

The QTcF correction method may be automated and reported by some ECG machines, while it may sometimes have to be manually read. Where possible, even with automated reading, supplementation with manual reading is recommended. Manual reading can be performed as follows:

1. From the 12-lead ECG printout, choose Lead II, V5 or V6 as they usually best show the end of the T wave.
2. Measure the **QT interval** from the beginning of the QRS complex to the end of the T wave. This is the uncorrected QT. Measure at least three successive beats, with the maximum interval taken, in case these three beats differ.

a) Make an imaginary line on Q and on T on one heartbeat on the selected lead.

b) Count the number of small squares between Q and T: 8 small squares (in the example below).

c) Multiply the number of squares by the unit time per square (0.04 sec): 8 small squares X 0.04 sec **= 0.32** seconds.

d) Multiply the result by 1000 to change seconds to milliseconds: **QT = 320ms.**

3. Similarly, measure the RR interval.
4. Calculate the QTcF using a medical calculator (online or from a smartphone application) or using the formula below.

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

5. QTcF intervals may be interpreted using *Table 13* below.

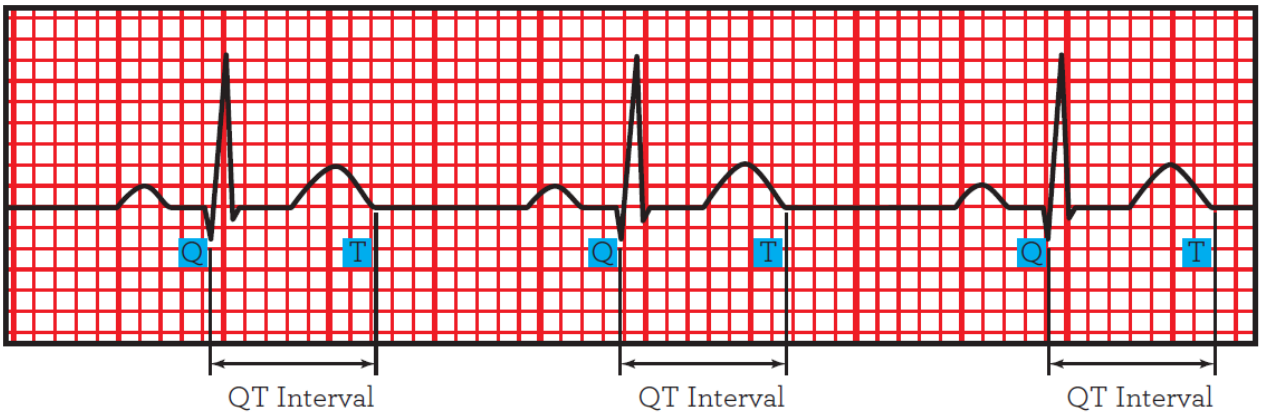

Figure 6: Sample of an ECG tracing showing the QT intervals

5.4. Management of adverse effects

Before starting treatment, the patient should be counselled in detail about the potential adverse effects of the prescribed medicine regimen, and when to notify a health-care provider. Prompt evaluation, diagnosis and treatment of adverse effects is extremely important, even if the adverse effect is not particularly dangerous. Patients may have significant fear and anxiety about an adverse effect if they do not understand why it is happening. These emotions in turn may worsen the perceived severity of the adverse effect, as in the case of nausea and vomiting. Preventive treatment should be applied where necessary, e.g. Pyridoxine (vitamin B6) 50 mg for every 250 mg of cycloserine for all patients receiving cycloserine to minimise neurological adverse effects. Pyridoxine is also routinely added to regimens containing linezolid or high-dose isoniazid.

Psychosocial support is an important component of the management of adverse effects, and DOT providers should educate patients about their adverse effects and encourage

them to continue treatment. Patient support groups can provide psychosocial support to patients.

If the adverse effect is mild, treatment should be continued with the help of ancillary medicines if needed. Most adverse effects diminish with time, and patients may be able to continue receiving the medicine.

Options for managing adverse effects include the following (see also *Annex 3*)

- Reassurance and psycho-emotional support,
- Ancillary and/or symptomatic treatment of an adverse effect while continuing the anti-TB regimen,
- Reducing the dose and/or dosing frequency of an offending medicine,
- Suspending the offending medicine,
- Discontinuation of the offending medicine(s),
- Substituting the offending medicine(s),
- Suspending the entire regimen, and
- Complete discontinuation of treatment.

Complete discontinuation of therapy because of adverse effects is rarely necessary. Proper management of adverse effects begins with patient education.

Table 13: Interpreting ECG QTcF intervals

QTcF	Male	Female	Action needed
Normal	<430ms	<450ms	If feasible, supplement with manual reading
Borderline	430-450ms	450-470ms	Supplement with manual reading
Prolonged	>450ms	>470ms	Supplement with manual reading Perform more frequent ECG monitoring Monitor electrolytes closely
	Increase of 60ms from baseline		
Dangerous	≥500ms		Discontinue Bdq, Dlm and all QT prolonging medicines

6. MANAGEMENT OF CLOSE CONTACTS OF DR-TB PATIENTS

6.1. Overview

Close contacts of MDR-TB and XDR-TB patients are defined as people living in the same household, or spending many hours a day together with the patient in the same indoor living space.

Contact investigation is an integral part of managing DR-TB. All close contacts of DR-TB patients should be evaluated for symptoms using the standard TB symptom screening questionnaire. Attention should be paid to those contacts who are below the age of 5 years, and those who have HIV infection. Management of these contacts depends on whether they have symptoms of TB or not.

The use of second-line anti-TB medicines for chemoprophylaxis in DR-TB contacts is currently not widely recommended. In addition, strains infecting close contacts of MDR-TB TB patients are likely to be resistant to isoniazid, therefore the widely-used isoniazid preventive therapy is unlikely to work.

6.2. Asymptomatic contacts

Close contacts of known DR-TB patients should receive careful clinical follow-up every 3 months for a period of at least two years.

- They should be offered screening tests for active TB as well as an HIV test.
- Asymptomatic contacts who are HIV positive, should be offered anti-retroviral therapy and TB screening at every visit per the national guidelines. Isoniazid preventive therapy may also be offered as a general standard of care, not necessarily related to the current (DR-TB) contact.
- Asymptomatic contacts who are under the age of 5 years should be further evaluated with a tuberculin skin test. If the tuberculin skin test reaction is greater than 10mm in an HIV negative asymptomatic contact or greater than 5mm in an HIV infected asymptomatic contact, the clinical team may evaluate the contact for possible chemoprophylaxis[8], with expert consultation.

6.3. Contacts who develop symptoms and signs of tuberculosis

These patients should be evaluated by a medical officer, and should all be offered an HIV test, if not already done. An effort should be made to establish a bacteriological diagnosis (and obtain DST) in a patient with suspected DR-TB, including paediatric patients. It may be noted, though, that bacteriological confirmation may not always be

[8] Though not routinely recommended, chemoprophylaxis may be considered for children in certain circumstances.

possible in young children, and a negative test in a symptomatic child does not exclude disease. In addition to the routine evaluation and management of presumptive TB case, the following should be performed:

- Bacteriological testing on sputum, gastric aspirate or any other appropriate specimen (tests include rapid DST and TB C/DST).
- Chest X-ray examination.
- Tuberculin skin test (in children).

If active TB is strongly suspected or confirmed, an empirical regimen based on the resistance pattern of the index case is warranted, particularly for small children and immunocompromised adults.

7. RECORDING AND REPORTING FOR DRUG RESISTANT TB

7.1. Case registration

Any patient with TB must be classified in terms of anatomical site, history of previous treatment, bacteriological status including drug resistance and HIV status. Once a diagnosis of DR-TB is confirmed, or if a decision to commence empirical treatment for DR-TB is made, this and other relevant information is then recorded in the following tools:

1. District Drug-resistant TB register,
2. Drug-resistant TB Patient Booklet (also known as the DR-TB Treatment Card), and
3. Electronic TB Manager (*eTB Manager*).

7.1.1. Classification based on anatomical site

- Pulmonary tuberculosis (PTB) refers to a case of TB involving the lung parenchyma. This will be the most common form of drug-resistant TB.
- Extrapulmonary tuberculosis (EPTB) refers to a case of TB involving organs other than the lungs, e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. EPTB cases could be either bacteriologically confirmed or clinically diagnosed. However, for a diagnosis of drug resistant EPTB to be made, there must be bacteriological confirmation of resistance, or a positive contact history with a case of DR-TB.

7.1.2. Classification based previous treatment

A patient with TB can either be new or previously treated.

- **New** refers to a patient who has never received anti-TB treatment, or has received less than one month of anti-TB treatment at the time of diagnosis.
- **Previously treated** refers to a patient who has previously received 1 month or more of anti-TB treatment. Previously treated patients may be further registered as follows:
  - **Relapse:** A patient who was previously treated for TB and whose most recent treatment outcome was cured or treatment completed, and who is subsequently diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

- **After loss to follow-up**: A patient who had previously been treated for TB and was declared lost to follow-up at the end of the most recent course of treatment.
- **After failure of first treatment with first-line medicines**: A patient who has received first-line treatment for TB and in whom treatment has failed.
- **After failure of retreatment regimen with first-line medicines**: A previously treated TB patient who has received a retreatment regimen with first-line medicines and in whom the retreatment has failed.
- **Other previously treated patients:** A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented.

Additionally, previously treated patients may be categorised by the type of anti-TB treatment previously received, which can be either

- Previously treated with first line medicines, or
- Previously treated with second line medicines.

