National Guidelines
for
Programmatic Management of
Drug Resistant Tuberculosis

NATIONAL PROGRAMME FOR TUBERCULOSIS CONTROL AND CHEST DISEASES

SEPTEMBER 2015

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FOREWORD

The emergence of drug resistance to first-line anti tuberculosis drugs (FLD) is a major threat to effective global TB control activities. Multidrug resistant TB (MDR-TB) and rifampicin resistant TB (RR-TB) is on the gradual rise mainly due to irrational use of anti TB drugs. This trend has been observed in Sri Lanka too, though we have managed to maintain it very low figures with the well-structured TB control services and through monitoring of treatment adherence.

This National Guidelines for the Programmatic Management of Drug Resistant Tuberculosis (PMDT) is an advent of a great effort taken by NPTCCD with the help of local and international expertise in this context. This will be much more important for the diagnosis, treatment and prevention of MDR-TB/RR-TB in the country.

I take this opportunity to deliver my sincere thanks to those who has contributed enormously to become this publication a realty.

I believe that this publication will be useful for all health professionals to update the knowledge and to manage drug resistant TB more effectively and prevent further spread.

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PREFACE

The National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) has prepared this Programmatic Management of Drug Resistant Tuberculosis (PMDT) manual to give guidance for proper management of drug resistant TB (DR-TB) in Sri Lanka.

It contains the diagnosis, management, infection control, psychosocial wellbeing and reporting system related to DR-TB. The content of this book is formulated according to the WHO guideline of DR-TB management & companion handbook of DR-TB management, with alterations to match the country protocol.

Initiation of drafting the guideline was done in 2011 by Dr. Shantha Devi Thotticamath, WHO international consultant and was finalized by Dr. Vineet Bhatia, independent consultant of WHO, in 2015 September. Consultant Respiratory Physicians of Sri Lanka, Consultant Microbiologist of NTRL, Deputy Director, Consultant Community Physicians, MDR-TB Coordinators and Medical Officer (Health Informatics) of NPTCCD contributed for the formulation of the guideline.

This book is intended to all clinicians who are dealing with DR-TB management, for the proper management of DR-TB patients.

I extend my heartfelt thanks to Dr. Vineet Bhatia, Dr. Shantha Devi, Dr. Wijitha Senaratne and all other local contributors, for the tremendous assistance given. I am also very thankful to WHO and GFATM for the assistance given in publishing this document.

Dr. K. N. Gamini Senevirathne
Director
NPTCCD

CONTENTS

ABBREVIATIONS

ADR	adverse drug reaction
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CD4	CD4+T lymphocyte
CDS	Central Drug Stores
CP	continuation phase
Cs	cycloserine
CSOs	civil society organizations
DCC	District Chest Clinic
DOT	directly observed treatment
DOTS	Directly Observed Treatment Short course
DR-TB	drug resistant tuberculosis
DRS	drug Resistance surveillance
DST	drug sensitivity testing
DTCO	District Tuberculosis Control Officer
E	ethambutol
EPTB	extrapulmonary Tuberculosis
Eto	ethionamide
GDF	Global Drug Facility
H	isoniazid
HCW	health care worker
HIV	human immunodeficiency virus
IC	infection control
IP	intensive phase
ITL	intermediate tuberculosis laboratory
ITR	individual treatment regimen
IUATLD	International Union Against Tuberculosis and Lung Disease
Km	kanamycin
Lfx	levofloxacin
LJ	Lowenstein-Jensen
LPA	line probe assay
MDR	multidrug- resistant tuberculosis

MO	Medical Officer
MOTT	mycobacteria other than tuberculosis
MTB	*Mycobacterium tuberculosis*
NGOs	non-governmental organizations
NHRD	National Hospital for Respiratory Diseases
NNRTI	non-nucleoside reverse transcriptase inhibitors
NPTCCD	National Programme for Tuberculosis Control and Chest Diseases
NTP	national tuberculosis control programme
NTRL	National Tuberculosis Reference Laboratory
PAS	p-amino salicylic acid
PDR	poly drug-resistant
PI	protease inhibitors
PMDT	programmatic management of drug resistant tuberculosis
PPE	personal protective equipment
PTB	pulmonary tuberculosis
R	rifampicin
S	streptomycin
SLD	second-line drugs
SNRL	supra-national reference laboratory
TB	tuberculosis
TDR	totally drug resistant tuberculosis
WHO	World Health Organization
XDR-TB	extensive drug resistant tuberculosis
Z	pyrazinamide

CHAPTER 1

BACKGROUND INFORMATION ON MULTI DRUG AND EXTENSIVE 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 135 countries including 63 countries that have continuous surveillance systems based on routine diagnostic drug susceptibility testing of all TB patients (WHO 2012). It is estimated by WHO that in 2013, almost half a million (480,000) new cases of MDR-TB emerged globally and 210,000 such cases died. The proportion of new cases with MDR-TB has not much changed in recent years. However, there are serious epidemics of MDR-TB in some countries. Globally, 5% of TB cases are estimated to have MDR-TB. Among new TB cases (that account for most of the global TB burden), an estimated 3.5% have MDR-TB. The proportion is higher among people previously treated for TB, at 21%.

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 (2.2, range: 1.6-2.8%) 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 16% (range: 11-21%). However, given the large numbers of TB cases in the SEA Region, this translates to totally 89 000 (range: 75,000–100,000) estimated MDR-TB cases among the notified pulmonary TB cases, accounting for 30% of the world's MDR-TB cases in 2013.

A new threat to TB control is emerging in the form of extensive drug resistant TB (XDR-TB) defined as in-vitro resistance to isoniazid and rifampicin along with resistance to any of the quinolones and one of the second-line injectable anti-TB drugs. 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/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 drug resistant TB (DR-TB), describes the case finding and treatment strategies including referral for bacteriological examination, provide description of treatment regimen and dosages, 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 National Tuberculosis Control Programme (NTP) staff , in implementing the PMDT strategy.

CHAPTER 2

TB CONTROL ACTIVITIES IN SRI LANKA

TB control activities in Sri Lanka are 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. Country has been achieving the global targets of 70% case detection and 85% treatment success among newly diagnosed smear positive cases since 2004 which has been fairly stable over the past 10 years.

From 2005 onwards, TB microscopy services were decentralized to over 100 health facilities and have now been expanded over to more than 160 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.

TB control programme in Sri Lanka is also committed to the End TB strategy adopted by the World Health Assembly in 2014 and will work collectively with the global community to eliminate TB as per the targets established in the End TB strategy.

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 DCCS of Colombo and 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 and Gampaha DCCs, all other DCCs are under the administrative purview of the respective Regional Directors of Health Services.

