

National Guidelines for Programmatic Management of Drug Resistant Tuberculosis

**National Programme for Tuberculosis Control and Chest Diseases
Sri Lanka**

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EDITORS AND CONTRIBUTORS

Chief Editors

Dr. Muhammad Asif	WHO Consultant
Dr. Bandu Gunasena	Consultant Respiratory Physician

Writing panel

Dr. Nirupa Pallegatte	Deputy Director, NPTCCD
Dr. Wijitha Senaratne	Consultant Respiratory Physician
Dr. Dushani Jayawardhana	Consultant Microbiologist, NTRL
Dr. Onali Rajapakshe	Consultant Community Physician, NPTCCD
Dr. Pramila Liyanage	Consultant in Health Informatics, NPTCCD
Dr. N.H.S Nadeeka	Actg. Consultant Community Physician, NPTCCD
Dr. Nazneen Nazeer	Senior Registrar (Community Medicine), NPTCCD
Dr. Kaushalya Rajapaksa	National PMDT Coordinator, NPTCCD

Contributors

Dr. Geethal Perera	Consultant Respiratory Physician
Dr. D Madegedera	Consultant Respiratory Physician
Dr. Saman Kularatna	Consultant Respiratory Physician
Dr. Eshanth Perera	Consultant Respiratory Physician
Dr. Manil Peiris	Consultant Respiratory Physician
Dr. H.S Samankantha	Consultant Respiratory Physician
Dr. W.L Dilisha	Consultant Respiratory Physician
Dr. Nayana De Silva	DTCO Colombo
Dr. Chinthika Dissanayake	DTCO Badulla
Dr. Arany Koneshwaran	DTCO Batticaloa
Dr. Devika Vijayathunga	DTCO Ampara
Dr. Jeewani Samaraweera	DTCO Polannaruwa
Dr. Anjana Senanayake	DTCO Nuwaraeliya
Dr. Iresha Samanmali	DTCO Galle
Dr. A.Thyaseelan	DTCO Mullaithivu
Dr. R Maniwasakan	DTCO Jaffna
Dr. Niluka Lakmali	DTCO Matara
Dr. Deepthini Vaidyaratna	DTCO Anuradhapura
Dr. Suraj Suresh Kumara	DTCO Trincomalee

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FOREWORD

Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat to the global commitment to end the TB epidemic. Despite lower levels of MDR-TB and rifampicin resistance tuberculosis (RR-TB) in Sri Lanka, owing to effective national TB control activities, the gradual rise in resistance to first line anti TB drugs is a cause for concern.

Recognizing the critical importance in tackling drug resistance before it took deep root, the National Programme took a timely initiative of developing the National Guidelines for the Programmatic Management of Drug Resistance Tuberculosis back in 2015.

However, with new evidence realized with respect to diagnostic modalities, treatment regimens and preventive strategies for drug resistance TB, the ingenuity of the National programme to revise the guideline for improved patient centred care is highly appreciated.

I earnestly hope that this revised publication would serve as a valuable and effective guide to all relevant health professionals to update their knowledge for effective management of drug resistance TB in the country.

My heartfelt appreciation to all authors and stakeholders for their invaluable contribution.

Dr. Asela Gunawardane
Director General of Health Services
Ministry of Health

PREFACE

With the view of improving the management of drug resistance TB (DR-TB) in Sri Lanka, the National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) has taken the timely initiative to revise the current edition of the guideline for Programmatic Management of Drug Resistance Tuberculosis (PMDT) taking into consideration recent evidence that have come to light in the areas of diagnosis and treatment.

The foremost modifications to the guidelines include amendments in treatment regimens, application of new diagnostic tools, and revised outcome definitions among many others. Active drug safety monitoring and management, and key research areas related to DR-TB are the novel add-ons to the manual.

The revision process was performed under the spearhead of Dr. Muhammad Asif, the international consultant, together with Dr. Bandu Gunasena, the local consultant with tremendous contributions from Consultant Respiratory Physicians of Sri Lanka, Consultant Microbiologist from the NTRL, the Deputy Director, Consultant Community Physicians, Consultant Health Informatics, Senior Registrar in Community Medicine and the PMDT Coordinator of the NPTCCD.

The revised guideline is intended for all clinicians involved in the management of drug resistance TB in order to update their knowledge which would enable in providing an effective and patient centred care.

I extend my sincere gratitude to both the chief consultants, international and local, and all other contributors for their tireless effort and immense support. I also acknowledge the assistance rendered by the WHO and the GFATM in the publication of this document.

Dr. H.D.B Herath

Director

NPTCCD

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ABBREVIATIONS

AFB	Acid Fast Bacillus
AE	Adverse Event
ADR	Adverse Drug Reaction
aDSM	Active Drug Safety Monitoring and Management
CRP	Consultant Respiratory Physician
CCC	Central Chest Clinic
CXR	Chest Xray
DST	Drug Susceptibility Testing
DOTS	Directly Observed Treatment Short Course
DRS	Drug Resistant Survey
DM	Diabetes Mellitus
DCC	District Chest Clinic
DTCO	District TB Control Officer
EPTB	Extra Pulmonary TB
FQ	Fluoroquinolone
FLDs	First line drugs
GX	GeneXpert MTB/RIF
GDF	Global drug facility
Hr TB	Isoniazid Resistant TB
IPC	Infection Prevention and Control
ITL	Intermediate TB Lab
LJ	Lowenstein-Jensen
LPA	Line probe Essay
MDR TB	Multidrug Resistant TB
MO	Medical Officer
NPTCCD	National Program for TB control and chest Diseases
NSP	National Strategic plan
NTRL	National TB reference Lab
OLTR	Oral Longer Treatment Regimen
OSSTR	Oral Standardized Shorter Treatment Regimen
PTB	Pulmonary TB
PLHIV	People Living with HIV
PMDT	Programmatic Management of Drug Resistant TB
PDHS	Provincial Director of health services
RDHS	Regional Director of Health Services
rGLC	Regional Green Light Committee
RR TB	Rifampicin Resistant TB
SAE	Severe/Serious Adverse Event
SLDs	Second Line Drugs
SLIs	Second Line Injectable
XDRTB	Extensively Drug Resistant TB
WHO	World Health Organization

SUMMARY OF MAJOR CHANGES IN PMDT GUIDELINES 2021 UPDATE

- Second line anti TB drugs (SLD) are regrouped (A, B, C) by the WHO based on assessment of relative benefits to harms.
- Kanamycin and capreomycin are no longer to be the part of treatment of RR/MDR-TB regimens. Only Amikacin or Streptomycin is to be used under certain conditions.
- All oral standard shorter RR/MDR TB regimen as preferred option if eligibility criteria are met and any changes in OSTR to be done under operational research.
- Use of BPaL (6-9 moths) regimen for pre XDR TB-patients to be considered following operational research.
- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis(Hr TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. It is not recommended to add injectables.
- When deciding on the treatment regimen (choice between short and long regimens), preference of the patient should be taken into account.
- Pre XDR TB to be used as official term when RR/MDR TB plus any of the FQs are resistant, similarly the definition of XDRTB has been revised.
- Most of outcome definitions of RR/MDR TB have been revised.
- A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option, ensuring the best mode of providing DOT and adherence to it as well.
- Active drug safety monitoring and management (aDSM) is applicable to all RR TB patients
- Diagnosis of DR TB should be based on newer RR/MDR TB diagnostic tools
- Country capacity to diagnose and treat DR TB should be developed further and this should include ability to perform DST to bedaquiline (Bdq), linezolid (Lzd), clofazimine (Cfz) and delamanid (Dlm).
- It is desirable to repeat sputum culture monthly while on treatment for DR TB

1. BACKGROUND INFORMATION ON MULTI DRUG AND EXTENSIVELY DRUG RESISTANT TB

Multi Drug Resistant Tuberculosis (MDR-TB), which is defined as resistance to both isoniazid and rifampicin, is emerging as a major threat to global tuberculosis control. Countries with a high prevalence of MDR-TB generally have a history of poor tuberculosis (TB) control in the past. The problem of MDR-TB has been growing over the past several years and mathematical modelling suggests that unless there is a concerted effort to stop MDR- TB, it would become a major health problem in several continents. The global initiative taken by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD/The Union) to ascertain the extent of the problem through anti-TB Drug Resistance Surveillance (DRS) Programme was established in 1994 and at present data is available on 169 countries including 113 countries that have continuous surveillance systems based on routine diagnostic drug susceptibility testing of all TB patients (WHO 2020). It is estimated by WHO that in 2019, almost half a million (465,000) new cases of MDR-TB emerged globally and 182,000 such cases died. The global proportion of RR-TB estimated to have MDR-TB in 2019 stands at 78% (WHO-Global TB report, 2020).

Although globally the proportion of new cases with MDR-TB remains stable, at national level the proportion of TB cases with MDR/RR-TB should be interpreted within the overall context of the country's TB epidemic (WHO-Global TB report, 2020). Globally, among new TB cases (that accounts for most of the global TB burden) an estimated 3.3% (95%CI; 2.3-4.3%) have had MDR/RR-TB while the proportion is higher among previously treated for TB at 18% (95%CI; 9.7-27%).

Well-functioning National TB control programmes in the WHO South East Asia (SEA) Region achieving high treatment success rates has resulted in maintaining a slow but steady decline in TB incidence rates during the past decade. This has also led to low levels (2.5%, range: 1.9-3.3%) of multi drug-resistance (MDR) among newly detected TB cases. Among previously treated TB cases in the Region, MDR-TB rate is estimated to be higher, around 14% (range: 7.7-21%). However, given the large numbers of TB cases in the SEA Region translates to a total 171, 000 (range: 117,000–236,000) estimated MDR-TB cases among the notified pulmonary TB cases, accounting for 37% of the world's MDR-TB cases in 2020. (WHO-Global TB report, 2020).

A new threat to TB control is emerging in the form of extensive drug resistant TB (XDR-TB). Strains of XDR-TB are readily transmissible and outbreaks have been reported in some parts of the world. TB/HIV co-infection compounds the problem. Therefore, there is an urgent need

to strengthen NTP to prevent the emergence of MDR, Pre XDR and XDR-TB cases. Newly named totally drug resistant TB (TDR-TB) is also emerging, that is resistant to all anti -TB drugs tested in the laboratory. The framework for management of MDR-TB presented in these guidelines will be integrated into the basic TB control strategy of the National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) as MDR-TB prevention and control is an integral part of the National TB control programme in Sri Lanka.

This Programmatic Management of Drug-resistant Tuberculosis (PMDT) guideline is designed to facilitate early identification of cases likely to have DR-TB , describes the case finding and treatment strategies including referral for bacteriological examination, provide description of treatment regimen and doses, case definitions, patient registration categories, types of drug resistance, management of adverse reactions, infection control measures, treatment outcomes, role of various partners and stakeholders and the responsibilities of NPTCCD staff in implementing the PMDT strategy.

2. TB CONTROL ACTIVITIES IN SRI LANKA

TB control activities in Sri Lanka have been integrated with the general health services since 1970. The Directly Observed Treatment Short course (DOTS) strategy was adopted in 1997 and the Stop TB strategy in 2006 with a gradual expansion of services, now covering the entire population in all 25 administrative districts. The detection of incident TB cases (all forms) in the country has ranged between 60%-69% for the last two decades since 2006. The treatment success rate has been around 85% of notified cases of rifampicin susceptible, for the last few years and 68% for MDR-TB for the 2017 cohort (End term TB Review-Report 2020)

From 2005 onwards, TB microscopy services were decentralized to over 100 health facilities and have now been expanded to around 170 facilities in the country. TB patients diagnosed at various peripheral governmental facilities above are referred to the respective District Chest Clinic (DCC) for initiation of treatment followed by treatment closer to the homes of patients.

The TB control programme in Sri Lanka has developed its National Strategic Plan (NSP) for 2021-2025 well in line with achieving targets established in the End TB strategy adopted by the World Health Assembly, working collectively with the global community to eliminate TB. The new NSP focuses on improved case detection with special emphasis on children, introduction and scaling up of TB preventive treatment, reinforcement of private sector engagement in TB diagnosis and management, strengthening monitoring and evaluation system and operational research.

2.1. Organizational structure of NPTCCD

NPTCCD is a decentralized unit within the Ministry of Health (Figure 2.1). It is headed by the Director who is reporting to the Deputy Director General (Public Health Services)-I of the Ministry of Health. The Central Unit, National Tuberculosis Reference Laboratory (NTRL), Central Drug Stores of the NPTCCD, and Central Chest Clinic (CCC), Colombo and DCC Gampaha are under the direct administrative purview of the Director, NPTCCD.

District level TB control activities are carried through DCCs. There are 26 DCCs, one in each district (in Ampara district there are two DCCs as Ampara and Kalmunai). Except for the Colombo CCC and Gampaha DCC, all other DCCs are under the administrative purview of the respective Regional Directors of Health Services.

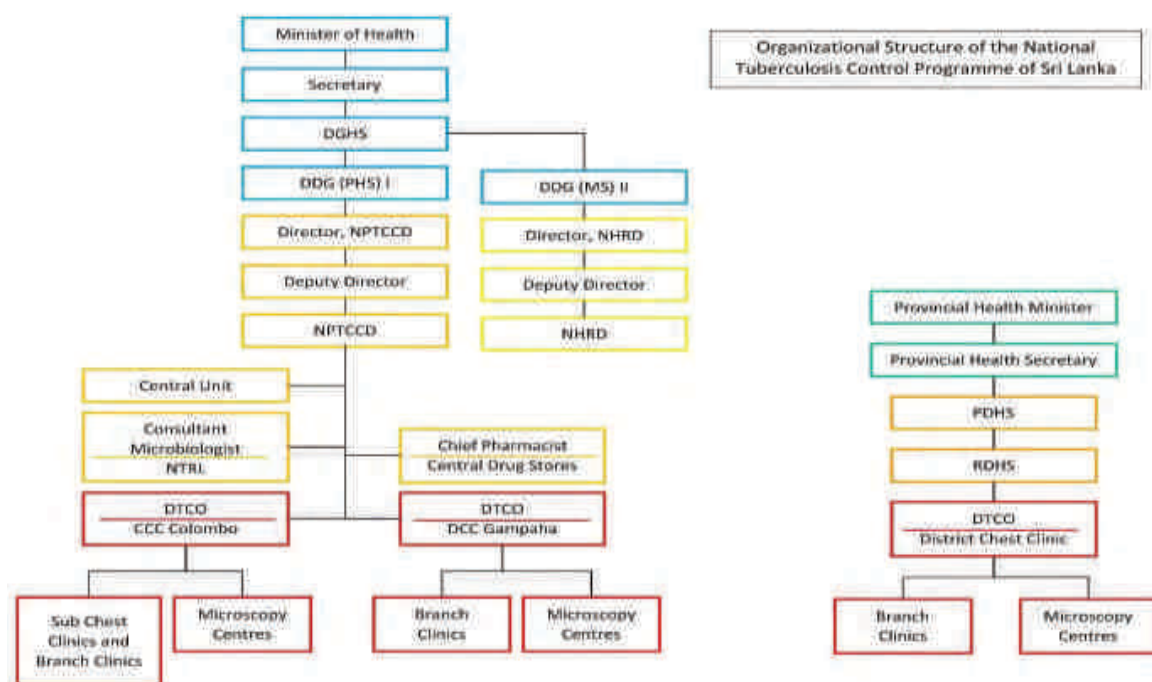


Figure 2-1: Organizational structure of the National Tuberculosis Control Programme in Sri Lanka

The District Tuberculosis Control Officer (DTCO) is the focal point for tuberculosis control activities in each district. Based on the service requirements one or more branch clinics at different healthcare facilities are functioning on a regular basis under the DTCOs. For TB case detection a network of around 170 microscopy centres is functioning throughout the country. In addition to the NTRL, four intermediate TB culture laboratories are functioning in Kandy, Ratnapura, Galle and Jaffna with plans to establish two more intermediate TB culture laboratories in Batticaloa and Anuradhapura districts in coming years. Drug Sensitivity Test (DST) facilities for first line and second line (Fluoroquinolones and Amikacin) anti-TB drugs are available only at NTRL. Line Probe Assay (LPA) facilities are available for second-line anti-TB drugs (Fluoroquinolones and Amikacin) within the country at the time of writing these guidelines. DST for Bdq, linezolid (Lzd), clofazimine (Cfz) and Xpert/XDR TB modules will be established at NTRL by 2022.

2.2. Epidemiology of TB in Sri Lanka

Given that Sri Lanka is a low burden country for TB, conducting a prevalence survey is not perceived as cost effective. However, an inventory survey is a pipeline project to be carried out in the near future. The reported incidence of TB in 2019 is 64 per 100,000 population in Sri Lanka. A total of 8434 all forms of TB were notified in the same year. Table 2.1 shows the estimated burden of TB in Sri Lanka.

Table 2-1: Tuberculosis burden in Sri Lanka (WHO, country profile for Sri Lanka, 2020)

	Estimated Year	Rate*	Number
Total TB Incidence (all forms /100,000 /year)	2019	64	14,000
HIV-negative TB Mortality	2019	3.6	770
HIV-positive mortality	2019	0.02	4
HIV-positive TB incidence	2019	0.05	11
MDR/RR-TB incidence	2019	0.13	27

*Rates per 100,000 population

2.3. Epidemiology of HIV in the country

Sri Lanka has a low HIV prevalence. The estimated number of people living with HIV/AIDS in Sri Lanka for the year 2020 was 3994 with an adult (15-49 years) prevalence rate of <0.1%. According to the national HIV/AIDS surveillance data, the number of HIV cases detected was 363 in 2020. TB/HIV co-infection was reported among 33 out of 6679 TB patients with known HIV status in 2020 (WHO, 2020).

2.4. MDR-TB

Sri Lanka has a low burden of drug-resistant TB with an estimated 27 rifampicin-resistant (RR) or multidrug-resistant (MDR) TB cases appearing each year which translates into an incidence rate of only 0.13/100 000 population (end-term TB review report,2020).

Sri Lanka thus far has conducted two national level surveys on anti-mycobacterial drug resistance of *Mycobacterium tuberculosis*; one in 2005/2006 and the latest in 2017. The latest survey was carried out in a total of 1643 patients enrolled for treatment at all 26 chest clinics across the country (1512 newly diagnosed and 131 previously treated cases). While Xpert (MTB/RIF) positivity for MTB was 91.4%, culture positivity was 71.7%. A total of 11 patients were detected with RR-TB (7 new and 4 previously treated). Of these eleven patients (11/1519) only two cases (2/1519) were reported to have MDR-TB (DRS- SL, 2017). The rates of RR/MDR TB were 0.56% in new and 5.1% for previously treated cases (rGLC report for Sri Lanka, 2019).

However, according to WHO estimates for 2019, the proportion of TB cases with RR/MDR TB cases is 0.1% for new and 3.3% for previously treated (WHO –country profile, 2020).

Table 2.2 shows numbers of RR/MDR-TB cases notified, and patients enrolled for MDR-TB treatment annually in Sri Lanka for the period of 2010-2010.

Table 2-2: RR/MDR-TB cases notified and patient enrolment for treatment in Sri Lanka (End-Term TB review report, 2020)

Year	Notified RR/MDR-TB cases	Patients started on MDR-TB treatment	Treatment initiated
2010	15	6	40.0%
2011	24	10	41.6%
2012	8	5	62.5%
2013	12	4	30.0%
2014	13	11	84.6%
2015	15	13	86.6%
2016	23	17	73.9%
2017	32	22	68.8%
2018	32	13	40.6%
2019	21	20	95.2%
2020	14	14	100.0%

2.5. TB case finding and treatment strategy

Case finding is a collective effort of screening of presumptive TB cases (in whom TB is suspected) attending outpatient departments as well as inpatients of hospitals by implementing the diagnostic algorithm as per National Guidelines. In addition, active screening of high-risk groups with special focus on prison inmates contribute to the cases routinely detected. While sputum for microscopy and chest x-rays are done for all presumptive TB patients, Xpert MTB/Rif is carried out for all those who are sputum positive in line with the universal DST policy. However, Xpert MTB/Rif is also endorsed as an initial investigation for presumptive MDR- TB and for presumptive TB in identified high-risk groups as well.

According to the national policy, all close contacts (household, workplace and others) of all TB (PTB, EPTB) patients are screened for TB.

All new cases are treated with 2HRZE/4HR regimen. Patients who give a history of prior anti-TB treatment of one month or more (previously treated) are tested with Xpert MTB/Rif and treated with 3HRZE/5HRE for Rifampicin sensitive patients, at present. Fixed dose combination drugs are used at all stages of treatment.

Intensive phase treatment is given under supervision by a DOT provider and during the continuation phase, drugs are supplied for a duration of two weeks to one month at the chest clinic or branch clinics for self-administration. During the continuation phase drug compliance is monitored by pill count and by checking the emptied foils.

3. FRAMEWORK FOR EFFECTIVE CONTROL OF DR TB

Diagnosis treatment and prevention of DR TB is an integral part of NTP. Therefore, the PMDT programme is integrated into the basic NTP strategy. PMDT activities are categorized under the following components.

3.1. TB control framework as applied to the DR TB –PMDT strategy

- Sustained political and administrative commitment.
- Appropriate case finding and diagnosis strategy using quality assured globally accepted rapid molecular tests, cultures and DST.
- Appropriate treatment strategies that use second line drugs under globally accepted standards.
- Uninterrupted supply of quality assured second line drugs.
- Recording and reporting system designed for DR TB control programme that enables evaluation of performance, monitoring and treatment outcome.

3.1.1 Sustained political and administrative commitment

- Essential to establish and maintain the other four components of control framework.
- Administrative support for NTP to implement effective TB control policies.
- Address the factors leading to the emergence of drug resistance.
- Long term investment on staff and resources.
- Coordination between government institutions, non-governmental bodies, local and international agencies.
- Long term financial support.
- Central and provincial level commitment.

3.1.2 Appropriate case finding and diagnosis strategy using quality assured globally accepted rapid molecular tests, culture and DST

- Rational triage of patients for testing of drug resistance.
- Appropriate use of WHO endorsed rapid tests as well as culture and DST with internal and external quality assurance.
- Close collaboration with supranational TB reference laboratory for proficiency testing.

3.1.3 Appropriate treatment strategies that use second line drugs under globally accepted standards

- Rational treatment design.
- Ensure DOT throughout whole treatment duration.
- Active monitoring and management of adverse events.
- Obtaining services of properly trained human resources.

- Treatment adherence through patient centered approach.
- Health education and psychosocial support.

3.1.4 Uninterrupted supply of quality assured second line anti TB drugs

- Ensure the availability of quality assured second line drugs without interruption
- Drug management should take into consideration the short half-life of second line drugs and the storage conditions to assure the predicted shelf life.
- Procurement process should take into account the limited number of suppliers for quality assured second line drugs
- Strengthen the inventory management capacity at sub national level
- All precautions need to be taken to minimize wastage of drugs

3.1.5 Recording and reporting system designed for DR TB control programme that enables evaluation of performance, monitoring and treatment outcome

- Effective reporting and recording system supported by introduction of electronic documentation
- Documentation of laboratory results
- Monitoring treatment delivery and the response to treatment throughout the whole duration of treatment
- Effective functioning of PMDT committees at national level and at PMDT implementation sites for regular review of performance.

4. DEFINITIONS AND CLASSIFICATIONS

This chapter describes types of drug resistance, bacteriological definitions for drug resistance, case definitions, patient registration categories and treatment outcome definitions which are important in cohort analysis procedures for DR-TB patients who are treated under PMDT strategy.

4.1. Types of drug resistance

- **Drug resistance among previously treated cases (acquired resistance).** Presence of resistant strains of *M. tuberculosis* in a patient who has previously received at least one month of anti-TB therapy. Inadequate dosage or duration, inappropriate drug combinations, treatment with substandard drugs and erratic treatment lead to proliferation of drug resistant organisms or acquisition of drug resistance by organisms which are previously sensitive.
- **Drug resistance among new cases (primary resistance).** Presence of resistant strains of *M. tuberculosis* in a newly diagnosed TB patient who has never received anti-TB drugs or has received them for a period of less than one month. This means that the patient has been infected with organisms which are already drug resistant, likely from exposure to a person who harbours a drug resistant bacillus.
 - **Wild type resistance.** In a colony of *M. tuberculosis* there can be few organisms which are resistant to a given anti-TB drug not because of previous exposure to that drug but due to spontaneous genetic mutations. Such drug resistance is known as wild type resistance. When anti-TB drugs are used in combination, the organisms which are wildly resistant to one drug are killed by another drug in the combination. Monotherapy leads to selection of drug resistant organisms and their proliferation.

4.2. Causes of drug resistance

MDR-TB/other types of DR-TB is entirely a man-made phenomenon and is an indicator of poor management of TB patients by the entire health system. The common causes of MDR/DR-TB are given in Table 4.1

Table 4-1: Common Causes of MDR/DR-TB

Service factors	Patient factors
<ul style="list-style-type: none"> - Prescribing incorrect chemotherapy (wrong combination of drugs, doses and duration) - Failure to ensure a regular and uninterrupted drug supply - Poor case management – incomplete and irregular treatment, where patients are not directly observed taking their drugs - Use of drugs of unproven bioavailability/unsure quality - Adding one new drug at a time to a failing (or failed) anti-TB drug regimen - Inappropriate treatment regimen in patients with history of previous TB treatment including irrational use of second-line drugs (SLD) - Not referring TB patients to the state health sector for treatment and patients being forced to purchase drugs which they cannot afford - Regular services not being accessible in terms of distance, transport facilities and/or convenient timing for the patient - Failure to educate patients and the family about the disease, treatment approach and failure to stress the importance of adhering to treatment throughout the prescribed period 	<ul style="list-style-type: none"> - Not taking the full prescribed number of drugs - Taking less than the prescribed dose - Taking drugs irregularly or discontinuing treatment before the prescribed period - Adverse effects to anti-TB drugs - Social psychological and economic barriers. preventing proper treatment - Malabsorption or other concomitant illness - Alcoholism and substance abuse leading to non-adherence - Lack of family support. - Lack of knowledge about the disease and its treatment

4.3. Significance of MDR-TB

- Commonly used first-line anti-TB drugs are no longer effective.
- MDR-TB is more difficult to treat, and it requires treatment with ‘reserve’ or second-line anti-TB drugs (SLD) which are not as potent as first-line drugs (FLD) and have to be given for at least twenty months.
- These drugs are more toxic to the patients and have more severe adverse reactions (ADRs).
- The SLD are more expensive than the standard FLD.
- The outcome of treatment is poor, and the mortality rate is high.

4.4. General definitions of resistance used in DR TB

- **Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB):** caused by *M. tuberculosis* strains resistant to isoniazid and susceptible to rifampicin
- **Mono-resistance:** TB in a patient, whose infecting isolates of *M. tuberculosis* are resistant in vitro to one of the first line anti-tuberculosis drugs except rifampicin. Rifampicin mono resistance is categorised separately.

- **Poly-resistance:** TB in a patient, whose infecting isolates of *M. tuberculosis* are resistant in vitro to more than one first-line anti-tuberculosis drug, other than to both isoniazid and rifampicin.
- **Multi drug resistant TB (MDR-TB):** TB caused by *Mycobacterium Tuberculosis* (*M. tuberculosis*) strains that are resistant to at least both rifampicin and isoniazid with or without resistance to other first or second-line TB medicines
- **Pre-XDR-TB:** TB caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any of the fluoroquinolone (levofloxacin/moxifloxacin) (1)
- **Extensively Drug Resistant TB(XDR-TB):** TB caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A drug (Bdq, linezolid) (1)
- **Rifampicin resistance (RR):** Resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti TB drugs except Isoniazid.

Reference: (1) WHO 2021; Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis

4.5. Classification according to the site affected

4.5.1 Pulmonary tuberculosis (PTB)

PTB is TB involving the lung parenchyma & tracheobronchial tree. A patient with both pulmonary and extra-pulmonary TB will be classified as pulmonary TB. Miliary TB is classified as pulmonary TB because there are lesions in the lung parenchyma as well.

4.5.2 Extrapulmonary tuberculosis (EPTB)

TB of organs other than the lung parenchyma & tracheobronchial tree.

4.6. Classification based on history of previous anti-TB treatment

Each RR/ MDR-TB patient commenced on second-line drug regimen should be classified in two different ways:

4.6.1 Classification for the purpose of assigning appropriate treatment regimen

- **New:** A patient who has received no or less than one month of first line anti-TB treatment. Patients are placed in this group if they had sputum collected for DST at the start of a new treatment regimen with FLD or within one month of starting FLD and were then switched to a second-line treatment regimen because MDR-TB was later confirmed. (even if they had received more than one month of new treatment with FLD by the time the results of DST received and were started with second-line treatment).

- **Previously treated with FLD only:** A patient who has been treated for one month or more for TB with FLD only.
- **Previously treated with SLD:** A patient who has been treated for one month or more for TB with one or more SLD, with or without FLD.

4.6.2 Classification for the purpose of registration

Patients are assigned to a registration group based on the most recent treatment history at the time of collecting the biological specimen that was used to confirm MDR-TB or RR-TB.

The registration groups are the established groups used in the DOTS recording and reporting system, with additional subgrouping of patients treated after failure.

The groups are as follows:

- **New:** A patient who has received no or less than one month of anti-TB treatment.
- **Relapse:** A patient whose most recent treatment outcome was “cured” or “treatment completed”, and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy, molecular tests or culture.
- **Treatment after lost 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. (This was previously known as treatment after default).
- **Treatment after failure of first line regimen for new cases:** A patient who has received treatment for TB (with first line drugs as for a new case) and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.
- **Treatment after failure of first line regimen for retreatment cases:** A patient who has received re-treatment for TB with first line drugs and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.
- **Other previously treated:** A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented

Patients placed on second-line anti-TB medications usually belong to one of the following groups:

- **Confirmed RR-TB or MDR-TB.** Confirmed resistance to Rifampicin or both Rifampicin and Isoniazid
- **Presumptive RR-TB or MDR-TB:** All possible efforts should be taken to get tested by Xpert MTB/RIF prior to initiation of treatment. However, on rare occasions, in the absence of RR/MDR TB confirmation, presumptive RR/MDR TB patients can be treated with MDR TB regimen with the best judgment of treating physician in line with consultation with

committee. If Xpert shows RR susceptibility, then FL LPA should be carried out to evaluate for INH resistance.