7.1.3. Classification based on bacteriological status and drug resistance

Patients with TB can either be bacteriologically confirmed or clinically diagnosed. Bacteriological confirmation can either be through molecular methods, mycobacterial culture or smear microscopy. Bacteriologically confirmed cases are further classified based on resistance to the main medicines as follows:

- *Multi-drug resistance (MDR):* Resistance to at least isoniazid and rifampicin.
- *Extensive drug-resistance (XDR):* MDR plus resistance to any fluoroquinolone, and at least one injectable second-line medicines (capreomycin, kanamycin, or amikacin)
- *Mono-resistance:* Resistance to one anti-TB medicine. *Rifampicin mono-resistance (Rif Mono)* is of special interest because patients with rifampicin monoresistance are managed the same way as those with MDR-TB.
- *Poly-drug resistance (PDR):* Resistance to more than one anti-TB medicine, but not both isoniazid and rifampicin.
- *Rifampicin resistance (RR):* resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB medicines. It

includes any resistance to rifampicin, in the form of monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

- *Rifampicin resistance by GeneXpert (RifXpert)*: resistance to rifampicin detected using Xpert MTB/RIF genotypic test. This is an interim classification pending further drug susceptibility test results to guide final classification. It should be noted that this may be with or without resistance to other anti-TB medicines and the final classification may be rifampicin monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

Patients may be placed on second-line anti-TB treatment based on a confirmed or presumptive diagnosis of drug resistance.

- **Confirmed drug resistance** (usually MDR, XDR, PDR, RifMono or RifXpert), for which there is bacteriological confirmation of the type of resistance
- **Presumed drug resistance**, referring to patients put on second line treatment without bacteriological confirmation of the resistance they are being treated for.

7.1.4. Classification based on HIV status

HIV status must also be recorded at registration (*positive/negative/unknown*), and if unknown, point of care counselling and testing is recommended. In addition, for those who are positive, the antiretroviral treatment status should be recorded, bearing in mind that all HIV positive TB patients are expected to be on antiretroviral therapy. The ART regimen, start date and the cotrimoxazole start date must also be recorded.

7.2. Bacteriological monitoring and interim outcome classification

7.2.1. Initial bacteriological classification

For a patient to be considered bacteriologically confirmed at the start of a second line treatment regimen, the following criteria must be met:

- At least one pre-treatment culture, smear, genotypic test was positive;
- The collection date of the sample on which the culture or smear or Xpert MTB/RIF was performed was less than 30 days before, or 7 days after, initiation of second line TB treatment.

7.2.2. Sputum conversion

Sputum conversion (smear or **culture)** is defined as two sets of consecutive negative smears or cultures, from samples collected at least 30 days apart in a patient who was

initially smear/culture positive[9]. Both bacteriological techniques (smear and culture) should be used to monitor patients throughout therapy.

Conversion date refers to the date of the first set of negative cultures and smears. Culture conversion rate at 6 months is used to assess programme performance.

7.2.3. Interim outcomes

At regular intervals, quarterly cohorts are monitored for conversion, whether still on treatment, and adverse outcomes (death, failure and loss to follow up). Each regional team must monitor cohort interim outcomes every three months. The conversion rate at 6 months may be used as a proxy for successful progression of treatment.

7.3. Final treatment outcomes

All patients should be assigned a final outcome when they complete the treatment regimen and/or at the end of the cohort reporting period. This outcome should be registered in the DR-TB treatment register, on the Patient Booklet and the relevant electronic symptoms. Any of the following final outcomes may be assigned:

- **Cured**: Treatment completed as recommended by the national policy without evidence of failure *and* three (3) or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
- **Treatment completed:** Treatment completed as recommended by the national policy without evidence of failure *but* no record that three (3) or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
- **Treatment failed:** Treatment terminated or need for permanent regimen change of at least two anti-TB medicines because of:
    - Lack of conversion by the end of intensive phase; or
    - Bacteriological reversion in the continuation phase after the conversion to negative; or
    - Evidence of additional acquired resistance to fluoroquinolones or second-line injectable medicines; or
    - Adverse drug reactions (ADRs).
- **Died:** A patient who dies of any cause during the course of treatment.
- **Lost to follow-up:** A patient whose treatment was interrupted for two or more consecutive months.

[9] When assessing bacteriologic progress, the date the *sputum was collected* is used, and not the date the results were obtained

- **Not evaluated:** A patient for whom no treatment outcome is assigned (this includes cases ‘transferred out' to another treatment unit and whose treatment outcome is unknown).
- **Treatment success:** The sum of Cured and Treatment Completed.

A patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown may have the outcome assigned as *not evaluated***.** Patients who have *transferred in* should have their outcomes reported back to the treatment unit at which they were originally registered.

7.4. Cohort analysis

All patients should be analysed in two different cohorts:

- **The treatment cohort** includes only patients who start treatment. It is defined by the date of start of treatment.
- **The diagnostic cohort** includes patients diagnosed with DR-TB (identified in the DST Register by date of diagnosis or DST result) during a specific period.

8. PREVENTION OF TRANSMISSION

8.1. Preventing transmission in health-care facilities

As with all air-borne diseases, facilities caring for patients with DR-TB should ensure adequate interventions to prevent nosocomial transmission of TB (please refer to the *National Tuberculosis Infection Control Guidelines).*

8.1.1. Administrative infection control measures

An infection control plan (ICP) must be formulated for every facility and/or department. It should outline responsibilities of staff and the patient separation policy, among other things. The administration should be able to support the ICP, including providing quality assurance to the measures outlined therein. Staff trainings and regular screening for TB are essential for all those working in direct contact with DR-TB patients.

Patients with DR-TB should be physically separated (preferably isolated) from other patients. DR-TB patients should further be separated according to type of resistance, sputum conversion status and duration of treatment. All patients with DR-TB should be provided with surgical masks to prevent them from emitting infectious droplets, and should use these when indoors. Sputum collection should preferably be performed outdoors.

The principle of 'FAST' for TB infection control will apply, as follows:

- **F**inding cases quickly, by use of rapid molecular methods and expediting results,
- **A**ctive case finding through cough surveillance, and screening all those at risk for first line and second line drug resistance,
- **S**eparating safely, especially until effective treatment based on DSTs begins, and
- **T**reat effectively, with the appropriate regimen on molecular drug susceptibility testing results.

Ongoing patient education will foster the cooperation of patients in implementing infection control measures. Increasing community awareness, including education of family members/contacts may also help to reduce transmission of DR-TB.

8.1.2. Environmental infection control measures

Facilities caring for patients with DR-TB should have an *'open window policy'* in all areas used by presumptive TB patients, confirmed TB patients and DR-TB patients to promote natural ventilation. Fans may help to enhance dilution of air if used with open windows. Candle smoke, burning paper or a vaneometer can be used to determine if airflow direction is indeed from the 'clean' to the 'contaminated' area.

Where upper room ultraviolet germicidal units are installed, they require regular maintenance, and must be kept on all the time for them to be effective. They should be cleaned at least twice a year and lamps replaced every year.

8.1.3. Personal respiratory protection

All people entering rooms used by DR-TB patients should put on respirators (N95 'masks'). *Common surgical masks should not be worn by health care workers as they do not prevent the acquisition of TB infection*, and they must never be worn together with N95 respirators as they cause improper fitting, thus increasing the risk of acquiring TB. Visitors to rooms used by patients with DR-TB should also be given N95 respirators; otherwise visitation should occur outdoors.

8.2. Prevention of transmission in the community

Patients with TB (including DR-TB) should be started on the appropriate treatment as soon as possible after diagnosis to prevent transmission. In addition, efforts should be made to screen all close contacts at risk of acquiring drug resistance with the aim of diagnosing those with the disease early.

If patients with DR-TB are managed on an ambulatory basis, they should be encouraged to practise cough hygiene, and spend most of their time outdoors, particularly during the early stage of treatment. They should also be encouraged to sleep in separate rooms from children and people infected with HIV where possible. Where patients are known to be highly infectious (high bacillary load as shown on smear microscopy), it is preferable that they be managed in a hospital at first. They should be given surgical or paper masks to wear when in contact with others, whether at home or in hospital.

In the homes, windows should be kept open as often as possible. Where feasible, informal dwellings may be renovated to include or enlarge window openings.

Family members and household members of patients with DR-TB should be educated to support the patients swallow their treatment, as it is only when effective treatment is taken properly that cessation of transmission is assured. Direct observation of treatment (DOT) is preferable.

The clinical team should monitor monthly sputum smears and cultures to ensure that any reversion (from negative to positive), or persistent infectiousness is addressed early to prevent further transmission.

8.3. Management of patients who refuse treatment

Patients who refuse to take treatment may pose a continued risk of transmission to their contacts. Treatment for DR-TB, like any other treatment, respects the patient's right to autonomy and therefore can only be administered with consent. However, adequate counselling should be provided to the patient and his or her family to ensure that they understand the implications of not taking the treatment on their health and that of others. Patients and their immediate contacts should be equipped with full knowledge regarding treatment for them to make an informed decision.

Where a patient does not agree to take treatment, the immediate circle of contacts may be called upon to assist, as it is in their best interest to prevent them getting infected. Should this not work, that circle may be expanded to include especially influential figures such as religious leaders, political leaders, traditional authorities and/or employers. It should be noted that while confidentiality is respected as a fundamental right, it may be necessary to disclose information regarding a disease of public health concern for the greater good of preventing continued transmission. It should also be noted that when such disclosure occurs, the key message should be that *this form of TB is curable; transmission will be prevented if treatment is taken properly and affected individuals are expected to resume their previous function (particularly employment) when they recover*.

Where all efforts to convince the patient to take treatment have failed, and the patient is deemed a significant public health risk, the team may seek legal advice to apply *Public and Environmental Health Act (No.1 of 2015)*. This act has provisions for:

- Detention of individuals with infectious disease in a designated place of isolation until they are no longer a public health risk (Section 11 of the Act), and
- Prosecution of individuals who knowingly expose others to infectious disease (Section 17 of the Act).

It should be borne in mind that these measures should be last resort, but may still not address the most effective way of cutting transmission – taking effective treatment.

9. HIV AND DRUG-RESISTANT TUBERCULOSIS

9.1. Overview

HIV infection is a significant challenge for the prevention, diagnosis, and treatment of DR-TB, and mortality rates among HIV-infected patients with DR-TB are relatively high. Essential components in the management of DR-TB in HIV infected persons include the following:

- Early diagnosis of DR-TB and HIV,
- Prompt treatment with adequate regimens,
- Sound patient support, and
- Strong infection control measures.