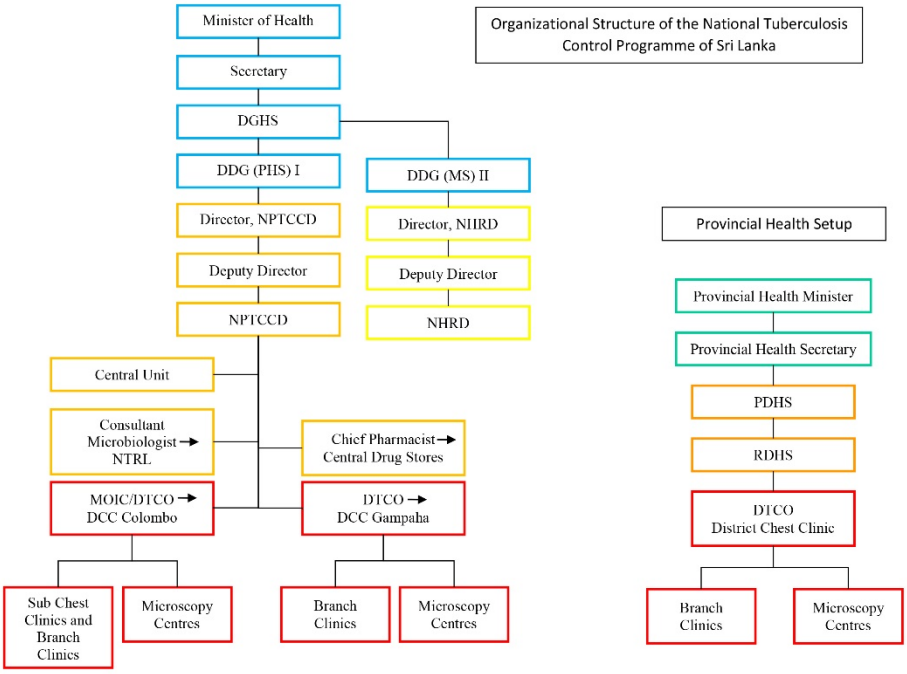

Figure 2.1: Organizational structure of the National Tuberculosis Control Programme in Sri Lanka

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 160 microscopy centres are functioning throughout the country. In addition to the NTRL, two Regional TB Culture Laboratories are functioning in Kandy and Ratnapura. It is planned to establish more Regional TB Culture Laboratories in Jaffna, Karapitiya, Batticaloa and Anuradhapura districts. Infrastructure has been upgraded in Jaffna and Karapitiya while the infrastructure work at other two laboratories is yet to be done. DST facilities for first line anti-TB drugs are available only at NTRL. There are no Drug Sensitivity Test (DST) facilities for second-line anti-TB drugs within the country at the time of writing these guidelines.

However there is a plan to establish these facilities in the country in near future

2.2 Epidemiology of TB in Sri Lanka

It is difficult to assess exactly the current TB burden in Sri Lanka in the absence of recent representative epidemiological studies. The last disease prevalence survey was conducted in 1970/1971. The reported incidence of TB in 2013 is 66 per 100,000 population in Sri Lanka. A total of 9,498 all form 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

	Source	Estimated Year	Rate*	Number
Incidence rate (all forms / 100,000 / year)	WHO (2014)	2013	66	14000
Prevalence rate (all forms / 100,000)	WHO (2014)	2013	103	22000
Mortality rate (deaths / 100,000 / year)	WHO (2014)	2013	5.9	1300
Incidence rate (HIV positive/ 100,000/ year)	WHO (2014)	2013	0.7	150
MDR-TB among new cases (%)	WHO (2014)	2013	0.2	13
MDR-TB among previously treated cases (%)	WHO (2014)	2013	0.55	2
MDR-TB among notified pulmonary TB cases	NPTCCD (Quarterly reports)	2014	--	13

* Rate per 100,000 population

2.3 Epidemiology of HIV in the country

Sri Lanka has a low HIV prevalence. The estimated number of adults living with HIV/AIDS in Sri Lanka for the year 2013 was 2900 with an adult prevalence of <0.1%. According to the national HIV/AIDS surveillance data, the number of HIV cases detected was 229 in 2014 and106 up to end of June in 2015[1]. TB/HIV co-infection was reported among 37 out of 4650 TB patients with known HIV status in 2013(WHO 2014).

[1] http://www.aidscontrol.gov.lk/web/ accessed 21 September 2015

2.4 MDR-TB

Prevalence data of MDR-TB is not available on a countrywide basis. Sri Lanka had undertaken a *Mycobacterium tuberculosis* drug resistance surveillance in 2005/2006 on 1036 patients enrolled for treatment at all chest clinics (905 newly diagnosed and 93 previously treated cases). Culture positivity was 57.4% (62% for new and 36.6% for previously treated cases). The drug resistance to any drug was 1.4% on new and 8.8% for previously treated cases. Only one case (1/595) was reported to have MDR-TB. Table 2.2 shows numbers of MDR-TB reported annually in Sri Lanka.

Table 2.2: MDR-TB cases reported in Sri Lanka

Year	New TB cases		Retreatment TB cases	
	No tested	No positive for MDR-TB	No tested	No positive for MDR-TB
2005	659	07	417	25
2006	613	03	336	13
2007	926	01	388	07
2008	759	03	323	05
2009	813	00	419	04
2010	839	05	378	06
2011	1080	04	408	09
2012	1069	01	238	04
2013	1317	00	512	03
2014	1338	05	624	06

2.5 TB case finding and treatment strategy

Case finding is done by active screening of presumptive TB cases (patients in whom TB is suspected) attending the outpatient departments and among inpatients of hospitals by implementing the diagnostic algorithm as per National Guidelines. For contact screening, diagnosed TB patients are advised to bring all children who are close contacts below 5 years of age, diabetics, and those on immunosuppressive medications irrespective of symptoms and any other contacts if they have symptoms.

All new cases are treated with 2HRZE/4HR regimen. Patients who give a history of prior anti-TB treatment of one month or more are treated with

retreatment regimen 3RHZE/5RHE or 2HRZES/1HRZE/5HRE (see manual on the management of TB in Sri Lanka).

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 once-a-week at the chest clinic or branch clinics for self-administration.

CHAPTER 3

FRAMEWORK FOR EFFECTIVE CONTROL OF MDR-TB

Prevention, treatment and control of MDR-TB is an integral part of the NTP. Therefore PMDT programme will be integrated into the basic TB control strategy of the NTP. The following five essential components of the approach to MDR-TB management will be integrated into the NTP.

3.1 TB control framework as applied to the drug-resistant TB – PMDT Strategy

- Sustained political and administrative commitment
- Appropriate case-finding and diagnosis strategy using quality assured rapid molecular tests, culture and DST
- Appropriate treatment strategies that use second-line drugs under proper case management conditions in alignment with globally accepted standards.
- Uninterrupted supply of quality assured second-line anti-TB drugs
- Recording and reporting system designed for MDR-TB control programme that enables performance monitoring and evaluation of treatment outcomes

3.1.1 Sustained political and administrative commitment

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

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

- Rational triage of patients for testing drug resistance
- Appropriate use of WHO endorsed rapid tests as well as Quality assured culture and DST with internal quality control and external quality assurance
- Close relationship with supranational TB reference laboratory for proficiency testing
- Linking of all sectors involved in the management of TB patients

3.1.3 Appropriate treatment strategies that use second-line drugs under proper case management conditions in alignment with globally accepted standards

- Rational treatment design
- Ensure DOT throughout the whole treatment duration
- Active monitoring and management of adverse effects
- Properly trained human resources
- Treatment adherence through patient centric approach and psycho- social support

3.1.4 Uninterrupted supply of quality assured second-line anti-TB drugs

- Ensure availability of quality assured second-line drugs without interruptions
- Drug management should take into consideration the short shelf life of second-line drugs and the storage conditions required to maintain proper shelf life
- Procurement process must take into account the limited suppliers of quality assured second-line drugs
- Strengthening the inventory management capacity at sub national level

3.1.5 Recording and reporting system designed to enable the performance monitoring and evaluation of treatment outcomes

- Effective recording and reporting system
- Documentation of laboratory results
- Monitoring treatment delivery and treatment response for the whole duration of treatment
- Introduction of electronic recording and reporting system
- Effective functioning of PMDT committee at national level and the PMDT site committees implementing sites for regular review of performance.