- **Poly-/mono-resistant TB without rifampicin resistance.** Some of these patients may have second-line anti-TB drugs added to their treatment.
- **Pre-XDR TB & XDR TB** (confirmed or presumptive): Patients may be started on Pre-XDR TB or XDR-TB treatment on the basis of a laboratory diagnosis or in its absence, because of significant risk for example close contacts.

4.7. Treatment outcome definitions of MDR-TB patients

Following are the updated definitions to be used to document treatment outcome and these definitions apply to both DS and DR TB (2).

Treatment failed

A patient whose treatment regimen needed to be terminated or permanently changed^(a) to a new regimen or treatment strategy^(a)

Cured

A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response^(b) and no evidence of failure.

Treatment completed

A patient who completed treatment as recommended by the national policy, whose outcome does not meet the definition for cure or treatment failure.

Died

A patient who died^(c) before starting treatment or during the course of treatment.

Lost to follow-up

A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

Not evaluated

A patient for whom no treatment outcome was assigned

Treatment success

The sum of cured and treatment completed.

Notes:

a Reasons for the change include:

- no clinical response and/or no bacteriological response (see note 'b');

- adverse drug reactions; or
- evidence of additional drug resistance to medicines in the regimen.

b “Bacteriological response” refers to bacteriological conversion with no reversion.

- “Bacteriological conversion” describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are negative.

- “Bacteriological reversion” describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

c Patient died for any reason.

5. STRATEGIES FOR CASE FINDING AND DIAGNOSIS OF DR-TB

Quality assured laboratory plays a key role in the management of DR-TB patients. Case finding strategies should not be separately considered for DR-TB, rather it should be addressed as holistic approach to find cases for TB/DR-TB as one approach.

This chapter focuses on the strategies used to identify suspected patients with different forms of DR-TB that includes RR-TB, MDR-TB, pre-XDR-TB, XDR-TB and Hr-TB and the diagnostic methods available to detect and confirm TB/DR-TB.

5.1. Strategy for case finding of DR-TB patients

Following strategies are used to improve DR-TB case finding:

1. Identification of risk groups for DR-TB
2. Screening of all presumptive DR-TB systematically using diagnostic algorithm
3. Identification of DR-TB cases from microbiologically positive patients using Universal DST

5.1.1 Identification of Risk groups for DR-TB

Case finding should be carried out in risk groups for:

- RR/MDR
- Pre XDR and XDR
- INH resistant TB (Hr TB) -Mono and Poly DR TB other than RR/MDR TB

5.1.1.1 Case finding for RR/MDR TB

The first step in case finding begins with identification of presumptive DR-TB cases. DR-TB should be suspected in the following categories of patients and their sputum should be sent for rapid molecular tests (Xpert MTB/RIF), and for further drug susceptibility testing in order of priority.

As per NPTCCD policy, following groups of patients should be tested by Xpert MTB/Rif as the initial diagnostic test:

- a) Symptomatic contacts of MDR-TB patients or those asymptomatic contacts screened with CXR having changes suggestive of TB.
- b) First line regimen failures and non-converters/ delayed sputum conversion.

First line treatment failure (patients who are on treatment with first line drugs for a new episode of TB) and patients remaining sputum smear positive at 2nd month after first line treatment.

- c) Patients with history of repeated treatment interruptions.
- d) All other previously treated TB patients.
- e) Patients with TB/HIV co-infection.

- f) Children
- g) Institutionalized patients e.g., prisoners
- h) Drug addicts.
- i) Healthcare workers.
- j) Those who return from abroad with active TB.
- k) TB patients treated outside the NTP.

5.1.1.2 Case Finding for Pre XDR and XDR TB

Following are high risk and high priority for Pre XDR and XDR TB and should be tested with SL LPA/ MTB/XDRTB or Liquid culture

1. Non-responders of RR/MDR TB treatment (non-converters of culture by month 4 of treatment or worsening clinically/radiologically during treatment)
2. Failure of RR/MDR TB treatment
3. Previous history of treatment with group A and group B anti-TB drugs
4. Close contact of RR/MDR TB or pre-XDR/XDR TB patients
5. Non-responders/failures of Hr TB treatment (repeat Xpert assay and perform other tests as mentioned above)

5.1.1.3 Case finding for Hr TB

Following are priority patients to be tested for Hr TB

1. Failure of initial TB regimen with Xpert MTB/RIF result Trace (T) or Trace Indeterminate (TI)
2. Failure of retreatment TB regimen with Xpert MTB/RIF result “T or TI”
3. Close contacts of Hr TB patients
4. Among non-converters of DS-TB treatment, when RR-TB has been excluded
5. Others as per physician’s clinical judgment

NOTE: point, 1, 2, 3 are the priority patients for testing with FL LPA, while others depend upon resources available for testing.

5.1.2 Screening of all presumptive DR-TB patients systematically using diagnostic algorithm

It is important to follow diagnostic algorithm to screen the presumptive DR-TB cases systematically and use existing diagnostic tests optimally to detect all DR-TB cases. Xpert MTB/RIF, Culture and microscopy as the initial tests will improve case detection and early detection of rifampicin resistance, permits drug susceptibility for both first line drugs and other drugs used to treat DR-TB and also allow monitoring response to treatment.

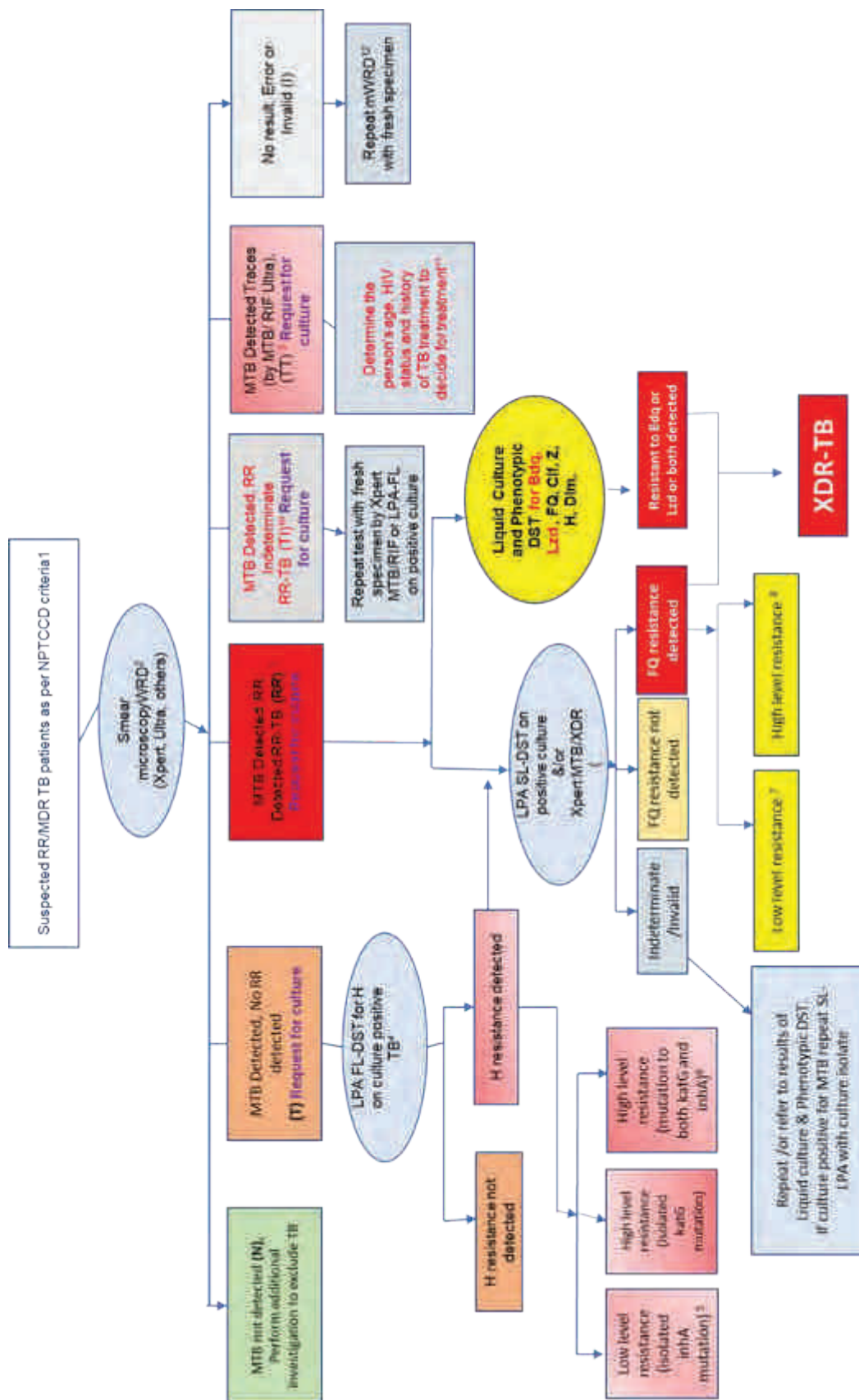


Figure 5-1: Diagnostic Algorithm

Footnote to Diagnostic Algorithm

1. According to NPTCCD policy and criteria: Symptomatic MDR contacts, New or Retreatment failure, Non or delayed converters, Repeated treatment interrupters, Previously treated, Children, TB/HIV Co-infection, Prisoners (institutionalized), Drug addicts, Health workers, Active TB patients from abroad
2. molecular WHO recommended diagnostics (Xpert MTB/RIF assay, Xpert MTB/RIF ultra-assay, Others- TrueNat or other centralized Dx platforms)
3. For patients without risk factor(s), repeat Xpert result is necessary to determine as MDR/RR-TB patients.
4. Priority patients to perform LPA FL:
 - o First line drug regimen failures, Retreatment cases (lost to follow up and relapse), Hr-TB contacts, Non-converters, Clinical judgment of physician
5. Consider high dose H in (1) Hr-TB regimen, (2) individualized DR-TB regimen if regimen construction with group A-C does not meet required 4/ 5 effective drugs.
6. Eto is unlikely to be effective and thus not to be used in longer DR-TB regimen.
7. Not eligible to enrol in OSSTR.
7. Mutations A90V, S91P, D94A in gyrA, mutations N538D and E540V in gyrB detected and therefore high dose Moxifloxacin is likely to be effective. Performing phenotypic DST for Mfx at clinical breakpoint to exclude resistance is recommended.
8. Mutations D94N/ D94Y, D94G and D94H in gyrA detected and therefore Mfx cannot be considered as an effective medicine.
9. All Trace calls by MTB/RIF Ultra result provide no information on RR.
10. Treat as DS-TB; (proceed liquid culture and if culture positive to perform 1st line LPA or pDST). Review treatment based on DST result.
11. Not to repeat Ultra. Use clinical judgement for treatment decisions
12. Repeat Xpert MTB testing is preferable than FL LPA because it has a lower Level of detection (LOD) than the FL-LPA.

5.1.3 Identification of DR-TB cases from microbiologically positive patients using Universal DST

All microbiologically positive (smear positive) patients should be tested for rifampicin resistance using rapid molecular diagnostic, Xpert MTB/RIF to detect drug resistance early as per the national policy.

All rifampicin resistant cases detected from Xpert assay should be tested with LPA for first line drugs (rifampicin and isoniazid) and second line drugs (fluoroquinolones and amikacin).

5.2. Diagnostic methods

The effective management of TB relies on the rapid diagnosis of TB and rapid detection of drug resistance. This requires access to rapid and accurate diagnostic tests, as well as rapid and accurate DST for all TB patients.

For many years, smear microscopy and solid culture have been used to diagnose TB. Both these tests have drawbacks of their own. Microscopy is less sensitive and drug susceptibility is not available. Culture on the other hand takes long time.

However, there are array of newer diagnostic tests now which are rapid, accurate and reliable.

To obtain reliable results from these tests, it is important to have a good quality specimen from the patients. Patients should therefore be clearly advised on collection of specimens properly.

5.2.1 Specimen collection and transport

Patients will be advised to provide two sputum specimens, one for smear microscopy and one for Xpert assay on the first day presented to the health care provider, and two sputum specimens, one for smear microscopy and one for culture on the following day.

The specimens will be collected in clean, transparent, wide mouthed bottle for microscopy. Sterile universal bottles or sterile transparent disposable containers should be used for Xpert assay and culture.

Specimens should be transported to the laboratory as soon as possible and at 2-8°C for Xpert assay and culture through a courier who usually is a minor staff employee of the respective DCC with a request form for bacteriological examination. (Refer Laboratory Manual for Tuberculosis Control for more information)

One sample should be sent to the nearest facility where Xpert MTB/RIF test is available (National Tuberculosis Reference Laboratory (NTRL) at Welisara and 29 other facilities where Xpert testing is available). The other sample should be sent to the nearest culture facility which could be National Tuberculosis Reference Laboratory (NTRL) at Welisara or an Intermediate Tuberculosis Laboratory (ITL).

Such specimens can originate from the DCCs, other government health institutions or the private sector health institutions.

Other government health institutions and private sector health institutions are also free to send sputum and other specimens for bacteriological examination on presumptive MDR-TB patients along with properly filled TB 06 form. However, in such situations, it is advisable to send such specimen through the respective DCCs.

a. Respiratory specimens in children

In children, usually less than eight years of age who are unable to expectorate, early-morning fasting gastric aspiration/lavage can be collected. Induced sputum (Refer the Lab manual) is also feasible, can be performed in all age groups and has a slightly higher mycobacterial yield. Gastric aspirates should be immediately transported to the laboratory and the stomach acid neutralized by adding 100mg of sodium bicarbonate before transport.

b. Extrapulmonary specimens

As per recent WHO recommendations in adults and children with signs and symptoms of extra pulmonary TB, Xpert MTB/RIF or Xpert MTB/RIF Ultra may be used on lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens as the initial diagnostic test depending on the site involved. Xpert MTB/RIF can be performed on stool specimens obtained from children (low evidence). (Refer Laboratory Manual for Tuberculosis Control for more information).

5.2.2 Patient registration

Register of Referral for Bacteriological Examination, from which presumptive DR-TB patients can be identified, should be maintained at all District Chest clinics (see Annexure I-b).

5.2.3 TB diagnostic tests

1. Smear microscopy

The role of smear microscopy in the DR-TB care is for two specific reasons

- i) To make decision on performing FL-LPA as FL – LPA cannot be performed on smear negative specimens directly.
- ii) For microbiological follow up to decide response to treatment

Smear microscopy is a low-cost and essential frontline tool for diagnosis of TB (but not drug-resistant TB). However, with the more advancements in rapid molecular tests availability the role of smear microscopy is being phased out gradually. NPTCCD and NTRL plans to use CXR, and Gene Xpert based algorithm for presumptive TB patients to diagnose TB and RR-TB.

The sputum smears are stained using the Ziehl-Neelsen staining method and examined with a bright field binocular microscope and graded according to WHO grading for AFB microscopy. Auramine staining with a fluorescence microscopy is also used instead of bright field microscopy especially in high microscopy workload centres and can increase sensitivity by more than 10%.

Microscopy for AFB cannot distinguish viable from non-viable organisms nor differentiate between drug-susceptible and drug-resistant *M. tuberculosis*. Thus, its usefulness in drug-resistant TB treatment monitoring is limited.

A repeat sample from all smear positive patients should be tested with Xpert to exclude rifampicin resistance as per universal DST policy

2. Genotypic testing (molecular tests)

Genotypic methods have considerable advantages when PMDT is being scaled up, in particular with regard to their speed, the standardization of testing, potential high throughput and reduced requirements for biosafety.

Nucleic acid amplification technologies (NAAT) e.g.: Xpert/MTB RIF, LPA hold promises for significant gains in speed and performance for DST. Currently, three types of genotypic testing are used within the national TB laboratory network: Xpert MTB/RIF assay, Genotype MTBDR plus Test, and Genotype MTBDR sl Test. Xpert MTB/XDR will be available from this year for patient categories mentioned above. In addition, three other WHO recommended molecular tests will be used for some targeted group of patients or area: chip-based molecular test (TrueNat), and Whole Genome Sequencing (WGS)

I. Xpert MTB/RIF and Xpert MTB/RIF Ultra assay

a. *Xpert MTB/RIF*

Xpert MTB/RIF assay is an automated cartridge- based nucleic acid amplification test for simultaneous detection of TB and rifampicin resistance. Xpert MTB/RIF is a fully automated molecular diagnostic test that can detect DNA of mycobacterium tuberculosis complex (MTBC) and common mutations associated with rifampicin resistance (*rpoB* gene mutation) directly from sputum specimens within two hours.

The assay has similar sensitivity, specificity and accuracy as culture on liquid media and can be used from both smear positive and negative specimens.

Currently, Xpert MTB/RIF assay is available at 29 sites in the country. It is expected that the results of test should be available within 2 days of receiving the sputum specimen at the laboratory.

b. *Xpert MTB/RIF Ultra*

The Xpert MTB/RIF Ultra assay (hereafter called Xpert Ultra) uses the same GeneXpert platform as the Xpert MTB/RIF test with improved sensitivity and reliability of detection of

MTBC and rifampicin resistance. However, the higher sensitivity of Xpert Ultra is accompanied by a slight loss of specificity.

The Xpert Ultra assay can detect very small numbers of non-viable or non-replicating bacilli, particularly in patients with a history of TB treatment (i.e., completed within the past 5 years). Such non-viable bacteria may also be detected by the other molecular WRDs though less frequently. The increased sensitivity and loss of specificity are primarily related to the Xpert Ultra “trace” call for MTB. Therefore, MTB trace result provides no information on rifampicin resistance.

c. Xpert MTB/XDR

Xpert MTB/XDR TB cartridge is helpful in detection of resistance to fluoroquinolones (FQ), ethionamide (Eto), amikacin (Am) and Isoniazid. This new tool will be used in line with NPTCCD policy.

II. Line Probe Assays

There are two types of LPAs to detect DR-TB

- FL LPA is used to detect resistance to First line drugs rifampicin and isoniazid
- SL LPA is used to detect resistance to fluoroquinolones and aminoglycosides

Following are the recommendations for use of FL-LPA and SL-LPA.

a. FL-LPA

WHO in 2020 recommended using FL-LPA in the following situations:

1. Sputum smear-positive specimen or a cultured isolate of MTBC,
2. FL-LPAs may be used as the initial test instead of phenotypic culture-based DST to detect resistance to rifampicin and isoniazid.

Conventional culture-based DST for isoniazid may still be used to evaluate patients when the LPA result does not detect isoniazid resistance. This is particularly important for populations with a high pre-test probability of resistance to isoniazid.

b. SL-LPA

WHO in 2020 recommended using SL-LPA in the following situations:

1. For patients with confirmed MDR/RR-TB,
2. SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to FQ and Am
3. SL-LPA tests are also useful for detecting FQ resistance before starting therapy for Hr-TB

These recommendations apply to the use of SL-LPA for testing sputum specimens, irrespective of the smear status and cultured isolates of MTBC from both pulmonary and extra pulmonary sites.

As per NPTCCD policy, all RR/MDR diagnosed patients are subject to be tested by SL LPA at baseline to diagnosis FQ resistance and Am resistance.

Interpretation of mutations detected in LPA

a. For isoniazid:

katG mutation is associated with high-level resistance to isoniazid and the use of isoniazid even at higher dose is less likely to be effective.

inhA promoter and katG is associated with high-level resistance to isoniazid and it cannot be considered as an effective drug.

b. For Moxifloxacin:

SL-LPA has probes to detect mutations within genes (gyrA plus gyrB) that are associated with resistance to fluoroquinolones.

Genoscholar PZA-TB II (Nipro) is used to detect resistance to pyrazinamide

III. Next-generation Sequencing/ Whole Genome Sequencing

Next-generation sequencing (NGS) or whole genome sequencing (WGS) is a powerful tool with the capacity to improve tuberculosis management and control through the rapid and accurate detection of all clinically relevant mutations, and thereby the rapid diagnosis of DR-TB in clinical specimens.

WGS is currently the only approach that has the ability to interrogate hundreds of genome-wide targets in parallel and simultaneously test for resistance to multiple first and second-line anti-TB drugs. As a result, it can detect rare mutations that are typically missed by rapid molecular assays. Sequencing also allows species identification, genotyping, and detection of mixed populations and hetero resistance in a sample

Currently, WGS is not available at NTRL.

3. TB Cultures

Both solid and liquid cultures are used for MDR-TB diagnosis and monitoring. But after introducing Xpert MTB/RIF tests in NPTCCD, culture is usually used to conduct diagnostic culture and DST for first- or second-line drugs when molecular tests are either not available or inconclusive as well as for follow up cultures to monitor the patient's response to treatment.

To optimize treatment regimens for DR TB, complex drug regimens can include any remaining first-line and second line drugs to which the organisms are susceptible from different groups

of anti TB drugs. Therefore, reliable DST of these anti-TB drugs is crucial for the management of MDR-TB and for preventing emergence of additional drug resistance in these patients. DST will be performed on isolates from newly diagnosed patients and monthly thereafter throughout the treatment.

However, culture-based methods are time consuming and require sophisticated laboratory infrastructure, qualified staff, and strict quality assurance mechanisms. For these reasons, phenotypic DST is being progressively replaced by molecular-based DST for first line and second line drugs.

Culture based DST methods also requires biosafety measures. All procedures involving the handling of specimens for culture and DST should be carried out in a high-risk TB laboratory with BSL 3 facilities.

At NTRL, DST is performed:

- Using solid media (LJ medium) for first line drugs, streptomycin, isoniazid, rifampicin, ethambutol
- Using liquid media (automated BACTEC MGIT) for streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide

If the sample is found to be contaminated, the sender is informed by the laboratory to send two further sputum specimens. DST results indicating RR/ MDR-TB is sent as soon as possible to the sender, the DTCO of the relevant district and to the PMDT coordinator. Results is communicated over the telephone which is followed by a written report by post and by e-mail.

5.3. Quality assurance of DST

- A comprehensive laboratory quality assurance system is essential to ensure that the results of DST are accurate, reliable, and timely.
- Quality control should be performed on new batches of test kits and reagents (new lot testing) to ensure that the testing material is in good condition for use and that the transport and storage conditions have not affected the assay performance. Quality control should also be performed by new personnel prior to testing clinical specimens to assess their competency.
- Proficiency of drug susceptibility testing carried out at each laboratory should be assessed annually by participating external quality assurance programme.

5.4. Recording and reporting

All positive results should be informed to requesting clinician over the phone on the same day the result is available. Report of the result should be sent by poste or sent through courier most often a to the DCC or relevant institute

5.5. Sputum examination during treatment

Sputum examination and culture should be done monthly to monitor response to treatment during the course of treatment for DR TB. Two sputum samples will be collected at each follow up, into sterile universal bottles and sent to the NTRL or the regional ITL for direct smear and culture.

Table 5-1: Tests to monitor response to treatment

Test	Frequency
Smear	Monthly
Culture	Monthly

Table 5-2: Summary of Drug Susceptibility Tests

	Diagnostic Platform	Test Name	Turnaround Time	Description and comments
Phenotypic DST	Solid Culture and DST	Lowenstein-Jensen	2-8 weeks (for positive culture)	Egg-based medium, inexpensive. First- and second-line DST can be done.
			8 weeks (for negative culture)	
	Liquid culture and DST	MGIT®	21 days (For positive culture)	Present recommended standard for TB culture and test of choice for DST confirmation. Fully automated system exists with MGIT 960. First- and second- line DST can be done.
			42 days (for negative culture)	
Genotypic DST	Molecular Testing	Line Probe Assay (LPA)	3 days - direct 21 days-indirect	<p>DNA targets are amplified by PCR and hybridized to immobilize oligonucleotide targets.</p> <p>Genotype MTB DR_{plus} test identifies MTBC, isoniazid resistance by detecting KatG and inhA gene mutations and rifampicin resistance by rpoB gene mutation.</p> <p>Genotype MTB DR_s/ test identifies MTBC, fluoroquinolones resistance by detecting gyrA gene and gyrB gene mutation, aminoglycosides and cyclic peptides resistance by rrs gene and eis gene mutation. Can be done directly from smear positive samples or from liquid /solid culture positive colonies. Genoscholar PZA-TB II (Nipro) is used to detect resistance to pyrazinamide</p>
		Xpert® MTB/RIF	2 hours	The test that uses nested real-time PCR (cartridge-based) to identify MTBC and rifampicin resistance by detecting rpoB gene mutation. Can be done directly on smear-positive or smear-negative specimens.
		Xpert MTB/XDR	90 minutes	Xpert MTB/XDR detects resistance to isoniazid, ethionamide, fluoroquinolones and amikacin. Can be done on smear positive or negative samples.

6. TREATMENT FOR DR TB

Once DR TB is diagnosed, it is important to proceed further with patient enrolment in a timely manner and to adopt the procedures outlined in guidelines. The aim of NPTCCD is for early diagnosis and treatment initiation of RR/MDR TB and ideally there should be no gap between the number of RR/MDR TB diagnosed and treated. This chapter will describe treatment strategies of all types of diagnosed DR TB patients who are RR/MDR TB, Pre XDR, XDR TB and role of PMDT committees and the importance of counselling and patient centred care approach.

The probability of treatment success in MDR/RR-TB patients depend upon patients will and strong adherence to treatment, as well as severity of the disease, resistance patterns and co-morbidities and access to health care (e.g. regimens with sufficient effective agents, medications of good quality, attention to adverse events and patient psycho-social support)

6.1. PMDT committees, Role and Responsibilities

Once the diagnosis of RR/MDR-TB is confirmed by NTRL, the results of rapid test and/or culture and DST is forwarded to the referring unit and the PMDT coordinator. The PMDT coordinator informs the relevant DTCO and ensures that the patient is traced and is admitted to the NHRD as it is the only inward care facility for drug resistant TB cases in the country.

NPTCCD has established the central PMDT committee and PMDT site committees which will be responsible for treatment decisions, monitoring and evaluation of DR TB treatment.

Once the pre-treatment evaluation is done (most likely at NHRD) the site PMDT committee would decide whether to keep the patient for inward care at NHRD or to send for ambulatory DOT at relevant DCC

After admission, the PMDT site committee of the inward treatment facility (currently NHRD) decides the treatment regimen after the pre-treatment evaluation. Initially the patient is treated in-ward. For the management during the ambulatory period, the patient is referred to the relevant CRP & DTCO. Further decisions on management of individual patient should be taken by the relevant site committee headed by CRP.

6.1.1 PMDT Central Committee

PMDT central committee will be the apex body for the implementation of programmatic management of drug resistant tuberculosis activities in Sri Lanka.

Box 6-1: PMDT Central Committee Roles and Responsibilities

Composition
<ul style="list-style-type: none"> • Director NPTCCD(Chairperson) • Deputy Director NPTCCD (member) • All Consultant Community Physicians NPTCCD (member) • Consultant in Health Informatics NPTCCD (member) • All Consultant Respiratory Physicians NHRD (member) • All Consultant Respiratory Physicians Central Chest Clinic Colombo(member) • Consultant Respiratory Physician Colombo South Teaching Hospital(member) • Consultant Microbiologist NTRL (member) • DTCOs of Colombo and Gampaha Districts(member) • PMDT coordinator (Member/ Secretary) • Chief pharmacist Central Drug Stores
Duties & Responsibilities
<ul style="list-style-type: none"> • Progress evaluation of all diagnosed MDR-TB patients • Ensure that DRTB patients are admitted where indicated, commenced on appropriate treatment, monitored and followed up as per national guidelines. This includes ensuring timely discharge from inward care and referral to appropriate DCC with relevant clinical details' • Ensure that the details of the patients are entered into the DR-TB or MDR-TB Site Register and updated appropriately. The PMDT coordinator would communicate the relevant details to the DTCO concerned. • Review the progress of patients on second-line anti-TB drugs and where indicated, submit suggestions to relevant site committee regarding management of individual patient' • Coordinate with other site committees to ensure that exchange of patients on DRTB treatment takes place in the proper manner • Ensure regular uninterrupted supply of SLD.
Operational Guidance
<ul style="list-style-type: none"> • The PMDT site committee at NHRD shall convene three monthly. • In addition, the committee shall convene at any time when important decisions have to be taken. • Any other non-member person may be called upon to the committee meetings on the discretion of the chairman or upon request made by a member of the committee. • A member or non-member secretary should be appointed to the committee • All meeting proceedings shall be minuted. • The PMDT coordinator to the committee shall take minutes of the meeting. • Minutes of each committee meeting shall be tabled and approved at the next committee meeting.

6.1.2 Site committee of the National Hospital for Respiratory Diseases

The evaluation and decision on second-line anti TB drug treatment for MDR-TB patients are taken at the National Hospital for Respiratory Diseases (NHRD). As per new guidelines all the patients may not be to hospitalized, instead the decision on ambulatory DOT needs to be made on a case by case basis. The composition, roles, and responsibilities of the site committee of the NHRD differs from those of other site committees. All drug resistant TB

patients admitted to the NHRD and/or managed under the care of DCC Gampaha falls under the purview of this site committee.

Box 6-2: Roles and Responsibilities of NHRD Site Committee

Composition
<ul style="list-style-type: none"> • Director NHRD(Chairman) • Deputy Director NHRD(Members) • One Consultant Community Physician NPTCCD (Members) • Consultant in Health Informatics NPTCCD (Member) • All Consultant Respiratory Physicians NHRD (Members) • Consultant Microbiologist NTRL (Members) • DTCO of Gampaha District • PMDT coordinator (Member/Secretary) • Chief pharmacist Central Drug Stores (CDS) (Members) • One Public Health Inspector from the NHRD and one PHI from DCC Gampaha (Members) • Any other relevant Officers (Members)
Duties & Responsibilities
<ul style="list-style-type: none"> • Pre-treatment evaluation of all DR-TB patients referred for admission. • Deciding on the SLD treatment regimen for individual patients • Ensure that patients are admitted to the MDR-TB ward for initial phase of the treatment • Ensure that the details of the patients are entered into the DR-TB or MDR-TB Site Register and updated appropriately • Ensure that the details of each patient including the discharge from the MDR-TB ward and referral to the DCC of patient's residence are communicated to the relevant DTCO in a timely manner • Review the progress of patients on second-line anti-TB drugs and make decisions regarding the total management of individual patients. • Coordinate with other site committees when DR-TB patients are exchanged between NHRD site committee and other site committees. • Report to the PMDT central committee on the progress of DR-TB patients
Operational Guidance
<ul style="list-style-type: none"> • The PMDT site committee at NHRD shall convene monthly. • In addition, the committee shall convene at any time when important decisions have to be taken. • Any other non-member person may be called upon to the committee meetings at the discretion of the chairman or upon request made by a member of the committee. • The PMDT coordinator should be appointed as the secretary to the committee • All meeting proceedings shall be minuted. • The secretary to the committee shall take minutes of the meeting. • Minutes of each committee meeting shall be tabled and approved at the next committee meeting. • Minutes of all site committee meetings shall be submitted to the PMDT central committee.