All patients with DR-TB should be offered an HIV test and, if positive, should be on ART and achieve adequate viral suppression. Those that are HIV negative should be educated on preventive measures and offered condoms.

9.2. Concomitant treatment of DR-TB and HIV

The treatment of DR-TB in patients with HIV is similar to that in patients without HIV, with the following notes:

- All HIV positive patients with DR-TB are eligible for antiretroviral therapy (ART). ART plays a crucial role in reducing the mortality DR-TB/HIV.
- Adverse effects are more common in patients with HIV. Some toxicities are common to both anti-TB treatment and ART, which may result in increased incidence of adverse events.
- Monitoring needs to be more intense for both response to therapy and adverse effects.
- Immune reconstitution inflammatory syndrome (IRIS) may complicate therapy.

9.3. Initiating antiretroviral therapy in patients with DR-TB

All patients with HIV and TB are eligible for ART, but treatment for DR-TB takes priority. The timing of ART depends on such factors as the patient's tolerance of the anti-TB medicines and the degree of immunosuppression as measured by the CD4 count as well as the presence of other opportunistic infections. In general, ART should

be started as soon as the patient can tolerate it (usually within 2-8 weeks), bearing in mind that the current ART is lifelong and requires more commitment.

9.4. Initiating DR-TB treatment in patients already receiving antiretroviral therapy

There are two issues to consider in patients who are diagnosed with DR-TB while on ART:

- Whether modification of ART is needed due to medicine interactions or to decrease the potential of overlapping toxicities. This is necessary for patients on nevirapine or protease inhibitors for whom rifampicin containing TB treatment regimens are being considered, as well as those on tenofovir where there is a considerable risk of nephrotoxicity.
- Whether the presentation of active DR-TB in a patient on ART is an indication of ART failure. All patients receiving ART at the time of initiating treatment for DR-TB should be evaluated for ART failure in line with the *National Guidelines for Antiretroviral Therapy*. If ART failure has been diagnosed, it is not recommended to begin a new second-line ART regimen at the same time as initiation of a DR-TB regimen. Instead, the switch to the second-line ART regimen may be made two to eight weeks after the start of DR-TB treatment.

Table 14: Important medicine interactions in the treatment of HIV and DR-TB

ART MEDICINES	ANTI-TB AGENTS	INTERACTIONS	COMMENTS
Protease inhibitors lopinavir/ritonavir atazanavir/ritonavir	Rifampicin	Rifampicin decreases lopinavir level	Causes hepatotoxicity. GIT side effects Avoid atazanavir in patients with TB
Protein Inhibitors ritonavir/lopinavir	Bedaquiline	Increase levels of bedaquiline	Avoid the use of bedaquiline in patients who are infected with DR-TB and HIV Consider delamanid
NNRTIs: Efavirenz/nevirapine/etravirine	Bedaquiline	Decrease levels of bedaquiline	Consider delamanid
Buffered didanosine	Fluoroquinolones	Reduces absorption of fluoroquinolone	Avoid didanosine or separate administration by at least 6 hours

10. MANAGING PATIENTS WHO HAVE FAILED TREATMENT FOR DR-TB

10.1. Assessment of patients at risk for failure

All patients who show clinical, radiological or bacteriological evidence of progressive active disease, or re-appearance of disease after the 4th month of treatment, should be considered as being at high risk for treatment failure. Vigilance is thus particularly required for the following patients:

- Patients who have been treated for DR-TB before,
- Contacts of known XDR-TB patients,
- Contacts of patients who have failed or died on TB treatment,
- Patients with known poor adherence, and
- Patients with HIV and inadequate virologic suppression.

10.2. Patients who remain smear or culture positive at four months or later during treatment

The following steps are recommended in such patients:

- Health workers should confirm through non-confrontational interviews with the patient and DOT provider that the patient has adhered to treatment, including review of treatment card.
- The treatment regimen should be reviewed, including dosages and appropriateness of the regimen in relation to the DST reports. If the regimen is deemed inadequate, a new regimen should be designed.
- The bacteriological results should be reviewed. One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not necessarily indicate failing treatment. Repeated culture and smear-negative results in a patient with clinical and radiological deterioration suggests a condition other than MDR-TB.
- Evaluate for other conditions that may decrease absorption of medicines (e.g. chronic diarrhoea or vomiting).
- Review the current and previous radiological findings. A computer tomography (CT) scan of the thorax may be warranted. If the disease is localised and surgical

resection is feasible, it should be considered (this involves consulting a cardiothoracic surgery team).

Adding one or two medicines to a failing regimen should be avoided. Consultation with the NTLP at this stage is essential. Many patients who fail treatment will be discharged from the failing regimen and an outcome of 'treatment failed' assigned. Following this, and consultations with the NTLP, a new regimen should be designed following the principles outlined in *Table 4*. For most of these patients, this will be the *individualised regimen for complicated patients,* and some may have to be referred to a larger treatment centre in Windhoek, Oshakati or Rundu.

10.3. Suspending treatment

There are times when suspension of medical treatment is warranted. The most important considerations in suspending anti-TB therapy are:

1. *The patient's quality of life*: the medicines used in MDR-TB treatment have significant adverse effects, and continuing them while the treatment is failing may cause additional suffering.
2. *The public health concern*: continuing a treatment that is failing can amplify resistance in the patient's strain, resulting in highly resistant strains which may cause subsequent infection of others.

Examples of situations when treatment can be suspended are:

- Temporarily,
    - Adverse effects, pending treatment resumption when the patient's condition has stabilised.
    - Multiple interruptions or selective intake by the patient, to prevent amplification of resistance, until such a time that the adherence issues have been addressed.
    - Failure to secure all the doses to achieve a complete regimen, such as due to non-availability.
- Permanently,
    - Severe and/or intractable adverse effects with significant impact on the patient's quality of life, such that treatment cannot be continued any more. In such cases, the outcome of 'treatment failure' may be assigned.
    - Total failure by the medical team to design an effective regimen after adequate consultation. The team should be confident that all the medicines have been

ingested and that there is no possibility of adding other medicines or carrying out surgery.

The approach to suspending therapy should start with discussions among the clinical team involved in the patient's care. A social worker should always be invited to take part in these discussions. Once the clinical team decides that treatment should be suspended, in consultation with the NTLP, a clear plan should be prepared for approaching the patient and the family. It is not recommended to suspend therapy before the patient and/or family understands and accepts the reasons to do so, and agrees with the supportive care offered.

10.4. Palliative care after suspending treatment

Several supportive measures can be used once the therapy has been suspended. It is very important that medical visits continue and that the patient is not abandoned. In instances where the suspension was due to poor adherence, the team must make it clear that treatment would still be available if improved adherence is assured.

Other supportive measures to consider are summarised in *Table 15*.

Table 15: Supportive measures for patients who have failed treatment for DR-TB

INTERVENTION	COMMENTS
Pain control and symptom relief	Paracetamol, or codeine with paracetamol, gives relief from moderate pain. Codeine also helps control cough. Other cough suppressants can be added. If necessary, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable.
Relief of respiratory insufficiency	Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from symptoms of respiratory insufficiency and may be offered if available.
Nutritional support	Small and frequent meals are often best for a person with terminal or severe illness. It should be accepted that the intake will reduce as the patient's condition deteriorates and during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
Regular medical visits	When therapy stops, regular visits by members of the treating team and the support team should not be discontinued.
Continuation of ancillary medicines	All necessary ancillary medications should be continued as needed. Depression and anxiety, if present, should be addressed.
Hospitalisation, hospice care or nursing home care	Having a patient die at home can be difficult for the family. Hospice-like care should be offered to families who want to keep the patient at home. Inpatient end-of-life care should be available to those for whom home care is not available.
Preventive measures	Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important.
Infection control measures	The patient who is taken off anti-TB treatment because of failure often remains infectious for long periods of time. Strict infection control measures should be continued.

11.PATIENT CENTRED CARE AND PSYCHOSOCIAL SUPPORT

11.1. Overview

Drug-resistant TB disproportionately affects poor members of the society and those who are otherwise socially disadvantaged or marginalised. The disease often takes away the patients' livelihood, income, dignity and rights to fulfil their responsibility temporarily or permanently. Often, patients are left with a disability arising from either the disease or an adverse effect of the medicine.

The patient-centred approach consists of enabling patients to exercise their rights and fulfil their responsibilities with transparency, respect and dignity, by giving due consideration to their values and needs. This section will cover additional treatment support required by patients.

11.2. Pre-treatment assessment

All patents with DR-TB must be assessed by a social worker at the beginning of treatment. The social worker's assessment provides a platform to:

- Listen to the patient's concerns about their diagnosis and the treatment,
- Know the patient, his or her family, and existing social support structures for each individual patient,
- Evaluate livelihood, source of income and estimate the loss thereof due to treatment,
- Assess the need for material support and the quantities required,
- Prepare for contact investigation,
- Identify influential figures in the patient's life who are key to the patient's decision-making process. It may be necessary, such as in the case of the employer, to reach out, educate and negotiate with the influential figure to facilitate adherence to treatment,
- Identify potential barriers to treatment,
- Address any misconceptions and reinforce the key messages already provided by other members of the team, particularly on the disease and its treatment, and
- Provide counselling as needed.

A rehabilitation professional should also assess the patient, paying particular attention to:

- The patient's pre-treatment occupation. It is preferable to maintain the patient's skills and abilities during prolonged hospitalisation and treatment.
- Pre-treatment disabilities, if any. Pre-treatment hearing should be assessed and recorded.
- Disabilities caused by the disease. These are usually related to the site of the disease (e.g. spinal TB causing para-paresis), or decreased mobility (e.g. muscle wasting, contractures).
- The patient's interests, favourite pastimes and hobbies.

11.3. Providing psycho-emotional support

Patients diagnosed with DR-TB often find the diagnosis devastating, and they usually go through different psycho-emotional states (denial, anger, bargaining, depression and acceptance). The patient's state at any given time will influence how he/she relates to the health care workers and his/her overall attitude to treatment. In addition, the changes in life circumstances brought about by the disease and its treatment may directly or indirectly affect the patient and their families, potentially leading to social or psychological complications.