CHAPTER 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 MDR-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 less than one month of treatment. This means that the patient has been infected with organisms which are already drug resistant, likely from exposure to a person who harbours 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 drug resistant TB (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:

4.2.1 Service factors

- Prescribing incorrect chemotherapy (wrong combination of drugs, dosages 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 patient 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 and/or convenient timing for the patient.
- Failure to educate patient and the family about the disease, treatment approach and failure to stress the importance of adhering to treatment throughout the prescribed period.

4.2.2 Patient factors

- Not taking the full prescribed number of drugs.
- Taking lesser 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 reserve drugs are more expensive than the standard first-line drugs.
- The results of treatment are poor and the mortality rate is high.

4.4 General definitions of resistance

- **Mono-resistance:** TB in a patient, whose infecting isolates of M. tuberculosis are resistant in vitro to one of first line anti-tuberculosis drug 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):** Tuberculosis in a patient, whose infecting isolates are resistant in vitro to both isoniazid and rifampicin with or without resistance to other first-line drugs.
- **Extensively drug resistant (XDR-TB):** TB in a patient, whose infecting isolates of M. tuberculosis are resistant in vitro to both

rifampicin and isoniazid along with resistance to any quinolone and one of the second-line Injectable anti-TB drugs.

- **Rifampicin resistance (RR):** Resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti TB drugs except Isoniazid.

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 and were then switched to a second-line treatment regimen because MDR-TB was later confirmed. They should be considered “new” if DST was performed within one month of the start of treatment (even if they had received more than one month of new treatment with FLD by the time the results of DST returned and they 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 sub grouping 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.
- Presumptive RR-TB or MDR-TB. Patients may be registered and started on second-line anti-TB treatment on the basis of significant risk for drug resistance and before laboratory confirmation of resistance, or on the basis of a rapid molecular result. All attempts should be made to confirm microbiologically the status of resistance in such cases at the soonest possible.
- Poly-/mono-resistant TB without rifampicin resistance. Some of these cases may have second-line anti-TB drugs added to their treatment.
- XDR-TB (confirmed or presumptive). Patients may be started on XDR-TB treatment on the basis of a laboratory diagnosis or, in its absence, because of significant risk.

4.7 Treatment outcome definitions of MDR-TB patients

Sputum culture conversion is defined as two sets of consecutive negative cultures taken 30 days apart. The specimen collection date of the first negative Culture is used as the date of conversion

- **Cured**: An MDR-TB patient who has completed treatment according to the programme protocol and has at least three or more consecutive negative cultures from samples collected at least 30 days apart after the intensive phase. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient will be considered cured, only if this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

- **Treatment completed**: An MDR-TB patient who has completed treatment according to the programme protocol without evidence of failure, but does not meet the definition for cure because of lack of bacteriological results; i.e. fewer than three or more consecutive cultures were found negative after the intensive phase because patient was unable to produce sputum for culture.

- **Died**: An MDR-TB patient who dies for any reason during the course of MDR-TB treatment.
- **Failed**: Treatment will be considered to have failed if treatment is terminated or need for permanent regimen change of at least two anti-TB drugs because of
    - Lack of conversion by the end of the intensive phase or
    - Bacteriological reversion[2] in the continuation phase after conversion to negative; or
    - Evidence of additional acquired resistance to fluoroquinolones and/or second-line injectable drugs; or
    - Adverse drug reactions.
- **Lost to follow-up**: A patient on second-line drugs whose treatment was interrupted for two or more consecutive months.
- **Not evaluated:** A patient for whom no treatment outcome is assigned due to any reason.
- **Treatment success:** The sum of Cured and Treatment completed.

[2]Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failure, reversion is considered only when it occurs in the continuation phase. Only single culture positive with improving clinical picture may be due to errors.

CHAPTER 5

STRATEGIES FOR CASE FINDING AND DIAGNOSIS OF DR-TB

The diagnosis of DR-TB is essentially laboratory based. Therefore quality assured laboratory plays a key role in the management of DR-TB patients. This chapter describes identification of probable MDR-TB patients, bacteriological tests that will be used in confirming the diagnosis of MDR-TB.

5.1 Strategy for case finding of DR-TB patients

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 culture with DST in order of priority.

Category A[3]: High risk cases for drug resistance

a. Symptomatic contacts of MDR-TB patients or those asymptomatic contacts screened with CXR and found to have changes suggestive of TB
b. First line regimen failures and non-converters/delayed sputum conversion
    i. Patients who continue to remain sputum smear positive after 3 months of retreatment with FLD or failures of retreatment with FLD
    ii. Patients who continue to remain sputum smear positive after 2 months of new treatment regimen with FLD or failures of new treatment regimen with FLD
c. Patients with history of repeated treatment interruptions
d. All other previously treated TB patients

[3]The categorisation of risk cases is temporary and only for prioritisation for using GeneXpert tests. The categories will be used only till such time the country has enough capacity to test all cases at risk of drug resistance

Category B: Patients with moderate or low risk of drug resistance but in whom the risk of mortality or chance of spread of resistant bacillus to contacts is high

e. Patients with TB/HIV co-infection,
f. Institutionalized patients e.g.:- prisoners
g. Drug addicts
h. Healthcare workers
i. Those who return from abroad with active TB.
j. TB patients treated outside the NTP.

In some cases classified as low risk, clinical judgement would have to be used to determine if they could be high risk e.g. a health care worker (HCW) working in a facility where MDR-TB is being treated will be considered high risk for drug-resistance.

Xpert MTB/RIF tests will also be used in smear negative patients (including paediatric cases) and extra-pulmonary cases (except pleural fluid which is considered a sub-optimal sample. The current WHO recommendations also do not cover blood, stool or urine samples). However this testing policy comes into effect from 2016, when additional machines are available and installed. Till such time, priority is being given to high risk DR-TB cases.

From presumptive DR-TB cases, two sputum specimens in sterile universal bottles should be collected. One sample should be sent to the nearest facility where Xpert MTB/RIF test available (National Tuberculosis Reference Laboratory (NTRL) at Welisara for now and from 2017 other facilities). 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) for culture & DST. Such specimens can originate from the DCCs, other government health institutions or the private sector health institutions. Patients will be continued on first line treatment till the Xpert MTB/RIF, LPA (results of which will be ready early if done) and DST results of culture - are available. If the sample is found to be contaminated, the sender should be informed by the laboratory to send two further sputum specimens. DST results

indicating RR/ MDR-TB should be sent as soon as possible to the sender, the DTCO of the relevant district and to the PMDT coordinator. Results should be communicated over the telephone which should be followed by a written report by post and by e-mail.