6.1.3 PMDT Site Committee

PMDT site committees other than the NHRD site committee will be established at district level whenever DRTB patients are under their care. Whenever there are no such patients the PMDT site committee will cease to function and will be re-convened by the DTCO once new patients are enrolled. During the non-functioning of the site committee, the DTCO may be appointed

as the focal point for all DRTB patients. Considering service needs of districts with high burden, any other Medical Officer other than the DTCO may be appointed as the focal point for DRTB. Requests for such appointments should be forwarded to the PMDT central committee. The PMDT central committee will make such appointments after the situation is analysed and all factors are taken into consideration.

Box 6-3: Roles and responsibilities of PMDT site committee

Composition
<ul style="list-style-type: none"> • CRP(Chairperson) • DTCO (DTCO will be the chairman in the absence of CRP) (Member) • Focal point for DR-TB (DTCO or MO of DCC) (Member) • Pharmacist (Dispenser or any other personnel who handles second-line drugs in the absence of pharmacist) (Member) • Public Health Inspector (Member) • Any other relevant Officer/s(Member)
Duties & Responsibilities
<ul style="list-style-type: none"> • Review the progress of patients on second-line anti-TB drugs and make decisions regarding the total management of individual patients. • Ensure that MDR-TB/XDR TB/pre XDRTB patients are admitted to the MDR-TB ward at NHRD for the initial phase of the treatment. If any patient is not in a position to get admitted/ refused to be admitted, site committee should make decisions on the best course of management and should ensure arrangements for the same. • Ensure that the details of the patients are entered into the DR-TB or MDR-TB Site Register and updated appropriately • Coordinate with other site committees when DRTB patients are exchanged between NHRD site committee or other site committees. • Report to the PMDT central committee on the progress of individual drug resistant TB patients • Report to the PMDT central committee on managerial and other issues pertaining to management of drug resistant TB in districts.

6.2. Key Points for MDR/RR-TB Treatment

6.2.1 Patient Education and counselling

- Patient education is an essential component of any DR-TB control program and is important for gaining interpersonal trust and opportunities of communication between patients and medical personnel.
- Provision of emotional & social support to DR-TB patients may increase the likelihood of adherence.
- The education and counselling should be considered equally with the other components of the DR-TB program (such as case detection and diagnostics, drug supply, etc.)
- The patient's knowledge and understanding of his/her role in achieving a successful treatment outcome is an essential component for the management of DR-TB.
- Strict DOT is the mainstay of TB/DR TB treatment to improve the treatment success rate, to reduce the transmission of TB and to reduce morbidity and mortality

6.2.2 Referral for DR TB Management

The DTCO will trace the MDR-TB/XDRTB and pre XDRTB patient and refer to NHRD or to the nearest inward treatment facility if available for initiation of treatment, after counselling.

A copy of the TB treatment card, DST result and duly filled referral form for second-line treatment should be sent with the patient. Patients referred to the MDR-TB/XDRTB/Pre XDRTB treatment initiation site for treatment with the completed referral form will be admitted to the hospital and the Respiratory Physician and the PMDT coordinator informed regarding the admission. The DTCO will also send a copy of the request for MDR-TB XDRTB/Pre XDRTB treatment by post to the PMDT coordinator. The PMDT coordinator informs the DTCO about receipt of patient and treatment initiation in the ward.

6.2.3 Pre-treatment Evaluation

Following are strongly recommended before the treatment initiation is considered:

- Ahead of enrolment on DR-TB treatment, all patients should receive appropriate counselling to enable informed and participatory decision-making.
- Ensure that patients are appropriately informed about their available treatment options (longer or shorter treatment)
- Ensure patient-centred approach to the delivery of care including social and psychological support and any other issue or challenges that may affect treatment adherence.
- Active monitoring of TB drug safety and management (**aDSM**) is essential for all patients enrolled on DR-TB treatment including evaluation of history and tendency/risk for Adverse drug reactions (ADRs) to second line drugs,
- Initial pre-treatment assessment should include:
 - Microbiological assessment with fresh specimens for liquid culture and DST (for first line and second line drugs) and for FL-LPA and SL – LPA to reconfirm DRTB and DST.

Good history (including past episodes of TB & treatment received, co-morbidities & their treatment, drug allergies, smoking, alcohol consumption, family background/support, employment, socio economic status). Investigations – CXR (other radiological investigations where appropriate), FBC, FBS, S. creatinine, S electrolytes, S bilirubin, SGPT, ECG, echocardiography (where appropriate), HIV status, pregnancy test (where appropriate), audiometry (with Am containing regimens). Psychological assessment. Thyroid function tests.

6.3. DR TB Treatment Strategies

In Sri Lanka oral regimens have been started in 2020 and NPTCCD will continue enrolling patients on the following regimens.

- 1. Standardized Shorter all oral Treatment Regimen (OSSTR)** 9-12 months duration as preferred treatment regimen for MDR/RR-TB patients provided that certain eligibility criteria are met.
- 2. All oral Longer Treatment regimen** (minimum 18 months duration) is applicable for RR/MDR-TB patient found ineligible for shorter regimen.
- 3. BPaL Regimen** (Bdq, Pretomanid and Lzd) is applicable for patients with FQ resistance

for a duration of 6-9 months to be used under operational research (While BPAL regimen will be considered as operational research or will be implemented once WHO recommendations come to implement BPAL under programmatic conditions)

6.4. General Principles of MDR/RR-TB Treatment

The following general principles of MDRTB/RR-TB should be followed for regimen designing and the objective should be “no harm practice” keeping in view the effectiveness and safety of the regimen designed.

At the time of enrolment patients should be informed about available options of treatment (longer or shorter) and shared decisions should be made between doctor and patient for the choices of treatment. However, doctor providing treatment/treatment providers have to be vigilant about choosing the right treatment option for patients keeping in mind history of TB and anti TB drugs in the past, comorbid conditions, severity of the disease and contraindications for drugs. A shorter all oral Bdq containing regimen is a preferred option in eligible patients as it has multiple benefits for the patients and program

- Review patient's full history of previous treatment, DST results, comorbid conditions, and concomitant drugs in use
- Assessment for underline cardiac, liver, kidney disease, peripheral neuropathy, and anaemia should be done. Baseline anaemia of some degree is likely to be present in chronic TB/MDR-TB patients due to TB itself, or it could be multifactorial in aetiology, Lzd should be used with caution keeping in mind the severity of anaemia. Anaemia and Peripheral neuropathy can be more pronounced in MDR-TB/HIV co-infected patients.
- It is essential that a patient's DR strain be tested for the susceptibility to the drug, planned to be included in the regimen at the time of treatment initiation (FQ, Bdq, Lzd, Cfz, Z). Particularly susceptibility to FQ. Genotypic DST (SL LPA - GenoType MTBDRsl) can be used in both children and adults and as a direct and indirect test for DST to FQ. Xpert MTB/XDR is also another option for rapid DST to FQ, H and second line injectable (SLIs).
- Delays in initiation of treatment must be avoided in all circumstances as such delays would result in further worsening of the disease and increased risk of transmission. In turn it will lead to loss of confidence of the patient creating problems of compliance.
- After initial assessment of the patient based on microbiological, clinical and socioeconomic status the central PMDT committee would request the PMDT coordinator to discuss with the DTCO of the district and the patient regarding the possibility of ambulatory DOT.
- All steps should be taken to get DST results as early as possible to initiate appropriate DST based treatment. However, if there are delays then OSSTR/OLTR which are likely to be effective, should be started as early as possible and adjusted based on DST results, once they become available. This potentially life-saving treatment (OSTR/OLTR) should not be delayed awaiting lab results.

- For some medicines, DST results would present uncertainties (e.g., cycloserine, streptomycin, and ethambutol). "Likelihood of effectiveness" is generally assessed in the programmatic setting on the basis of one or more of the following:
 - i) confirmed susceptibility in the individual patient
 - ii) confirmed susceptibility in the presumed source case
 - iii) no known resistance to another drug which has cross-resistance to the medicine
 - iv) infrequent use of a drug in an area (low drug-resistance levels to a drug from surveillance activities)
 - v) no previous use of the same drug in a regimen that has failed in that particular patient

Below are the detailed treatment options available for DR TB patients and each option is selected, based on certain factors enlisted in each section.

1. Standardized All Oral Shorter Treatment Regimen (OSSTR)

WHO in December 2019 recommended all oral shorter treatment (9-12 months) for eligible MDR/RR-TB patients as preferred treatment regimen. In this recommendation, it simply replaced Amikacin with Bdq and Moxifloxacin high dose with Levofloxacin and the rest of the drugs and dosages remain the same.

4-6 (Bdq(6)-Lfx-Cfz-Eto-E-Z-Hh / 5 Lfxh-Cfz-Z-E

The above-mentioned regimen will simply replace the existing regimen by only replacing kenamicin with Bdq and moxifloxacin high dose with levofloxacin. However, the principles of treatment with oral STR are similar to those of Longer MDR-TB regimen with some exceptions, and these will be discussed in this chapter. All MDRTB patients are considered for shorter regimen if they do not have any of the following exclusion criteria.

Exclusion Criteria

- Patients having INAH resistance due to Kat G mutation detected during molecular diagnostic evaluation
- Children under 6 years of age, weighing less than 16kg
- Past exposure to one or more of the SLD including Bdq for more than one month (unless susceptibility is confirmed)
- Patient is known to have a strain resistant to fluoroquinolone, identified with Xpert MTB/XDR / SL LPA or phenotypic DST.
- Known resistance or suspected ineffectiveness to a drug in the shorter treatment regimen except Isoniazid*
- Patient who has known hypersensitivity to ≥1 drug in the shorter regimen
- Patients with extensive (or advanced) tuberculosis i.e., presence of bilateral cavitory disease or extensive parenchymal damage on chest radiography.

- Patient with severe extra pulmonary TB and other forms of TB i.e., Miliary TB/ disseminated TB or TB meningitis, bone TB, TB abdomen, bilateral TB pleural effusions, TB pericarditis
- HIV patients with Extra pulmonary disease
- Patients with renal insufficiency who may need adjustment of anti-tuberculosis medications (an estimated creatinine clearance (CrCl) less than 30 mL/min based on the Cockcroft-Gault equation)
- Patient has AST or ALT >5 times the upper limit of normal
- Patient has a QTc interval of > 500 ms
- Patient taking any medications which render the concurrent use of medicines in the STR contraindicated.
- Pregnancy

[*Determined by phenotypic DST or mutations in either inhA or katG genes (not both). The presence of mutations in both the inhA promoter and katG suggests that isoniazid at high dose and thioamides are not effective, and that the shorter regimen should not therefore be used.

Important Practice Points

- The initial phase consists of Bdq, levofloxacin, Cfz, ethambutol, high-dose isoniazid, pyrazinamide and Eto given daily (once a day) for 4 to 6 months. Bdq will be given for 6 months duration only (400 mg daily for the first 2 weeks followed by 200 mg three times per week for 22 weeks).
- The continuation of treatment consists of Levofloxacin, Cfz, ethambutol and pyrazinamide (once a day) for 5 months.
- Total duration of STR will depend on 4th month smear results, CXR response and clinical improvement as follows.
 - a. If smear is negative at the fourth month (given that PTB is not extensive radiologically and radiological response is observed), the initial phase will be only 4 months (Bdq to be continued till the end of 6 months), followed by 5 months of continuation phase. Then the total duration of treatment will be 9 months
 - b. If at 4th month the smear is positive, the initial phase will be extended for further 2 months, then the total duration of treatment will be 11 months. Extension to 12 months treatment is also applicable where CXR lesions are healing relatively slowly.
 - c. Failure will be declared at the end of the sixth month for those who have both positive smears at six months and with poor clinical and radiological response to treatment.

The Implementation Model

Strict regular monitoring is needed to ensure the required standard of care and with applicability of aDSM. The direct observation of treatment (DOT) and other supportive measures to ensure adherence will be applied for patients on the shorter MDR-TB regimen similar to the patients on the longer regimen. Admission to hospital may be indicated if there is a need as per judgment of the treating physician.

Table 6-1: Use of drugs during Intensive and continuation phase of OSTR

Drugs in SSTR \ Month	Initial Phase (4-6 months*, Bdq for 6 months)						Continuation Phase (5 months)				
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11
Ethionamide											
Isoniazid high dose											
Bedaquiline											
Levofloxacin											
Clofazimine											
Pyrazinamide											
Ethambutol											

**Intensive phase will be extended to 6 months if smear at 4 months is positive, CXR healing relatively slow or as per judgment of the treating physician*

- Drugs are given daily according to the dosages in table below and all drugs are to be given in a single dose. However, in patients with intolerance to Eto, dosages can be divided into twice daily dosing (for 500mg/day, 250 bd. For 750/day, 250mg mane and 500mg nocte)
- Bdq will be used as per recommended dosages for 6 months for patients with a body weight >30k kg as 400 mg daily for the first 2 weeks/14 days followed by 200 mg three days a week (Monday/Wednesday/Friday) for the next 22 weeks (total 24 weeks/ 6 months). For patients with a body weight between 16-30 kg the Bdq dose will be 200 mg tablet daily for 14 days, followed by 100 mg three days a week (Monday/Wednesday/Friday)
- Any modification in SSTR is not recommended and, such patients are switched to OLTR.

Recommended dosages for the anti-TB drugs used in Shorter MDR-TB Regimen:

Table 6-2: Weight-based dosing of anti-TB drugs used in Shorter MDR-TB Treatment Regimen for adults

Medicines	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years				
			30-35Kg	36-45Kg	46-55Kg	56-70Kg	>70 Kg
High-dose Isoniazid ¹	10-15 mg/kg	300 mg tab	1.5	1.5	2	2	2
Pyrazinamide	20-30 mg/kg	400 mg tab	3	4	4	4	5
		500 mg tab	2	3	3	3	4
Ethambutol	15-25 mg/kg	400 mg tab	2	2	3	3	3
Levofloxacin		250 mg tab	3	3	4	4	4
Ethionamide	15-25 mg/kg	250 mg tab	2	2	3	3	4
Bedaquiline	16-30 kg: Bdq dose will be 200 mg tablet daily for first 2 weeks, followed by 100 mg daily three time/week (M/W/F) for 22 weeks (total 24 weeks/ 6 months)						
	31 kg and above: 400 mg daily for the first 2 weeks followed by 200 mg three times/week (M/W/F) for 22 weeks (total 24 weeks/ 6 months)						
Clofazimine		100 mg cap or tab	1	1	1	1	1

¹Pyridoxine is given with isoniazid in patients at risk (e.g., Those with HIV or malnutrition)

Discontinuation of SSTR

The STR will have to be discontinued in the following situations and such cases should be discussed by using panel base approach:

- The baseline SL LPA or phenotypic DST shows resistance to the FQ and/or Bdq or Cfz
- Severe toxicity due to Bdq with QTcF prolongation or risk of QTcF prolongation, is not manageable or Hepatotoxicity is not manageable
- When there is a need to permanently discontinue a drug or more in the SSTR in line with the aDSM protocol.
- Sputum smears remain positive for up to 6 months, along with inappropriate treatment response (clinical and/or radiological deterioration) together with best judgement of the clinician
- Pregnancy during first 6 months of treatment

NOTE: For declaring failure of OSTR, please refer to definition of failure

2. Oral Longer-Term Regimen (OLTR)

Longer MDR-TB regimens with sufficient effective agents are known to increase the likelihood of cure and lower the risk of death in adults and children (*Ahmed et al 2018, and Harausz et al 2018*)

WHO in 2018 convened the Guideline Development Group (GDG) meeting and assessed the continuation to treatment outcome of individual drug used in previous longer regimens using primarily the estimates of effects from individual patient data meta-analysis 2018 (IPD meta-analysis). Following a thorough assessment of relative benefits to harms, recommendations were made for each drug and classified in to three groups:

Group A: fluoroquinolones (levofloxacin and moxifloxacin), Bdq and Lzd were considered highly effective and strongly recommended all three to be included in all regimens unless contraindicated.

Group B: clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice and at least one to be included as part of standard regimen.

Group C: included all other medicines that can be used when a regimen cannot be composed with Group A and B agents.

Recently, in 2020, WHO recommended that MDR/RR-TB patients with extensive TB disease, severe forms of extrapulmonary TB, those with resistance to fluoroquinolones or who have been exposed to treatment with second-line drugs > 1 month should be treated with an individualized longer regimen designed using the WHO priority grouping of medicines with a minimum duration of 18 months

In general, oral longer regimen composition is guided by the selection of individual drugs considered to be effective and need to combine sufficient drugs to maximize the likelihood of relapse-free cure without increasing toxicity. Regimens may be of standardized (fixed) composition or may be individualized in line with DST results, baseline contraindications to a drug in regimen, comorbid conditions, and concomitant drugs in use.

Apart from the ranking by balance of effectiveness and harms, choice is also determined by:

- a) Preference for composition of agents; the results of drug-susceptibility testing (DST).
- b) Reliability of existing DST methods; population drug resistance levels.
- c) History of previous use of the medicine in a patient; drug tolerability; and potential drug interactions.

Table below shows the overall approaches to design a longer MDR-TB regimen as opposed to the STR which is standardized. Based on the WHO 2019 consolidated guideline, the regimen is designed by selecting medicines sequentially going down from group A to group C.

Table 6-3: Grouping of SLD and recommendation for their use in longer MDR/RR-TB regimens^a

Groups	Steps	Medicines	Abbreviations
A	Include all three drugs to the regimen, if no contraindication	Levofloxacin OR	Lfx /Mfx
		Moxifloxacin	
		Bedaquiline ^{b,c}	Bdq
		Linezolid ^d	Lzd
B	Add one or both drugs	Clofazimine	Cfz
		Cycloserine OR	Cs, Trd
		Terizidone	
C	Add to complete the regimen, and when drugs from Group A and Group B cannot be used	Ethambutol	E
		Delamanid ^{c,e}	Dlm
		Pyrazinamide ^f	Z
		Imipenem-cilastatin OR	Imp-Cln, Mpm
		Meropenem ^g	
		Amikacin (OR Streptomycin) ^h	Am(S)
		Ethionamide ⁱ OR prothionamide	Eto, Pto
		P-aminosalicylic acid ⁱ	PAS

- a. This table is intended to guide the design of longer MDR-TB regimens. Drugs in Group C are ranked by decreasing order of preference for use subject to other considerations.
- b. Bedaquiline is usually administered 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally three times per week for 22 weeks (total duration of 24 weeks). The use of Bdq beyond 6 months still remains as off-label use.
- c. Both Bdq and Dlm may be used beyond 6 months and concurrently among patients who have limited other treatment options available, and if sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place.
- d. Use of Lzd for at least 6 months was shown to increase effectiveness, although toxicity may limit its use.
- e. Use of Dlm beyond 6 months and in patients below the age of 3 years should be taken by the central PMDT committee depending on the need.
- f. Pyrazinamide (Z) is added in the regimen unless there is clinical contraindication for its use and is added without DST. | In the regimen Z is only counted as an effective agent when DST results confirm susceptibility, if found to be resistant to pyrazinamide, then it should not be included in the regimen. |
- g. Every dose of Imipenem-cilastatin or meropenem is administered with oral clavulanic acid

(125mg), which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Imipenem-cilastatin or meropenem

- h. Amikacin and streptomycin are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin is unavailable and DST results confirm susceptibility (streptomycin resistance is not detectable with second-line molecular line probe assays and phenotypic DST is required). Kanamycin (Km) and capreomycin (Cm) are no longer recommended for use in MDR-TB regimens.
- i. Amikacin and streptomycin can be used when no other options of effective drugs are possible to compose a regimen.

Composition of MDR/RR-TB Treatment Regimens

Stepwise approach is used in constructing the regimens applicable for the country as a principle of MDR-TB treatment and regimen Construction.

Stepwise approach for regimen construction and treatment

1. If there are no contraindication to any of the group A drugs, preferably all three Group A agents (Lfx/Mfx, Bdq, Lzd) and at least one Group B agent (Cfz or Cs) should be included in the regimen
2. If only one or two Group A agents are used, then both Group B agents are to be included in the regimen and the rest should be chosen from group C to complete the regimen of at least 4 drugs which are likely to be effective. The group C agents should be added in the order of preference or as per patient's individual settings
3. Starting treatment with more than four effective agents may also be a practice and this provision is expected to apply to those with additional resistance or suspected resistance to fluoroquinolones or other medicines.
 - 3.1 If there is confidence in all four Group A and B agents and are included in the regimen then Group C agents are not required to be added.
 - 3.2 If there is confidence in three Group A and B agents and are included in the regimen then at least one Group C agent is added
 - 3.3 If two Group A and B agents are included and there is confidence in all of them then at least three Group C agents are added
 - 3.4 Mfx at higher doses may still be effective if minimum inhibitory concentration (MIC) of FQs is below the clinical break point. If MIC is high, then FQs should not be used even in higher doses.

4. The first six months of treatment consists of at least four effective or likely to be effective second-line agents
5. The remaining 12 months include the same agents except Bdq, bringing the total duration to 18 months minimum. However, it is important to remember that during the remaining 12 months of treatment at least one strong bactericidal drug should be part of the regimen.
6. All medicines are given seven days a week, apart from Bdq. Bdq is given daily for the first two weeks and three times weekly thereafter
7. Regimens without an injectable agent (i.e., all oral regimens) are considered not to have an intensive phase.
8. When an injectable has to be used, a minimum duration of 6 months treatment is given until 3 consecutive cultures are negative.
9. Bedaquiline use, beyond 6 months should be on case-by-case basis depending on treatment response and remaining number of effective drugs in the regimen after Bdq is stopped
10. The use of cardio toxic drugs (Mfx, Bdq, Dlm and Cfz) in combination should be with caution and with close monitoring. However, recent data shows that combined use of Bdq and Dlm could be safe and effect on QTc interval with co administration of both drugs is clinically modest (Dooley et al, 2019)
11. The use of Lzd for the whole duration is associated with better treatment outcomes and lower mortality but is expected to cause frequent toxic effects in a significant number of patients. The neurological toxicity is associated with duration, while haematological toxicity/ myelosuppression is dose related.
12. If baseline Grade 1 to grade 2 anaemia (8-10.5g/dl) and baseline peripheral neuropathy of grade 1 and 2 is reported, Lzd 600 mg daily (OD) or if programmatically feasible 300 mg BID may be used, but with close monitoring to avoid serious adverse effects
13. Lowering the dose of Lzd from 600 mg daily to 300 mg daily may reduce toxicity but its impact on treatment effectiveness is not known. Therefore, if dose of Lzd is reduced at the time of initiating treatment, another effective drug should be added to the regimen on case-by-case basis.
14. The addition of Pyrazinamide (Z) in the regimen is useful as it has synergistic effects when used in combination with strong bactericidal drugs (FQs, Bdq, Am) and strong sterilizing drugs (Bdq,Cfz). However, if a reliable DST source is confirming resistance to Z, it should not be used in regimen and is not counted as an effective drug.

15. Injectable, Am/S should only be used in regimen if there is documented susceptibility to them and appropriate monitoring for hearing loss is available. WHO also recommends to use Am, above the age of 18 years.
16. Where there is doubt about the effectiveness of a certain drug, it may still be included in the regimen. However, it should not be considered an effective alternative to the number of medicines needed in the regimen and clinical judgment is advisable to decide whether the benefit of its inclusion outweighs any added toxicity or pill burden, for example E, Cs, Eto, PAS
17. DST to Ethambutol (E) is not routinely recommended because of highly unreliable nature and unreproducible results. For pyrazinamide, BACTEC MGIT 960 liquid culture method is the only WHO recommended DST method, even though this testing is reportedly associated with a high rate of false-positive results of resistance. The detection of resistance conferring mutations in the *pncA* gene using DNA sequencing may be the most reliable method for the detection of pyrazinamide resistance although there is emerging evidence of non-*pncA* mutational resistance to pyrazinamide (WHO, 2018).
18. Panel -based approach is encouraged for management of MDR TB at all levels and in Sri Lanka, PMDT committees are well functional at all levels and should be followed for decision making and enrolment procedures
 - ❖ Basic principle of “never adding a single drug to a failing regimen” should always be applied in treatment of MDR-TB.
 - ❖ Active drug safety monitoring and management (aDSM) is applicable to all RR-TB patients; therefore, it is imperative to closely monitor patients for side effects of drugs in the regimen.
 - ❖ If the long-course regimen fails, treatment options will be very limited. The patient must be referred to the PMDT central committee.

Eligibility for OLTR

Following is generally to be considered for patients on OLTR enrolment.

- Not eligible for OSSTR
- MDR/RR-TB patients with extensive lung disease
- Severe forms of extrapulmonary TB
- With resistance to fluoroquinolones (Pre XDR, XDR TB), or close contacts of Pre-XDR and XDR TB or suspected resistance to FQs
- Who have been exposed to treatment with second-line drugs > 1 month

Following regimen will be used as standard practice and can be individualized if contraindication to a drug or ineffectiveness is suspected.

18 Bdq(6), Mfx, Lzd, Cfz

Note:

- *Apart from above-mentioned regimen, OLTR may be individualized keeping in view history of previous drug exposure, resistance pattern, underline patient condition/co-morbidities, contraindications etc*
- *If ineffectiveness to FQ is suspected, start with 5 effective drugs by adding Cs to the regimen and adjust once DST results are available*
- *If risk of cardiotoxicity is high, use Lfx instead of Mfx*
- *The results to FQ susceptibility should be available preferably within 8 days*
- *Cs or Eto can be added if intolerance to Lzd develops. Z is to be excluded if reliable DST shows resistance*
- *Bdq use can be extended beyond 6 months on a case-by-case basis. Total minimum duration of OLTR is 18 months but can be extended based on treatment response*

Contraindications and Drug Interactions

In line with WHO 2019 guidelines and regrouping of medicine, Bdq and Lzd will be part of standard MDR-TB regimen, while Dlm from group C is an important add on drug and a good choice to replace in cases of toxicities to front line agents. Short term regimen is standardized/fixed whereas long term regimen has to be composed taking many factors into consideration such as previous exposure to SLD, DST results, availability of drugs, concomitant treatment of co-morbidities, drug allergy, drug interactions and patient preference etc. Therefore, it is important that treating physicians have a thorough knowledge about these drugs, use best of their clinical judgement and seek further advice from other specialists in the field if needed when composing a treatment regimen.

Table 6-4: Contraindications and Precautions with Bdq, Dlm and Lzd (Source: End TB 2018 DR-TB

Drug Name	Relative contraindication	Precautions
Bdq, Dlm	History of syncopal episodes, secondary to ventricular arrhythmias or severe coronary artery disease Baseline ECG with QTc > 500 ms (repeated)	Use with caution if QTc > 450/470 ms in male/female patients. Weekly ECG monitoring and serum electrolyte screening should be performed if Bdq or Dlm is being used despite a cardiac contraindication. Dlm is less cardiotoxic than Bdq (new data has shown that QTc prolongation with combined use of Bdq and Dlm is clinically modest and safe)
Bdq,Lzd,Dlm	Severe renal Failure	Usually, no dose adjustment is required in mild to moderate renal failure severe renal failure/impairment need dose adjustment
Bdq	Severe hepatic failure	Try not to use if patient has severe liver function impairment ART should be adjusted if used in HIV cases particularly efavirenz containing regimen should be avoided
Lzd	Pre-existing mild to moderate peripheral neuropathy (based on Basic Peripheral Neuropathy Screening (BPNS), subjective sensory neuropathy scoring) Severe Myelo suppression and Anemia, moderate neutropenia	Special precautions when used in combination with Cs, high dose INH and diabetics. In mild to moderate Myelo suppression and Anemia Lzd can be used with lower doses, 300 mg daily or 600 mg alternative days with close monitoring

guideline)

Drug Interactions and Overlapping Toxicities with Bdq, Dlm and Lzd

It is essential to consider the drug- interactions with Bdq, Dlm and Lzd with other concomitantly used drugs. It may have various levels of impact causing either decreased or increased absorption, toxicity and adverse events. Patients should be given a card mentioning the drugs that should not be co-prescribed by doctors, while the patient is in ambulatory care in the community. Therefore, treating physicians should review all the medicines patients are taking when enrolling them on MDR-TB Treatment.

Drug Interactions with Bedaquiline

Following drugs should be avoided while using Bdq;

Strong/moderate inducers of cytochrome P450: These may decrease blood levels of Bdq:

E.g., Efavirenz, Rifamycins, Phenytoin, Carbamazepine, Phenobarbitone.

Strong/moderate inhibitors of cytochrome P450: These may increase serum concentration of Bdq: e.g. Ritonavir-boosted PIs, Oral azole antifungals (can be used up to two weeks): eg: Itraconazole, Fluconazole and Macrolide antibiotics other than azithromycin

Drug Interactions with Delamanid

First line Anti TB drugs (HRZE), as these drugs appear to reduce serum levels of Dlm.

Overlapping Toxicity with Bdq and Dlm.

Moreover, many other drugs also have overlapping toxicity when used with Bdq and Dlm:

Antipsychotic drugs (Haloperidole, Risperidone). Many anti-nausea drugs (Ondansetron, Granisetron, Domperidone, Chlorpromazine), Methadone and Cardiac drugs that may affect the heart rhythm (Amiodarone, Beta-blockers, Digoxin, Quinidine)

Linezolid and concomitant medicines that increase serotonin levels:

- Serotonin reuptake inhibitors (SSRIs): fluoxetine, paroxetine
- Tricyclic antidepressants: amitriptyline, nortriptyline
- Serotonin 5-HT₁ receptor agonists
- MAO inhibitors: phenelzine, isocarboxazid
- Other serotonergic agents: meperidine, bupropion, buspirone, quetiapine

For more information on drug safety and QT interval prolongation, please visit Woosley et al 2017, CredibleMeds.org

Regimen Options when there are base line contraindications to Bdq, Lzd

NOTE: these are examples only and regimen to be constructed in line with PMDT committee discussions

1. Baseline contraindication to Lzd (severe anaemia and peripheral neuropathy)

Suggested regimen in the presence of severe anaemia 18 Bdq(6), Mfx, Cfz, Cs, Z where Lzd is replaced with Cs. In patients with peripheral neuropathy at baseline where Cs too is contraindicated, Cs should be replaced with Dlm or Eto. Bdq can be extended beyond 6 months in case-by-case situations.