It is the responsibility of the health care workers to be empathetic and supportive during this time, and be sensitive to the patient's situation when recommending treatment approaches. Some members of the team, particularly social workers or clinical psychologists, will be better equipped to handle such situations. Intensive counselling is required is required early during treatment.

People often find solace in others who are in similar circumstances, hence the power of support groups. Every treatment facility which manages more than a few DR-TB patients is advised to have a support group. This group of patients (may even include former patients) should be assisted to meet regularly and discuss issues pertaining to patients. In this forum, patients may share information and provide support to each other. It is helpful if this support group is convened and moderated by a social worker, TB field promoter, or another team member who is not a nurse or doctor. Other team members may be invited to assist with education sessions.

11.4. Providing socio-economic support

Various forms of economic support are available to patients in Namibia. Social, disability and economic assistance consists largely of a universal benefit for the

patients provided by the state through Social Security as per Social Security Act of 1994 or through social assistance as provided for by the National Pension Act of 1992.

11.4.1. Social Disability grant

Any patient deemed by the medical officer to have a significant disability and is not formally employed may access this grant based on the following:

- Functional assessment by a state medical practitioner, and
- Patient with Namibian national documents e.g. birth certificate on national identity card

Patients without physical disability may be considered to have temporary functional impairment based on certain circumstances e.g. hospitalisation, which prevents such people from engaging in economic activity.

11.4.2. Social Security Sick-leave benefit

Patients who are formally employed and contribute to the Social Security Fund are eligible for this benefit, but not for the Social Disability grant. The sick leave benefit is payable when an employee is booked off-duty by a medical practitioner for 30 or more consecutive days and has exhausted paid sick leave days as provided under the Labour Act or contract of employment. The medical officer and the patient complete forms issued by the Social Security Commission to allow the patient to claim compensation for the period away from their place of employment.

11.4.3. Negotiating with employers

Patients are often worried about job security when they are sick and employers, on the other hand, may not understand the nature of the disease and may be inclined to terminate the employment of a sickly employee. The health care team is responsible for educating the employers and dispelling stigma surrounding the TB diagnosis. The team may negotiate on behalf of the patient since the duration of the sick – leave granted may be longer than what is allowed by that employer. Employers may need to be encouraged to take a supportive stance towards employees with infectious diseases; that way employees feel free to disclose and seek treatment, rather than hide their disease and spread it. In that same vein, if employers support treatment administration, they ensure that their employees are cured and they have a healthy workforce.

11.5. Other forms of socio-economic support

11.5.1. Income generating activities

Where feasible, patients should be encouraged and supported to engage in income generating activities. At facilities where this approach has been successful, support groups, social workers and/or rehabilitation professionals have been involved. This approach has the following benefits:

- Takes advantage of existing skill-pool among patients,
- Patients get to learn new skills,
- Patients are kept occupied, particularly those who would otherwise be unemployed or idle, and
- There is potential for patients to receive income and/or nutritional benefit from such a project.

Projects that have been successfully implemented in Namibia include gardening, small livestock farming, weaving and handicraft making.

11.5.2. Transport support

Patients with DR-TB on ambulatory treatment should be supported to ensure that they continue to access treatment. This can range from each patient being given a cash handout for using public transportation, to reimbursing costs incurred to providing a vehicle that transports patients to their follow-up visits. The aim of this support is to take away the cost of transport for accessing treatment from the patient. The local team may liaise with community based TB care providers to determine the best modalities in each setting.

11.5.3. Nutritional support

Patients with nutritional needs are eligible to receive supplementary feeding from the MoHSS. Additionally, where possible, all patients with DR-TB can be supported with food baskets and/or other available nutritional support packages. The local government administration often has food packages for vulnerable members of the community that can be negotiated for. In some settings, providing a meal to patients coming for DOT may be the best way to ensure adherence. The treating team may need to explore other ways that stakeholders, including the business sector can support the nutritional needs of patients.

11.6. Providing rehabilitation support

Based on the pre-treatment assessment, rehabilitation needs may vary. The goal of rehabilitation support is to promote emotional well-being, independence, physical ability and an enhanced quality of life while on treatment for DR-TB.

It is important for a rehabilitation professional to assess patients regularly and monitor the individual situation of each patient, and work together with the social worker and other members of the team. Issues to manage include the following:

- Establishing a ward plan for hospital settings to encourage functional independence in the activities of daily living,
- Supporting mobilisation and physical exercise, particularly for hospitalised patients,
- Providing entertainment support for hospitalised patient,
- Maintaining patients' occupational skills,
- Assisting patients develop new occupational skills while they are on treatment,
- Preventing and managing contractures, and
- Support for respiratory insufficiency.

REFERENCES

1. World Health Organization. *Definitions and Reporting Framework for tuberculosis–2013 Revision*. Geneva: WHO; 2013. http://apps.who.int/iris/handle/10665/79199.
2. World Health Organization. WHO treatment guidelines for drug resistant tuberculosis. 2016. http://www.who.int/tb/MDRTBguidelines2016.pdf.
3. KNCV Tuberculosis Foundation. Generic programmatic and clinical guide for the introduction of new drugs and shorter regimen for treatment of Multi / Extensively Drug- Resistant Tuberculosis. 2016.
4. GDI. The evaluation of effectiveness and safety of a shorter standardized treatment regimen for multidrug-resistant tuberculosis. 2015;(May):25.
5. World Health Organization. Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions. 2016;2015(June):1-14.
6. The Sentinel Project on Pediatric Drug-resistant TB. *Rapid Avice: The Use of Delamanid and Bedaquiline for Children with Drug-Resistant Tuberculosis*. Boston; 2016.
7. The Sentinel Project for Pediatric Drug-Resistant Tuberculosis. *Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide*. Boston; 2012.
8. World Health Organisation. *Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*. Geneva: WHO; 2014. http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf?ua=1&ua=1.
9. Curry International Tuberculosis Center and California Department of Public Health. *Drug-Resistant Tuberculosis A Survival Guide for Clinicians*. Third.; 2016.
10. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. *Eur Respir J*. 2012;40(5):1277-1286. doi:10.1183/09031936.00044812.

Annex 1: Regimen eligibility checklist

For all TB patients with resistance to rifampicin, by Xpert MTB/RIF or conventional DST			
Check	**Ask**	**Tick**	
A	A1- Has the patient been previously treated for DR-TB for >1 month?	YES	NO
	A2- Does this patient have extra-pulmonary TB		
	A3- Is there any reason to suspect that the patient has or will develop intolerance to any of the medicines in the STR		
	A4- Does the patient have severe lung damage (on the CXR), such as multiple bilateral cavities, extensive parenchymal damage, lung collapse?		
	A5- Is the patient pregnant?		
	A6- TB? Does the patient have a close contact who: a. Had XDR TB? b. Had resistance to fluoroquinolone or second-line injectable? c. Failed or is failing treatment for DR-TB? d. Died while on treatment for DR-TB?		
	If there is a 'YES' to any of the 6 questions, this patient is eligible for the individualised regimen, go to C below If 'NO' to all the above 6 questions, this patient is eligible for the STR, go to B below		
B	Trace results for second-line LPA, and conventional second line DST		
	B1- Is there resistance to a second-line injectable?		
	B2- Is there resistance to a fluoroquinolone?		
	If there is a YES to any of these 2 questions, this patient requires individualised regimen, go to D below. If the responses to both questions are 'No', or results unavailable, start the *Short treatment regimen (STR) for DR-TB.*		
C	Trace results for second-line LPA, and conventional second line DST		
	C1- Is there resistance to either a second-line injectable or FQ or both?		
	C2- Is there any YES on the answer to Question A6 (above)?		
	C3- Is there suspected intolerance to a second-line injectable or FQ?		
	If there is a YES to any of these 3 questions, go to D below If the response to all 3 questions is 'No', consult local DR-TB committee and start *Individualised DR-TB treatment regimen for uncomplicated patients.*		
D	Consult CCRC (national level) and start *individualised DR-TB treatment regimen for complicated patients.*		

Annex 2: Registering a DR-TB patient on *eTB Manager* (2016)

1. Switch on the computer or login to an electronic tablet or smartphone with internet access.
2. Open the web browser (Internet Explorer, Google Chrome, Firefox, etc.) by double clicking on the icon on the desktop or taskbar.
3. Type in the browser, www.etbmanager.org.na and press ENTER (For most browsers, you can skip the http://)
    - This must take you to the **ETB Manager Log-in** page
4. Type in your username and password provided to you by an administrator and click ENTER.
    - You will be taken to the ETB Manager homepage
    - If you do not have a login name or password, request one from the NTLP
5. Click on **CASES** and the summary of the cases in your Unit/Region will appear
6. If you have DST results, click on **NEW CASE** and a search entry field will appear (this is a confirmed case)
    - If you do not have DST results, click on **NEW SUSPECT** instead and a similar search entry field will appear (this is a non-confirmed case for which we would like to provide treatment nevertheless)
    - Suspects can be changed to confirmed cases later by clicking **CASES** on the home page, then **HEALTH UNIT** (name) > **PATIENT** (name) > **SUSPECT FOLLOW-UP**
7. Type in the patient's name and date of birth and click **SEARCH**
    - A list of existing records with similar names will appear
8. If you want a new notification, without amending the existing records, click **NEW PATIENT.**
    - If you are re-registering a patient whose records exist, click on the appropriate name
9. Then click GO **TO NOTIFICATION FORM**
    - The **Notification form** page will appear
10. Complete all fields for the PATIENT DATA, PREVIOUS TB TREATMENTS, and MEDICAL CONSULTATIONS information that you have and click **SAVE** at the bottom of the page.
    - If there's any key information missing or inconsistent, the system will show you, and will not allow you to proceed
    - This information can be modified later if you click **CASES** on the home page, then **HEALTH UNIT** (name) > **PATIENT** (name) > **CASE DATA** (tab) > **EDIT**
11. You have now entered all the case data and now have to enter the following data
    - Exams
    - Medical consultations