5.2 Sputum collection and transport system

At all District Chest Clinics a Register of Referral for Bacteriological Examination, from which presumptive DR-TB patients can be identified, should be maintained (see Annexure I-b). Patients will be advised to provide 2 sputum samples (preferably consecutive early morning sputum samples). The specimens will be collected in sterile universal bottles and transported to the laboratory, as above, through a courier who usually is a minor staff employee of the respective DCC with a request form for bacteriological examination.

Other government health institutions and private sector health institutions are also free to send sputum samples for bacteriological examination on presumptive MDR-TB patients. However, in such situations it is advisable to send such samples through the respective DCCs or to send a copy of the request form sent to the respective DCC.

5.3 Procedures for bacteriological examination

Sputum smear microscopy for AFB will be done at all DCC laboratories and microscopy centers.

Xpert MTB/RIF tests will be done at the respective centres for detecting TB as well as resistance to rifampicin. It is expected that the results of test will be available within 2 days of receiving the sputum sample at the laboratory.

Cultures will be done at NTRL (National Tuberculosis Reference Laboratory) or at ITL (Intermediate Tuberculosis Laboratory). The DST will be done only at NTRL. All procedures of smear, molecular testing, culture and DST of these presumptive cases should be handled with appropriate bio-safety measures. The sputum smears will be done and will be graded.

5.4 Identification of *Mycobacterium tuberculosis* and drug resistance

1. **Culture and drug susceptibility testing (DST)**

   Acid-fast Bacilli (AFB) examined under the microscope cannot differentiate between

   1. species of acid fast bacteria
   2. live and dead bacilli
   3. drug-susceptible and drug-resistant *M. tuberculosis*.

Therefore, the main use of microscopy for drug-resistant TB is limited to assessing the infectiousness of patients and confirming that microbes growing on (or in) culture media are mycobacteria rather than contaminants. Microscopy gives early results that are not affected by transport delays or other reasons for false negative results of cultures. Furthermore sputum microscopy is cheap, easy to perform with minimum resources and man power. Microscopy will continue to be of value, and they should always be considered together with the clinical condition and culture results.

For culture, the processing of sputum and inoculation on to liquid culture or the Löwenstein-Jensen (LJ) media bottles will be done according to standard steps. The LJ culture bottles will be incubated at 37°C and read weekly till colonies are observed. If there is no growth until the 8th week, the result will be given as *"culture negative"*. Liquid media will be incubated in automated culture systems or in incubators up to 6 weeks before issuing a negative result. Growth in liquid media will be detected using machine specific detection systems and microscopy.

Delays in specimen transport, excessively harsh or insufficient, decontamination, poor-quality culture media or incorrect incubation temperature can adversely affect the culture yield. Laboratory errors, such as mislabelling or cross-contamination between specimens during aerosol-producing procedures, may lead to false-negative or false-positive results. In this context, laboratory findings should always be correlated with the patient's clinical condition and any diagnostic/relevant test should be

repeated. If necessary, a single culture with low colony counts should be repeated on two fresh samples as soon as possible. Persistent positive cultures or any positive culture combined with clinical or radiological deterioration should be regarded as significant when making decisions on starting second-line drugs. Currently NTRL uses following methods for culture.

1. LJ Medium
2. Liquid Culture.

2. Xpert MTB/RIF® test

Automated real time PCR (Xpert MTB/RIF® using the GeneXpert platform)

The Xpert MTB/RIF® system gives two pieces of information:

1. Presence of *M. Tuberculosis* (MTB) in the specimen
2. Presence of genetic mutations for Rifampicin resistance.

It works on a real-time PCR basis and identifies genetic sequences of the bacteria. It is a highly automated (only 3 manual steps required) test run in a closed system with one cartridge per sample, thus it is less prone to contamination than other PCR based tests. Published results from evaluation studies have showed that for detection MTB, the assay has sensitivities of 98 % for smear-positive, culture positive samples, and 72 % for smear-negative, culture-positive samples (sensitivity can reach 90% if the test is repeated 3 times).

For Rifampicin resistance, the sensitivity compared with conventional DST on culture is 97.6%. The test has a high negative predictive value (>98%), Therefore negative rifampicin- resistance can be considered to be true negative.

False positives for rifampicin resistance can occur, especially if the pre-test probability of the patient having MDR-TB is less than 10%. Therefore, confirmation tests will be done for all patients testing positive for rifampicin resistance with Xpert MTB/RIF® when they belong to a low risk category. This should be with another sputum sample using the Xpert MTB/RIF® or

LPA on culture isolate. Further, all cases also undergo culture and DST using solid or liquid media as per the current national policy.

Additionally, Xpert MTB/RIF® does not eliminate the need for conventional microscopy, culture or DST, all of which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin. Due to the fact that Xpert MTB/RIF® can detect dead bacilli, it is not used as a substitute for monitoring cultures while patients are on second-line TB treatment.

3. Line probe assays (LPA) (HAIN test®)

This is also a molecular method that provides results in 2-3 days depending on the capacity of the laboratory staff. Unlike the Xpert MTB/RIF®, it has numerous steps and needs a highly equipped laboratory with high level of biosafety.

LPA also allows for the detection of both rifampicin and isoniazid resistance. The commercial HAIN® tests are very good at detecting rifampicin resistance among smear-positive patients (sensitivity and specificity >99%), however, the HAIN® test for Isoniazid has a lower sensitivity (about 70%). Further, the LPA/ Hain test cannot be used in smear negative patients.

Constraints of HAIN® testing remain the high cost, high infrastructure requirement, high level of technical training and the risk of cross-contamination. Currently LPA is done on culture isolates and not directly on sputum samples.

5.5 Drug susceptibility testing (DST)

Drug Susceptibility Testing will be performed at baseline for diagnosis of DR-TB at the NTRL, using the proportion method. DST will be done on a single sample only if two or more specimens of the same patient yields an isolate.

Susceptibility to isoniazid (H), rifampicin (R), streptomycin (S) and ethambutol (E) will be tested. Priority will be given for testing H resistance in those cases where R resistance has already been tested with Xpert MTB/RIF. Testing for resistance to S and E will depend on resources available and the judged need. For each strain, the number of organisms resistant to each drug concentration will be expressed as a percentage of the number of organisms growing on the drug free slope. Resistance is defined as 1% or more growth.