2. Baseline contraindication to Bdq (cardiac causes given in table 6.7)

18 Lfx, Lzd, Cfz, Cs, Z: when Bdq is contraindicated because of cardiac reasons, Dlm too is contraindicated for the same reason.

3. Baseline contraindication to both Bdq and Lzd

6 Am, Lfx, Cfz, Cs, Z / 12 Lfx, Cfz, Cs, Z

- Cardiac contraindication to Bdq are contraindications to Dlm too. However, Dlm is not contraindicated in liver disease.
- Use Am, only if found susceptible with no baseline contraindication and having appropriate monitoring by Audiometry in place.
- Other options like Imp/Mpnm or Eto can be used if required
- Am designed to be given for 6 months if 4 consecutive cultures are negative. However, it needs to be stopped early if toxicity develops.

6.5. Treatment of MDR/RR-TB with additional resistance and non-responders (failures) to RR/MDR TB Treatment

6.5.1 Treatment principles for the management of MDR-TB with additional resistances and failures

The diagnosis of additional resistance on top of MDR-TB may be revealed at the beginning or after MDR-TB treatment is started.

1. The basic principle is to have at least 4 effective drugs in the beginning and at least 3 drugs to be continued throughout when Bdq or Dlm is stopped after 6 months.
2. It is imperative that all diagnosed MDR-RR TB isolates should be tested for DST and currently available rapid molecular DST LPAs and Xpert/MTB XDR TB modules make the results available quickly.
3. As per revised definition of XDR TB, it is crucial to send samples for phenotypic DST for Bdq and Lzd .
4. The DST result to FQ should be known as soon as possible and regimen needs to be adjusted accordingly.
5. However, if there are delays in obtaining results, treatment initiation with the best empirical regimen should not be delayed.
6. Designing longer regimens for MDR-TB patients with additional resistance follows the same principle as those without additional resistance.
7. With the emergence of new drugs, repurposed drugs, and analytical results of currently used SLDs, it is considered that usage of large numbers of drugs is probably no longer required.
8. Individualized longer regimen is designed based on resistance, tolerance, and prior use of drugs from group A, B and C, to have at least 4 effective drugs in the initial and 3 in the latter part of the treatment.
9. The duration of treatment is minimum of 18 months and can be extended based on the patient's response to treatment.

Table 6-5: Suggested Regimens for use in Pre XDR and XDR TB

Type of DR TB	Suggested Regimen Option	Comments/Remarks
Baseline FQ resistance (Pre XDR TB) with exposure to Bdq, Lzd less than 14 days*	BPaL Regimen (Bdq, Pretomanid, Lzd for 6-9 months)	1. Currently applies only under operational research at designated sites only 2. Follow the set eligibility criteria
For patients with fluoroquinolones resistance and not eligible for BPaL (Pre-XDRTB)	<ul style="list-style-type: none"> • 12 Bdq Lzd Cfz Cs, Z/6 Lzd Cfz Cs, Z • 12Bdq, Dlm(6), Lzd, Cfz, Cs/6Lzd, Cfz, Cs • 18Bdq, Am (6), Cfz, Cs, Z, E 	1. Use E or Eto, if Z resistance 2. If Lzd is contraindicated at baseline then use Dlm instead or Am (if susceptible with close monitoring) 3. Bdq can be extended to 12 months or throughout treatment duration on case-by-case basis 4. Once Bdq is stopped and if DST suggests Mfxh sensitivity, Mfx high dose can be added 5. Dlm is very expensive and its availability for all FQ resistant patients may not be guaranteed
For Patients with FQ resistance plus resistance to Bdq or Lzd (XDR TB)	<p>If there is resistance to Bdq; 6 Lzd, Cfz, Cs, Dlm, Z/12 Lzd, Cfz, Cs, Z</p> <p>If there is resistance to Lzd or Lzd is contraindicated: 6Bdq, Cfz, Cs, Dlm, Z/12 Bdq, Cfz, Cs, Z</p> <p>If resistant to both Bdq and Lzd 6Cfz, Cs, Dlm, Am, Z/12Cfz, Cs, Dlm, Z (Imp/co-amoxclav)</p>	1. If no confidence on E, Z then choose Eto, PAS in regimen 2. Where possible use Mfxh, but avoid using together with Bdq/Dlm 3. Option of Imp/CIs can be used as required 4. For all above, treatment duration can be extended beyond 18 months as per treatment response

*WHO is recommending exposure to Bdq or Lzd for not more than 14 days for BPaL eligibility, but in field settings keeping 14 days exposure history will limit BPaL eligibility, TB Alliance and KNCV are recommending exposure not more than 28 days

NOTE: these are examples only and regimen to be constructed in line with PMDT committee discussions.

6.6. Treatment regimens for MDR/RR-TB failures

NOTE: The followings regimens are examples only and the regimens are constructed based on DST results, previous exposure to drugs in failed regimen and contraindications to a drug in line with PMDT committee guidance

Table 6-6: Treatment regimens for RR/MDR TB failures

Type of DR TB	Suggested Regimen Option	Comments/Remarks
Failure of all oral SSTR	<ul style="list-style-type: none"> • 18 Lzd, Cfz, Cs, Dlm (6), PAS or Z/E • 12Lzd, Dlm (6), Am (6) Cs, PAS /6 Lzd,Cs,imp/co-Amxclv, PAS, Mfxh 	<ol style="list-style-type: none"> 1 DST guided regimen 2 if FQ susceptibility is confirmed, it can be part of the regimen 3 Mfxh can be effective if, low level of FQ resistance is reported, and can be added once Amk is stopped 4 Z/E use only if susceptible
Failed by MDR-TB all oral longer treatment /Relapse or recurrence of MDR-TB	6 Amk, Dlm, Eto, Cs,PAS, ((Lfx/Mfx)/ 12 Dlm (6), Imp-Cln with Am- Clv(6) Eto Cs ,PAS(Lfx/Mfxh)	<ol style="list-style-type: none"> 1 DST to FLD and SLDs should guide further modifications where necessary 2 Use Am on susceptible isolates and design regimen based on previous exposure to SLDs and likely effective drugs. 3 Imp-Cln with Amx-Clv may be used as required, but avoid two injectables during same phase 4 If susceptible to FQ, high dose Lfx or Mfx can be used, if resistant to FQ then FQ can be used in line with level of resistance reported (Mfx h only) 5 Extending the use of Dlm for the whole duration is a possibility if there is no other option 6 If Cs was used as a part of the previous failing regimen, it cannot be reused

6.6.1 Treatment Duration of All oral Longer Regimen

As per new WHO guidelines, 2019 for all longer MDR-TB regimens duration following is recommended.

- A total minimum duration of 18 months
- A treatment duration of 16 months is recommended after culture conversion
- The treatment duration may be modified as per patient's response to treatment
- Prolonging the treatment beyond 18 months may be considered in patients with additional resistance, late converters, extensive disease XDR-TB and in the presence of other risk factors for failure or relapse of treatment.

6.6.2 BPaL (Bedaquiline, Pretomanid and Linezolid) Regimen

Globally there are continuous efforts to shorten the duration of MDR TB treatment. As result of studies done in this regard BPaL regimen (6-9 months duration) has been introduced which is currently recommended by the WHO to be used under operational research in the treatment of Pre XDR and XDR TB.

Inclusion and Exclusion Criteria

Inclusion criteria

A patient, who:

1. is diagnosed as TB in any of the following circumstances irrespective of HIV status:
 - a. has a laboratory-confirmed resistance to at least rifampicin and fluoroquinolones; or
 - b. Has been treated for MDR-/RR-TB and has documented non-response to treatment*, and a decision has been made by the PMDT Committee to shift the patient to the BPAL regimen; or
 - c. Has been treated for MDR-/RR-TB and has documented intolerance, and a decision has been made by the PMDT Committee to shift the patient to the BPAL regimen; and
2. is willing and able to give informed consent to be enrolled in the operational research (OR) and adhere to the OR procedures and the follow-up schedule (signed or witnessed consent if illiterate).
3. is at least 18 years old at the time of enrolment and has a body weight of ≥ 35 kg; and
4. is willing to use effective contraception if a pre-menopausal married woman.

*Applies to conventional longer and Injectable shorter regimen only

Exclusion criteria

A patient, who:

1. has a known severe allergy to any of the BPAL component drugs; or
2. has DST showing resistance to any of the component drugs, or documented XDR TB
3. has been previously exposed to any of the component drugs or Dlm for more than 14 days*.
4. has a form of extrapulmonary TB that would require treatment of longer duration than for pulmonary TB (e.g., TB meningitis, other central nervous system TB, or TB osteomyelitis); or
5. is pregnant or breastfeeding; or planning to conceive within the next year
6. has one or more of the following medical conditions
 - Baseline QTc of > 500 ms and not correctable
 - Baseline Grade 3 peripheral neuropathy
 - Baseline severe anaemia (Hb < 8.0 g/dl which is un-correctable)
 - Baseline moderate thrombocytopenia (Platelet $< 75000 / \text{mm}^3$)
 - Baseline moderate neutropenia (Neutrophil count $< 1000 / \text{mm}^3$)
 - Baseline ALT/AST $> 3 \times$ upper limit of normal
 - Baseline Serum creatinine of $> 3 \times$ upper limit of normal

**WHO is recommending more than 14 days of previous exposure of Bdq and or Lzd as BPAL exclusion and TB Alliance and KNCV are in favour of more than 28 days of Bdq and or Lzd exposure as this seems more practical and feasible at country level. It is entirely a country decision to keep 14 days or 28 days as exclusion criteria for BPAL keeping in view country context and timely availability of FQ susceptibility results.*

Table 6-7: Dosing of component drugs for adults (aged 18 and over) [and adolescents] based on a minimum of 26 weeks treatment

Drug	Dose	Total number of tablets
Bedaquiline (100 mg tablets)	400 mg once daily for 2 weeks, then 200 mg 3 times per week for 24 weeks afterwards	200
Pretomanid (200 mg tablets)	200 mg once daily	182
Linezolid (600 mg tablets)	1200 mg once daily (adjustable only after 4 weeks) BPaL	264 to maximum of 364 (based on Nix trial)

The BPaL regimen is given for a duration of 6-9 months (26 – 39 weeks):

The standard treatment duration is 6 months. If the sputum culture taken after the patient has taken 4 months of treatment is still positive, the patient can receive an additional 3 months of treatment (total 9 months) provided the patient is clinically well and /or improving.

Note:

If NTPCCD plans to conduct BPaL operational research, comprehensive BPaL protocols need to be developed and followed for further information. The ZeNIX trial results are promising to use 600 mg daily instead of 1200 mg of Lzd and WHO recommendations are awaited on this.

Table 6-8: Dosing of medicines used in second-line multidrug-resistant-TB regimens by weight band (patients 15 years or older)

Group	Drug	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years ^a					Usual maximum daily dose ^b	Comments
				30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg		
A	Levofloxacin	— ^c	250 mg tab	3	3	4	4	4	1.5 g	
			500 mg tab	1.5	1.5	2	2	2		
			750 mg tab	1	1	1.5	1.5	1.5		
	Moxifloxacin	Standard dose ^{c,d}	400 mg tab	1	1	1	1	1	400 mg	
		High dose ^{c,d}	400 mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg	
B	Bedaquiline	— ^c	100 mg tab	4 tabs od for first 2 weeks; then 2 tabs od three times a week for 22 weeks					400 mg	
	Linezolid	— ^c	600 mg tab	(<15 y)	(<15 y)	1	1	1	1.2 g	
	Clotazimine	— ^c	50 mg cap or tab ^e	2	2	2	2	2	100 mg	
			100 mg cap or tab ^e	1	1	1	1	1	100 mg	
	Cycloserine or terizidone	10–15 mg/kg	250 mg cap	2	2	3	3	3	1 g	
C	Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3	—	
	Delamanid	— ^c	50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	200 mg	
	Pyrazinamide	20–30 mg/kg	400 mg tab	3	4	4	4	5	-	
			500 mg tab	2	3	3	3	4		
	Imipenem-cilastatin	— ^c	500 mg + 500 mg powder for	2 vials (1 g + 1 g) bd					-	To be used with clavulanic acid.

				injection, vial (10 mL)	1 vial 3 times per day or 2 vials bd							
Meropenem	— ^c			1 g powder for injection, vial (20 mL)	2.5 mL	3 mL	3–4 mL	4 mL	4 mL	-		To be used with clavulanic acid.
Amikacin	15–20 mg/kg			500 mg/2 mL solution for injection, ampoule	2.5 mL	3 mL	3–4 mL	4 mL	4 mL	1 g		
Streptomycin	12–18 mg/kg			1 g powder for injection, vial	Calculate according to the dilution used					1 g		
Ethionamide or prothionamide	15–20 mg/kg			250 mg tab	2	2	3	3	4	1 g		Once daily dose is advised, however can start with 2 divided doses until tolerance improves.
P-aminosalicylic acid	8–12 g/day in 2–3 divided doses			PAS sodium salt (equivalent to 4 g PAS acid) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd	12g		
				PAS acid (4 g) sachet	1 bd	1 bd	1 bd	1 to 1.5 bd				
Isoniazid	4–6 mg/kg (standard dose) ^d			300 mg tab	2/3	1	1	1	1			100 mg isoniazid tablet can facilitate the administration of certain dosages.
	10–15 mg/kg (high dose) ^d			300 mg tab	1.5	1.5	2	2	2	-		Pyridoxine is given with isoniazid in patients at risk (e.g. those with HIV or malnutrition).
Clavulanic acid ^g	— ^c			125 mg clavulanic acid as amoxicillin/clavulanate, 500	1 bd	1 bd	1 bd	1 bd	1 bd	–		Only to be used with carbapenems
Other medicines ^f												

target levels in an average adult patient. In patients <30 kg, the schedule for those aged <15 years should be followed, unless otherwise indicated. If multiple dose options are given for one weight band, the lower or higher option should be selected, depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg per day should be aimed for, and is more feasible with oral or parenteral fluids, and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range, to minimize the adverse therapeutic consequences of over- and under-exposure, respectively (especially for injectable agents, Lzd and fluoroquinolones).

- b. Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.
- c. No weight-based dosing is proposed.
- d. The higher dose may be used except when: there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption, or other reasons; or the strain has low-level drug resistance.
- e. Tablets are expected to become available in the near future.
- f. Amoxicillin/clavulanic acid is only recommended as a companion agent. Because of a lack of data from the latest analysis on longer MDR-TB regimens in adults, gatifloxacin, isoniazid and thioacetazone are not included in the grouping table of medicines used for longer regimens. Pretomanid is recommended to be used only as part of the package of the BPaL regimen.
- g. Only available in combination with amoxicillin as co-amoxycylav (e.g., 500 mg amoxicillin/125 mg clavulanic acid fixed-dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.
- h. Use for age 14 years or older

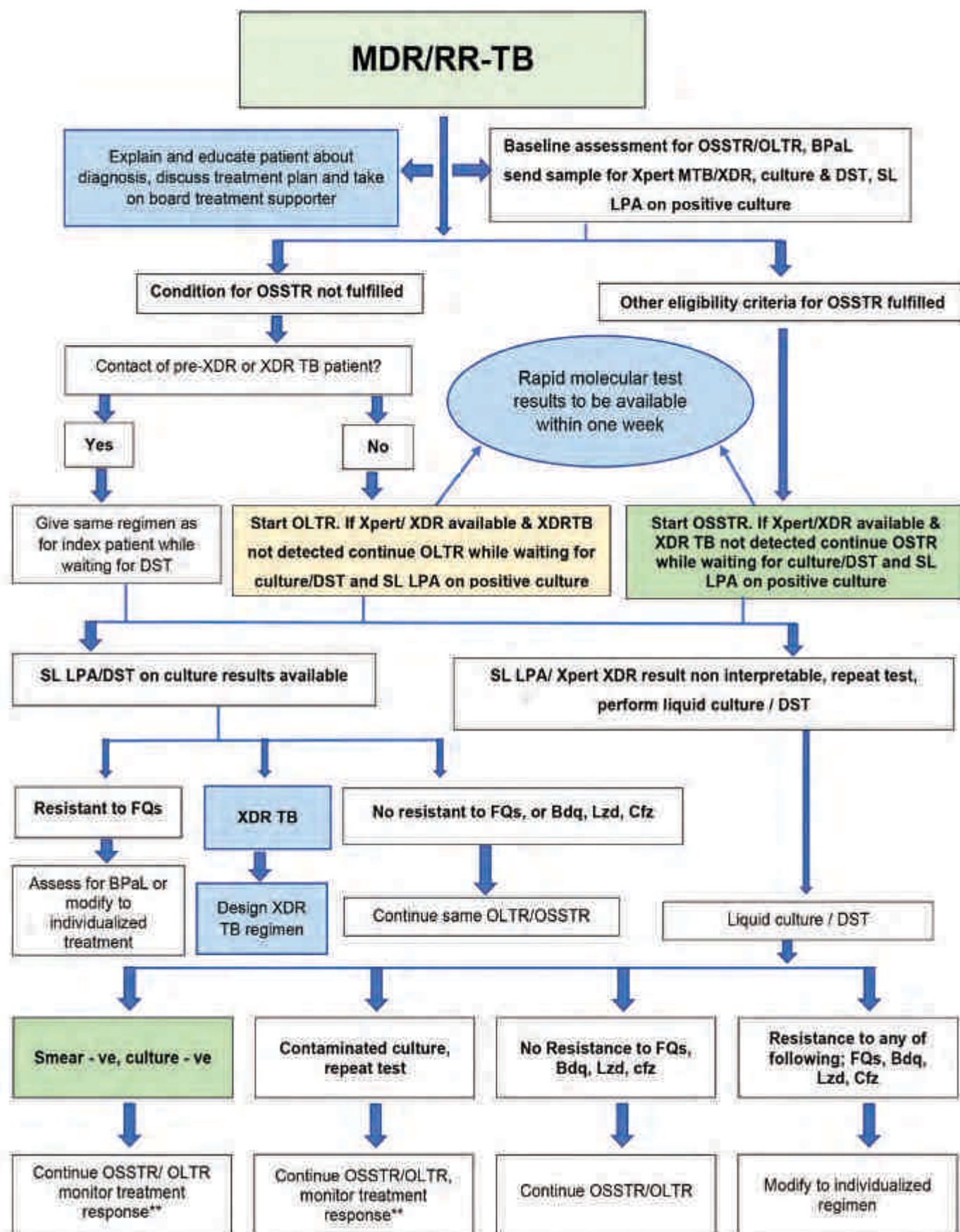


Figure 6-1: MDR/RR Treatment Algorithm

Note:

**It is recommended to get the rapid DST results for FQs before the start of treatment, although this testing should not delay the start of treatment. SL-LPA can be used on sputum smear-positive or smear-negative specimens, although a higher indeterminate rate will occur when testing smear-negative specimens. However, with widely availability of Xpert-XDRTB test the problem of delayed DST results will be solved for majority of patients.*

*** If the patient is responding well to treatment and there is significant improvement clinically and radiologically then continue treatment with OSTR otherwise shift to OLTR after thorough assessment and in case-by-case situation*

7. TREATMENT OF ISONIAZID RESISTANT TB (HR TB), MONO AND POLY DR TB

When implementing Hr TB treatment, one should make sure that the HRZE(FDC) +Lfx regimen is administered only in patients in whom **resistance to isoniazid is confirmed and resistance to rifampicin has been excluded**. Testing for resistance to fluoroquinolones, prior to treatment initiation (preferably with SL LPA) is desirable among such patients. It is also important to test for resistance to pyrazinamide and adjust treatment if necessary. DST for E has no practical implication on treatment. Empirical treatment of Hr TB is not recommended.

7.1. The Scenarios and action required in Hr TB patient management

In practice the following scenarios will be encountered, and appropriate actions should be taken.

Hr-TB is confirmed before TB treatment is started:

- Treatment with the (H)REZ-Lfx is started immediately.
- If the diagnosis is strongly presumed (e.g., close contacts of a confirmed Hr-TB source case) but results of drug susceptibility testing are still pending the regimen may be introduced.

If pre-treatment drug susceptibility test results show susceptibility to isoniazid, then levofloxacin is stopped, and the patient continues treatment in order to complete a 2HREZ/4HR regimen.

Hr-TB is confirmed after starting the treatment with 2HREZ/4HR regimen:

- This applies to patients who developed isoniazid resistance while on first-line treatment, at this point rapid molecular testing for rifampicin resistance must be done (or repeated).
- Once rifampicin resistance is excluded, a full 6-month course of (H) REZ-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.
- If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB treatment regimen keeping in view the previous exposure to drugs in Hr TB treatment.

7.2. The treatment principles for Hr/mono/poly DR TB

Following should be considered for Hr TB management;

1. It is imperative to perform Xpert MTB/RIF in all mono and poly-DR TB patients, before enrolling them on treatment; this excludes those with R resistance, as such patients require full MDR-TB treatment.

2. Always rule out FQ resistance and send quality specimens for DST (SL LPA) to exclude FQ resistance before enrolling patients on mono and poly DR-TB treatment regimen.
3. If the patient is new and H resistance is reported during FLD treatment, the regimen 6(H)RZE,Lfx may suffice and extension beyond 6 months may be considered case by case. If Lfx cannot be added in Hr TB treatment due to various reasons, then treating with 6HRZE is also an option.
4. For patients who are failures of IR or retreatment regimen with H resistance, or where additional resistance is suspected (to E or especially to Z) or where Lfx cannot be used, an individualized regimen should be designed in consultation with experts. This is because treatment of such patients remains a grey area and WHO has not provided clear guidance as to how they should be treated. Treatment of such patients with RZELfx regimen carries a risk of sub optimal treatment and development of resistance to Lfx'. Moreover, DST to Z & E might not be available and DST to E is unreliable and there is also a chance that Xpert and FL LPA may not detect Rif resistance if resistance is due to genetic mutation other rpoB gene. Therefore, both Xpert and LPA may miss RIF resistance, particularly hetero resistance with mutations that cause fitness loss, and this may be more encountered with Phenotypic DST (pDST) (Van Deun et al 2020). Thus, Whole Genome Sequencing (WGS) could be the best solution. The poor treatment outcomes and amplification of resistance to FQ in INAH resistance/ Rifampicin sensitive treatment is because of missed rifampicin resistance (Van Deun et al 2020).

Therefore, a stronger regimen at baseline should be designed with at least three to four drugs likely to be effective. Therefore, drug from Lzd, Cs, Eto can be considered for such cases (WHO 2018). Bdq, Dlm are not recommended in Hr/Rs TB treatment and Mfxh can be considered in Hr TB treatment when low level FQ resistant is reported, though plasma peak concentration and exposure to Mfx decreases significantly when used with Rifampicine. There is also a risk of QTc prolongation with Mfxh.

5. The basic principle to treat mono and poly DR-TB (Rif susceptible) **is to have at least 3 to 4 drugs likely to be effective**. It is the decision of the treating physician keeping in view the previous H/O exposure to anti TB drugs, previous treatment outcome and DST patterns, whether to treat as H resistant TB or to place patients on full MDR TB treatment considering it as a proxy of MDR TB.
6. Assess and address adherence issues in patients who failed FLD, because mostly the problem remains noncompliance to treatment and in such cases none of the treatment can be helpful.
7. Treatment prolongation up to 9 months may be considered for patients with extensive cavitory disease or in patients who are slow to convert to negative smear/culture.

8. **Xpert MTB/RIF should be repeated after 1st and 2nd months** of Hr TB treatment. If smear is reported positive after negative smears and if rifampicin resistance is found, the patient is switched to MDR-TB regimen.
9. These recommendations also apply to children and HIV patients
10. Monitoring should be done as in the case of drug sensitive TB treatment regimen.
11. Principle of never adding a single drug to a failing regimen should be maintained at all times.

7.3. Examples of treatment regimens for mono and poly DR-TB

Table 7-1: Examples of regimens for mono and poly DR-TB other than RR-TB

Background History/ resistance pattern	Regimen	Comments
H resistance in new patients	R(H)ZE, Lfx for 6 months If Lfx cannot be used, then 6R(H)ZE is also an option	Rule out and exclude FQ resistance by SL LPA/pDST
H resistance among patients who are FLD failure/retreatment cases	6-9 RZE, Lfx, Lzd	If Lzd cannot be given, then choice could be Cs
Resistance to H&Z	6-9 HRE-FDC, Lfx, Lzd	Same as above
Resistance to H&Lfx +/- Z	6-9 HRE (FDC), Lzd, Cs, Eto	Assess case by case and design regimen. In doing so Cfz should not be an option as it has cross resistance with Bdq therefore exposure to Cfz may render future use of Bdq less/ineffective. Furthermore, it is rational to commence oral longer MDR TB regimen rather than adding multiple SLD from group C.

Follow up monitoring of Hr TB patients

1. Principles of monitoring will be as same as that for DS TB. However monthly smear is necessary to closely monitor these patient's treatment response and to detect early failures. Other monitoring measures include baseline and monthly LFT, visual checks if complains of blurred vision, peripheral neuropathy assessment at baseline and monthly, Blood Counts and Blood picture at baseline and monthly to monitor haemoglobinopathies. Baseline ECG should be done; however, monthly ECG may not be required as Lfx has low cardiotoxicity profile until unless there is underline risk of electrolytes imbalance.
2. Repeat Xpert MTB/RIF monthly for at least 2 months to see if Rif resistance has developed
3. Culture routinely not to be performed unless necessary or DST is required
4. Hr TB patients to be registered in SLD register for drug consumption from 2nd line agents, but should not be included in RR/MDR TB cohort

5. Monitor separately for Hr TB detection, testing, treatment coverage and outcomes from other DS TB and RR/MDR TB patients.
6. Generally, outcomes are given after 6-9 months of treatment and outcome definitions of DS-TB are applied.
7. aDSM does not apply to Hr/Poly DR TB patients
8. Post-outcome follow up at month 6 and 12 applies

7.4. Dosages for Hr TB

Table 7-2: Dosage with 4-drug FDC (RHZE) - Adults

Weight bands in adults	4-drug adult FDC RHZE-150/75/400/275*	Levofloxacin 250mg
35-49 kg	3 tablets	3 tablets
50-64 kg	4 tablets	4 tablets
65-75 kg	5 tablets	4 tablets

**patients <35 kg may receive 3 tablets/day and patients >75 kg may receive 6 tablets/day if they tolerate this dose*

Table 7-3: Dosage with 3-drug FDC (RHZ) - Children

Weight bands in children*	3-drug paediatric FDC RHZ-75/50/150	Ethambutol 100mg	Levofloxacin 100mg
4-7 kg	1 tablet	1 tablet	1 tablet
8-11 kg	2 tablets	2 tablets	2 tablets
12-15 kg	3 tablets	3 tablets	3 tablets
16-24 kg	4 tablets	4 tablets	4 tablets

** In children weighing 25 kg or more the adult schedule shown in the previous section is followed.*

If levofloxacin 100mg dispersible tablet is not available, the 250mg tablet can be used with 6(H)REZ in children aged 0-14 years, based on a slightly different weight band from the above:

Table 7-4: Dose for levofloxacin 250 mg

Weight	Levofloxacin 250mg
5 - 6 kg	½ tablet / day
7 - 9 kg	¾ tablet / day
10 – 15 kg	1 tablet / day
16 – 23 kg	1.5 tablets / day
24 – 30 kg	2 tablets / day
31 kg +	Follow adult schedule (up to 1g / day)

8. TREATMENT OF DR-TB IN SPECIAL SITUATIONS

This chapter outlines the management of drug resistant TB in special conditions and situations. The emphasis should be to carefully consider selection of regimen, which is safe, effective and to closely monitor the treatment due to potential risks in such patient groups.

8.1. Pregnancy & DR TB Treatment

Most second-line drugs are toxic to the fetus. Before starting any second-line treatment, all women of childbearing age should have a pregnancy test. If the test is negative, contraception must be recommended. The use of oral contraceptives is not contraindicated during MDR-TB treatment, but several second-line drugs may cause vomiting. Anti TB drugs and oral contraceptives should not be taken together as vomiting immediately after such drug administration will affect the efficacy of both contraception and anti TB treatment. Therefore, ingestion of anti TB drugs and oral contraceptives should be done several hours apart.

- Pregnancy is not a contraindication for treatment of active drug-resistant TB, but DR-TB poses great risk to the lives of both the mother & fetus.
- The risks and benefits of treatment should be carefully considered, with the primary goal to protect the health of the mother and child, both before and after birth.
- Most pregnant patients should be started on treatment as soon as the diagnosis is made
- Treatment may be delayed until the second trimester when the patient is very stable with minimum disease as majority of teratogenic effects occur during 1st trimester. Risks and benefits should be carefully evaluated. However, it is better to start treatment with safer options
- Counselling should be done in line with relevant family, religious, cultural and social dynamics.
- Treat with three or four oral second-line anti-TB drugs which are likely to be highly effective plus pyrazinamide and regimen should be reinforced with other drugs as needed immediately postpartum (*WHO 2014*)
- Despite limited data on safety and long-term use of fluoroquinolones, cycloserine, paraaminosalicylic acid (PAS) in pregnancy, they are considered the drug of choice for MDR-TB treatment during pregnancy. Clofazimine has been used extensively in leprotic pregnant patients and use of it in pregnant DR-TB patients so far had not reported serious consequences. Similarly, Bdq has been used in pregnant women in South Africa with no apparent adverse events and recently in 2020 WHO too recommended to use in pregnancy.
- Ethionamide should be avoided as can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.
- Amikacin and Streptomycin are contra-indicated during pregnancy.

- There are no relevant data on use of Lzd in human pregnancy.
- In pregnancy, a longer regimen should be individualized to include components with an established safety profile.
- Therefore, the most suitable option of regimen will be 6 (Bdq, Lfx, Cfz, Cs, Z)/12 (Lfx, Cfz, Cs, Z).
- The termination of pregnancy should be the last choice of action if it would carry a significant risk to mothers' life. The decision will be heavily influenced by the religion and culture.
- If some of the effective drugs were withheld because of the pregnancy, they can be added back postpartum to make a more complete regimen. (WHO 2014)
- Total duration is same as for non-pregnant women.
- The child should receive Bacillus Calmette–Guérin (BCG) vaccination at birth as per national policy.