- Additional information
- Treatment

12. EXAMS: Click on **EXAMS** and enter all the HIV, laboratory and X-ray information
    - Please note that your case may not be validated if HIV information is missing or if you classify a DR-TB case without entering DST results. Also, rifampicin resistance on Xpert is not the same as monoresistance.
    - Click **SAVE** at the bottom of the page
    - This information can be modified later if you click **CASES** on the home page, then **HEALTH UNIT** (name) > **PATIENT** (name) > **EXAMS** (tab) > **EDIT**
    - This is also where you enter follow-up smears, culture, X-rays and DSTs
13. MEDICAL CONSULTATIONS: Click on **MEDICAL CONSULTATIONS** tab to update all the relevant clinical observations by date, from the initial to follow-ups. For each visit, a weight and comment on DOT is needed.
    - Click **SAVE** at the bottom of the page
    - This information can be modified later if you click **CASES** on the home page, then **HEALTH UNIT** (name) > **PATIENT** (name) > **MEDICAL CONSULTATIONS** (tab) > **EDIT**
    -
14. ADDITIONAL INFORMATION: Click on **ADDITIONAL INFORMATION** to enter information on:
        - Comorbidities and associated factors
        - Contacts evaluation
        - Social Support
        - Adverse events
    - Click **SAVE** at the bottom of the page
    - This information can be modified or updated later if you click **CASES** on the home page, then **HEALTH UNIT** (name) > **PATIENT** (name) > **ADDITIONAL INFORMATION** (tab) > **EDIT**
15. TREATMENT: Click on **TREATMENT** (tab) to **START TREATMENT** and select appropriate/proposed regimen.
    - For each medicine, the dose and the duration may be adjusted.
    - Click **SAVE** at the bottom of the page.
    - This information can be modified or updated later if you click **CASES** on the home page, then **HEALTH UNIT (**name) > **PATIENT** (name) > **TREATMENT**(tab) > **OPTIONS**
    - In addition, clicking the MONTH on the 'Treatment card' will allow you to insert DOT information

16. ISSUES: This is not a mandatory tab. The **ISSUES** tab can be used to communicate issues with the National team or other supervisors. To submit a new issue, click **CASES** on the home page, then **HEALTH UNIT** (name) > **PATIENT** (name) > **ISSUES** (tab) > **NEW**
    - Enter the Issue title and issue details and SAVE.
    - To respond to an issue, just enter response in space provided and **ADD**
17. WAIT for validation by the CCRC/National team. You may sms or email the patient name to the CCRC team to remind them to check and validate the case. VALIDATION is by the CCRC or National team. VALIDATION means the notification details have been accepted and the proposed treatment has been approved.
18. Update all the tabs regularly
19. The MANAGEMENT tab is for generating reports

Annex 3: Management of Adverse Events (AEs)

Background

Prompt evaluation, diagnosis and treatment of adverse events is extremely important component of active drug safety monitoring (aDSM), even if the adverse event is not particularly dangerous.

Before starting treatment, the patient should be counselled in detail about the potential adverse event of the prescribed medicine regimen, and when to notify a health-care provider.

Preventive treatment should be applied where necessary, e.g. Pyridoxine (vitamin B6) 50 mg for every 250 mg of cycloserine or at preventive dose of 50-100 mg /day (up to 150 mg) for patients receiving Isoniazid or Linezolid (to minimize peripheral neuropathy, neurological adverse event and myelosuppression).

Psychosocial support is an important component of the management of adverse effects, and DOT providers should educate patients about their adverse effects and encourage them to continue treatment. Patient support groups can provide psychosocial support to patients.

Any relevant clinical event (adverse events or reactions) and any required additional diagnostic testing and/or therapy will be recorded. All serious adverse event (SAEs) should be notified within 24 hours to the Therapeutics Information and Pharmacovigilance Centre (TIPC).

Management of AEs should take patient safety and treatment need into consideration. For minor AEs, re-assurance to enhance adherence is needed. For AEs that need additional evaluation and/or medical treatment, a treatment decision structure (consultation back-up for DOT provider), additional tests and ancillary medicines should be available and accessible, free of charge.

If drug(s) thought to cause the AE need to be removed from the regimen, replacement might be required, especially in the intensive phase when the bacillary load is high. Replacement of drugs should take the clinical condition and bacteriological status of patients into account. Ensure that the regimen contains at least 4 medicines with known effective drugs [20]. Any decision must be made on the basis of careful case review (if necessary consult DR-TB committee for guidance).

Severity grading scale of adverse events and main laboratory parameters

All SAEs and AEs should be graded for severity according to the provided Severity Grading Scale (grades 1-4). For those AEs not described in the Severity Grading Scale, the general definition of clinical severity should apply.

Severity grading scale of adverse events

Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 LIFE-THREATENING
Transient or mild discomfort (<48 hours) without limitation of normal daily activities*. No medical intervention or corrective treatment required	Mild to moderate limitation of normal daily activities*. Minimal medical intervention or corrective treatment required	Marked limitation of normal daily activities* Medical intervention, therapy, stop or reduction of the offending drug is required. Possible hospitalization	Severe limitation of normal daily activities*. Medical intervention and corrective treatment required almost always in a hospital setting.

*The term 'activity' covers basic self-care functions such as bathing, dressing, toileting, transfer/movement, continence and feeding; but also, usual social and functional activities or adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Severity grading scale of main laboratory parameters

Parameter (units)	Hb (g/dl)	Platelets ($/mm^3$)	Neutrophils ($/mm^3$)	AST (UI/l)	ALT (UI/l)	Creat. (µmol/l)	K+ (mEq/l or mmol/L)
Normal values	>12	>150,000	>1,500	*	*	*	3.5-5.0
Grade 1	10-11.9	100,000-149,999	1,000-1,500	1.5 < 2.5 x ULN	1.5-<2.5 x ULN	1.1 – 1.5 x ULN1.1-1.5 x ULN	3.2-3.4
Grade 2	8- 9.9	50,000-99,999	750-999	2.6-5.0 x ULN	2.6-5.0 x ULN	1.6 – 3 x ULN1.6-3.0	2.8-3.1
Grade 3	6-8	20,000-49,999	500-749	5.1-10 x ULN	5.1-10 x ULN	3- 6 x ULN6xULN	2.5-2.7
Grade 4	<6	<20,000	<500	>10 X ULN	>10 x ULN	> 6 x ULN	<2.5

*Normal values vary from laboratory to laboratory and might be slightly different in men, women and children. (check normal parameters for your laboratory)

ULN= upper limit of normal

Clinical Management of adverse events

Management of Adverse Events

11.6.1.1.Prolonged QT interval

Possible anti-TB drug causes: Bdq, Dlm, Mxf, Cfz,

Normal Values	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Male: ≤450 **Female: ≤470**	Not applicable (N/A)	Male: >450-500 ms Female: > 470 -500 ms	> 500 ms ***or*** ≥ 60 ms above baseline	Life-threatening consequences (e.g., Torsade de Pointes, other associated serious ventricular dysrhythmia)
Action	N/A	Monitor more closely; at least weekly ECG until QTcF has returned to grade 1 or less. Check electrolytes and replete as necessary	Stop the suspected causative drug. Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug. Hospitalize and replete electrolytes as necessary.

Check and replace serum electrolytes

- Check Serum potassium (K^+), ionized calcium (ionized Ca^{++}), and magnesium (Mg^{++})
- Abnormal electrolytes are most commonly due to the injectable and should be corrected.
- If low potassium is detected: urgent management with replacement and frequent repeat potassium testing (often daily or multiple times a day). Check magnesium and ionized calcium and compensate as needed. (If unable to check, give oral empiric replacement doses of magnesium and calcium).
- **Check TSH**: if hypothyroidism found treat accordingly.

11.6.1.2.Hypokalaemia

Possible anti-TB drug causes: Am, Km, Cm, S

Normal value	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
3.5- 5.0 (mmol/L)	3.4-3.2	3.1-2.8	2.7-2.5	<2.5
Action	Continue injectable. Start oral potassium slow K***** 600 mg = 8 mEq: 1 tab twice daily. **Monitor K monthly**	Continue injectable. Start oral potassium slow K* 600 mg = 8 mEq: 2 tab twice daily Oral Magnesium gluconate: 1000 mg twice daily. **Monitor K every 2 weeks** and adjust the slow K dose accordingly	Continue injectable. Oral potassium: Slow K* 600 mg = 8 mEq: 2 tab thrice daily Oral Magnesium gluconate: 1000 mg twice daily **Monitor K every 1-2 days** and adjust dose accordingly	Stop injectable temporarily. Hospitalization**.** Start IV potassium in addition to oral. Replace magnesium and other electrolytes **Monitor K 1 hour after replacement and repeat till K is >2.8 mmol/L**

Oral potassium and magnesium should be administered either two hours before or four to six hours after fluoroquinolones as they can interfere with fluoroquinolone absorption**.**

Replacing serum electrolytes

- Replacement of 40 mEq of potassium increase 1 mEq/L the potassium.
- Oral replacement: The replacement varies 40 mEq to 80 mEq day. Usually patients don't tolerate more than 6-tab slow k (diarrhea, nausea). Doses should be divided to two or three times a day (no more than 20 mEq per dose)
- * The formulations of oral potassium chloride variates by manufacturer and countries. Slow- release versions are common in low resources settings. One slow K 600 mg tab contains 8 mEq of potassium. **Adjust the number of pills according to the formulation available.**
- Hypokalemia may be refractory if concurrent hypomagnesemia is not also corrected.
- If unable to check serum magnesium, give empiric replacement therapy in all cases of hypokalemia with oral magnesium gluconate 1000mg twice daily.
- In refractory cases, can be given spironolactone 25 mg/ day or Amiloride 5-10 mg/day orally (decrease of potassium and magnesium wasting).

FOR HOSPITALIZED PATIENTS:

If severe hypokalemia (K ≤ 2.5 mmol/L or symptomatic hypokalemia): give Intravenous potassium concurrently with oral potassium replacement.