5.6 Time for testing and reporting: turnaround time

Table 5.1: Time for testing and reporting: turnaround time

Test	Description	Target
Smear microscopy	Time between receipt of specimens for smear at the laboratory and result reporting	24-48 hours
Solid culture	Time between receipt of specimens for culture at the laboratory and availability of result.	2-6 weeks average for smear-positive samples and 4–8 weeks average for smear-negative samples
Liquid culture		8-21 days average for smear-positive samples and 2–6 weeks for smear-negative samples
Solid media DST	Time between inoculation of DST and availability of result (mean, range and 90th centile). For total DST TAT add this value to culture TAT.	7 weeks from culture positivity
Liquid media DST		2 weeks after inoculation of isolates
LPA	Time between receipt of specimens for LPA at the laboratory and availability of result (mean, range and 90th centile).	3-5 days for direct LPA on specimens (longer if batching of tests). For indirect LPA, add the culture TAT for total TAT (longer if batching of tests)
Xpert MTB/RIF	Time between receipt of specimen for Xpert MTB/RIF at the laboratory and availability of result.	24-48 hours

5.7 Sputum examination during treatment

Sputum examination will be done on a monthly basis from second month onwards in the intensive phase (IP) and every two months in the continuation phase (CP). 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. At any time during the CP, if the sputum becomes culture positive and identified as MTB, sputum specimens will be

collected for culture and direct smear every month for the next three months.

5.8 Infection control and bio-safety in the laboratory

Transmission of DR-TB is a recognized risk for laboratory workers. The specimen has to be handled in a Class 2 Biological Safety Cabinet for all procedures of smear, culture and DST. Instructions on safe handling of specimens have to be strictly followed. The biomedical waste generated in the laboratory should be disposed of in accordance with the national Biomedical Waste Management Guidelines (Ministry of Health, 2008). The health workers, who report signs and symptoms suggestive of tuberculosis, will have their sputum examined and chest X-ray taken.

5.9 Quality assurance

To ensure that results of DST are reliable - a system of quality assurance has been developed for the NTRL. As a part of Internal Quality Control, susceptibility testing has to be performed on the standard H37Rv strain whenever each new batch of drug containing LJ media are prepared.

Proficiency of drug susceptibility testing is being assessed annually by the Mycobacteriology Unit at the Institute of Tropical Medicine, Antwerp, Belgium.

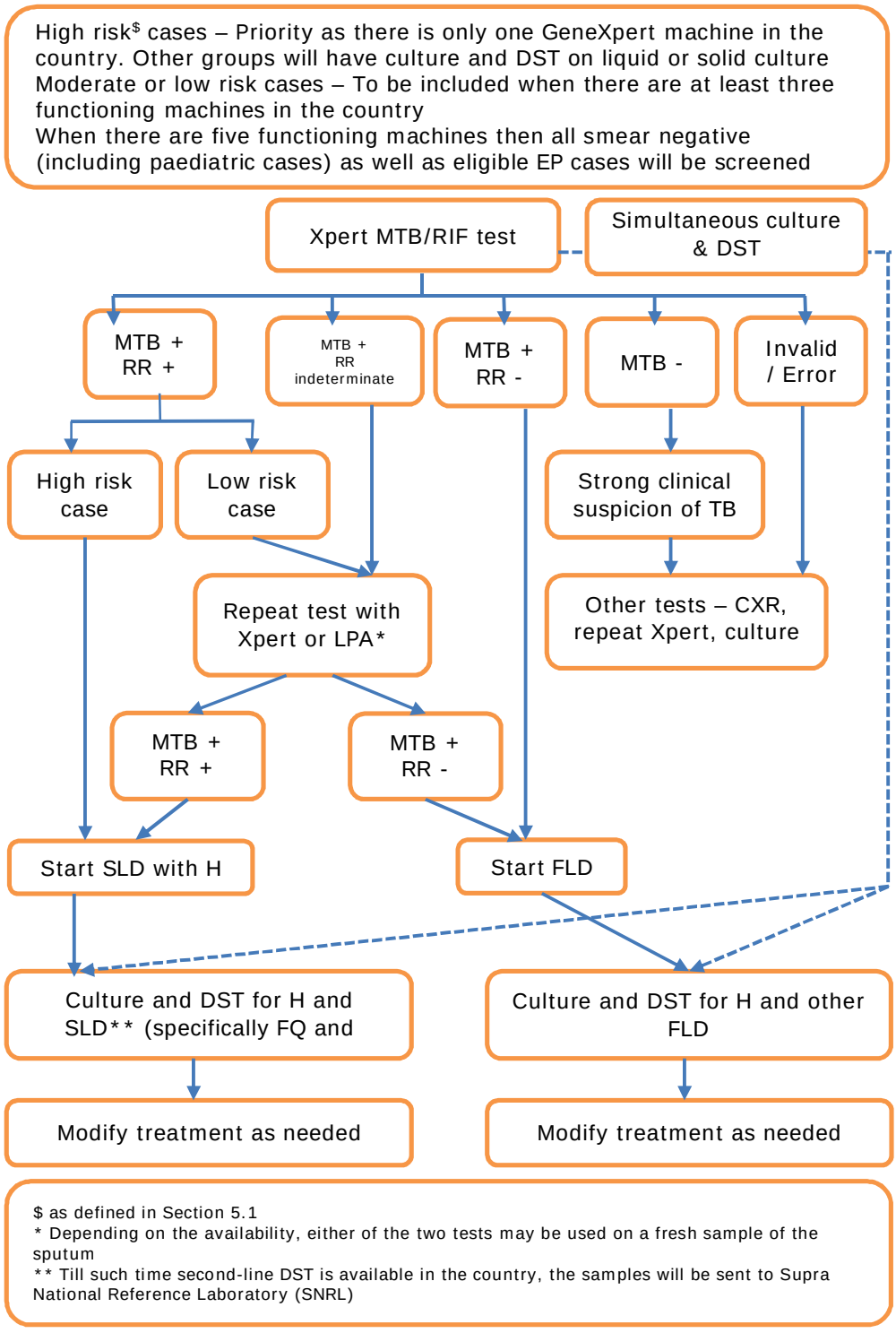

Figure 5.1: Algorithm for detection of DR-TB using molecular diagnostic techniques

The country policy as of now recommends that the Xpert MTB/RIF test needs to be backed up with culture and DST test. The procedure for collecting and transporting sputum have already been described earlier (Procedure for specimen collection and transport is at Annexure V).

CHAPTER 6

TREATMENT OF MDR-TB

Any patient on whom drug-resistant TB is diagnosed and treatment indicated with second-line drugs will need carefully formulated regimens. This chapter describes the standardized approach to treat patients with MDR-TB, the rationale and the role of counselling in ensuring patient compliance while on the regimen. Standard treatment regimen for MDR-TB should always be backed up by the DST results.

If a case is found to be Rifampicin (R) resistant using Xpert MTB/RIF test among any of the high risk categories (close contact of MDR-TB, treatment failure of new or retreatment, non-converters of first line treatment or a case of repeated treatment interruption of first line drugs), such cases will be immediately started on second-line treatment including isoniazid (H) while waiting for results of DST to H. However if a case from low risk category is found to be RR on Xpert MTB/RIF, then the clinician may decide to get another test done on Xpert MTB/RIF or LPA using another sputum sample. Upon confirmed diagnosis of RR/ MDR-TB, patients are admitted to NHRD or another designated treatment site for the initiation of treatment with SLD(it is planned that there will be at least 2-3 additional treatment sites for initiation of treatment with SLD in the future) for the initiation of treatment. NHRD and all such facilities will have an isolation ward with proper infection control measures in place for treatment of MDR-TB patients.