Treatment regimen for MDR/RR-TB in pregnancy

6 Bdq, Lfx, Cfz, Cs, Z / 12 Lfx, Cfz, Cs, Z

- *Cfz is relatively safe in pregnancy based on experience in human use in leprosy patients and now developing experience in MDR-TB.*
- *FDA classifies Bdq in safety class B in pregnancy, in south Africa Bdq in pregnancy has shown to be safe.*

8.2. Breastfeeding

Breastfeeding is not a contraindication for MDR-TB treatment as anti TB drugs excretion in breast milk is minimal which is unlikely to cause harmful effects to the neonate. However, the benefit of breastfeeding has to be weighed against the risk of exposure to MDR-TB infection by the infant. Infant formula can only be considered an alternative to breastfeeding if all required resources are available and appropriate training has been provided. If the infection prevention can be maintained through personal protection like mask to the mother and breast feeding is done in a well-ventilated area breast feeding it is preferred over bottle feeding. If not, the option is to keep the baby away from the mother as long as she is contagious, and to collect the mother's milk using a breast pump and bottle-feed the baby with breast milk until it is safe to reunite mother and child.

8.3. Treatment of MDR-TB in children

8.3.1 Diagnosis of MDR/RR-TB in Children

Diagnosis of MDR-TB among children can be challenging and requires a high level of suspicion. Under field conditions, it may take several weeks from the time a child first presents with signs and symptoms of TB and the receipt of test results, during which time a child can rapidly deteriorate. Thus, it is important to consider initiating MDR-TB therapy in

the absence of bacteriologic confirmation in line with consultation with pediatrician expert in TB/MDR-TB.

GeneXpert Ultra and culture in liquid media should be prioritized in children. All relevant and available tests should be considered; performing multiple tests on one or more samples of a variety of specimen types significantly increases the diagnostic yield.

8.3.2 Confirmed and clinically diagnosed MDR-TB in children and approach to management

MDR-TB in children can either be confirmed (they have clinical TB disease and a sample taken from the child shows MDR-TB) or clinically diagnosed (the child has clinical TB disease and has risk factors for drug resistance).

Some definitions to consider to establish diagnosis in children are:

- **Confirmed MDR-TB:** MDR-TB is isolated from the child
- **Probable MDR-TB:** Symptoms/ signs and/or radiology consistent with TB disease in a child who has been exposed to an adult with infectious MDR-TB (>80% concordance between drug susceptibility test (DST) patterns in diseased children and the likely source case)
- **Possible MDR-TB:** Child is not improving after 2-3 months of first-line treatment (with confirmation of treatment adherence and exclusion of likely alternative diagnosis)
or
Close contact with a patient who: died from TB; failed TB treatment or is a TB retreatment case

8.3.3 Treatment Principles of MDR-TB management in Children

Sometimes treating MDR-TB in children becomes challenging as either some drugs age cannot be used in certain age groups, or it is difficult to monitor side effects. Many second-line drug formulations are not child-friendly, and preparation can be labor intensive. However, there are now child-friendly, quality assured formulations available from the Global Drug Facility: pyrazinamide, ethambutol, levofloxacin, moxifloxacin, ethionamide, isoniazid, and cycloserine and hopefully delamanide will also be available soon.

- The principles of regimen design for adults, also apply for children based on the WHO recommended regimen design as per grouping of SLDs.
- As per WHO 2018 recommendation, always attempt to treat children with injectable-free regimens, especially in very young children and those with mild disease and if there is no other option and Injectable has to be added then close monitoring by audiometry is crucial.
- Drugs with good penetration to CNS should be used in MDR-TB meningitis.
- Regimens should consist of at least 4 drugs to which the organism is likely to be effective and susceptible and unnecessary/additional drugs should be avoided to avoid toxicity

- WHO in 2020 guidelines recommends Bdq for the treatment of children aged 6 years and above and the use of Dlm for the treatment of children aged 3 years and above[#].
- In children with fluoroquinolone resistance or in whom there are limited treatment options, extension beyond 6 months and combination of Bdq and/or Delamanid could be considered on a patient-by-patient basis with careful monitoring
- Regimens will need to be designed for each individual patient—taking into account unique resistance patterns and toxicity risks
- Linezolid being group A drug has good efficacy, but its use has been associated with frequent toxicity and related toxicities are duration dependent. Therefore, its use ~~for~~ throughout the duration of treatment cannot be recommended.
- In children with HIV and MDR-TB co infection, simultaneous use of Bdq and efavirenz should be avoided as efavirenz lowers the concentrations of Bdq.
- Ethionamide (in the absence of Inh A gene mutation) and PZA are also options to be used if susceptibility is documented. PAS can also be used if no other effective option is left.
- The duration of therapy in children should depend upon the site and severity of disease; children with non-severe disease can be treated for 9 to 12 months while children with severe disease will require 12-18 months of therapy depending on their clinical progress.

[#] In recent WHO rapid communication August 2021, it is recommended to use Bdq and Dlm in all age groups. This will be implemented as per NPTCCD country level decision in line with consultation with central MDR TB committee.

8.3.4 MDR/RR-TB Treatment Regimens for Children

1. Under 3yr, paediatric RR/MDR TB regimen (FQ-resistant and FQ-sensitive cases)

- FQ sensitive: 18 Lfx,Lzd,Cfz,Cs
- FQ resistance: 18 Lzd,Cfz,Cs,Z,Eto

2. 3-5 yrs paediatric regimen (FQ-resistant and FQ-sensitive)

- FQ sensitive: 18 Lfx,Lzd,Cfz,Cs
- FQ resistant: 6 Dlm, Lzd,Cfz,Cs,Eto / 12 Lzd,Cfz,Cs,Eto

3 Years and above paediatric regimen

Please follow as per adult all oral shorter/longer regimens protocols

Note:

- The duration of therapy in children depend upon the site and severity of disease and clinical response
- Children with severe disease should be treated for 18 months while children with non-severe disease may need less than 18 months of therapy (9-12 months) depending on their clinical/radiological progress.

Table 8-1: Dosing of medicines used in second-line multidrug-resistant-TB regimens by weight band

Group	Drug	Weight-based daily dose ^b	Formulation	Weight bands among patients not yet 15 years old ^a						Usual upper daily dose ^b	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg	
A	Levofloxacin	15–20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g
			250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)	
	Moxifloxacin	10–15 mg/kg	100 mg dt	0.8	1.5	2	3	4	(>14 y)	(>14 y)	400 mg
			400 mg tab ^c	2 mL ^c	3 mL ^c	5 mL ^c	0.5 or 0.75	1	(>14 y)	(>14 y)	
	Bedaquiline	-	100 mg tab	-	-	-	1 tab od M/W/F for 22 weeks	4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks	4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks	-	Only in patients aged >5 years (lower dose from 15–29 kg; higher dose from >29 kg).
			20 mg dt	-	-	-	10 dts od for 2 weeks; then 5 dts od M/W/F for 22 weeks	20 dts od for 2 weeks; then 10 dts od M/W/F for 22 weeks	20 dts od for 2 weeks; then 10 dts od M/W/F for 22 weeks	-	
B	Linezolid	15 mg/kg od in <16 kg 10–12 mg/kg od in >15 kg	20 mg/mL susp	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL ^d	600 mg
			600 mg tab ^c	0.25	0.25	0.25	0.5	0.5	0.5	0.75 ^d	
	Clofazimine	2–5 mg/kg	50 mg cap or tab ^e	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg
			100 mg cap or tab ^e	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg
	Cycloserine or terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine) ^c	1	1	2	3	4	(>14 y)	(>14 y)	1 g

	P-aminosalicylic acid	200–300 mg/kg in 2 divided doses	PAS acid (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	Full dose can be given once daily if tolerated.
			PAS sodium salt (equivalent to 4 g PAS acid) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	
Other medicines	Isoniazid	15–20 mg/kg (high dose)	PAS sodium salt 60% w/w (9.2 g; equivalent to 4 g PAS acid) sachet	1.5 g bd	2–3 g bd	3–4 g bd	4 or 6 g bd	6 or 8 g bd	8–12 g bd	300 mg isoniazid tablet can be used in patients >20 kg. Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in those aged <5 years and 25 mg od in those aged >4 years).
			50 mg/5 mL soln	8–10 mL	15 mL	20 mL	–	–	–	
			100 mg tab	1	1.5	2	3	4	(>14 y)	
	Clavulanic acid ⁱ	-	62.5 mg clavulanic acid as amoxicillin/clavulanate, 250 mg/62.5 mg, powder for oral solution, 5 mL	2 mL bdi	3 mL bdi	5 mL bdi	8 mL bdi	10 mL bdi	(>14 y)	Only to be used with carbapenems.

(>14 y): follow the separate dose schedule for patients older than 14 years of age; alt: alternate; bd: two times a day; cap: capsule; dt: dispersible tablet; g: gram; im: intramuscular; iv: intravenous; kg: kilogram; mL: milliliter; mg: milligram; M/W/F: Monday, Wednesday, Friday; soln: solution; susp: suspension; tab: tablet.

a. Dosages were established by the guideline development groups for the WHO guidelines on drug-resistant tuberculosis treatment (2018 and 2020 updates) and the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in

pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients >30 kg, follow the schedule for >14 years old unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for and is more feasible with oral or parenteral fluids and when solid forms of different dosage are available. Fractioning of tablets into halves or less should be avoided if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure respectively (especially for injectable agents, Lzd and fluoroquinolones).

- b. Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.
- c. Dissolving in 10 mL of water may facilitate administration in patients in lower weight bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).
- d. In individuals >44 kg a dose of 600 mg od is proposed.
- e. Tablets are expected to become available in the near future.
- f. May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.
- g. Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways.
- h. Dosing closer to the upper limit of the mg/kg/day is more desirable. For iv use, the volume may be increased.
- i. These agents are only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (isoniazid).
- j. Only available in combination with amoxicillin as co-amoxycylav. Only to be used with carbapenems, in which case they are given together, e.g., 125 mg bd or 125 mg 3 times daily in the 24–30 kg weight band.

8.4 DR-TB and HIV Co-infection

The treatment of DR-TB in PLHIV is not different from the treatment in HIV-negative people. They can receive either short treatment regimen or a long-course regimen, based on the criteria. If the TB/HIV patient is already on ART, it is to be continued. If not yet on ART, it must be prescribed according to the recommendations of the National AIDS Program (NAP) and started early regardless of CD4 count, as soon as the patient is tolerating MDR-TB treatment, possibly within 8 weeks. All TB/HIV patients must receive cotrimoxazole preventive therapy (CPT). All patients co-infected with HIV and MDR-TB must be managed at the DR-TB Centre.

The DR-TB therapy in PLHIV is complicated by:

- cumulated drug toxicities
- Drug-drug interaction
- other co-infections exacerbating drug toxicity
- malabsorption of drugs leading to treatment failure
- paradoxical worsening of TB symptoms when ART is started (Immune Reconstitution Inflammatory Syndrome or IRIS: see national HIV/AIDS Guidelines).

The risk of adverse drug reactions in PLHIV treated with second-line TB drugs increases with the degree of immunosuppression. ART and anti-TB drugs have potential overlapping or additive toxicities and the identification of the source of adverse effects is difficult. It is often impossible to link side effects to a single drug. Using agents with shared adverse effect profiles is not the preferred option but often, the benefit of the drugs outweighs the risk. Increased monitoring of adverse effects is recommended rather than disallowing a certain combination.

The main overlapping toxicities between the second-line drugs and the anti-retroviral drugs commonly used when treating TB/HIV co-infected patients (TDF, 3TC and EFV) are shown in table 11. A full listing can be found in table 8.1 in the *WHO MDR Guidelines 2014*.

Table 8-2: Potentially overlapping adverse effects between ART drugs and second-line drugs used to treat PLHIV with MDR-TB

ART drug	Second-line drug	Adverse effect
EFV	Cs (Eto, FQ, H)	CNS toxicity Depression
EFV, AZT	Cs, Bdq	Headache
Many ART drugs	Z, H, Bdq (Eto, PAS, FQ)	Hepatotoxicity
AZT	Lzd (H)	Bone marrow suppression
AZT, 3TC	Lzd	Lactic acidosis
All ART drugs	Eto, PAS	Abdominal pain
Most ART drugs	Eto, PAS, Bdq, Dlm, H, E, Z	Nausea, vomiting
Most ART drugs	Most Second-line drugs	Skin rash
Most ART drugs	Bdq, Dlm, Mfx, Cfz	Prolongation of Q-T interval

Concomitant use of Bdq with efavirenz (EFV) is not recommended due to possible decrease in blood levels of Bdq. EFV should be replaced by nevirapine (NVP) and if Dorategravir is available it is preferred to be used with BDQ. PIs can be used with Bdq but should be administered with extreme caution and close clinical monitoring.

Please see more information in table below.

Table 8-3: Possible drug-drug interactions between antiretroviral and the new TB drugs (adopted from End TB guidelines 2018)

	Drugs	Instructions
ARVs to avoid with Bdq	EFV (Using EFV with Bdq will result in low levels of Bdq)	Use NVP or integrase inhibitor instead of EFV. Allow a 5-day washout of EFV. (Substitute NVP on day 1 and then start MDR regimen 5 days later). If patient is critically ill with MDR-TB, no washout period is necessary. When switching back to EFV after ending treatment with Bdq, this can be done immediately after Bdq is stopped
	Ritonavir containing protease inhibitors (PIs) (Using ritonavir with Bdq will result in high levels of Bdq)	If possible, use an ARV regimen with no PI. One possible solution is to substitute the PI with an integrase inhibitor (INSTIs), e.g., dolutegravir (DTG) or raltegravir (RAL). If a ritonavir-containing PI must be used, check ECG every two weeks.
ARVs to avoid with Dlm	None	Dlm has very little drug-drug interactions with ARVs, and no extra drug monitoring or regimen adjustment is needed.

Patients receiving ART and MDR-TB treatment must be closely monitored. Daily DOT is obligatory, because the large pill burden and the many side effects may compromise treatment adherence. Whenever adverse effects occur, they must be treated without delay. At the same time, it is important to be alert for signs and symptoms of malabsorption: diarrhoea, abnormal stools, poor nutritional status, evidence of vitamin deficiencies, weight loss, etc.

Diarrhoea should be treated aggressively as it may lead to decreased drug absorption and impair correct treatment.

8.5 Patients with Extra Pulmonary DR-TB and DR-TB meningitis

Patient with DR-TB with EPTB can be initiated in SSTR except those with severe form of EPTB (TB meningitis, Bone TB, Miliary TB, Disseminated TB, TB pericarditis) and PLHIV with EPTB.

Patient with DR-TB meningitis should not be treated with the STR nor with the standard MDR long-course regimen because several of the drugs in those regimens penetrate poorly into bone and soft tissues and the CSF. Therefore, it is imperative to design appropriate regimen having sufficient drugs which can cross the blood brain barrier.

Following table should be followed while designing an effective regimen to treat DR TB meningitis.

Table 8-4: Drugs with good Penetration into CNS for DRTB Treatment

Drug	CNS Penetration
Amikacin	Poor penetration except in the presence of meningeal inflammation
Bedaquiline	No data available; studies ongoing
Clofazimine	Limited data available
Cycloserine	CSF levels similar to serum levels
Delamanid	Limited human data but good CSF penetration in mice: studies ongoing
Ethambutol	Poor penetration
Ethionamide	CSF levels similar to serum levels, but higher end dosing (20 mg/Kg), recommended in children
Isoniazid	20% of serum concentrations except in the presence of meningeal inflammation
Levofloxacin	65% of serum concentrations
Linezolid	Animal studies showed CSF levels at 30% of serum levels: widely used in humans with excellent results
Meropenem	Excellent
Moxifloxacin	Good penetration in animals
PAS	Poor penetration except in the presence of meningeal inflammation
pyrazinamide	CSF levels similar to serum levels

Ref: 1: WHO companion Handbook for treatment of MDR TB, 2016

2: Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide 2019

Some forms of EPTB, when treated, may show a paradoxical worsening. This is quite common in patients co-infected with TB and HIV (Immune Reconstitution Inflammatory Syndrome or IRIS: see national HIV/AIDS Guidelines). In certain types of EPTB, and also if IRIS occurs, adjuvant steroid therapy may be helpful.

8.6 Patients with chronic liver disease

Many anti-TB medications have the potential to cause hepatotoxicity, and their use must be carefully contemplated in the setting of severe liver dysfunction. Possible anti-TB drugs that can cause hepatotoxicity are R, Z, H, Cfz, PAS, Eto/Pto, Bdq, Clavulanic acid. Fortunately, the most important second-line anti-tuberculosis drugs used for treatment of drug-resistant disease do not affect the liver. Among the first-line drugs used in MDRTB, Z is the most hepatotoxic, followed by R and H. RHZ hepatotoxicity is more when they are used in combination than when used alone. Z hepatotoxicity is mostly dose dependent while R & Z hepatotoxicity is idiosyncratic and dose dependent. Among the second-line drugs, Eto and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with fluoroquinolones. Lfx is less hepatotoxic than Mfx.

Hepatitis itself is not contraindication to start DR-TB treatment unless liver enzymes are raised to unacceptable level i.e 5-fold increase in liver enzyme. Patients with history of liver disease can receive the usual anti-TB drug regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carriage, and recent history of acute hepatitis or excessive alcohol consumption. In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Treatment of drug-resistant TB in the setting of liver failure is complicated and depends on the degree of liver damage. A long-course regimen with at least 4 non-hepatotoxic drugs is required. However, as per newly WHO recommended regimen, the drugs from group A and B are safe to use.

If a patient with acute hepatitis requires MDRTB treatment and if it is not possible to differ the treatment until the acute episode has resolved and liver enzymes become normal, treatment with non-hepatotoxic drugs may have to be started.

Key messages for anti TB drugs induced hepatotoxicity;

- Rule out Viral hepatitis and Alcoholic Hepatitis
- ALT-AST Levels indicate degree of liver inflammation and liver cell damage- ALT is more specific for liver injury
- If ALT, AST levels are reported >5 times above the upper limit of normal in an asymptomatic patient, or in symptomatic when levels are above 3 times the upper limit of normal, stop all anti TB drugs, check liver enzymes weekly
- Reintroduce drugs once liver enzymes return to normal, with least hepatotoxic drug first and add one drug by one every 3-4 days, while monitoring LFTs
- If Z or Cfz or H^h is the likely offending drug, stop the offending drug and introduce a safer

substitute. Similarly, in longer regimens if Z is the likely offending drug, stop Z permanently and introduce a safer drug instead.

For more information, please refer to aDSM chapter and side effects management

8.7 DR Patients with chronic kidney disease (CKD)

In DR-TB patients with renal insufficiency, the dosing of the second-line drugs that are cleared by the kidneys will have to be adapted if the creatinine clearance is <30ml/minute. The general strategy is to have an interval between dosing rather than to decrease the daily dose. There should be careful monitoring of nephrotoxicity during treatment.

Table 8-5: Dosing recommendations of anti-TB drugs in adult patients with creatinine clearance <30 ml/min

Drug	Change in frequency	Recommended dose and frequency
Isoniazid (H)	No change	300 mg once daily, or 900 mg 3 times/week
Rifampicin (R)	No change	600 mg once daily, or 600 mg 3 times/week
Pyrazinamide (Z)	Yes	25– 35 mg/kg/dose 3 times/week (not daily)
Ethambutol (E)	Yes	15–25 mg/kg/dose 3 times/week (not daily)
Levofloxacin (Lfx)	Yes	750 –1000 mg/dose 3 times/week (not daily)
Moxifloxacin (Mfx)	No change	400 mg daily
Cycloserine (Cs)	Yes	500 mg/dose 3 times/week
Ethionamide (Eto)	No change	15–20 mg/kg/day (can be in divided doses)
Para-aminosalicylate (PAS)	No change	4 gm/dose twice daily
Linezolid (Lzd)	No change	600 mg daily
Clofazimine (Cfz)	No change	100mg daily
Amikacin (Am)	Yes	12–15 mg/kg/dose 2–3 times/week
Bedaquiline (Bdq) and Delamanid(Dlm)	no change with mild to moderate renal dysfunction but use with caution in severe renal disease	

8.8 Patients with diabetes mellitus

The outcomes for patients who have both TB and diabetes are poorer than for TB patients without diabetes. In Sri Lanka diabetes mellitus (DM) is the most common and prevalent co-morbid condition among RR/MDR TB patients. DM must be managed and monitored closely throughout the treatment of drug-resistant TB. If the patient is on oral hypoglycaemic agents, he/she may need to be switched to insulin for the duration of the MDR-TB treatment if the diabetic control is unsatisfactory. None of the anti-TB drugs are contraindicated.

Patients with diabetes and MDR-TB may be at increased risk of adverse events since many of the anti-TB drugs have side effects that place diabetic patients at special risk. Patients with

long-standing diabetes may have underlying renal impairment that can be worsened by the second-line injectable drugs. Neuropathy is a common complication of diabetes and also can be worsened by several drugs used to treat MDR-TB such as high-dose INH, cycloserine, Lzd and the fluoroquinolones.

Some preliminary evidence suggests that improving glycaemic control can lead to better TB treatment outcomes and reduced risk of relapse and recurrence.

Patients with diabetes may have decreased gastric motility (gastroparesis) and may be at increased risk of nausea and vomiting with medications like Eto or other MDR-TB drugs. Gastric paresis should be treated ideally with domperidone (caution with QT prolonging drugs), but metoclopramide is also effective. Diabetic patients are at a high risk of developing peripheral neuropathy and some of them can have preexisting peripheral neuropathy. Lzd, Cs, Hh can cause or worsen preexisting neuropathy. Therefore, close monitoring and appropriate timely action in this regard is necessary.

9. ACTIVE DRUG SAFETY MONITORING AND MANAGEMENT (aDSM)

DOT providers, nurses in the hospital and clinicians will monitor and record all the minor to major adverse effects. Laboratory screening tests and a checklist will be used routinely as recommended (Table 10.1). The initial evaluation serves to establish a baseline and will identify patients who are at increased risk of adverse drug reactions or poor outcomes.

Training of medical staff on close monitoring and management of ADRs

Training of health staff will be done to identify and manage ADRs. Close monitoring of patients is necessary to ensure that the adverse effects of second-line drugs are recognized quickly by health-care personnel. The ability to monitor patients for adverse effects daily is one of the major advantages of DOT over self-administration of RR/MDR-TB treatment. The majority of adverse effects are easy to recognize. Usually, patients will complain about symptoms attributable to adverse drug effects. However, it is important to have a systematic method of patient monitoring since some patients may be reticent about reporting even severe adverse effects. Further, it is easier to reverse some of the side effects in early stages rather than in late stages when some of the damages may have become permanent. DOT workers should be trained to screen patients regularly for symptoms of common adverse effects, i.e., rashes, gastrointestinal symptoms (nausea, vomiting, and diarrhoea), psychiatric symptoms (psychosis, depression, anxiety, and suicidal ideation), jaundice, hearing disturbances, visual disturbances and neurological symptoms (peripheral numbness and fits). DOT providers should be able to identify ADR and refer patients to DCC. Most of the ADRs could be managed by the DTCO/Chest Physician of the DCC. If required, hospitalisation should be arranged either in chest wards in the district, if this facility is available or at NHRD. Decisions regarding alteration of second-line regimen due to ADR should be taken by the treating Chest Physician in consultation with the PMDT site committee and Central PMDT committee.

Laboratory screening is invaluable for detecting certain adverse effects that are more occult.

9.1. Availability of ancillary drugs

All the ancillary drugs for managing ADRs will be made available in local health facilities as part of the general health care system. Commonly used ancillary drugs for specific adverse effects are given in Table 9.4.

9.2. Objectives Of aDSM

Overall, aDSM aims to detect, manage, and report suspected or confirmed drug toxicities in a timely fashion. The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second line (SL) treatment for DR-TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines.

9.3. Definitions

1. **Active drug-safety monitoring and management (aDSM):** active and systematic clinical and laboratory assessment of patients while on treatment. As per recent WHO 2018 recommendation, aDSM applies to all patients on MDR/RR-TB treatment with (a) new anti-TB drugs, such as Bdq and Dlm; (b) new DR-TB regimens, such as the shorter (or 9-month) MDR-TB regimen; or (c) XDR-TB regimens on new/repurposed drugs, in order to detect, manage and report suspected or confirmed drug toxicities.
2. **Adverse event (AE):** any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, that does not necessarily have a causal relationship with its treatment.
3. **Adverse drug reaction (ADR):** a reaction to a anti TB drug that is noxious and unintended, and which occurs at doses normally used in humans.
4. **Causality assessment:** the evaluation of the likelihood that an anti TB drug was the causative agent of an observed adverse reaction.
5. **Serious adverse event (SAE):** an AE which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. SAEs that do not immediately result in one of these outcomes but require an intervention to prevent it from happening are included. SAEs may require a drastic intervention such as termination of the drug suspected of having caused the event.
6. **AE of special interest:** AE documented to have occurred during clinical trials and for which the monitoring program is specifically sensitized to report regardless of its seriousness, severity or causal relationship to TB treatment
7. **AE of clinical significance:** AE that is either a) serious (SAE), b) of special interest, c) leads to a discontinuation or change in the treatment, or d) is judged as otherwise clinically significant by the clinician

The second line drugs have a lot of side effects. Adverse events (AEs) and adverse drug reactions (ADRs) may occur during treatment of DR-TB with various severity grading. This national guideline adopts DR-TB treatment regimens recommended by WHO as “new and repurposed drugs” are now part of standard regimen, therefore, aDSM is applicable to all the MDR/RR-TB patients.

Often, AEs or ADRs are the reason for treatment irregularities or inadequate therapy. Timely recognition and proper management of AEs or ADRs will help avoid these. All health workers dealing with DR-TB must be able to recognize AEs and ADRs and know how to manage or refer accordingly and to record and report in a timely manner as per NPTCCD aDSM protocols. NPTCCD has adopted Core Package of aDSM which means only SAEs/ADRs are reported.

9.4. Important Elements of aDSM

There are three fundamental elements of aDSM to achieve the above objectives:

1. Active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.
2. Recording and reporting: All AEs must be recorded properly using aDSM recording and reporting forms (patient's booklet and patient's card) and all Serious Adverse Events (SAEs) must be reported using reporting tools as per NPTCCD aDSM protocols by *email*. For any serious AEs/ADRs, the reporting must be done within 24 to 36 hours from its onset. Recording and reporting of AEs/ADRs are as equally important as clinical monitoring and management of the AEs/ADRs.

Seriousness is defined by the outcome of an adverse event. SAE is one that leads to any of the following;

1. Death
2. Threat to life
3. Hospital admission /prolonged hospitalization
4. Permanent disability
5. Other serious medically complication
6. Congenital anomalies in the foetus.

Severity is defined by the impact on the patient's ability to function. It is graded on a scale of 1 to 5, as shown below:

Table 9-1: Grading of adverse events

Grade	Severity	Description
Grade 1	Mild	Small or transient inconvenience that does not limit normal daily activity. No need for medical intervention or corrective treatment.
Grade 2	Moderate	Partial limitation of normal daily activity. In some, but not all cases, medical intervention or corrective treatment is necessary. No need to discontinue the treatment.
Grade 3	Severe	Limitation of normal daily activity. Medical intervention and corrective treatment, often requiring hospitalization, are necessary. The responsible drug may have to be stopped temporarily, until the symptoms have disappeared.
Grade 4	Life threatening	Very severe limitation of normal daily activity. Medical intervention and corrective treatment, requiring hospitalization, are necessary. The responsible drug may have to be stopped indefinitely.
Grade 5	Death	Death related to adverse event

9.5. Management of AEs or ADRs

Management options include measures taken to alleviate the signs and symptoms of adverse reactions with careful individual case review, such as: a) reassurance, if AE is minor b) lowering the dose of the offending drug, c) stopping the drug, d) drug replacement; e) providing ancillary medications and f) other interventions (surgery, transfusion, psychological support, etc.).

For a number of drugs, the toxicity is dose dependent. Reducing the dosage may be an effective method of managing these adverse effects. *But attention! The reduced dose must still be effective!* If the serum level of the drug is too low, it will compromise the treatment regimen. This is particularly the case for Eto and Cs. **Lowering the dose by more than one weight class (according to dosages table) for the long-course regimens should be avoided.**

Serious adverse events would be avoidable by systematic aDSM implementation and replacement with an appropriate drug. (eg, replacement of Am with non-nephrotoxic drug in a patient who has Grade I ototoxicity).

Particular attention needs to be paid to the side effects of Lzd, a potent but toxic drug used as a part of standard regimen. Monitoring the adverse drug reactions of Lzd requires specific investigations:

Table 9-2: Severity grading scales and suggested action for common AEs (adopted from End TB Guidelines 2018)

Severity grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
1. Peripheral neuropathy Possible anti-TB drug causes: E, Lzd, Cs, H, S, FQ, Pto/Eto . Other causes: DM, HIV, malnutrition				
Paraesthesia (Burning, tingling, etc.)	Mild discomfort: no treatment required; and/or BPNS (Brief Peripheral Neuropathy Screen) subjective sensory neuropathy score 1-3 on any side.	Moderate discomfort: non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort: or narcotic analgesia required with symptomatic improvement; and/or BPNS subjective sensory neuropathy score 7-10 on any side.	Incapacitating; or not responsive to narcotic analgesia.
Action	Stop Cs and Lzd. If symptoms improve, consider restarting these drugs. Consider restarting Lzd at a lower dose (300mg daily or 600 mg thrice weekly). If Cs is not essential to the regimen, consider suspending the drug.	Stop Cs and Lzd. If symptoms improve, consider restarting Cs. Do not reintroduce Lzd. Provide symptomatic relief	Same as Grade 2.	Same as Grade 2.
2. Myelosuppression (anemia, thrombocytopenia, or neutropenia) Possible anti-TB drug causes: Lzd. Possible other causes: AZT, cotrimoxazole, Viganciclovir				
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL
Platelets decreased	75,000 – 99,999/mm ³	50,000 – 74,999 /mm ³	20,000 – 49,999/mm ³	< 20,000 /mm ³
Absolute neutrophil count low	1500 - 1000/mm ³	999 - 750/mm ³	749 - 500/mm ³	<500/mm ³

Action	Monitor carefully and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly).	Monitor carefully and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly); in case of Grade 2 neutropenia, stop Lzd immediately. In case of Grade 2 anemia, consider erythropoietin (EPO). Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd immediately. In case of Grade 3 anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose once toxicity has decreased to Grade 1.
3. Prolonged QT interval Possible anti-TB drug causes: Cfz, Bdq, Mfx, Dlm, and Lfx (a mild QT prolonging drug) Possible other causes: Other drugs, e.g., erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, antipsychotics (all have some risk, including haloperidol, chlorpromazine and risperidone), many anti-nausea drugs (ondansetron/granisetron, domperidone), methadone, and some anti-retrovirals); genetic causes such as long QT syndrome; hypothyroidism				
Prolonged QTcF	QTcF 450 – 480 ms.	QTcF interval 481 – 500 ms.	QTcF \geq 501 ms without signs/ symptoms of serious arrhythmia.	QTcF \geq 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.
Action	Monitor more closely; at least weekly ECG until returned to less than grade 1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.
4. Optic nerve disorder (optic neuritis) Possible anti-TB drug causes: Lzd, E, Eto/Pto, Cfz,.				

Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40[6/12] or better)	Limiting vision in the affected eye (worse than 20/40[6/12] but better than 20/200[6/60])	Blindness (20/200[6/60] or worse) in the affected eye
Action	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.
5. Hepatitis Possible anti-TB drug causes: Z, H, R, Pto /Eto, Bdq, Cfz, PAS, clav , alcohol use, unknown herbal/traditional medicine Possible other causes: unknown				
ALT (SGPT)	1.1 – 3.0 x upper limit of normal (ULN)	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST (SGOT)	1.1 – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen if the patient is asymptomatic. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation or until the patient develops symptoms of liver toxicity when the treatment is withheld.	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.
6. Acute kidney injury Possible anti-TB drug causes: S, Am, Possible ART causes: Tenofovir (TDF) - rare				
Acute kidney Injury	Creatinine level increase of >0.3 mg/dL above base line; creatinine 1.5 - 2.0 times the upper limit of normal.	Creatinine 2 - 3 times above baseline.	Creatinine >3 times baseline or >4.0mg/dL; hospitalization indicated	Life-threatening consequences: dialysis indicated

Action	Consider stopping aminoglycosides until creatinine has returned to baseline. Restarting aminoglycosides may be considered after discussing with nephrologists	Stop aminoglycosides until creatinine has returned to baseline. Restarting aminoglycosides may be considered after discussing with nephrologists or substitute with a non-nephro-toxic drug.	Stop aminoglycosides until creatinine has returned to baseline. Restarting aminoglycosides may be considered after discussing with nephrologists or substitute with a non-nephrotoxic drug.	Stop aminoglycosides until creatinine has returned to baseline. Restarting aminoglycosides may be considered after discussing with nephrologists or substitute with a non-nephrotoxic drug.
7. Hypokalemia and hypomagnesemia Possible anti-TB drug causes: Am, S. Possible ART causes: TDF(rare)				
Hypokalemia	3.4 - 3.0 mEq/L	2.9 - 2.5 mEq/L	2.4 - 2.0 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium <i>with</i> paresis, ileus or life-threatening arrhythmia
Action	Continue injectable. Start oral potassium replacement therapy. Check serum magnesium and replace if necessary.	Continue injectable. Start aggressive oral potassium replacement therapy. Replace magnesium as necessary.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.
Hypomagnesemia	0.60-0.70 mmol/L	0.45-0.59 mmol/L	0.30-0.44 mmol/L	<0.30 mmol/L
8. Hypothyroidism Possible anti-TB drug causes: Eto/Pto, PAS. Possible ART causes: d4T				
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting iADL (instrumental activities of daily living) *	Severe symptoms: limiting self-care ADL * hospitalization indicated	Life-threatening consequences: urgent intervention indicated
Action	Continue anti-TB drugs.	Continue anti-TB drugs. Start thyroxine.	Continue anti-TB drugs. Start thyroxine.	Stop all anti-TB drugs. Start thyroxine.

9. Hearing loss Possible anti-TB drug causes: S, Am, Possible other causes: none. WHO classification grading scale for hearing loss: (In the case of moderate hearing loss, the range for children is 31-60 dB)				
Hearing loss	40dB Slight/Mild	41-60 dB Moderate	61-80 dB Severe	Over 81 dB Profound
	Difficulty hearing and understanding soft speech, speech from a distance, or speech against a background of noise.	Difficulty hearing regular speech, even at close distance.	May only hear very loud speech or loud sounds in the environment, such as a fire truck siren or a door slamming. Most conversation speech is not heard.	May perceive loud sounds as vibrations
Action*	Consider stopping aminoglycosides and replace with non-ototoxic drug of equal efficacy	Stop Am/S or consider decreasing frequency if further hearing loss is a concern and no effective alternative option is available. Initiate discussion with patients about risks and benefits of aminoglycoside. Consider replacing an injectable agent with a non-ototoxic SLD. Do NOT substitute with a single drug. If the treatment is failing, add additional SLD	Consider stopping or decreasing aminoglycoside frequency (e.g. MWF). Discuss with patients the risks and benefits of further aminoglycoside use. In most cases of Grade 1-3 hearing loss due to aminoglycosides should be stopped and replaced with a non-ototoxic SLD. Do NOT substitute with a single drug if the treatment is failing, add additional SLD	In cases of complete hearing loss, some clinicians may continue aminoglycoside as the damage is already done. Consider suspension of aminoglycosides if ongoing use contributes to worsening tinnitus or vestibular disturbances (or if some hearing might be still preserved). Add additional SLD as needed.
* Any form of new onset hearing loss needs discontinuation of aminoglycosides and decision to restart has to be discussed with otolaryngologists				

9.6. Causality Assessment of the Serious Adverse Event (SAEs):

For all SAEs, the *first level Causality Assessment* can be done at the DR-TB treatments centers/TB hospitals by the treating doctor using the Adverse Event Causality Assessment definitions and Flowchart given below: This will be helpful in recognizing the drugs responsible for the adverse event and to stop the offending drug early to reduce the progression further. However, all reported SAEs are presented and discussed later in the National committee for aDSM, for causality assessment and reporting,

CAUSALITY ASSESSMENT

Causality assessment (CA) is an integral part of clinical management. In TB, evaluating the likelihood that a TB medicine was the causative agent of an observed adverse reaction, forms part of clinical evaluation. While the details of the systematic method of conducting CA may not be familiar to the practitioner, the overall approach is not too different from the clinical practice followed when evaluating any patient on treatment.

CA involves making an attribution or describing the *relationship* between the AE and an exposure by a physician or any other health care professional with the right expertise which forms part of clinical monitoring and management. This determination must be recorded both in the patient's medical record as well as in a case report form. For aDSM, CA should be made primarily at the country level and by consulting the relevant data sources close to where the event occurred. Attributing a relationship requires a systematic process and is one of the main reasons why data are collected in aDSM. CA, once done, attributes a level of certainty between the event and the exposure, ranging from certain to unrelated.

CA is conducted by the members of the National aDSM committee, who also comprise the National PMDT committee, with the participation of other designated members. CA should be conducted using a systematic tool provided later in this section, involving inputs from the panel of experts beyond the treating physician. The steps in doing CA are as follows:

- The hospital site provides all details relevant to the SAE to the national level (within 24 hours to the NPTCCD and the National Medicines Regulatory Authority (NMRA) aDSM focal points)
- The hospital site will forward all other details to the NPTCCD aDSM Focal Point (within 72 hours from SAE detection) in the Case Summary section of the SAE Form, including the following key data elements:
 - a) medical history (including concomitant disease),
 - b) other risk factors (social factors, alcohol use, substance abuse, etc.),
 - c) details of drugs taken: names, doses, routes,
 - d) start and stop dates and indications for use,

- e) description of adverse event, including clinical description, baseline, monthly and ad hoc laboratory results, and date of onset / end and
 - f) evolution of event, severity, seriousness, and outcome.
- The aDSM Focal Point forwards the completed SAE Form to the Clinicians and all others who are involved in CA, and other aDSM committee members
 - The NPTCCD aDSM Focal Point schedules a CA meeting within 15 days from detection of a SAE.
 - Prior to the meeting, each member of the CA team will individually review the SAE Form guided by the WHO-Uppsala Monitoring Centre (UMC) Causality Algorithm or the Naranjo ADR probability scale.
 - During the CA meeting, the individual CAs will be considered until a **Causality Consensus** is arrived at.

The goal for CA is to decrease inter-individual differences in the assessment of a given event, classify the likelihood of a relationship between the drug and the event, and improve scientific evaluation.

Table 9-3: The WHO-UMC Classification System for causality assessment

Causality term	Definition	Assessment criteria
Certain	<u>Clearly caused by the exposure</u> <i>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</i>	<ul style="list-style-type: none"> Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) Re-challenge satisfactory, if necessary
Probable/Likely	<u>Likely to be related to the exposure</u> <i>There is evidence to suggest a likely causal relationship and the influence of other factors is unlikely.</i>	<ul style="list-style-type: none"> Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Re-challenge not required
Possible	<u>May be related to the exposure</u> <i>There is some evidence to suggest a causal relationship (e.g., because the event occurs within a reasonable time after administration of the</i>	<ul style="list-style-type: none"> Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear

	trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	
Unlikely	<u>Doubtfully related to the exposure</u> There is little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after administration of the study regimen). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

The on-line SAE Form/ soft file received by the NPTCCD should be entered/ reviewed/ updated regularly to the National SAE Database by the NPTCCD Focal Point in a format linked with the Global aDSM Database sharing the same key variables to facilitate data transmission and contribution of the data from the country to the Global Database.

9.7. Management of Side Effects

Table 9-4: Minor to Major Side Effects and Management

Adverse Effect	Suspected Agent	Suggested Management	Comments
Rash, allergic reaction and anaphylaxis	Any drug	<ol style="list-style-type: none"> 1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols. 2. Eliminate other potential causes of allergic skin reaction (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include: <ul style="list-style-type: none"> • Antihistamines • Phototoxicity may respond to sunscreens, but these can also cause rash 	<ol style="list-style-type: none"> 1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flashes, itching, palpitations can be caused with isoniazid. If this occurs, advise patients to avoid foods that precipitate the reaction. 3. Any drug that resulted in anaphylaxis or Steven-Johnson syndrome should never be reintroduced to the patient, not

		<ul style="list-style-type: none"> • Dry skin may cause itching (especially in diabetics); liberal use of moisturizing lotion is recommended. <p>Dry skin as well as generalized darkening of skin are common and significant problem with Cfz.</p> <p>4. Generalized skin reactions such as itchy maculopapular rash, urticaria need stopping of all drugs as any drug can be the cause of such a rash. Once the rash resolves, drugs should be started one by one starting with drugs which are least likely to cause skin rash in that order. Each drug should be commenced with a lower dose and the dose increased to recommended dose over 3 – 4 days. If a drug is found to cause rash during this process of challenge, that drug should be suspended.</p> <p>5. Suspend permanently any drug identified to be the cause of a serious reaction.</p>	even as a challenge.
Nausea and Vomiting Without elevated transaminase	Eto, Pto, PAS, H,Z, Amx/ Clv,	<p>1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis; initiate rehydration therapy if indicated and correct any electrolyte disturbances.</p> <p>2. Initiate stepwise approach to nausea and vomiting.</p> <ul style="list-style-type: none"> • Phase 1: Adjust medications and conditions without lowering overall dose: <ul style="list-style-type: none"> • Give the Eto/Pto at night • Give Eto or PAS twice or thrice daily. • Give a light snack (biscuits, bread, rice, tea) before the medications. • Give PAS 2 hours after other anti-TB drugs • Phase 2: Start antiemetic(s): <ul style="list-style-type: none"> • Metoclopramide 10 mg 30 minutes before anti-TB medications. • Ondansetron 8 mg 30 minutes before the anti-TB drugs and again 8 hours after. Ondansetron 	<p>1. Nausea and vomiting is 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 and patients should be advised about this side effect.</p> <p>2. Creatinine and electrolytes should be checked if vomiting is severe. Give IV fluids and replace electrolytes as needed.</p> <p>3. Ondansetron (not recommended with QT Interval prolonging drugs) is serotonin 5-HT₃ receptor antagonist and considered to have strong anti-emetic properties. It is on the WHO essential drug list. A number of other anti-emetics from this class of serotonin 5-HT₃ receptor antagonists exist. Trying different antiemetics, even if from the same class, may be helpful for some patients.</p>

		<p>can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used) For refractory nausea 24 mg 30 minutes before the dose can be tried.</p> <ul style="list-style-type: none"> • Phase 3: Decrease dose of the suspected drug by one weight class if this can be done without compromising regimen. Rarely is it necessary to suspend the drug completely. 	
Diarrhoea and/or flatulence	PAS, Eto/Pto	<ol style="list-style-type: none"> 1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 4. Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe. 5. Fever and diarrhoea and/or blood in the stools indicate the diarrhoea may be secondary to something other than a simple adverse effect of the anti-TB drugs. 	<ol style="list-style-type: none"> 1. Consider other causes of diarrhoea: <ul style="list-style-type: none"> • Pseudo-membranous colitis related to broad-spectrum antibiotics such as the FQs is a serious and even life-threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are danger signs of possible p s e u d o - membranous colitis. <ul style="list-style-type: none"> • Lactose intolerance, especially if a patient has been exposed to new foods in a hospital not normally part of their diet.
Hepatitis	Z, H, R, Alcohol,	<ol style="list-style-type: none"> 1. If enzymes are more than 5 times the upper limit of normal, stop all hepatotoxic drugs and continue with non-hepatotoxic medications (an example of non-hepatotoxic drugs are the injectable agent, fluoroquinolone and cycloserine, Lzd). 2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol-induced hepatitis being the two most common causes) and treat any identified condition. 3. Consider suspending most likely agents permanently. Reintroduce remaining drugs one at a time, with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely culprit 	<ol style="list-style-type: none"> 1. History of previous drug hepatitis should be carefully analysed to determine most likely causative agent(s); these drugs should be avoided in future regimens.

		is not essential, consider not re-introducing it.	
Hypothyroidism	Eto/Pto, PAS	<p>Drugs can be continued while replacing Thyroxin. If these drugs are not essential, they can be replaced with alternative drugs.</p> <p>If that is not possible, endocrinologists' opinion is sought with regard to continuation of these drugs while replacing thyroxin</p> <p>Thyroid functions are repeated every 6 months if the patients are on these drugs</p>	<p>Symptoms of hypothyroidism include:</p> <ol style="list-style-type: none"> 1. fatigue 2. somnolence 3. cold intolerance 4. dry skin, 5. coarse hair 6. constipation, 7. Occasional depression and inability to concentrate. <p>Completely reversible upon discontinuation of PAS and/or ethionamide/prothionamide.</p> <p>The combination of ethionamide/prothionamide with PAS is more frequently associated with hypothyroidism than is the individual use of each drug.</p>
Arthralgias	Z, Fluoroquinolones	<ol style="list-style-type: none"> 1. Lower dose of suspected agent (most commonly pyrazinamide), if this can be done without compromising regimen. 2. Discontinue suspected agents, if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. <p>There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present, it should be used.</p> <ol style="list-style-type: none"> 3. If acute swelling, redness, and warmth are present in a joint, consider aspiration for diagnosis (gout, infection, autoimmune disease, etc).
Electrolyte disturbances (Hypokalaemia and hypomagnesaemia)	Am, S	<ol style="list-style-type: none"> 1. Check potassium. & Perform, ECG 2. If potassium is low, also check magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalemia). 3. Replace electrolytes as needed. Dose oral electrolytes apart from FQ as they can interfere with FQ absorption. 	<ol style="list-style-type: none"> 1. If severe hypokalemia is present, consider hospitalization. 2. Amiloride 5–10 mg per day or spironolactone 25 mg per day may decrease potassium and magnesium wasting and is useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhea
Nephrotoxicity (Renal toxicity)	S, Am, Possible ART: TDF	<ol style="list-style-type: none"> 1. Discontinue suspected agent. 2. Consider other contributing etiologies (NSAIDs, diabetes, 	<ol style="list-style-type: none"> 1. History of diabetes or renal disease is not a contraindication

		<p>other medications, dehydration, congestive heart failure, obstruction, etc.) and address as indicated.</p> <p>3. Monitor creatinine (and electrolytes) closely, every 1 to 2 weeks.</p> <p>4. Consider changing injectable agent to a safer and effective drug i.e Bdq, Lzd, Dlm</p> <p>5. Adjust all TB medications according to the creatinine clearance, refer to nephrologist for opinion and management. See notes under section 8.7.</p>	<p>to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure.</p> <p>2. An example of how to calculate a creatinine clearance based on the serum creatinine</p> <p>3. Renal impairment may be permanent.</p>
Hearing loss (also see vestibular toxicity above)	S, Am,	<p>1. Document hearing loss and compare with baseline audiometry if available. (Some degree of hearing loss occurs with most patients, starting with high-frequency loss).</p> <p>2. If early symptoms of hearing loss are then discontinue the injectable agent and replace with other suitable drug (Bdq, Lzd, Dlm) if this can be done without compromising the regimen.</p>	<p>1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry should be done at the start of MDR-TB therapy. Baseline audiometry is also recommended on those who complain of hearing impairment, elderly patients and children.</p> <p>2. Hearing loss mostly is irreversible or permanent (often permanent).</p> <p>3. Continuing the injectable agent despite hearing loss almost always results in deafness.</p> <p>4. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial to determine if a patient with hearing loss can benefit from their use.</p>
Myelosuppression (anemia, thrombocytopenia, or neutropenia)	Lzd, Possible other causes: AZT, cotrimoxazole. TB itself, iron deficiency, GI bleeding also causes of anaemia,	<p>Lzd associated Myelosuppression is very common, approximately 18-21% of patients taking Lzd may experience anemia/ Myelosuppression.</p> <p>If the patient has thrombocytopenia or neutropenia, this is more likely to be due to Lzd.</p> <p>In mild to moderate Anaemia/Myelosuppression, continue close monitoring and consider dose reduction of Lzd to 300 mg daily or 600 mg</p>	<p>Lzd associated anaemias/ myelosuppression is dose related and may occur in few days after start of treatment</p> <p>Many chronic TB/DR TB patients may have iron deficiency anemia at baseline due to inflammatory process and production of hepcidin and influencing iron homeostasis</p> <p>Monitor full blood count regularly</p>

		<p>alternative day and seek expert opinion.</p> <p>In severe and life-threatening situation (grade 3-4) stop Lzd immediately.</p> <p>Start blood transfusion.</p> <p>Consider Erythropoietin with specialist advice.</p> <p>Restart Lzd at reduced doses, once severity has become to grade 1.</p> <p>If necessary stop, Lzd and consider other safer drugs.</p>	
Peripheral Neuropathy (PN)	Cs, Lzd, H, H, FQs, rarely Pto/Eto, E	<p>1. Increase pyridoxine to maximum daily dose (200 mg per day).</p> <p>2. The neuropathy associated with Lzd is common after prolonged use and often extremely painful and irreversible. For this reason, if nerves are permanently damaged, Lzd should be immediately stopped and not reintroduced when symptomatic neuropathy develops (grade 2 or above). Consider additional anti-TB drugs to reinforce the regimen.</p> <p>3. Consider whether the dose of cycloserine, Lzd, isoniazid, Eto can be reduced without compromising the regimen.</p> <p>3. Initiate medical therapy:</p> <ul style="list-style-type: none"> • NSAIDs or paracetamol may help alleviate symptoms. • Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime; the dose may be increased to a maximum of 150 mg). Do not use QT prolonging drugs. <p>Tricyclic antidepressants with selective serotonin reuptake inhibitors (SSRIs) antidepressant drugs (fluoxetine, sertraline). Avoid Lzd and Amitriptyline together because of risk serotonergic syndrome.</p>	<p>1. Nutritional status is important to see as low BMI increase the risk of PN with use of Lzd, Cs</p> <p>2. Lzd associated PN may be a result of disrupted mitochondrial function in neurons.</p> <p>3. Patients with co-morbid disease (e.g., diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here.</p> <p>4. Neuropathy may be irreversible, but many patients experience improvement when offending agents are suspended. However, the neuropathy associated with Lzd is common after prolonged use and often permanent (for this reason suspension of this agent should be considered when neuropathy develops).</p>

		<ul style="list-style-type: none"> Carbamazepine, an anticonvulsant, at 100–400 mg twice daily can be tried. Carbamazepine is a strong inducer of CYP3A4 and should not be used with bedaquiline or Dlm. Gabapentine: 100-300 mg daily at night or 100 mg tds, is a good drug to treat PN and many clinical trials support its use Culprit medication may be discontinued and changed with alternative drugs so that the regimen is not compromised. 	
Depression	socio economic factors/consequences, social stigma, burden of chronic Cs, fluoroquinolones, H, Eto/Pto	<ol style="list-style-type: none"> Assess and address underlying socioeconomic issues. Assess patients for co-existing substance abuse/alcoholism and refer to treatment if appropriate. Initiate individual counselling (or group counselling if the patient is smear- and culture-negative). When depression is significant, initiate antidepressant therapy (amitriptyline, fluoxetine or similar, it may be necessary to refer to a psychiatrist for management). Tricyclic antidepressants and SSRIs should not be given together and should not be given to patients on Lzd. Also avoid with QT prolonging drugs. Lower dose of suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and Eto to 500 mg daily to see if the depression is lessened is a common strategy). Discontinue suspected agents if this can be done without compromising regimen. 	<ol style="list-style-type: none"> Socioeconomic factors and chronic illness should not be underestimated as contributing factors to depression. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine if possible. Question the patient regarding suicidal ideation any time the depression is judged to be more than mild.
Suicidal ideation	Cs, H, Eto/Pto/FQ	<ol style="list-style-type: none"> Hospitalize the patient and put under 24- hour surveillance. Discontinue cycloserine. Request psychiatric consultation. 	<ol style="list-style-type: none"> Keep the patient in the hospital until risk of suicide has passed. If no improvement occurs after holding cycloserine, stop H and/or Eto/Pto/FQ

		<p>4. Initiate antidepressant therapy.</p> <p>5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable or stop altogether.</p>	
Other psychotic symptoms	Cs, H, FQs, drug abuse, heavy alcohol consumption	<p>1. Stop suspected agents for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high-dose isoniazid.</p> <p>2. If moderate to severe, initiate antipsychotic therapy (haloperidol).</p> <p>3. Hospitalize in a ward with psychiatric expertise if the patient is at risk to himself/herself or others.</p> <p>4. Increase pyridoxine to maximum daily dose (200 mg per day).</p> <p>5. Lower dose of suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising regimen.</p> <p>6. Discontinue suspected agents if this can be done without compromising regimen.</p> <p>7. Once all symptoms resolve and the patient is off cycloserine, anti-psychotic therapy can be tapered. If cycloserine is continued at a lower dose, anti-psychotic therapy may need to be continued and any attempts at tapering should be done with a psychiatrist trained in the adverse effects of second-line anti-TB drugs.</p>	<p>1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy (and discontinue upon completion of MDR-TB therapy).</p> <p>2. Previous history of psychiatric disease is not a contraindication to the use of cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment.</p> <p>3. Some patients will tolerate cycloserine with an antipsychotic drug, but this should be done in consultation with a psychiatrist as these patients will need special observation and this should only be done when there is no other alternative.</p> <p>4. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.</p> <p>5. 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.</p>
Seizures	Cs, H, fluoroquinolones	<p>1. Hold cycloserine, FQs and isoniazid pending resolution of seizures.</p> <p>2. Initiate anticonvulsant therapy in consultation with a neurologist (carbamazepine, phenytoin, or valproic acid are most commonly used).</p> <p>3. Increase pyridoxine to maximum daily dose (200 mg per day).</p>	<p>1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued.</p> <p>2. 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.</p>

		<p>4. Check serum electrolytes including potassium (K⁺), sodium (Na⁺), bicarbonate (HCO₃⁻), calcium (Ca²⁺), magnesium (Mg²⁺), chloride (Cl⁻).</p> <p>5. 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.</p> <p>6. Seek expert opinion</p>	<p>(Do not include cycloserine if an alternative drug is available).</p> <p>3. Patients with a history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy.</p> <p>5. Always check creatinine in patients with new-onset seizures. 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.</p>
Optic neuritis	E, Lzd, H,	<p>1. Stop Lzd/ ethambutol. Do not restart.</p> <p>2. Refer a patient to an ophthalmologist.</p>	<p>1. The most common drug responsible is ethambutol. Lzd can also cause ON and combination of E and Lzd enhances the risk.</p> <p>2. Usually reverses with cessation of ethambutol, LZD</p> <p>3. Improve diabetic control in diabetic patients</p>
Metallic Taste	Eto/Pto, FQs	<p>1. Encourage the patient to tolerate this side effect.</p> <p>2. Sucking hard candy or chewing gum can be helpful.</p>	<p>1. Normal taste returns when treatment is stopped.</p>
Gynecomastia	Eto/Pto	<p>1. Breast enlargement can be a troublesome side-effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported.</p> <p>2. Encourage patients to tolerate this side effect</p>	<p>1. Resolution occurs after treatment is stopped</p>

10. MONITORING AND SUPERVISION

Patients should be monitored closely for regularity of drug intake, development of ADRs and signs of treatment failure. Clinically, the most important way to monitor response to treatment is through regular history-taking, physical examination and reviewing periodical sputum and blood tests.

10.1. Monitoring and supervision during treatment

Treatment of each MDR-TB patient should be closely monitored based on the checklist available in Annexure III. The outcome of treatment depends on the intensity and quality of monitoring and supervision of treatment.

Opinion from other specialists such as endocrinologist, venereologist, psychiatrist, neurologist, dermatologist, paediatrician, obstetrician (for females of childbearing age) and nephrologists should be sought when necessary, as decided by the treating chest physician.

Table 10-1: Standard parameters for monitoring

Monitoring	Recommended Frequency
Clinical evaluation by physician	At baseline (hospital admission) and on monthly basis until conversion. Then every 2–3 months In particular, clinical monitoring for hypothyroidism if receiving Eto / prothionamide and/or PAS; monitor for hepatitis while receiving pyrazinamide
Psychological assessment by psychiatrist	If indicated at baseline and during treatment
Pregnancy test	Baseline for women of childbearing age and repeat if indicated
HIV test	At baseline, repeat if clinically indicated
Weight assessment by physician or nurse	At baseline (hospital admission), then monthly until conversion; Thereafter every 2 months
Monitoring of side effects by DOT Plus Provider	At every DOT
Sputum smear and Sputum culture	Monthly from 2nd month until conversion and every two/three months thereafter throughout treatment (on two samples each time)
Drug susceptibility testing (DST)	At baseline only for diagnosis of MDR-TB and repeat if culture is positive even after 4 months of treatment
Chest radiograph	At baseline, then every 6 months or as suggested by the treating physician
Serum creatinine	At baseline, then monthly while receiving an injectable drug
Liver functions/ Enzymes	At baseline and monthly
Blood CP/CBC	At baseline and monthly if on Lzd

Serum Electrolytes	At baseline, then monthly while receiving Bdq/Dlm or an injectable drug
Thyroid stimulating hormone (TSH)	At baseline and every 6 months if receiving Eto and/or PAS
Peripheral Neuropathy *	At baseline and monthly while on Lzd and Cs
Audiometry	Should ideally be done at baseline if Am is part of regimen and then monthly
Visual acuity	Should ideally be done at baseline and monthly while on Lzd
ECG	At baseline, after 2 weeks and monthly while on Bdq/Dlm
Blood Sugar Test	At baseline and monthly if diabetic to monitor glycaemic control

*Verbal screening for sign and symptoms, proceed to examination and apply tests if indicated and grade it

Table 10-2: Recommended schedule for monitoring (for details see above table 10.1)

Month	Clinical consultation	Weight	Smear	Culture	DST	CXR	LFT ^{\$}	CR, K ⁺	TSH	Audiometry*	HIV testing	
0 (baseline)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
1	Every two weeks	Every two weeks	✓	✓	Repeat if culture positive			✓			repeat if indicated	
2			✓	✓				✓		✓		
3			✓	✓				✓				
4	✓	✓	✓	✓				✓				
5	✓	✓	✓	✓				✓				
6	✓	✓	✓	✓		✓		✓	✓			
7	✓	✓	✓	✓				✓				
8	✓	✓	✓	✓				✓		✓		
9	✓	✓	✓	Every two months					If on injectable			If on injectable
10	✓	✓	✓									
11	✓	✓	✓									
12	✓	✓	✓			✓						
Until completion	Every two months	monthly	Monthly			6 Monthly						

^{\$} repeat if symptoms of hepatotoxicity observed

*monthly if the patient reports hearing problems

10.2. Process of sputum collection and transport

Both sputum microscopy and culture will be done at the NTRL or Regional culture laboratory during follow-up. Sputum samples are collected in sterile universal containers/bottles (two samples each time) and sent to the respective laboratories as described in Chapter 5.

10.3. Handling treatment interruptions

Person in charge of the DOT unit with support of PHI will be responsible for tracing MDR-TB patients who interrupt treatment. Every effort should be made to trace them within one day of interrupting treatment. Non-confrontational discussions with the patient (with and without the presence of the DOT provider) on the reasons why the doses have been missed should be conducted. All the missed doses must be completed in both IP and CP. The schedule for follow up will be revised accordingly. If the doses are missed often, the PMDT committee should be consulted.

10.4. Management of patients returning after treatment interruption

If the patient returns after treatment interruption, sputum will be taken for smear, culture and DST for first line drugs and wherever possible for second-line drugs and the PMDT committee will take a decision on further management based on duration of previous treatment, period of interruption and the status of sputum smear and specifically the culture.

10.5. Follow up: post-treatment monitoring

Once the patient has completed the course of treatment, the assessment has to be performed every 6 months during the next 2 years. The assessment should include the following:

- Signs and symptoms for TB
- Sputum direct smear and culture for AFB
- Body weight
- Chest X-ray

11. TREATMENT ADHERENCE

In view of the long duration of hospitalization and prolonged nature of overall treatment, special efforts may be required to ensure adherence to treatment.

11.1. Education and counselling of patients and their families

All patients and their families should receive education and counselling about DR-TB, its treatment, potential adverse drug reactions and the need for adherence with therapy. Educational interventions should commence at the time of referral for diagnosis, start of therapy and continue throughout the course of treatment. Education can be provided by the attending doctors, nurses, community health workers, and other HCWs. Materials need to be appropriate to the literacy levels of the population, culturally sensitive and available in all three languages (Sinhala, Tamil and English)

11.2. Treatment delivery settings

In PMDT projects in other countries, multiple strategies are used for the delivery of DR-TB treatment, including hospitalization, clinic-based, and community-based care. Regardless of the mode of delivery, key in the management of DR-TB is the assurance of a steady supply of medications provided to the patients free of charge through a reliable network of trained DOT providers. Care should be delivered by a multidisciplinary team of providers including physicians, nurses, and community health workers or volunteers.