Dosing: 10 -15 mEq /h IV and 80 meq orally every six to eight hours. Recheck serum potassium 1 hour after infusion. Repeat IV replacement every 6 to 8 hours until serum potassium is ≥ 2.8 mmol/L.

The normal preparation of a potassium chloride infusion is 40mEq in200Ml of normal saline over 2-4 hrs. Do not exceed an infusion rate of 20 mEq/hr(100mL/hr).

Magnesium replacement:

Dosing: 2000 mg/day. If Mg can be measured and is less than 1.0 increase the dose up to 3000 mg- 6000 mg if Mg IV (doses greater than 2000 mg are usually given IV). Magnesium IV:

The normal preparation is magnesium sulfate2g in100mLor4 gin250mLof5 % dextrose or normal saline. Do not exceed an infusion rate of 150mg/min (2gin100mL administered over one to two hours,4gin 250mL administered over two to four hours). Repeat until serum K is > 2.8mmol/l.

Other considerations:

- Check an ECG in patients with significant serum electrolyte disturbances.
- Drugs that prolong the QT interval should bed is continued inpatients with evidence of QTc interval prolongation.
- Electrolyte abnormalities are reversible upon discontinuation of the injectable. Even after suspending the injectable, it may take weeks or months for this syndrome to disappear, so electrolyte replacement therapy should continue for several months after completion of the injectable phase of DR-TB treatment.

11.6.1.3.Nephrotoxicity

Possible anti-TB drug causes: Am, Km, Cm, S

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Creatinine	1.1 - 1.5 x U/LN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required
Creatinine clearance* Normal value Male: 97-137 ml/min Female: 88-128 ml/min Cr Cl grading [22]	>90ml/min	60-89ml/min	30-59ml/min	15-29 ml/min Note: < 15 ml/min is grade 5 and requires dialysis.
Action	Continue monitoring	Reduce injectable to 3 times a week dosing at 12-15mg/kg	Reduce injectable to 2 times a week dosing at 12 mg/kg	**Stop injectable.** Monitor creatinine and electrolytes weekly till creatinine returns to normal. Adjust the other drugs dosages

Suspend the injectable permanently if the nephrotoxicity recurs despite intermittent dosing, and add additional anti-TB drugs to reinforce the regimen (Bedaquiline, Delamanid or Linezolid)

Consider other causes of renal insufficiency (pre-renal, intrinsic renal and post-renal).

***Creatinine clearance formula:**

Weight (Kg) x (140 – Age) x (constant)

Serum creatinine µmol/L

Constant: 1.23 for men and 1.04 for woman

If creatinine is reported in mg/dL multiply by 88.4 to convert to µmol/L

When **Cr Cl < 30 ml/min**, stop the injectable and monitor creatinine and electrolytes weekly until returns to normal. **Adjust all the TB medications according to table 18 in annex C.**

Then reintroduce the injectable at a dose of 12-15 mg/kg/ per dose 2 or 3 times per week, monitoring creatinine weekly. If the creatinine continues to rise suspend the injectable permanently and add additional anti-TB drug (Bdq, Dlm or Lzd).

11.6.1.4.Hearing loss

(ANRS scale)

Possible anti-TB drug causes: Am, Km, Cm, S

AUDIOMETRY TEST:

Exclude causes of conductive hearing loss: ear wax, otitis media, tympanic perforation

**Attain a baseline record of the hearing status of a person prior to treatment initiation*

Perform a monthly audiogram that includes speech frequencies (500-4000 Hz) and higher up to 8000 Hz.

Calculate the average hearing loss (AHL) for each ear:

sum the loss in dB at each frequencies of 500-1000-2000-4000 Hz (if a frequency is not perceived consider a loss of 120 dB) and divide by 4. You have the average of the best ear and the bad ear

Then calculate the Weighted Average Hearing Loss (WAHL) for both ears:

WAHL= (Average of the best ear multiply by 7) + (Average of the worst ear multiplied by 3). Divide the total by 10

Normal Values	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Profound
0-20 dB	**21-40 dB** Speech perceived if voice is normal, difficulties arise if voice is low-pitched or distant from the subject. Most of the daily life noises are perceived	**41-70 dB** Speech is perceived if the voice is loud. The subject understands better what is being said if he can see his/her interlocutor.	**71-90 dB** Speech is perceived if the voice is loud and close to the ear. Loud noises are perceived.	**>90dB** Speech is not perceived at all. Only very loud noises are perceived.

Action:

Confirm results on repeated test in the same visit before any change in the treatment.

Before reducing or stopping a drug: Think carefully, consult other experts.

If ototoxicity is detected early, it may be possible to stop the injectable, preventing progression of the hearing loss.

If vestibular disorder (vertigo, dizziness, imbalance, disequilibrium, nausea and vision problems) injectable should be stopped.

Patient with no hearing loss at baseline:

Injectable	Continue injectable but consider reducing the frequency to 3 times per week and perform more frequent audiometry	Stop the injectable and replace by new drugs Bdq, Dlm or Lzd. Refer to audiologist	Stop the injectable and replace by new drugs Bdq, Dlm or Lzd. Refer to audiologist	Stop injectable and replace by new drugs Bdq, Dlm or Lzd. Refer to audiologist

Patients with hearing loss at baseline: consider reducing frequency or stopping the injectable if there is a worsening of 1 grade of hearing loss compared with baseline

Hearing Aid	Counselling.	hearing aids usually recommended	Certainly, hearing aids are needed. If not available, lip-reading and signing should be taught.	Hearing aids may help understanding words but additional rehabilitation needed and lip-reading and sometimes signing essential

- *Five percent of the world's population has disabling hearing loss (>40dB in better ear in adults and > 30 dB in children). This includes one third of 65 years old. Hence, it is important to attain a baseline record of the hearing status of a person prior to treatment initiation.
- **Patient at higher risk of ototoxicity: previous use of aminoglycoside, elderly, renal insufficiency, pre-existing hearing problems, receiving other ototoxic medications**
- The toxicity to the eight-cranial nerve concerns the vestibule (dizziness) and the cochlea (hearing loss), and is irreversible.
- The frequencies between 500 Hz and 4000 Hz are considered to be those of a normal conversation
- The higher frequencies (4000-8000 Hz) are the first to be affected; the frequencies of the human voice come next.
- Hearing loss becomes perceptible for patients at a frequency <4000Hz when it reaches 25-30dB. When patients mention hearing loss there is already a severe degree of loss.
- Children: above 4 years can perform pure tone audiometry. Below 4 years refer to audiologist.
- Hearing loss should always be compared to baseline measurements and ototoxicity is defined as any of:
    - (a)20dB decrease at any one frequency
    - (b) 10dB decrease at any two adjacent frequencies
    - (c) loss of response at three consecutive test frequencies where responses were previously obtained.

11.6.1.5.Hepatotoxicity

Possible anti-TB drug causes: Z, H, Eto (Pto), Lzd, Cfz, Bdq, Mfx

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
ALT (SGPT)	1,25 – 2,5 x ULN	2,6 – 5,0 x ULN	5,1 – 10,0 x ULN	> 10,0 x ULN
AST (SGOT)	1,25 – 2,5 x ULN	2,6 – 5,0 x ULN	5,1 – 10,0 x ULN	> 10,0 x ULN
Action	Continue treatment Patients should be follow until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment Patients should be followed until resolution (return to baseline).	**Stop all drugs,** including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	**Stop all drugs,** including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.
If JAUNDICE: Stop all anti-TB drugs until resolution				

Consider other potential causes of hepatitis: viral (hepatitis B and C), HIV, alcohol).

Avoid potentially hepatoxic non-tuberculosis drugs.

Reintroduction of anti-TB drugs

- Check ALT/AST once a week. Reintroduce anti-TB drugs once liver enzymes return to at least Grade 2.
- Anti-TB drugs should be reintroduced in serial fashion. The least hepatotoxic drugs should be added first: Km-E-Cfz-Mfx. Then introduce the more hepatotoxic one by one every three days: Eto-H-Z while monitoring liver function tests after each one to identify the responsible drug.
- If reintroduction leads to signs of hepatotoxicity, stop the suspected drug and replace it by another if it is essential for the treatment (do not replace H and Z). Follow transaminases monthly.
- If patient is on ART and experienced Nevirapine (NVP) hepatotoxicity, they should not be re-challenged with NVP.

11.6.1.6.Peripheral neuropathy

Possible anti-TB drug causes: Lzd, Cs, H, S, Km, Cm, H, FQ, Pto/Eto, E

Possible other causes: Diabetes Mellitus, alcohol, HIV infection, Vitamin B deficiency, hypothyroidism and other drugs

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Action	Stop offending drugs (Lzd, High dose INH). If symptoms improve after 2 weeks consider restarting Lzd at a lower dose.	**Stop Lzd and do not reintroduce**.	**Stop Lzd and do not reintroduce.**	**Stop Lzd and do not reintroduce.**

Suggested management strategy

- All patients taking High dose INH and linezolid should receive 100 mg of pyridoxine (Vitamin B6) day.
- The neuropathy associated with Linezolid is common after prolonged use and often extremely painful and irreversible. For this reason, Linezolid should be immediately stopped and not reintroduced when symptomatic neuropathy develops (grade 2 and above).
- Symptomatic relief:
    - Increase pyridoxine (Vitamin B6) to a maximum of 150 mg.
    - Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
    - Tricyclic antidepressants have also been used successfully. Start amitriptyline 25 mg at bedtime. The dose may be increased to a maximum of 150 mg daily for refractory symptoms.
    - Carbamazepine may also be effective in relieving pain and other symptoms of peripheral neuropathy. **Carbamazepine is a strong inducer of CYP3A4 and should not be used with Bedaquiline or Delamanid.**

11.6.1.7.Myelosuppression (anaemia, thrombocytopenia, and/or neutropenia)

Possible anti-TB drug causes: Lzd

Possible other causes: AZT, Cotrimoxazole, HIV Infection, chemotherapy

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Absolute neutrophil count	1000 – 1300/mm^3	750 – 999/ mm^3	500 – 749/mm^3	< 500/ mm^3
Haemoglobin	8,5 – 10, 0 g/dl	7,5 – 8,4 g/dl	6,5 – 7,4 g/dl	< 6,5 g/dl
Platelets, decreased	100.000 – 124.999 /mm^3	50.000 – 99.999 /mm^3	25.000 – 49.999 /mm^3	< 25.000 /mm^3
WBC, decreased	2.000 – 2.500 /mm^3	1.500 – 1.999 /mm^3	1.000 – 1.499 /mm^3	< 1.000 /mm^3
Action	Monitor carefully, and consider reduction of dose of Lzd to 300mg daily	Monitor carefully, and consider reduction of dose of Lzd to 300mg daily; in case of Grade 2 neutropenia, **stop Lzd immediately.** Restart at reduced dose once toxicity has decreased to Grade 1.	**Stop Lzd immediately.** Restart at reduced dose once toxicity has decreased to Grade 1.	**Stop Lzd immediately.** Consider BLOOD transfusion or erythropoietin. Restart at reduced dose once toxicity has decreased to Grade 1.