Patients are registered in the RR/ MDR-TB register maintained by the DTCO/ PMDT coordinator and a RR/MDR-TB number is given. The same number is allotted to the patient throughout treatment. Patients are commenced on a standardized regimen of second-line anti-TB drugs. On completion of inward phase, patients are referred to respective DCC for continuation of remaining treatment. The treatment should be directly observed for the whole duration of treatment.

6.1 PMDT committees

After the diagnosis of RR/MDR-TB is carried out by NTRL, the result 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 or another identified treatment site.

NPTCCD has formulated the central PMDT committee and PMDT site committees which will be responsible for treatment decisions, monitoring and evaluation of treatment with SLD.

After admission, the PMDT site committee of the inward treatment facility 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.

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.

Composition

1.	Chairman	Director NPTCCD
2.	Member	Deputy Director NPTCCD
3.	Members	All Consultant Community Physicians NPTCCD
4.	Members	All Consultant Respiratory Physicians NHRD
5.	Members	All Consultant Respiratory Physicians Central Chest Clinic Colombo
6.	Member	Consultant Respiratory Physician Colombo South Teaching Hospital
7.	Member	Consultant Microbiologist NTRL
8.	Members	DTCOs of Colombo and Gampaha Districts

9.	Member	PMDT coordinator (Member Secretary)
10	Member	Chief pharmacist Central Drug Stores

Duties and Responsibilities

- Formulate and regularly update the national policies and guidelines for programmatic management of drug resistant tuberculosis
- Formulate and revise as and when necessary a monitoring and evaluation mechanism for programmatic management of drug resistant tuberculosis
- Ensure that the MDR-TB national register is updated and managed properly
- Provide the technical guidance for the management of drug resistant tuberculosis
- Assess the infrastructure, resource needs including human resources and training needs for management of drug resistant tuberculosis and provide recommendations for improvement.
- Forecast the annual requirement and monitor the procurement and supply chain of second-line anti TB drugs.
- Routinely review the implementation status of PMDT activities and progress on the PMDT expansion plan in Sri Lanka
- Decision making and facilitating establishment of drug resistant TB treatment sites in selected districts
- Appointment of focal points for drug resistant TB at districts
- Ensuring social wellbeing of MDR-TB patients

Operational guidance

- The PMDT central committee shall convene at a frequency of once in three months' time.
- In addition, the committee shall convene at any time when there are important decisions have to be taken.
- Progress of all MDR-TB patients on treatment presented by MDR-TB coordinator / relevant DTCO should be reviewed. Therefore CRPs

and DTCOs who have MDR-TB patients under their care should be invited for the central committee meeting.

- 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.
- All meeting proceedings shall be minuted.
- The Secretary to the committee shall take minutes of the meeting.
- Minutes of the each committee meeting shall be tabled and approved at the next committee meeting.

Site committee of the National Hospital for Respiratory Diseases

In the current practice, 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 well as treatment initiation and the larger part of the intensive phase treatment is done after the patient is admitted to the designated MDR-TB ward at the NHRD. Therefore, the composition, roles and responsibilities of the site committee of the NHRD differs from the other site committees. All drug resistance TB patients admitted to the NHRD and/or managed under the care of DCC Gampaha falls under the purview of this site committee.

Composition

1.	Chairman	Director NHRD
2.	Member	Deputy Director NHRD
3.	Member	One Consultant Community Physician NPTCCD
4.	Members	All Consultant Respiratory Physicians NHRD
5.	Member	Consultant Microbiologist NTRL
6.	Member	DTCO of Gampaha District
7.	Member	PMDT coordinator (Member Secretary)
8.	Member	Chief pharmacist Central Drug Stores (CDS)
9.	Member	One Public Health Inspector from the NHRD and one PHI from DCC Gampaha
10.	Member	Any other relevant Officer/s

Duties and Responsibilities

- Pre-treatment evaluation of all diagnosed MDR-TB patients
- 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 making decisions regarding the total management of individual patients.
- Coordinate with other site committees when management of drug resistant TB patients are exchanged between NHRD site committee and other site committees.
- Report to the PMDT central committee on the progress of individual drug resistant TB patients

Operational guidance

- The PMDT site committee at NHRD shall convene monthly.
- In addition, the committee shall convene at any time when there are 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 secretary to the committee shall take minutes of the meeting.
- Minutes of the 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.

PMDT site committees

PMDT site committees other than the NHRD site committee will be established at district level whenever drug resistant TB 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 site committee, the DTCO may be appointed as the focal point for all drug resistant TB patients. Considering service needs of districts with high burden, any other Medical Officer other than the DTCO may appoint as the focal point for drug resistant TB. Request for such appointment should be forwarded to the PMDT central committee. The PMDT central committee will make such appointments after the situation is analyzed and all factors are taken into consideration.

Composition

1.	Chairman	CRP
2.	Member	DTCO (DTCO will be the Chairman if there is no CRP)
3.	Members	Focal point for DR-TB (DTCO or MO of DCC)
4.	Member	Pharmacist (Dispenser or any other personnel who handles second-line drugs in the absence of pharmacist)
5.	Member	Public Health Inspector
6.	Member	Any other relevant Officer/s

Duties and Responsibilities

- Review the progress of patients on second-line anti-TB drugs and making decisions regarding the total management of individual patients.
- Ensure that MDR-TB patients are admitted to the MDR-TB ward at NHRD for initial phase of the treatment. If any patient is not in a

position to get admitted/ refused to be admitted 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 management of drug resistant TB 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 Referral for MDR-TB management

The DTCO will trace the MDR-TB patient and refer to NHRD or the nearest treatment initiation site, after counselling. A copy of the TB treatment card, DST result and duly filled referral form for second-line treatment (see Annexure I-c) should be sent with the patient. Patient referred to the MDR-TB treatment initiation site for treatment of MDR-TB 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 treatment by post to the PMDT coordinator. The PMDT coordinator informs the DTCO about receipt of patient and treatment initiation in ward.

6.3 Pre-treatment evaluation

All confirmed MDR-TB patients will be subjected to pre-treatment evaluation prior to start of the second-line treatment regimen. Pre-treatment evaluation will include a thorough clinical evaluation by a respiratory physician, with chest radiograph, relevant haematological and bio-chemical tests (see Annexure I-d)

Since the drugs used for the treatment of MDR-TB are known to cause more adverse effects, proper pre-treatment evaluation is essential to,

a) Identify already existing co morbidities
b) Have baseline levels of screening parameters for future reference.
c) Identify patients who are at increased risk of developing such adverse effects.

These include screening for diabetes mellitus, liver disease, drug or alcohol abuse, mental illness, renal insufficiency, thyroid function, pregnancy and lactation. All presumptive MDR-TB patients will be offered HIV counselling and testing. Patients on MDR-TB treatment who are not already tested for HIV will be counselled and tested for HIV. If they are found to be HIV positive, then they will have freely access to further counselling, ART and CD4 counts.

Management of patients with any of these conditions is likely to vary from the standard practice depending on the condition and may require more intense monitoring.