11.2.1 Initial in-patient care

When a presumptive DR-TB case is confirmed to have RR/ MDR-TB, the respective DTCO who referred the patient for investigation, will be informed of the DST result by the NTRL. The DTCO will confirm the address of the patient and will arrange for the patient's referral and admission to the NHRD or designated treatment site with the DST result, duly filled PMDT referral for treatment form and a copy of the treatment card. The patient will be hospitalized initially in most cases for necessary pre-treatment evaluations. Once the PMDT site committee decides upon second-line treatment for the patient, the patient is counselled, consent obtained for treatment and hospitalization, second-line treatment card opened, an RR/MDR-TB patient identity card issued to the patient, and second-line treatment initiated. The PMDT coordinator will be informed, who will then register the patient in the second-line treatment register. During the period of hospitalization, the patient will be monitored for drug tolerance and counselled and motivated for adherence for the prolonged treatment.

11.2.2 Ambulatory care

One week prior to discharge from the hospital, the PMDT coordinator/ DTCO will inform the pharmacist of the CDS to send three-month supply to the respective DTCO who in turn will send one-month supply of drugs to the peripheral DOT provider.

At the time of discharge, the patient will be given one-week supply of drugs from the treatment site to cover for the period of travel. The patient will report to the DTCO and will be referred to the peripheral DOT provider after counselling.

For collection of the follow-up sputum samples for direct smear and culture, the patient will need to go to their respective DCC, where the DTCO will arrange for the samples to be collected and transported to the NTRL. In case the DCC is located far from the patient's residence, sputum samples will be arranged to be collected by a health worker closer to the patient's residence. The patient will need to return to the local PMDT site for the decision to end treatment, for managing severe adverse drug reactions and for any change of regimen or dosage. All referrals from the DTCO to the PMDT site or vice versa should be made on the PMDT referral for treatment form.

11.3. Adherence

Adherence to second-line therapy is made more difficult by its prolonged treatment regimens, with larger numbers of drugs that have more serious adverse effect profiles. Therefore MDR-TB patients are at risk of not being able to appropriately adhere to treatment, an essential element to prevent the amplification of resistance with the potential for community-wide spread and virtually no chance of cure for the patient. MDR-TB treatment can be successful with high overall rates of adherence when adequate support measures are provided. These measures include enablers and incentives for delivery of DOT to ensure adherence to treatment and may include the following.

- Reimbursement of travel expenses to patient and attendants for visits to DCC and NHRD
- Emotional support to patient and family
- Peer education on RR/MDR-TB treatment
- Early and effective management of adverse drug reactions
- Incentives for the non-governmental DOT providers

A support of Rs 5,000/- per month for the first 6 months of treatment through the provincial social service department has been approved. Mechanisms to ensure easy access to this facility need to be ensured by respective DTCOs in coordination with the provincial health office.

11.4. Directly observed therapy

Because RR/MDR-TB treatment is the last therapeutic chance for patients and there is a high public health consequence if MDR-TB therapy fails, it is recommended that all patients receiving second-line treatment for MDR-TB receive daily DOT wherever they are receiving the treatment be it in the community, health centres or within the hospital setting i.e. every dose of second-line treatment is to be given under DOT by an appropriate and acceptable DOT provider. DOT should be provided in a way that does not introduce undue burdens to

patients and their families. Long transportation times and distances, short clinic operation hours and difficulty in accessing services may all contribute to a decreased efficacy of DOT.

11.4.1 Who can deliver DOT for RR/MDR-TB patients?

MDR-TB patients are most likely to be hospitalized during the initial part of the IP. CP treatment should be supervised by a DOT provider daily. The DOT provider should be acceptable and accessible to the patient and accountable to the system. DOT providers should be adequately trained, supervised and supported to deliver DOT to MDR-TB patients.

11.4.2 Maintaining confidentiality

The HCWs should explore the need of the patient to maintain strict confidentiality of the disease. In some cases, this may entail working out a system where the patient can receive medication without the knowledge of others.

11.5. Digital Technologies for Medication Adherence

Three digital solutions for medication adherence are supported with evidence to be used as per recommendation by the WHO. These include short messaging services (SMS), event monitoring device for medication support (EMM) and video-supported treatment for TB (VOT).

NPTCCD has recently initiated implementation of an SMS campaign aimed at promoting awareness on TB among medical officers and improving adherence to treatment in TB patients. This will be integrated with the ePIMS and automated SMS notifications will be sent to both DS and DR-TB patients and their DOT providers regularly and also at treatment interruptions.

In addition, NPTCCD has planned to explore the possibility of using smart medication containers (an EMM) and as a pilot and will be introduced to DR-TB patients and at-risk (for interruption) patients in selected settings. These devices enable automatic logs and notifications to the healthcare provider when treatment is interrupted. Moreover, NPTCCD will also consider using Video based DOT platform for RR/MDR TB patients.

11.6. Socio-economic interventions

Socio-economic problems should, as far as possible, be addressed to enable patients and their families to adhere to the MDR-TB treatment. In many settings, these problems have been successfully tackled through the provision of “incentives” and “enablers” for the patients. Enablers refer to goods or services that make it easier for patients to adhere to treatment. Incentives refer to goods or services that are used to encourage patients to adhere to therapy. The programme will also engage with appropriate NGOs/agencies to aid in providing appropriate socioeconomic interventions.

11.7. Social and emotional support

Having MDR-TB can be an emotionally devastating experience for patients and their families; there may be stigma attached to the disease and this may interfere with adherence to therapy.

In addition, the long nature of MDR-TB therapy combined with the adverse effects of medications may contribute to depression, anxiety and further difficulty with treatment adherence. The provision of emotional support to patients may improve chances of adhering with therapy. This support may be provided formally in the form of support groups or one-on-one counselling with trained providers. Informal support can also be provided by physicians, nurses, community workers or volunteers, and family members.

11.8. Nutrition support for MDR-TB patients

Drug-resistant TB treatment (as with all TB treatment) and care should contain integrated nutritional assessment counselling and support for the duration of the illness. Without nutritional support, patients can become enmeshed in a vicious cycle of malnutrition and disease. The second-line anti-TB medications can also further decrease appetite, making adequate nutrition a greater challenge. Providing free food probably does improve weight gain during treatment, and is thought to improve quality of life but further research is necessary.

While being admitted to a hospital, a high protein diet is arranged through the hospital services. In addition, a government funded nutrition supplementary programme, Thripasha scheme is also in place which is also expected to help treatment adherence.

11.9. Follow-up of the non-adherent patient

When a patient fails to attend a DOT appointment, a system should be in place that allows prompt patient retrieval. The DOT provider should contact the patient on the same day to find out why the patient has not appeared for the DOT and ensure that treatment is resumed promptly and effectively. The situation should be addressed in a sympathetic, friendly, and non-judgmental manner. Every effort should be made to listen to reasons for why the patient missed a dose(s) and to work with the patient and family to ensure treatment continuation.

11.10. Early and effective management of adverse drug reactions

Although rarely severe, the adverse effects of second-line anti-TB drugs can be highly debilitating for patients. Patients experiencing higher rates of adverse drug reactions may be at increased risk of non-adherence. Therefore, early and effective management of adverse drug reactions should be part of adherence-promotion strategies in the management of MDR-TB. In most cases, management of the adverse effects can be accomplished using relatively simple and low cost interventions without compromising the integrity of the MDR-TB treatment regimen in line with aDSM guidelines.

11.11. Death audit

The DTCOs should conduct an in-depth audit of all the deaths of MDR-TB patients occurring prior to initiation of treatment or during treatment. This would be beneficial in understanding the causes leading to the deaths and guide the programme in taking appropriate action to prevent them in future. The results of the death audit would be discussed by the PMDT site

committee as well as the central PMDT committee to improve management of other patients and prevent deaths, wherever possible.

11.12. Adherence promotion strategies for second-line treatment

- Directly observed therapy
- Social and financial support
- Effective management of adverse drug reactions

12. INFECTION CONTROL IN CONTEXT OF DR-TB

Transmission of TB is a recognized risk in health care facilities and communities, especially in resource-limited settings where transmission is facilitated by inadequate TB infection control measures. TB infection control has three components. By order of importance, they are as follows: administrative controls, environmental controls and personal respiratory protection.

12.1. Components of infection control

Administrative, environmental and personal infection control measures will be taken to minimize the transmission of MDR-TB. Currently available infection control measures for susceptible TB will be strengthened.

12.1.1 Administrative controls

The administrative controls include policies and procedures intended to promptly identify and treat infectious cases so that additional precautions can be taken. Important aspects of administrative control measures are;

1. Triage of people with TB signs and symptoms, or with TB disease,
 - Promptly identify people with TB symptoms or confirmed TB cases
 - Separate from other patients
 - Place in an adequately ventilated area. As far as possible the waiting areas for patients with chest symptoms should have adequate natural ventilation. Access to the consultation rooms will be from open space rather than closed corridors
 - Be diagnosed as a matter of priority (i.e., fast tracked)
2. Respiratory separation / isolation of people with presumed or known infectious TB or RR/MDR TB (especially smear-positive cases) from other patients
 - Identify infectious patients after triage
 - People with infectious TB should be seen at times or in places away from other people
 - Separate PLHIV and immune -compromised patients from presumptive or confirmed TB patients
 - Patients with drug resistance especially MDR and XDR should be separated and isolated

3. Prompt initiation of effective TB treatment of people with TB disease
 - Initiate treatment as soon as possible for bacteriologically or clinically diagnosed patients
4. Ensure measures to minimize the spread of droplet nuclei by educating patients and the families on cough etiquette and respiratory hygiene
 - Minimize the number and duration of visit to outpatient department while they are still infectious.
 - Advice to cover mouth and nose with a tissue when coughing or sneezing; If a tissue is not available, cough or sneeze into your upper sleeve.
 - To use nearest waste receptacle to dispose of the tissue after use.
 - Perform hand hygiene (e.g., hand washing with non-antimicrobial soap and water, alcohol-based hand rub, or antiseptic hand wash) after having contact with respiratory secretions and contaminated objects/materials.
 - When infectious patients are moving through areas, surgical mask may be useful.

12.1.2 Environmental controls

Installation of ventilation systems reduces the number of infectious particles in the air. High efficiency particulate air filtration and ultraviolet germicidal irradiation should be considered when MDR tuberculosis is being treated.

In warm climates, infection control can be assured most effectively by strong natural ventilation (i.e. open windows in opposite walls for presumptive or confirmed TB cases). Natural ventilation is cost effective but depends on climatic conditions.

Design of rooms, patient waiting areas and airflow needs should be considered before building construction for patients in TB health care settings.

12.1.3 Personal respiratory protection (special masks N95)

In addition, when administrative and environmental controls cannot provide complete protection, the third line of defence against nosocomial TB transmission is the use of masks. Because they are visible and relatively expensive, health workers assume that supplying personal masks alone will prevent TB transmission. However, they cannot be worn continuously and are likely not to be in use when unsuspected TB cases or unsuspected MDR-TB is encountered. Staff protection can be assured only by masks with a high-efficiency air-intake filter and fitting tightly around the face so that no air can come in from besides the mask.

Patients will also wear personal masks to minimize dispersal of bacilli when they talk, cough, yawn or sneeze. These can be simple surgical masks; they will retain the droplets expelled by the patient effectively.

Personal respiratory protection

- a. Ensuring the use of particulate respirators (e.g., N85 masks, FFP2) by staff.
- b. Surgical masks to the patients

In case a patient is being treated for RR/ MDR-TB in the private sector or a health facility outside the public health system, all the infection control practices as listed above will be valid as well. The private sector hospitals will ensure proper triage of all chest symptomatic and referral of those like to have TB/MDR-TB when TB management facilities are not available within the health facility.

12.2. Essential actions for effective TB infection control safety without stigma

12.2.1 Include patients and community in advocacy campaigns

The community should be well-educated about TB infection, prevention, and control. Patients should understand that they should know their TB status and have a right to rapid TB diagnosis and treatment. They should know that TB can be spread by coughing and expect health care settings and community services to require persons coughing to cover their mouths when coughing. They should understand that HCWs may wear personal respiratory protection sometimes or that they may be asked to wear a mask to protect others. Safety without stigma should be the goal--a request to wear a mask or provide sputum outside, or in a well-ventilated room should not be stigmatizing but is part of a safer clinic for everyone.

12.2.2 Develop an infection control plan

All facilities should have an infection control (IC) plan, facilities and a person or a team responsible for IC.

12.2.3 Ensure safe sputum collection

Collecting and processing sputum are an essential part of the diagnosis of TB. Sputum collection can be potentially hazardous for HCWs and other patients. HCWs should explain to patients that safety without stigma is the goal of good TB infection control and that sputum be collected outside. However, the cabins located outside should also have sufficient ventilation and air-change to ensure no cross infection between people sequentially using the cabin for sputum collection.

12.2.4 Promote cough etiquette and cough hygiene

Every facility should have a poster on TB infection control and cough etiquette in at least the outpatient department waiting area, admissions area, and casualty department. Patients

should be instructed to cover their mouths and nose when coughing, with a bended forearm (near elbow), cloth such as handkerchief or clean rag, paper tissues, or paper masks.

12.2.5 Triage TB suspects for "fast-track" or separation

All patients should be screened upon arrival for chronic cough (i.e., >2 weeks), fever, weight loss, night sweats, haemoptysis, or contact with a person with TB. Persons likely to have TB should be "fast-tracked" for rapid diagnosis and care services or should be asked to wait near an open window or in a comfortable area separate from the general waiting room (outside when possible). Community-based treatment models should be encouraged. Patients with known or suspected drug-resistant TB should be separated from general ward patients and from other TB suspects.

12.2.6 Assure early diagnosis and initiation of treatment

Patients likely to have TB should move to the front of the queue for all services and should undergo prompt evaluation for TB. All presumptive TB patients are subjected to CXR and Sputum examination (Microscopy and/or Xpert). Sputum collection should be done away from other people. Sputum specimens are sent to a quality-assured laboratory for AFB smear and /or Xpert. Anti TB treatment begins immediately when a diagnosis of TB is made.

12.2.7 Improve room air ventilation

Patient waiting areas should be open and well-ventilated. Windows and doors should remain open when possible, to maximize cross ventilation. Appropriately placed simple fans can assist ventilation. Where weather permits, using open-air shelters with a roof to protect patients from sun and rain are recommended. Patients should not wait for services in narrow, poorly ventilated corridors. Hospitals where patients with drug-resistant TB receive care should provide separate patient wards or rooms with good ventilation. Wall mounted fans or pedestal fans to promote unidirectional air flow should be preferred over ceiling fans which tend to mix the air within the room.

12.2.8 Protect HCWs

HCWs should know the symptoms of TB and should be regularly screened for TB and collect data in the healthcare worker register. Personal protective equipment (PPE) should be available at all places managing TB/ DR-TB cases. The health workers should receive training and regular orientation on proper usage of PPE.

12.2.9 Capacity building

Training on TB infection control practices should be incorporated into the broader infection control training at hospitals and facilities (e.g., hand washing, other respiratory and blood-borne infection control training).

12.2.10 Monitor infection control practices

Infection control committees should be established at all DCCs and the functioning of these should be monitored at central level. Supervision of infection control practices should be a part of every supervisory visit using the available check lists. On-site measures include examining medical records of a sample of TB patients, looking at the time interval from admission/first visit to suspicion of TB, suspicion of TB to ordering sputum for AFB, time from ordering to collection of sputum, collection of sputum to reporting of results/initiation of TB treatment and interviewing patients to discuss understanding of infection control, safety and stigma.

13. TRAINING ON DR TB MANAGEMENT

The training courses targets all health categories and non-health staff involved in DR TB management. The training programme will be coordinated and delivered by staff from NTP central office.

The full curricula of the training course on DR TB control include the following topics:

- DR TB –Definitions, case registration, bacteriology, and treatment outcomes
- Specific case finding strategies
- Laboratory services for essential laboratory examinations for DR TB
- Treatment strategies of DR TB
- Treatment of drug resistant tuberculosis in special situations
- HIV infection and DR TB
- Monitoring of treatment
- Management of adverse events
- Treatment adherence, missing doses and defaulter tracing
- Counselling
- Management of patients after DR TB treatment failure
- Management of contacts of DR TB patients.
- Recording and reporting systems

However, depending on the health category to be trained the course has to focus mainly on the related tasks to be accomplished by the staff under training as described below.

13.1. Training of staff at DCC

- PMDT guidelines
- Identification of presumptive DR TB cases as defined in the guidelines.
- Check on the possible reasons for non- conversion. E.g., poor compliance
- Schedule for follow up
- Procedure of sputum specimen collection and transportation to the appropriate laboratory with facilities to do culture and or molecular diagnostics, where Gene Xpert, LPA, culture for mycobacteria and drug susceptibility testing will be done.
- Filling of the request form for bacteriological examination in the special request form
- Tracing of patients reported to have RR or MDR TB
- Counselling patient and family.
- Discuss options of inward care and ambulatory care during intensive phase
- Arranging DOT for the full period of treatment and monitoring to detect and treat adverse drug reactions early
- Periodic assessment of patients on treatment as per guideline.
- Infection control measures

- Recording and reporting for PMDT.

13.2. Training of laboratory staff

13.2.1 laboratory technicians at the microscopy centres

- Collecting three sputum specimens of good quality in wide mouth, transparent, clean container for smear microscopy
- Educating patients on sputum collection, disposal, and respiratory hygiene

13.2.2 Laboratory staff of central laboratory

- Procedure of receiving sputum specimens
- Maintaining the register of presumptive MDR TB cases
- Handling and processing of specimens for molecular testing, culture, and DST, done at the NTRL.
- Reading results of the above tests
- Recording and reporting to the respective DCC
- Maintaining of the laboratory register for PMDT
- Schedule for follow up
- Quality assurance of culture and DST with SNRL
- Newer diagnostics
- Infection control and biosafety measures

13.3. Training for basic health staff

On the job training has to be regularly done by the DTCO and CRP of the DCCs. They are also responsible for the training of newly recruited health staff.

14. RESEARCH PRIORITIES FOR DRUG RESISTANT-TB

A rapid scaling up for an effective DR-TB management program entails implementation of effective and efficient strategies based on sound scientific evidence emphasizing the vital contribution of research.

The various types of research required to address priority areas related to DR-TB include and are not limited to fundamental, clinical, epidemiological, qualitative, and operational approaches with the common aim of producing results that are generalizable and aid in evidence-based decision making. Certain research topics and questions may be addressed from the systematic evaluation of routine collection of data from a well-established, rigorous recording and reporting system of the DR-TB program which could provide a platform for epidemiological and operational research.

The potential and relevant areas of research can be discussed under the following key priority areas most important to aid and expedite the scale-up of the programmatic management of drug resistant TB with subsequent maximization of constructive public health impact.

14.1. Diagnostic aspects

A tremendous laboratory support is essential, the lack thereof which compromises clinical management of patients, demonstrating the importance of research related to diagnostic aspects. Priority areas include:

1. Standardization of DST for 2nd line drugs.
2. Piloting of Xpert MTB/RIF as an initial investigation for all presumptive TB patients to enhance early RR detection: operability, feasibility, effectiveness, and efficiency
3. Extent of practise of Universal DST to enable RR detection
4. Use of Xpert MTB/XDR assay to detect resistance to isoniazid and second line drugs (fluoroquinolones and amikacin)

14.2. Treatment aspects

Documentation of MDR-TB burden and suboptimal treatment outcomes necessitates the need for research in this area. Priority areas include:

1. Modified oral shorter regimen: patient's response and effectiveness.
2. BPaL regimen for treatment of FQ resistance.
3. Effectiveness of standardized and individual regimens in adults and children.
4. DR-TB in special population (children, pregnant/breast feeding women, HIV co-infected patients, diabetics, etc).
5. Identification of surrogate markers for failure or relapse.
6. Cost effectiveness of various treatment approaches.

14.3. Programmatic aspects

Routine data informing operational experiences from the national program would provide operational guidance for scale up and implementation of MDR-TB treatment. The priority areas include:

1. Algorithms to select patients eligible for DST and 2d-line treatment in different settings, including special strategies for high-risk groups and use of rapid resistance testing methods.
2. Strategies for provision of 2nd-line treatment in different settings, including adherence and use of incentives and enablers.
3. Effectiveness of existing infection control measures and strategies for selecting and implementing infection control measures (for communities, households, and healthcare settings)
4. Human resource needs in the context of increased DR-TB treatment at all levels (specific to ambulatory or hospital settings), including training and continuing education
5. Evaluate existing laboratory capacity and strategies for rapid capacity building
6. Strategies to increase participation of private sector
7. Modelling the impact of various strategies in a given setting: type of treatment, timing of treatment introduction, infection control, and resistance pattern at initiation.

14.4. Epidemiological aspects

The coexistence and interaction of several risk factors, limited availability and quality of drug resistance data and limited quality of routine TB statistics necessitates to complement routine monitoring and evaluation activities with targeted research to obtain reliable data. Priority areas include:

1. Incidence, prevalence and mortality of drug resistant TB
2. Risk factors that promote drug resistance: type and quality of first line treatment, infection control practices, composition and referral to retreatment regimens, drug quality, M. Tuberculosis genotype, HIV prevalence, level of drug compliance

14.5. Other research areas

1. Management of drug resistant TB in special conditions and situations: children, HIV co-infected patients, substance abusers, pregnant women, prisoners, elderly patients, patients with low body mass index.
2. HIV infection and DR-TB: Interaction with HIV in acquisition of resistance, interaction between 2nd-line drugs and antiretroviral drug treatment, timing of antiretroviral drug treatment in drug-resistant TB patients
3. Adverse effects: Prevalence of adverse effects, most (cost-) effective protocols for management of adverse effects
4. Treatment delivery and adherence: factors promoting adherence

5. TB management in the context of Covid-19: in patients with past or concurrent TB, disease profile and outcomes of Covid-19 in this sub population,
6. Use of digital technologies in prevention and delivery of TB care services, especially during the Covid-19 pandemic.

15. SUPPLY CHAIN MANAGEMENT OF SECOND LINE ANTI TB DRUGS

Uninterrupted supply of high quality second line anti-TB drugs in adequate quantities is essential for successful management of drug resistant TB. At present, Sri Lanka procures second line anti TB drugs from Global Drug Facility via rGLC mechanism.

The drug Supply Chain Management cycle consists of four major components i. e. Selection, Procurement, Distribution and Use.

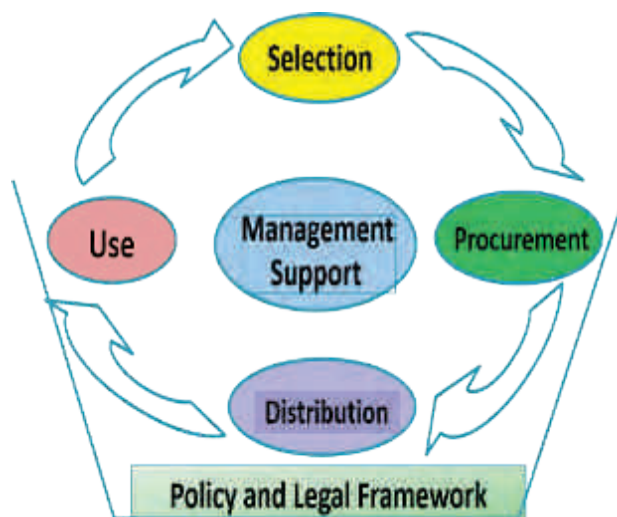


Figure 15-1: Drug Management Cycle

Selection of all second line anti-TB drugs for estimations and procurement is based on the standard regimens as indicated in guidelines of the Programmatic Management of Drug Resistant TB. The estimation of annual national requirements of drugs are carried out using the most recently updated version of WHO recommended software tool - Quan-TB (at present version 4.2 is used) by the Chief Pharmacist (CP) of the Central Drug store (CDS). The following information is required for drug estimations.

- Number of RR/MDR TB patients on treatment per year
- Treatment regimen adopted
- Stage of treatment (intensive phase/ continuation phase)
- Age of patients
- Annual increase adjustment of number of cases
- Buffer stock required
- Stock needed up to the lead time (reference date- date of calculation of last available stock until delivery of calculated new stocks)
- Stock ordered and pending delivery
- Stock in hand at the time of drug estimation

In addition, the requirement of pyridoxine 50 mg is added to the selected regimen assuming the average weight of a patient as 50kg -75 kg.

The PMDT coordinator provides required patient details and patient estimates based on the decisions taken at the central PMDT committee meeting to CP/CDS to facilitate the quantification.

Once quantification is finalized, online orders will be placed to Stop TB partnership/ GDF. Initiation of the procurement process by the GDF will happen after acceptance of the order by the GDF and fund transaction.

GDF requires at least 6 to 8 months lead time for the supply of drugs following placing an order.

Anti-TB drugs are usually transported by air. Once the consignment arrives at the airport it should be cleared within three days. The Medical Supplies Division (MSD) of the Ministry of Health is responsible for clearance of the consignments and their delivery to the CDS of NPTCCD.

Central Drug Stores is responsible for distribution of second line drugs to the National Hospital for Respiratory Diseases (NHRD) and to DCCs. Currently, the management of intensive phase of RR/MDR TB patients is carried out only at MDR TB ward in the NHRD, Welisara. When a patient is to be initiated on MDR-TB treatment, the PMDT coordinator will inform the pharmacist at the CDS to send second-line drugs to the central PMDT site (NHRD). Chief Pharmacist of NHRD is responsible for issuing drugs to the MDR TB Ward based on the weekly consumption.

Drugs for the management of the continuation phase are delivered to the respective District Chest Clinics. One week prior to discharge from the hospital, the PMDT coordinator will inform the Chief pharmacist of the Central Drug Stores to send a three-month supply to the respective DTCO.

At the time of discharge, the patient will be given one-week supply of drugs from the central PMDT site to cover for the period of travel.

Once the patient reports to the respective DTCO, he/she will be counselled and assigned to a reliable DOT provider agreed upon by the patient. Two weeks supply of drugs will be provided to the DOT provider following training.

Any unused drug for a patient at the periphery as a consequence of death/loss to follow-up will be returned to the DTCO. The DTCO will take the decision of returning the drugs to the Central Drug Stores or use the same for another RR/MDR-TB patient in his district based on the available shelf life of the remaining drugs after discussing with the PMDT coordinator and CP of CDS.

Annual requirement of XDR-TB, drugs will be estimated based on the decision taken at the PMDT central committee.

15.1. Storage of second line drugs

Harbour/ Airport warehouses

Once second line anti-TB drugs are imported to the country they are stored at the warehouses in the harbour or airport. Ideal storage condition is below 25° C.

Central Drug Stores/ Main stores at NHRD

All the second line anti-TB drugs are stored adhering to manufacturing instructions which is usually below 25°C in a clean, disinfected dry, well-ventilated storeroom out of direct sunlight. Drugs are stored in such a way separate 'lots' of drugs with separate dates of manufacture and expiry are clearly segregated and stored and drug 'lots' with the most recent expiry are issued first.

RR/MDR TB Ward / NHRD

One week's requirement of drugs for inward patients are stored in a drug storing cupboard in the ward. Separate containers are used for each patient and drugs are stored out of the direct sunlight and in an air-conditioned room ideally below 25°C. Nursing Officer in Charge of the Ward is responsible for supply chain management of the second line drugs.

District Chest Clinics

Quarterly requirements of second line drugs needed for the continuation phase for patients followed up at DCC should be maintained and stored under similar conditions as that of CDS. When issuing drugs to the outdoor dispensary of the DCC, only the daily requirement should be provided. Pharmacist of the DCC is responsible for drug supply and management, of the second line drugs.

Storage during transportation

During transportation drugs should be stored in such a way that they are not exposed to direct sunlight, or moisture. They should be kept below 25°C if the distance is too long.

15.2. Quality & Safety

Global Drug Facility provides WHO pre-qualified second line anti TB drugs. In addition, the GDF performs a series of quality checks throughout the production process, and up to the dispatch to recipient countries from the airport or seaport. Therefore, the quality of drugs until they are received by the CDS is assured.

If any potential quality failures such as breakages, damages, crusher, colour changes etc. are observed by DCC staff or any other user, they should be promptly reported to the CDS and samples should be sent to the National Medicines Quality Assurance Laboratory (NMQAL) for quality assurance tests.

Until quality assurance reports are available, the batch of the drug stock in question should be withheld after consultation of the CP of the CDS.

16. ROLE OF NGOs AND CSOs

While the national programme will make all efforts to provide a comprehensive set of patient centred services for all MDR-TB patients in need, it is possible that delivery of some of the planned services may be challenged by limitations in infrastructure and resources within the health system.

To overcome these challenges, the programme will actively seek the cooperation of all non-governmental organisations (NGOs) and civil society organisations (CSOs) that have a proven track record of working in TB care or another related health field. The envisaged role of NGOs and CSOs in PMDT is:

- Psychosocial support including counselling – The programme has elaborate plans to organise counselling support for all RR/MDR-TB patients. However, these patients need additional support from the NGOs and CSOs to integrate back into the community by reduction of stigma. Counselling of patients through peer groups, family members and community around the patients can effectively be carried out by people working at grass root level. Counselling support will also become important in case of treatment interruption where the community organisations can support patients in overcoming barriers to treatment adherence.
- Mobilising economic support – The treatment of MDR TB patients is prolonged and their earning capacity is diminished due to disease status. The financial support provided by the department of social services varies from Rs 500 to 5000 per month and is limited only for the first six months of treatment. Patients also may face procedural challenges to access these funds. Therefore, some patients may need additional economic support during the period of treatment. The NGOs and CSOs can provide support to the patients by coordinating with responsible officers for easy access to available money. These organisations can help patients and their families to uplift their economic status by introducing micro financial projects, self-employment etc.
- Rehabilitation services – Many of the patients on MDR-TB treatment lose jobs or face reduced earnings. Such patients will need support to enter a similar job or develop new skills to start earning again. NGOs can coordinate with the employers to advocate for jobs where possible. They can also organise skill development workshops for such patients along with other members of the society that can help them tide over any financial crisis that they may face because of the disease.
- Domestic fund mobilisation with targeted advocacy – Some of the NGOs working in the country have a good history of contributing to the national programme by mobilising domestic resources and providing support for infrastructure renovation. This would

specifically be helpful for expansion of PMDT services in the management of MDR-TB patients at the peripheries.