Suggested management strategy

1. All patients taking linezolid should also be receiving at least 100 mg of pyridoxine daily. This is largely to prevent myelosuppression, but may also prevent peripheral neuropathy.
2. Stop the causative drug immediately.
3. Monitor full blood counts regularly.
4. Hospitalize the patient and consider transfusion if the myelosuppression is severe.

11.6.1.8.Optic neuritis

Possible anti-TB drug causes: Lzd, E

Possible other causes: Multiple sclerosis, quinine, Herpes, Syphilis, Sarcoidosis, Cytomegalovirus (PLHV).

The first sign of optic neuritis is usually the loss of red-green color distinction. This is best tested using the Ishihara test. Other symptoms include central scotoma (loss of central vision or blind spot)

	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Optic neuritis is inflammation of the optic nerve resulting in permanent vision loss.	Visual changes causing minimal or no interference with usual social and functional activities.	Visual changes causing greater than minimal interference with usual social and functional activities.	Visual or changes causing inability to perform usual social and functional activities.	Disabling visual loss.
Action	**Stop Lzd or E immediately** if there are any suspicions of optic neuritis. Do not restart.	**Stop Lzd or E immediately** if there are any suspicions of optic neuritis. Do not restart.	**Stop Lzd or E immediately** if there are any suspicions of optic neuritis. Do not restart.	**Stop Lzd or E immediately** if there are any suspicions of optic neuritis. Do not restart.

Suggested management strategy

- Do not restart the suspected causative drug (linezolid or ethambutol)
- Refer patient to an ophthalmologist for further evaluation and management.
- Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.
- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention. Patients with advanced kidney disease are also at increased risk for optic neuritis.

11.6.1.9.Lactic acidosis

Possible anti-TB drug causes: Lzd

Possible other causes: AZT, 3TC

	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Lactate and pH	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without Acidosis	Increased lactate with pH < 7.3 without life threatening consequences	Increased lactate with pH < 7.3 with life threatening consequences
Action	Continue treatment regimen. Patients should be followed	**Stop Lzd immediately and do not reintroduce.**	**Stop Lzd immediately and do not reintroduce.**	**Stop Lzd immediately and do not reintroduce.**

	until resolution (return to baseline).			

Early signs and symptoms include **nausea, vomiting, abdominal pain, anxiety, and increased respiration rate and heart rate.** Late symptoms include lethargy, hypotension and septic shock. Early detection of lactic acidosis is important because full-blown lactic acidosis is often fatal.

Diagnosis: analysis of an arterial blood sample showing a low pH and high lactate: anion gap, metabolic acidosis, lactate > 5 mmol/L, increased lactate/pyruvate.

If laboratory is not available, start treatment with clinical features

Suggested management strategy

1. Stop linezolid and NRTIs if lactic acidosis occurs. Unfortunately, it may take months for the lactic acidaemia to resolve completely even after the causative drug is stopped.
2. Hospitalize patient and monitor serum electrolytes, renal function, arterial blood gas, and lactate levels.
3. Check vital signs frequently and provide supportive care. Sodium bicarbonate therapy to correct a low pH has not been shown to be of benefit in lactic acidosis.
4. After lactic acidosis resolves, do not restart the suspected offending medication.

11.6.1.10. Pancreatitis

Possible anti-TB drug causes: Bdq, Lzd

Other causes: gallstones, heavy and long-time alcohol use, high triglycerides

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Pancreatitis	Not Applicable	Symptomatic and Hospitalization not indicated	Symptomatic and Hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
	Continue treatment regimen. Patients should be followed until resolution (return to baseline).	**Stop Lzd immediately and do not restart.**	**Stop Lzd immediately and do not restart.**	**Stop Lzd immediately and do not restart.**

The most common symptoms and signs include severe epigastric pain (upper abdominal pain) radiating to the back in 50% cases, nausea and vomiting.

Suggested management strategy

1. Monitor liver function tests, amylase, lipase, and full blood count.
2. Provide supportive care.
3. Permanently discontinue Linezolid (or Bdq if suspected to be the cause of pancreatitis)

11.6.1.11. Gastrointestinal (Nausea and Vomiting)

Possible anti-TB drugs: Eto/Pto, PAS, Bdq
(less common H, E, Z, Amx/Clv, Cfz, Dlm)

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition

Management and comments

- Nausea and vomiting are universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at least in the initial period.
- Assess for danger signs including dehydration, electrolyte disturbances and hepatitis.
- Initiate rehydration therapy if indicated and correct any electrolyte disturbances.

Initiate a step-wise approach to manage nausea and vomiting.

Phase 1:

Give a light snack (biscuits, bread, rice, tea) before the medications. Give PAS with fruit juice.

Adjust medications and conditions without lowering the overall dose:

—Give Eto or PAS twice daily

—Give PAS two hours after other anti-TB drugs.

Another strategy is to stop the responsible medicine for two or three days and then add it back gradually increasing the dose (advise the patient that the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated).

Phase 2: Start antiemetic(s):

—Metoclopramide 10 mg, 30 minutes before anti-TB medications.

—Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. **Odansetron prolongs the QT interval; avoid with bedaquiline or delamanid.**

—If ondansetron is not available, promethazine can be used.) Promethazine25 mg PO,30 minutes before the anti-TB drugs (may be increased to 50 mg 3 times daily).

—Omeprazole or Ranitidine can also provide relief (omeprazole decreases the acid production, is also useful in the treatment of nausea).

Phase 3: Decrease dose of the suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.

Note: For patients, particularly anxious about the nausea, (and with "anticipatory nausea and vomiting") a small dose of an anti-anxiety medicine (5 mg of diazepam) can help when given 30 minutes prior to the intake of anti-TB drugs. Do not give diazepam longer than 2 weeks.

11.6.1.12. Gastritis

Possible anti-TB drug causes: Eto, Pto, PAS, Cfz, FQs, H, E, and Z

If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) initiate medical therapy (prolonged duration):

- Omeprazole 20 mg once daily (proton-pump inhibitors)
- Ranitidine 150 mg twice daily or 300 mg once daily (H2-blockers)
- Avoid the use of antacids as they decrease absorption of fluoroquinolones.

Stop any nonsteroidal anti-inflammatory drugs the patient may be taking.
Diagnose and treat for *Helicobacter pylori* infections.

11.6.1.13. Abdominal pain

Possible anti-TB drugs: Eto, Pto, Cfz, Lzd

Abdominal pain is most commonly gastritis. However, can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis (Lzd) and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent.
For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days).
Lower the dose of the suspected agent, if this can be done without compromising the regimen.
Discontinue the suspected agent if this can be done without compromising the regimen.
Severe abdominal distress has been reported with the use of clofazimine (deposition of Cfz crystal). Although these reports are rare, if this occurs, clofazimine should be suspended.

11.6.1.14. Diarrhoea

Possible anti-TB drugs: PAS, Eto/Pto

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Mild or transient; 3-4 loose stools/day or mild diarrhoea last < 1 week	Moderate or persistent; 5-7 loose stools/day or diarrhoea lasting >1 week	>7 loose stools/day or bloody diarrhoea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	Hypotensive shock or physiologic consequences requiring hospitalization

Management

1. Encourage patients to tolerate some degree of loose stools and flatulence.
2. Encourage fluid intake.
3. Check other causes of Diarrhea. Fever and diarrhea and/or blood in the stools indicate that diarrhea may be secondary to bacterial enteritis or pseudomembranous colitis (*C. difficile*) related to fluoroquinolone. If HIV positive assess CD4 and consider other possible causes (CMV, isospora, microsporidium)
4. Check serum electrolytes (especially potassium) and dehydration status if diarrhea is severe.
5. Treat uncomplicated diarrhea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per day.

11.6.1.15. Rash, allergic reaction and anaphylaxis

Possible anti-TB drugs: any drug

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Erythema; moderate pruritus	Extended maculopapular eruption (with or without pruritus)	Extensive papulovesicular eruption, palpable purpura, mist desquamation or ulcerations	Exfoliative dermatitis, mucous membrane involvement or erythema multiforme or suspected Stevens-Johnson or cutaneous necrosis requiring surgery
Continue the treatment and add ancillary medicines*.	Continue the treatment and add ancillary medicines*. Close monitoring. Stop the therapy if rash is worsening.	**Stop all therapy pending resolution of reaction.** Do not reintroduce the offending agent.	**Stop all therapy pending resolution of reaction**. **Hospitalization is required. Do not reintroduce the offending agent.**

Management

1. For serious allergic reactions (grade 3-4), stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols (including adrenaline). If Steven Johnson Syndrome treat with IV corticosteroid, IV fluids and IV broad spectrum antibiotic.
Suspend permanently any drug identified to be the cause of a serious reaction. Any drug that resulted in anaphylaxis or Stevens–Johnson syndrome should never be reintroduced

2. Eliminate other potential causes of allergic skin reactions (like scabies or other environmental agents).

3. *For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include
• Antihistamines
• Hydrocortisone cream for localized rash
• Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried
• Dry skin may cause itching (especially in diabetics), liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine.