6.4 Treatment regimen

The basic principle in the treatment of MDR-TB is to give at least four drugs to which the organisms are most likely to be susceptible (drugs which have not been used on that patient before) along with pyrazinamide. While there could be many possible regimens for MDR-TB, this fall into two broad groups:

(a) **Standardized treatment regimen (STR)** - Drug resistant survey data from representative patient populations are used to base the regimen design in the absence of individual DST. All patients with a confirmed diagnosis receive the same regimen in the beginning unless there is a known hypersensitivity to any of the second-line drugs.

(b) **Individualized treatment regimen (ITR)** - The treatment regimen is individualized for each patient depending upon the second-line

drug sensitivity profile. To start with, patients are started on standardised regimen and subsequently this is modified when DST results for second-line drugs are available.

6.4.1 MDR-TB treatment regimen for Sri Lanka

DST to second-line drugs is not currently available in Sri Lanka. Therefore, NTP of Sri Lanka will be using a Standardized Treatment Regimen for the treatment of MDR-TB cases under the programme. Standardized regimens are simpler to operate, order drugs and easy for the health workers to understand and do DOT.

6.5 Classes of anti-tuberculosis drugs

The classes of anti-tuberculosis drugs have traditionally been divided into first and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and Streptomycin being the first-line drugs. An alternative method of grouping the anti-TB drugs has been suggested by WHO as given in the Table 6.1 below.

Table 6.1: Grouping anti-tuberculosis drugs

Group	Description	Drug	Abbreviation
1	First-line oral anti-TB drugs	Isoniazid	H
		Rifampicin	R
		Ethambutol	E
		Pyrazinamide	Z
		Rifabutin	Rfb
		Rifapentine	Rpt
2	Injectable anti-TB drugs (injectable agents or parenteral agents)	Streptomycin	S
		Kanamycin	Km
		Amikacin	Am
		Capreomycin	Cm
3	Fluoroquinolones (FQs)	Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
		Ofloxacin	Ofx
4	Oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
		Prothionamide	Pto
		Cycloserine	Cs
		Terizidone	Trd
		p-aminosalicylic acid	PAS
		p- aminosalicylate sodium	PAS-Na

Group	Description	Drug	Abbreviation
5	Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)	Bedaquiline	Bdq
		Delamanid	Dlm
		Linezolid	Lzd
		Clofazimine	Cfz
		Amoxicillin/Clavulanate	Amx/Clv
		Imipenem/Cilastatin	Ipm/Cln
		Meropenem	Mpm
		High-dose isoniazid	High dose H
		Thioacetazone	T
		Clarithromycin	Clr

6.6 Regimen design

The following basic principles are involved in designing the regimen.

- Detailed history of anti-TB drugs taken by the patient in the past should be taken.
- Drugs and regimens commonly used in the country and the prevalence of resistance to first-line drugs should be taken into consideration while designing a regimen.
- Regimens should consist of at least four second-line drugs which are likely to be effective (including an injectable agent and a quinolone).
- Pyrazinamide should be added in spite of its previous use during the intensive phase of treatment and can be extended for the entire treatment duration if it is judged to be effective. Sensitivity to pyrazinamide is not currently available in the NTRL and many MDR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment where pyrazinamide remains active. Furthermore it is said that *M. tuberculosis* cannot acquire resistance to pyrazinamide easily.
- Where DST shows sensitivity to ethambutol, it should be added. However Streptomycin should be replaced with kanamycin/amikacin even if DST shows sensitivity to streptomycin.
- Oral drugs are administered for seven days a week throughout the treatment duration while injectable will be administered six days in

a week during the intensive phase. All drugs should be given in a single dose. In the event of patient not tolerating all drugs as a single dose, the dosage may be split and given twice-a-day for ethionamide, cycloserine and PAS.

- The drug dosage should be determined by body weight.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of 8 months and 4 months after culture conversion (intensive phase) whichever is longer.
- Treatment should be continued for at least 12 months after culture conversion (conversion is defined as two consecutive sputum samples taken 30 days apart are negative for direct smear and culture. Of the two consecutive negative samples the date of collection of the first sample is taken as the date of conversion).
- The total duration of treatment is at least 20 months.
- Each dose is given as DOT throughout the treatment. A treatment card is marked for each observed dose
- Early MDR-TB detection and prompt initiation of treatment are important factors in achieving successful outcomes.

6.7 Standardized treatment regimen (STR) used in Sri Lanka

Intensive phase	At least 8 (Km + Lfx + Eto + Cs + Z +/- E)
Continuation phase	At least 12 (Lfx + Eto + Cs +Z / +-E)

Km - Kanamycin	Cs - Cycloserine	E - Ethambutol
Lfx - Levofloxacin	Eto - Ethionamide	Z - Pyrazinamide

Cm and PAS Na will be kept as a reserve drug to be used in the event of intolerance to any of the drugs used in the regimen. Generally reserves drugs would be made available at Central level for 10% of cases expected to be on treatment.

6.8 Drug dosages and administration

Drug dosages for MDR-TB cases are decided according to the weight band as recommended in the 2015 Companion Handbook to the WHO guidelines for programmatic management of drug-resistant tuberculosis (WHO, 2015;). Monthly monitoring of weight and changing dose to the next weight band according to the weight gain is necessary.

All the oral drugs will be given in a single daily dosage on all 7 days of the week throughout the treatment while injectable will be given six days a week during the intensive phase. If intolerance occurs to ethionamide, cycloserine and/or PAS, these may be split into two dosages and the morning dose is administered as DOT. The evening dose will be self-administered. The empty strip of the self-administered dose will be checked the next morning during DOT. Pyridoxine (vitamin B_6) at a dose of 50 mg for every 250 mg of cycloserine should be administered to all patients on MDR-TB regimen.

Table 6.2 Weight-based oral anti-TB drug daily dosing in adults ≥30 kg

Drug	Daily Dose	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
Oral drugs						
Isoniazid	4–6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg
Rifampicin	8–12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Rifabutin	5–10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg once daily	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-aminosalicylic acid	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week for 22 weeks					
Delamanid	100mg twice a day for 6 months					
Clofazimine	200–300 mg (2 first months) then 100 mg daily					
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanic acid7/1	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanic acid8/1	80 mg/kg/day in 2 divided doses	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg
Injectable drugs						
Streptomycin	12–18 mg/kg once daily	500 mg	600 mg	700 mg	800 mg	900 mg
Kanamycin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg
Amikacin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg
Capreomycin	15–20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg

Table 6.3 Weight-based dosing for children

Drug	Daily dose	Maximum daily dose
Oral drugs		
Isoniazid	7–15 mg/kg for patients less than 30 kg	300 mg
Rifampicin	10–20 mg/kg for patients less than 30 kg	600 mg
Ethambutol	15–25 mg/kg	1200 mg
Pyrazinamide	30–40 mg/kg for patients less than 30 kg	2000 mg
Levofloxacin	5 years and under: 15–20 mg/kg split into two doses (morning and evening)	
	Over 5 years: 10–15 mg/kg once daily	
Moxifloxacin	7.5–10 mg/kg	
Cycloserine	10–20 mg/kg. (For older children who cannot swallow capsules, the capsules can be opened and dissolved in 10 ml water to aid administration)	
Prothionamide/ethionamide	15–20 mg/kg	
PAS	200–300 mg/kg for patients less than 30 kg	
Injectable drugs		
Streptomycin	20–40 mg/kg once daily	1000 mg
Amikacin	15–30 mg/kg once daily	1000 mg
Kanamycin	15–30 mg/kg once daily	1000 mg
Capreomycin	15–30 mg/kg once daily	1000 mg

6.9 Treatment initiation

The decision to initiate treatment will be taken by the PMDT site committee on the basis of pre-treatment evaluations. The consultant respiratory physician in-charge of the patient and the nursing staff are responsible for counselling patient and family opening a file and a treatment card for the patient and initiating treatment. Then the patient will be registered in the second-line treatment register that is maintained by the DTCO and PMDT coordinator.