- Advocacy/ awareness campaigns - The NGO and CSO which have members with technical background can support NTP or collaborate with other agencies in organising awareness campaigns for various associations so as to sensitise them to needs for screening drug resistance as well as proper treatment of TB as well as DR-TB.
- It is also pertinent that when all treatment options for DR TB patients are exhausted then a week knit palliative care system should be in place.

In addition, participation of NGO / CBO as members of the PMDT committees at central and district level is essential to provide operational inputs for making the services more accessible and convenient for the patients.

17. RECORDING AND REPORTING

This chapter describes the information system related to diagnosis and management of drug resistant TB cases, developed with the objective of recording and reporting of information needed to individual case management and monitoring programme performance.

The aims of the information system are twofold:

1. To aid staff of treatment units in providing optimum management for individual patients with drug-resistant TB.
2. To allow managers of TB programmes at different levels to monitor overall programme performance of drug-resistant TB control programmes and provide the basis for programme and policy developments.

17.1. Scope of the information system

The information system for treatment of DR-TB is based upon, and is an extension of, the main TB information system. The forms have therefore been designed to be as similar as possible to the standard forms used in TB programmes.

All recording and reporting systems are designed as per the WHO guidelines. A separate module in the electronic Patient Information Management System (ePIMS) has been developed and implemented on drug-resistant TB.

The information system is used to record information from initial investigation of a presumptive DR-TB patient through diagnosis, treatment, follow-up till an outcome is assigned. Further, the system also includes aggregate reports related to case finding, treatment progress and outcome of DR-TB patients.

17.2. Description of the recording and reporting formats

Separate formats are developed for recording and reporting. (See Annexes I-a to k). Below section outlines these formats.

17.2.1 Request form for TB culture, drug susceptibility and molecular testing – TB 06 (Annexure I-a)

This form has to be used when bacteriological examination (Culture, DST and GeneXpert) is requested. Form needs to be filled and sent with the sample to NTRL or the relevant laboratory.

17.2.2 Presumptive DR-TB Register (Annexure I-b)

This register has to be maintained at the DCC. All the presumptive DR-TB cases identified are entered in the register with the requested investigations. Once results are received, they are entered in the register and appropriate action needs to be taken.

17.2.3 PMDT referral for treatment (Annexure I-c)

This form is to be filled by the respective DCC referring the patient, sent to the DR-TB treatment centre.

17.2.4 PMDT Back-Referral for treatment and follow up Second-line Treatment Card (Annexure I-d)

This form is filled by the PMDT treatment site when referring a DR-TB patient back to the district after sputum conversion for further treatment and follow-up. The form contains the details of second-line treatment received by the patient at the PMDT site and other significant clinical details.

17.2.5 DR-TB Treatment Card (Annexure I-e)

This card is a key instrument for health staff who administer drugs to patients on a daily basis. When a decision is taken to initiate second-line treatment, a DR-TB Treatment Card is filled up by the Medical Officer of the treatment unit. The card has to be filled up completely since it is the primary source of information from which the second-line treatment register is periodically updated.

The original DR-TB Treatment Card will be retained by the PMDT coordinator and duplicate cards sent to the respective DTCO both by post and through the patient.

The card contains the following sections:

Page 1 of the Treatment Card:

- **Basic demographic information.** Name, sex, age, address.
- **DR-TB Registration Number.** This is a unique patient identification number assigned when registering a patient for DR-TB treatment. Previous district TB registration number can be recorded in the appropriate column.
- **The registration group of patients according to previous treatment:** The relevant registration group will be entered in the relevant space.
- **Drug Regimen**
- **Adverse Drug Reactions**
- **Treatment outcome**

Page 2 of the Treatment Card:

- **Monitoring of smear and culture:** Record the date, sample number and result of the monitoring smears and culture examinations. The smear and culture date that led to the patient being registered as second-line treatment case should also be recorded and this is recorded as 'prior registration'. Requirements for monitoring by smear and culture are described in Chapter 10.

- **DST:** Record the date and results of all DST performed on the treatment card.

Page 3 of the treatment card:

- **Record of daily observed administration of drugs:** One line per month which makes it easy to assess adherence. One box is checked for each day the treatment is administered.

17.2.6 DR-TB treatment register (Annexure I-f)

The register is filled by the DTCO/ PMDT coordinator when a patient is diagnosed and referred for DR-TB treatment. All patients with a positive laboratory confirmation for RR/MDR-TB are entered in the register and information such as smear, molecular test and culture results have to be updated on a monthly basis during the regular assessment of patients and treatment outcomes at the end of the treatment.

The second-line treatment register contains the following information:

- Date of registration
- RR/MDR-TB number
- Name/sex/age/address
- Treatment unit/ DOT centre
 - Site of the disease (PTB or EPTB; record as pulmonary if a patient has both)
 - Patient category (Registration group: new, relapse, after lost to follow up, after failure of first treatment, after failure of re-treatment, transfer in or other)
 - Date of DST and result (patients may have more than one DST: enter the DST that resulted in the patient being registered as MDR-TB patient). Date should be the date sample collected for culture and DST
 - Treatment regimen (date of treatment started and regimen used)
- Date of bacteriological examinations and results
- Treatment outcome
- Whether HIV testing is done, if yes, results.
- Comments: Information related to side effects, non-adherence and retrieval action taken etc. should be recorded in this section

17.2.7 DR-TB patient identity card (Annexure I-g)

This card includes all the general information related to the DR-TB patient, such as name and address, disease classification, type of patient and treatment category. The DTCO has to record on the back side of this card the date of the next appointment at the DCC and at the PMDT site when indicated. This card has to be kept with the patient.

17.2.8 Quarterly report on DR-TB case finding (Annexure I-h)

This report will be generated by the PMDT coordinator using information from the laboratory register and the second-line treatment register. This form is designed to report the number of presumptive DR-TB cases whose sputa were collected and received by the NTRL for bacteriological examination in the particular quarter. Suspects whose samples were collected but were not received by the NTRL due to various reasons (e.g., delay in transportation etc.) should not be included. Number of presumptive DR-TB cases tested, RR/MDR-TB cases diagnosed and initiated on treatment in the particular quarter (on the basis of the bacteriological results reported in the laboratory register) are recorded in block 1. The various subtypes of these will be recorded in block 2. The case finding report will be filled and submitted in the month following the end of the quarter e.g., report of the first quarter of 2021 will be filled and submitted in April 2021. The PMDT coordinator is responsible for submission of the report in a timely manner.

17.2.9 Quarterly report on the culture results of DR-TB patients registered 6-9 months earlier (Annexure I-i)

Each quarterly cohort defined by the date of the start of second-line treatment registration should have an interim or preliminary report after 6 months of initiation of treatment. This report should be developed by the PMDT coordinator based on the second-line treatment register. Since reporting at the end of treatment is very late (after two or even three years), preliminary results are desirable for all cohorts. The six-month interim report will be prepared 9 months past the closing date of the first quarter of a given cohort. Reporting at 9 months past the closing date, allows culture information for the first 6 months of treatment to be included for all patients reported in the respective cohort. For example, TB patients registered during the first quarter of 2021 should have the preliminary six month interim report filled out in January 2022. The number of patients who have negative smears or cultures at months 4, 5, and 6 (with at least two specimens collected for both smear and culture) gives an early estimate of the number of patients who are likely to be cured.

17.2.10 Quarterly report on the culture results of DR-TB patients registered 12-15months earlier (Annexure I-j)

Each quarterly cohort defined by the date of the start of second-line treatment should have a culture conversion report submitted after 12 months of treatment. This report should be developed by the PMDT coordinator, and the respective site committee based on the second-line treatment register. Since reporting at the end of treatment is very late (after two or even three years), preliminary results are desirable for all cohorts. The conversion results will be reported 15 months past the closing date of the notified cohort reported on.

Reporting at 15 months past the closing date, allows culture information for the first 12 months of treatment to be included for all patients reported in the cohort. For example, RR/

MDR-TB patients registered during the first quarter of 2021 should have the Culture Conversion Report filled out in July 2022.

17.2.11 Quarterly Report on treatment success of Second line Treatment (Annexure I-k)

This report is prepared by the PMDT coordinator. It shows the final result of treatment by year of treatment start. It is first completed 24 months after the last patient in the cohort started treatment. Most patients will have completed treatment by 24 months. Since a few patients may be on treatment for longer than 24 months, the form should be completed again at 36 months which will then be considered as the final report.

17.3. DR-TB Module in the electronic Patient Information Management System (ePIMS)

The DR-TB module of ePIMS is designed to capture individual patient information of diagnosed patients with drug resistant TB. Once a patient is diagnosed with DR-TB, the patient is registered in this system and the DR-TB registration number is issued automatically.

The module contains the following components.

1. DR-TB Patient registration: Captures demographic data, past TB history, co-morbidities, allergies, past medical and surgical history, social history and details related to initial diagnosis.
2. DR-TB Patient investigations: Captures investigation results done at initial and follow-up visits.
3. DR-TB Patient Treatment: Captures treatment details including drug regime, treatment centre and adverse effects.
4. DR-TB Patient post-treatment evaluation: Captures data related to evaluation after completion of treatment.
5. DR-TB Patient contact tracing: Captures data of all contacts of the DR-TB patient.
6. DR-TB Patient Site committee review: Captures the site committee decisions on management of the DR-TB patient.

Patient information is initially captured at the PMDT site where the patient is treated and follow up information is then captured at the DCC where the patient is followed up after completion of treatment. The module also facilitates preparation of DR-TB aggregate reports for programme management.

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ANNEXURE

Annexure I:	Formats of recording and reporting system
Annexure II:	Roles of various facilities and key staff under PMDT
Annexure III:	Check list for monitoring of patients being treated with second-line anti TB drugs
Annexure IV:	Instructions for collection & transport of specimens for TB culture and Xpert MTB/Rif test

Annexure I: Formats of recording and reporting system

- a. Request Form for TB Culture, Drug Susceptibility and Molecular Testing
- b. Presumptive DR-TB Register (Annexure I-b)
- c. DR-TB Referral for Treatment
- d. DR-TB Back-Referral for treatment and follow up Second-line Treatment Card
- e. DR-TB Treatment Card
- f. DR-TB Treatment Register
- g. DR-TB Patient Identity Card
- h. Quarterly Report on DR-TB Case Finding
- i. Quarterly report on the culture results of DR-TB patients registered 6-9 months earlier
- j. Quarterly report on the culture results of DR-TB patients registered 12-15months earlier
- k. Quarterly Report on treatment success of Second line Treatment

Annexure I-a: Request Form for TB Culture, Drug Susceptibility and Molecular Testing

National Programme for Tuberculosis Control and Chest Diseases

TB 06

REQUEST FORM TB CULTURE, DRUG SUSCEPTIBILITY AND MOLECULAR TESTING National TB Reference Laboratory, Welisara

Specimen		Date of Collection			Lab Use Only		Serial No	
Sputum	Other (Specify)	dd	mm	yy	Date of Receipt		Lab No.	
					dd	mm	yy	Culture
								DST

Last Name of the Patient (In Block Letters)

--	--	--	--	--	--	--	--	--	--	--	--

First Name/Initials of the Patient (In Block Letters)

--	--	--	--	--	--	--	--	--	--	--	--

Date of Birth	
yyyy	mm dd
Sex	M F

Contact Number	NIC/ID of Patient/Parent/Guardian	Patients Address:	Residential District:

Name of Sending Institution	Ward/Clinic	BHT/Clinic No	Forwarding DCC	Standard Card No.	District TB NO	Report to be Sent to

CXR	Not Done	Done			GeneXpert	Not Done	Done*						
		Changes present	No Changes	Report pending			MTB				RR		
							ND	H	M	L	VL	D	I

Test/s Requested		Indication		
Culture & DST	GeneXpert (MTB/RIF)	For Diagnosis	Follow-up (Indicate month M1/M2/M3**)	Other (Specify)

Probable Site	PTB	Smear +	EPTB	If EPTB, Site/s
		Smear -		

Treatment History	New	Previously Treated						
		Relapse	Failure	Loss to Follow Up	History Unknown	Other (Specify)	Known MDR	Known MOTT

Details of Treatment (Indicate drugs and duration)

Past ATT (Indicate periods of treatment)	Drugs/Regime	Duration
Present ATT (on date of specimen collection)	Not on ATT / On ATT (indicate regime)	Starting date

Current Sputum Smear Status of Follow Up Patients	
Positive	Negative

Does the patient belong to a Presumptive MDR group?	
Yes	No

*ND: Not Detected H: High M: Moderate L: Low VL: Very Low D: Detected I: Indeterminate

** Indicate month of follow-up e.g. M1/M2/M3

Previous Cultures Done

Lab Serial No.	ABST No.	MDR No.	Year	Result

Other Relevant Clinical Details (e.g. HIV /Other Causes of Immune Suppression/X Ray/Mantoux)

.....

.....

.....

.....

.....

Signature of Medical Officer:

Name:

Designation: HO/ MO/DTCO/SHO/REG/SR/VP/VS/

Please Refer to Lists Given to District Chest Clinic for the Following

- Indications for Culture - List 1
- Indications for Xpert MTB/RIF - List 2
- Presumptive MDR Groups -List 3

Laboratory Use Only

Lab Serial No:

Smear	Positive 3+		Positive 2+		Positive 1+		Positive scanty		Negative	
-------	----------------	--	----------------	--	----------------	--	--------------------	--	----------	--

Culture	Positive		Negative		Contaminated		Other	
---------	----------	--	----------	--	--------------	--	-------	--

Identification	MTB		Atypical		Other (Specify)	
----------------	-----	--	----------	--	-----------------	--

Results of Sensitivity Test

Result	Streptomycin	Isoniazid	Rifampicin	Ethambutol
Sensitive				
Resistant				

MLT /NTRL

Date:

Consultant Microbiologist/NTRL

Date:

Contact No.: 011-2956702 or 011-2951428 or 011-2951751 or 011-2958271 Ext 409, 138 or 421

Annexure I-b: Presumptive DR-TB Register

[illegible]

^a Referred from: District Chest Clinic/ Name of Hospital and Ward No/ Name of Private Hospital/ Name of other units

A - Contacts of DR-TB, **B** - First line regimen failures and non-converters/delayed sputum conversion, **C** - history of repeated treatment interruptions, **D** - All other previously treated TB patients, **E** - TB/HIV co-infection, **F** - Children, **G** - Institutionalized patients, **H** - Drug addicts, **I** - Healthcare workers, **J** - Those who return from abroad with active TB, **K** - TB patients treated outside the NTP

^c Culture results: **Neg**=Negative; **Pos**=Positive; **Con**=Contaminated; **Decom**=Decomposed

WWRD: **MTB:** **ND** - Not Detected, **H** - High, **M** - Medium, **L** - Low, **VL** - Very Low
RR: **D** - Detected, **I** - Indeterminate

LPA – Line Probe Assay

Results of DST: **R**= Resistance; **S**= Sensitive; **MS**= Moderately sensitive

Annexure I-c: DR-TB Referral for Treatment

District Chest Clinic			
Name of patient		Age	Sex: M/ F
Complete Address			
Mobile Number of Patient			

TB category	Site		DTB Number		Presumptive MDR TB category		
	Type						
Presenting Complaints with duration							
Comorbidities with duration							
laboratory test results							
WRD		LPA		Culture		DST	
Date	Result	Date	Result	Date	Result	Date	Result

Remarks			
Date			

Signature		Designation	
-----------	--	-------------	--

Annexure I-d: DR-TB Back-Referral for treatment and follow up

Name of Patient		Sex	
		Age	
		Telephone Number	
Complete Address		Date of Admission	
		Date of discharge	
		Initial Weight	
		Current Weight	
Details of DR-TB Confirmation and investigations			
WRD1	WRD2	Liquid Culture	Solid Culture
Other investigations		Sputum Status	
FBS		Culture 1	Regimen Changes
LFT		Culture 2	Date
S. Creatinine		Culture 3	Change and Reason
Hb		Culture 4	
WBC/DC		Culture 5	
CRP			
Na /K			
Consultant Referrals		Plan	
Eye		Intensive Phase	Continuation Phase
ENT			
Psychiatry			
Neuro		Future plan	
Cardio			
Other			

Annexure I-e: DR-TB Treatment Card

Patient's Name:		District:	
Address:		DOT provide Name:	
		Mobile No:	
		Supervising PHI:	
Sex	Date of Birth	Age	NIC No
Male <input type="checkbox"/> Female <input type="checkbox"/>			
Contact Number		DTB Registration Number	
Site: Pulmonary	Extra Pulmonary	If Extra pulmonary, site	
Date of DR-TB Registration		DR-TB Reg Number	
DR-TB Registration Group		Treatment Regimen	
New		Intensive Phase	
Relapse	<input type="checkbox"/>	Date started	<input type="checkbox"/> Cured
Treatment after lost to follow-up	<input type="checkbox"/>	Regimen	<input type="checkbox"/> Treatment completed
Treatment after failure of FLD (new)	<input type="checkbox"/>	Continuation Phase	<input type="checkbox"/> Treatment failed
Treatment after failure of FLD (retreatment)	<input type="checkbox"/>	Date started	<input type="checkbox"/> Died
Other previously treated	<input type="checkbox"/>	Regimen	<input type="checkbox"/> Lost to follow-up
			<input type="checkbox"/> Not evaluated
		Treatment Outcome of DR-TB	

Month of treatment	Sputum smear microscopy			Month of treatment	Culture		
	Date*	Sample No	Result		Date*	Sample No	Result/Remarks
Prior**				Prior**			
1				1			
2				2			
3				3			
4				4			
5				5			
6				6			
7				7			
8				8			
9				9			
10				10			
11				11			
12				12			
13				13			
14				14			
15				15			
16				16			
17				17			

[illegible]

Annexure I-f: DR-TB Register

Date registered	DR-TB number	Previous DTB number/s	Name in full	Sex		Complete address	Treatment unit/DOT centre	Site of disease (P/EP)	Registration group	Previous DR-TB history	DST results								DR-TB regimen	
				Age							S	H	R	E	Bdg	Lzd	Cfx	Dlm	Lfx	Date treatment started

Annexure I-g: DR-TB Patient Identity Card

District		DRTB No	
Full Name			
Complete Address			
Age		Sex	
Mobile No			

Previous District TB Numbers	
Treatment Regimen	
Treatment start date	Date of culture conversion
	Date of treatment outcome

Treatment Outcome	
-------------------	--

Date of appointment	Date attended	Signature of clinician	Comments

Annexure I-h: Quarterly Report on DR-TB Case Finding

Patients registered during:	Quarter	Year	Date of completion of the report
Name of PMDT coordinator			Signature

BLOCK 1: Presumptive DR-TB patients tested and confirmed RR/ MDR-TB cases registered and stated on Second line treatment during the quarter

Presumptive Group	A	B	C	D	E	F	G	H	I	J	K	Total
Presumptive DR-TB patients tested												
RR cases detected												
MDR-TB cases detected in the same quarter												
Pre-XDR cases detected in the same quarter												
XDR TB cases detected in the same quarter												
RR/ MDR-TB cases started on Second line treatment												
Number of contacts identified												

BLOCK 2: RR/ MDR-TB cases registered for treatment according 'Type' of cases

		New	Relapse	Treatment after lost to follow-up	Treatment after failure of FLD (new)	Treatment after failure of FLD (retreatment)	Other previously treated	HIV Status		
								Positive	Negative	Unknown
Male	<15 Y									
	>15 Y									
Female	<15 Y									
	>15 Y									

Annexure I-i: Quarterly report on the culture results of DR-TB patients registered 6-9 months earlier

Patients registered during:	Quarter	Year	Date of completion of the report
Name of PMDT coordinator			Signature

Total number of cases registered	Smear and culture results (of patients still on treatment)								Outcomes of other patients in the cohort			
	Smear Negative			Smear Positive			Smear Not done		Died	Lost to Follow up	Treatment Stopped for ADR	Treatment stopped for other reasons
	Cul Neg	Cul Pos	Cul NA	Cul Neg	Cul Pos	Cul NA	Cul Neg	Cul Pos				

Comments:

Annexure I-j: Quarterly report on the culture results of DR-TB patients registered 12-15 months earlier

Patients registered during:	Quarter	Year	Date of completion of the report
Name of PMDT coordinator	Signature		

Total Number of RR/MDR-TB cases registered	Culture result					Treatment stopped due to other reasons
	Culture Negative	Culture Positive	Culture Unknown	Died	Lost to follow-up	Treatment stopped due to ADR

Comments:

Annexure I-k: Quarterly Report on treatment success of DR-TB patients

Patients registered during:	Quarter	Year	Date of completion of the report	
Name of PMDT coordinator	Signature			

Category	Number registered	Cured	Treatment completed	Treatment failed	Died	Lost to follow-up	Not evaluated
New							
Relapse							
Treatment after lost to follow-up							
Treatment after failure of FLD (new)							
Treatment after failure of FLD (retreatment)							
Other previously treated							
Total							

Treatment failed		Not Evaluated		Remarks
Reason	Number	Reason	Number	

Annexure II: Roles of various facilities and key staff under PMDT

1. NPTCCD

1. Establish a National PMDT committee.
2. Develop a plan of action for implementation, expansion, and management of DR-TB in the country in consultation with the National PMDT committee.
3. Update the national PMDT policy and guidelines in coordination with the PMDT committee.
4. Review periodically the status of DR-TB and monitor PMDT programme performance in the country in coordination with the PMDT committee.
5. Plan and obtain sufficient financial and human resource for implementation, expansion and management of DR-TB throughout the country.
6. Periodically review the laboratory activities along with the Microbiologist and the NTRL staff.
7. Liaise with the international agencies for funding, technical and logistic support and organizing monitoring missions.

2. National Tuberculosis Reference Laboratory

1. Ensure the availability of staff at NTRL trained in DST for first and second-line drugs.
2. Assist in finalization of training modules for laboratory staff.
3. Organise training of the laboratory staff in coordination with the NPTCCD.
4. Undertake periodically on site evaluation for EQA in smear microscopy and culture facilities at the regional culture labs.
5. Obtain accreditation from the designated SNRL for first and second-line drugs and participate in periodic proficiency testing by the SNRL
6. Consolidate figures for presumptive DR-TB cases evaluated and identified on a monthly basis and report the same to PMDT coordinator
7. Perform DST for first and second-line drugs and ensure timely and prompt reporting.

3. PMDT coordinator

- Periodically review the implementation status and ensure that national guidelines are followed.
- Receive the DST results from the NTRL and enter the details in the Second-line treatment register.
- Conduct supervisory visits including patient visit and arrange social support as and when required.

- Ensure timely drug ordering and distribution.
- Maintain the Second-line treatment register.
- Ensure the initiation of treatment and patient discharges are communicated to the district medical officer on time.
- Will be responsible for data management and preparation of quarterly reports on Second-line treatment.

4. The National Hospital for Respiratory Diseases, Welisara and other designated treatment initiation sites

- Order pre-treatment investigations as per guidelines.
- Assess eligibility for Second-line treatment including a thorough clinical evaluation and put up the case to the PMDT site committee for evaluation.
- Motivate patient for hospitalisation.
- Get a consent form for treatment signed by the patient.
- Maintain Second-line Treatment Card.
- Inform PMDT coordinator upon initiation of treatment and one week prior to discharge.
- Periodic monitoring of the patient by the Consultant.
- Health education for patients regarding nature of disease, treatment, and basic infection control measures to be followed.
- Inform PMDT coordinator if a PMDT committee meeting is to be called for any reason.

5. The District Tuberculosis Control Officer

When presumptive DR-TB cases are referred

- Confirms that presumptive DR-TB cases identified are in accordance with the National PMDT Guidelines.
- Counsel the patient regarding the need for further investigations.
- Collect 2 sputum specimens in sterile McCartney bottle.
- Maintain a register for referral for culture/DST (Register of Presumptive DR-TB Cases)
- Arrange to transport specimens to the central laboratory within 4-days.
- Store collected specimens under refrigeration until despatch.

When the results are communicated from the lab:

- Enter the results in the Register of Presumptive DR-TB Cases Register
- Identify RR/ MDR-TB cases and contact them.
- Counsel the patient and refer him to the Welisara Chest hospital or designated treatment initiation site for management with a referral for treatment form and inform the PMDT coordinator.

When the patient gets discharged from NHRD

- Inform the respective PHC.
- Arrange to collect the drugs required for the patient.
- Send one month supply to the PHC where patient will be taking the treatment.
- Organise training of the respective PHC staff.
- Arrange and train a DOT provider who can give injection if patient is still on IP.
- Undertake regular monitoring and supervision to ensure that the patient management at the periphery is in accordance with the PMDT guideline.
- Advise patient to attend once in one-two months (as the case may be) to the chest clinic for evaluation including sputum smear microscopy at the DCC.
- Arrange to collect 2 sputum specimens as per the follow up schedule and transport to NTRL.
- If positive results are reported, patient would be referred to the PMDT committee for further evaluation.

6. Medical officer at the PHC and DCC:

- Will receive the patient referred for continuation of MDR-TB treatment
- Ensure drugs are available for the patient.
- Maintain patient treatment card (PMDT card).
- Counsel the patient and family members.
- Organise DOT for the patient.
- Ensure treatment adherence and prompt default retrieval actions.
- Arrange patient to be sent to the DCC every 2-months (from PHC)
- Monitor adverse drug reactions and manage the same.
- If severe and requiring admission, refer to the DTCO.

Annexure III: Check list for monitoring of patients being treated with Second-line anti TB Drugs

	Adverse Effect	Baseline	Month							
1	Poor Hearing / Loss of Hearing									
2	Dizziness / Giddiness									
3	Tinnitus/ ringing sound in ears									
4	Unstable Gait									
5	Confusion /Disorientation									
6	Aggressive / Depressed/ angry/ change in mood									
7	Loss of weight or excessive weight gain									
8	Loss of Appetite									
9	Nausea / Vomiting									
10	Itching /Skin Rashes									
11	Change in skin colour/ flushing									
12	Joint Pain									
13	Swelling of body									
14	Reduce Urine Output									
15	Altered Sleeping/ Lack of sleep (insomnia)									
16	Abdominal distention									
17	Epigastric Pain/ Abdominal pain									
18	Muscle Cramps									

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Month	M	___	___	M	___	___	M	___	___	M	___	___	M	___	___	M	___	___	M	___	___	M	___	___	
Date	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	___	
Sputum	Smear																								
	Culture																								
	DST 1 st line																								
	DST 2 nd line																								
Blood test	WBC																								
	N																								
	L																								
	E																								
	M																								
	Hb																								
	Hct																								
	Platelets																								
Chemistry	Na+																								
	K+																								
	Ca++																								
	Cl-																								
	Mg++																								
	Total bilirubin																								
	Glycemia																								
	BUN																								
	Creatinine																								
	Uric Acid																								
	ALAT																								
	ASAT																								

[illegible]

Annexure IV: Instructions for collection & transport of specimens for TB culture and Xpert MTB/ Rif test

1. Container

Universal bottle- Glass, reusable, sterile, transparent, screw-capped bottle with a wide neck. Use the bottles within the expiry date, mentioned on the bottle by the laboratory issuing the bottle.

Plastic, disposable, sterile, transparent, screw-capped bottle with a wide neck can also be used to collect the specimens.

2. Sputum Collection

If a patient has a productive cough, the patient is given a container on his first attendance. He should be instructed on how to collect the specimen, with demonstration/visual aids by a healthcare worker.

- Explain to the patient, the reason for Sputum examination
- Inform the patient the number of samples needed to be examined
- Give the patient the Universal container and demonstrate to the patient how to open and close the container.
- Ask the patient to rinse his mouth with plain water before collecting the sample.
- Drinking a glass of warm water may help to bring out the Sputum
- Place both hands on the hip and either sit or squat.
- Inhale deeply 2-3 times
- Cough out deep from the chest
- Open the container. Keep it close to the mouth and spit the Sputum into the container; avoid contaminating outside of the container
- Volume of the specimen collected should be 3-5 ml or up to the mark if indicated in the bottle.
- Avoid saliva or nasal secretions
- Close the container.
- 2 samples should be collected from each patient.
- Early morning samples are preferred whenever possible.



2.1 Safety conditions: Place of Sputum collection (Cough Area)

The risk of infection is very high when the patient coughs. Therefore,

- Patients should produce specimens in a designated cough area, outside in the open air or away from other people and not in confined spaces such as toilets. If there is no proper area outside to collect the sputum, use a separate, well-ventilated room.
- The cough area needs to be provided with a tap, sink, and a washable floor. The water drainage should be into a closed drainage system.

- Before the patient leaves the Laboratory, visually examine the Sputum sample for quality. If the sample is not good, ask the patient to cough again until a good sample is obtained.
- If patients cannot produce sputum, refer to the Medical Officer/Consultant Physician for instructions on induced samples.
- Bronchoscopic samples may be required in some patients.

3. Other specimens

The current WHO recommendations do not cover GeneXpert testing of Pleural Fluid, blood, stool or urine samples.

3.1 Aseptically collected fluids

Body fluids should be aseptically collected in a sterile container using aspiration techniques or surgical procedures.

3.2 Aseptically collected tissues

- Aseptically collected tissue specimens should be placed in sterile containers *without fixatives or preservatives*.
- Transbronchial biopsies, brushing (add 0.5 – 1 ml sterile saline to avoid drying)

4. Request Forms & Specimen labelling

- Request Forms should be located separately from specimen containers.
- Containers should be clearly labelled not on the cap but on the side.
- 2 consecutive samples of the same patient should be sent together. They should be labelled as 1st or 2nd sample.

5. Storage of specimens until transport to NTRL/ Intermediate Laboratory

Specimens should be transported to the Laboratory as soon as possible or within 72 hours of collection. If a delay is unavoidable the specimens should be protected from excessive heat & direct sunlight and refrigerated at 2°C to 8°C to inhibit the growth of unwanted micro-organisms. Sputum specimens can be kept refrigerated up to 7 days. **Extra-pulmonary specimens, however, should be submitted as soon as possible after collection.**

6. Transport container

1. Specimens should be transported in three-layer packaging using enough absorbent material so that if they are damaged or leak, the fluids will be absorbed.
2. Universal containers must be transported in Cool Boxes which should be robust and leak proof.
3. Ice packs should be included to maintain cold conditions during transport.

With each transport box an accompanying list must be prepared which identifies the specimens and the patients from whom the specimens were collected. Before dispatch from the health centre the following must be verified:

1. The number of specimen containers in the box corresponds to that on the accompanying list.
2. The identification number on each specimen container corresponds to the identification number on the accompanying list.
3. The accompanying list should have the necessary data for each patient.
4. The date of dispatch and the particulars of the health centre.