4. Once the minor rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause. The order or reintroduction can be: H, Z, Eto/Pto, FQ, Cs, E, PAS, Km (or Am/Cm)

11.6.1.16. Arthralgia/ Arthritis

Possible anti-TB drug: Z (less frequent FQ, Bdq)

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**

	Mild	Moderate	Severe	Life-threatening
Arthralgia (joint pain	Mild pain not interfering with function	Moderate pain, analgesics and/or pain interfering with function but not with activities of daily life (ADL)	Severe pain; pain and/or analgesics interfering with ADL	Disabling pain
Arthritis (inflammation involving a joint)	Mild pain with inflammation, erythema or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema or joint swelling; interfering with function, but not with activities of daily life (ADL)	Severe pain with inflammation, erythema or joint swelling and interfering with ADL.	Permanent and/or disabling joint destruction

Management:

- Give NSAIDs: ibuprofen 600 mg 3 times a day
- Rest the joint
- Initiate therapy with nonsteroidal anti-inflammatory drugs:
  Ibuprofen 400 to 800 mg three times a day or Indomethacin 50 mg twice daily
- Lower the dose or discontinue the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen.
- Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgia, although if gout is present it should be used.
- If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, TB arthritis etc.

11.6.1.17. Psychosis

Possible anti-TB drugs: Cs, H, Fqn, Eto/Pto

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Acute Psychosis (suicidal ideation, maniac status, hallucinations). Life-threatening consequences, threats of harm to self or others; **hospitalization indicated**

Management

The most likely drug is cycloserine followed by high dose isoniazid.

1. **Stop the suspected agent for a short period of time** (1–4 weeks) while psychotic symptoms are brought under control.

2. Always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.

3.. If moderate to severe symptoms persist, initiate **antipsychotic therapy (haloperidol).**

4.. **Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others**.

5.. Increase pyridoxine to the maximum daily dose (200 mg per day).

6.. Lower the dose of the suspected agent (most commonly cycloserine to 500 mg a day)

7.. Discontinue the suspected agent if this can be done without compromising the regimen.

8.. Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered off. If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist.

Some patients will need to continue antipsychotic treatment throughout DR-TB treatment (and discontinued gradually upon completion of treatment)

Previous history of psychiatric disease is not a contraindication to cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment. Avoid if there is an alternative.

Psychotic symptoms are generally reversible upon completion of DR-TB treatment or cessation of the offending agent.

11.6.1.18. Depression

Possible anti-TB drugs: Cs, FQ, H, Eto/Pto

Other causes: Psychological and socioeconomic circumstances, chronic disease.

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Mild depressive symptoms; and/or PHQ9 depression score 1-9.	Moderate depressive symptoms; limiting instrumental Activities of Daily Life (ADL); and/or PHQ9 depression score 10-14.	Severe depressive symptoms; limiting self-care ADL; hospitalization not indicated; and/or PHQ9 depression score 15-19.	Life-threatening consequences, threats of harm to self or others; PHQ9 depression score 20-27; and/or hospitalization indicated

Management:

- Anti-TB Therapy may contribute to depression. Depressive symptoms may fluctuate during the therapy.
- Asses and address underlying emotional and socioeconomic issues.
- Provide psychological support (for the patient and family)
- If depression is significant, initiate antidepressant therapy (amitriptyline, fluoxetine)
- Avoid serotonin reuptake inhibitors and tricyclic antidepressant with Lzd (risk of serotonin syndrome)
- Lower the dose of the suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and ethionamide to 500 mg daily.
- Discontinue the suspected agent if this can be done without compromising the regimen.

11.6.1.19. Seizures

Possible anti-TB drugs: Cs, H, FQ, Imp/Cln

First address other causes of seizures: infection, epilepsy, meningitis, encephalitis, alcohol withdrawal, hypoglycemia, cerebrovascular accident, malignancy or toxoplasma in PLHIV).
Then:
1. Hold cycloserine, fluoroquinolones and isoniazid pending resolution of seizures.
2. Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used).
3. Increase pyridoxine to the maximum daily dose (200 mg per day).
4. Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride.
5. Check creatinine level A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may be all that is needed to control the seizures
6. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.
Notes:
The anticonvulsant is generally continued until DR-TB treatment is completed or suspected agent is discontinued.
History of previous seizure disorder is not a contraindication to the use of agents listed here
if a patient's seizures are well controlled and/ or the patient is receiving anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available.)

11.6.1.20. Hypothyroidism

Possible anti-TB drugs: Eto/ Pto/PAS

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Sub-clinical hypothyroidism (TSH 6-10mIU/L, T4 free normal)	Simple Hypothyroidism without complications. Treatment required (TSH > 10 mIU/L)	Severe Hypothyroidism with clinical symptoms. Urgent treatment	Myxedematous coma

Management
Start treatment when TSH > 10 mIU/L
1. Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner:
• Young healthy adults can be started on 75–100 mcg daily
• Older patients should begin treatment with 50 mcg daily
• Patients with significant cardiovascular disease should start at 25 mcg daily.

2. Monitor TSH every month and increase the dose by 25 mcg until TSH normalizes (TSH < 5 mIU/L). Adjust the dose more slowly in the elderly and in patients with cardiac conditions.

Note: it could be considered to start treatment with TST >6 mIU/L to 10 mUI/L with low dose of levothyroxine (25 to 50 mcg)
Thyroid dysfunction resolves upon discontinuation of the cause agent. Hormone replacement must continue at least 2 to 3 months after completed DR-TB treatment.

Annex 4: Sample Central Clinical Review Council DR-TB consultation sheet

National Tuberculosis and Leprosy Programme: Tel 061-2035020, Fax 061-252740	
SITE/HOSPITAL	
DOCTOR and contact details	
District TB Coordinator and Contact Details	
PATIENT NAME, AGE, SEX	
DIAGNOSIS	
PROBLEM(S)	
HIV STATUS, LATEST CD4 & HAART REGIMEN	
MEDICAL HISTORY	
TB HISTORY (Date/year, initial Rx / retreatment, duration & outcomes, include any side effects)	1. 2. 3.
TB HISTORY SECOND LINE (Actual medicines, duration dates if possible, include any side effects)	
EXAMINATION & XRAY FINDINGS	
CURRENT SPUTUM (Date taken, DM, Culture, DST)	
OTHER INVESTIGATIONS DONE	
CURRENT TREATMENT (TB & Other –include side effects)	
PROPOSED TREATMENT (by district/regional team)	
SOCIAL CONSIDERATIONS **(**problems and how they are being addressed) Assessed by social worker (Y/N)	DOT (Y/N) .....Name of provider/organisation.....

SPUTUM EXAMINATION CHART

DATE TAKEN	DM-insert worst: *neg/+/++/+++* (and date received)	Culture MTB/MOTT/ Neg6wk/Neg2wk	Resistant: H/R/S/E Km/Ofx/Eto	Susceptible H/R/S/E Km/Ofx/Eto

H=Isoniazid, R=Rifampicin, S=Streptomycin, E=Ethambutol, Km=Kanamycin, Ofx=Ofloxacin, Eto=Ethionamide

ADDITIONAL COMMENTS/INFORMATION (please add another sheet if necessary):

.....

.....

.....

.....

PERSON REPORTING: .....

Fax number: ..... DATE.....

To be faxed to the CCRC: Fax 061-252740; Tel 061-2035020

Annex 5: Sample consent to treatment for DR-TB

REPUBLIC OF NAMIBIA

MINISTRY OF HEALTH AND SOCIAL SERVICES

CONSENT TO TREATMENT FOR DRUG-RESISTANT TUBERCULOSIS

I, _____, ID No_____, hereby consent to being admitted, investigated and treated for drug resistant tuberculosis. I have been informed that I have drug resistant TB, which as I have clearly understood, can spread to others and requires close monitoring to determine if the treatment that I am put on is working.

I have been told that I will receive daily injections for several months and that the treatment may continue for many months, up to two years or more. The actual duration of injections and my hospital stay will depend on when laboratory test results confirm that I am no longer able to spread TB to others.

I have been properly counselled that I may suffer side effects from this treatment, such as hearing loss and stomach upset. However, I have chosen to continue this treatment on my own free will because there are no other alternative medicines for my disease.

I may be admitted in hospital to prevent spreading tuberculosis to others and to make sure that I take the medicines every day under direct observation by a health worker. I may be transferred from one hospital to another which is better suited to manage my condition, as decided by the medical team. I fully consent to being discharged only after the medical team has confirmed and is satisfied that I am no longer able to spread TB to others.

To prevent the spread of TB to others I may be told to cover my mouth and nose with a surgical/hospital mask and I hereby undertake to do so immediately upon being requested to do so. I will not intentionally or negligently endanger the life of members of my family or public who do not have TB by violating any of the advice given to me to protect others during my treatment and will take all reasonable steps to avoid such an endangerment.

During the course of my admission, I will not leave the hospital without the written and signed approval of the nurse in charge of the ward. I understand the gravity and seriousness of having TB and I have chosen to stay in hospital out of my own free will in order to receive treatment; therefore, I shall abide by all of the terms and conditions set out in this consent form and generally by the rules and regulations of the hospital as outlined to me by the hospital authorities.

I further understand that, should I attempt to leave the hospital without consent during my treatment, physical force might be needed in order to restrain me from doing so, and that such restraint may be necessary to ensure my treatment period is completed and I agree to such.

I understand that to protect the effectiveness of the medicine the medical team will stop my medicine if:

- I interrupt the treatment myself, or
- there is evidence that the medicine will not work, or
- I suffer serious side effects, or
- I breach the conditions of treatment.

Furthermore, the hospital management reserves the right to ask me to leave the hospital if I disrupt smooth delivery of service at the hospital.

I have read the aforementioned and understand such and sign out of my own free will and without duress.

Signed:…… Date: ……..

Witness 1 (HCW) …… Witness 2 (relative/guardian)……