6.10 Hospitalization

The patients will be hospitalized initially during the intensive phase. Based on the clinical response and factors described below, a decision to decentralise treatment will be undertaken by the PMDT site committee. The decentralised treatment after discharge from the hospital will be provided by the DTCO and the staff of the relevant DCC under the supervision of CRP. In the event of a patient not being able to stay for the entire intensive phase, arrangements will be made by the concerned DTCO to ensure that the IP (including the injections) are given to the patient at the periphery. All the drugs will be administered daily under DOT.

The duration of admission/ hospitalisation during the Intensive Phase of treatment will be decided by the PMDT site committee based on:

1. Convenience of the patient and availability of a facility to administer injectable during ambulatory care
2. Absence of complications and serious adverse effects to the drugs

6.11 Assessment of patients at risk for failure

Patients who do not show signs of improvement after four months of treatment may be at risk for treatment failure. In all patients who show clinical, radio graphical or bacteriological evidence of progressive active

disease or reappearance of disease after month 4 of treatment should be considered as being at high risk for treatment failure.

The following steps are recommended in such patients:

- The treatment card should be reviewed to confirm that the patient has adhered to treatment. Non-confrontational discussions with the patient (with and without the presence of the DOT provider) on whether doses have been missed should be conducted.
- If persistently positive at month 4, discuss in the PMDT site committee and refer the case to central committee for advice on further management. Smear and culture positivity are the strongest evidence that the patient is not responding to treatment. One positive culture in the presence of otherwise good clinical response can be caused by a laboratory contaminant or error. In this case, subsequent cultures that are negative or in which the number of colonies decreasing, may indicate that the positive result does not indicate true treatment failure. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure.
- Other illnesses that may decrease absorption of medicines (e.g. chronic diarrhoea) or may result in immune suppression (e.g. HIV infection) should be excluded.
- If surgical resection is feasible, it should be considered.
- Consider additional nutritional support
- After 6-8 months of treatment, if the patient is doing clinically poorly with the Standard MDR-TB Regimen along with culture non-conversion, consider introduction of XDR-TB Regimen, as decided by the PMDT Site committee in consultation with the central PMDT committee. If clinically stable, but smear or culture positive past month four, monitor the patient closely and continue the standard MDR-TB regimen.
- Consider the possibility of previously undetected MOTT.

- Repeat chest x-ray as radiographic deterioration may indicate that the present regimen is not effective or may show other causes as to why the patient is clinically getting worse (i.e. pneumothorax, bulla, pleural effusions, malignancy).

Extensively Drug Resistant Tuberculosis (XDR-TB) regimen

To confirm the diagnosis of XDR-TB, DST for at least second-line injectable drugs and quinolones should be available (see definition of XDR-TB). Since second-line DST facility is not yet available in Sri Lanka diagnosis of XDR-TB will be only a presumptive diagnosis when there is no response to MDR-TB regimen. Therefore designing a treatment regimen is also based on a best available option. As per the Companion Handbook to WHO guidelines for PMDT, there is very limited data on the different clinical approaches to XDR-TB. Analysis of available data did indicate that success in XDR-TB patients was highest if at least six drugs were used in the intensive phase and four in the continuation phase. The following steps are recommended for an XDR-TB regimen:

- Use pyrazinamide and any other Group 1 agent that may be effective.
- Use an injectable agent to which the strain is susceptible and consider an extended duration of use. If resistant to all injectable agents consider designing the regimen with an injectable agent that the patient has never used before or consider designing the regimen without an injectable agent.
- Use a higher-generation fluoroquinolone such as moxifloxacin or gatifloxacin.
- Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.
- Add two or more Group 5 drugs (consider adding bedaquiline or delamanid[4]).

[4]These two new drugs are not available in the country at the time of writing these guidelines. In case these drugs are introduced, the programme will issue separate guidelines for their inclusion in the appropriate regimen.

In the absence of second-line DRS and based on the current recommended MDR-TB regimen, the following regimen will be used for diagnosed or presumed XDR-TB cases:

- Intensive phase 12 (Z+Cm+Mfx+Cfz+Lzd+NaPAS+Amx/Clv)
- Continuation phase 12 (Z+Mfx+Cfz+Lzd+Amx/Clv)

It is expected that the programme may need XDR-TB regimen for 1-2 patients annually.

6.12 When to stop treatment, without a cure:

Decision to stop treatment will be taken by the PMDT site committee in consultation with Central PMDT committee under the following conditions:

1. Patient develops serious adverse drug reactions.
2. Persistent positive sputum cultures, deteriorating clinical condition (weight loss and respiratory insufficiency) with progressive radiological changes despite addition of proposed XDR-TB Regimen, as decided by the PMDT committee. This should be considered after 8 – 12 months of XDR-TB treatment. Appropriate explanation to patient and family members should be ensured.
3. Treatment suspension in such a situation should be a collective decision of the treating physician and the clinicians in the central PMDT committee following detailed discussions.

6.13 Patient centred directly observed therapy (DOT)

Because MDR-TB treatment is the last therapeutic option for many patients and because there is a high public health consequence if a treatment for MDR-TB fails, all patients receiving treatment for MDR-TB should receive DOT ideally throughout treatment. Current policy of the NPTCCD is to admit the patient to NHRD for inward observed treatment for initiation of treatment (see Hospitalization) followed by observed treatment in the community preferably by a HCW in a health facility. DOT should be provided in a way that it does not introduce undue burden to patients and their families.

While the MDR-TB patient is undergoing pre-treatment evaluation, the DTCO should ensure an initial home visit to verify the address and meet the family members. A DOT provider (who is preferably a HCW), should be identified in consultation with the patient. The DOT provider should be given training for drug administration and to identify possible adverse effects during treatment, and the frequency of follow up.

6.14 Counselling for patient and family

Patients should receive counselling on the nature and duration of treatment, need for regular treatment and possible side effects of these drugs and the consequences of irregular treatment or pre-mature cessation of treatment. It is advisable to involve close family members during the counselling, since family support is an essential component in the management. Patients should be advised to report if he/she experiences any unusual problem. Female patients and their spouses should receive special counselling on family planning.

Health education and counselling is provided to all patients and family members at different levels of healthcare from the DCC and NHRD. It is started at the initial point of contact and carried out on a continuous basis. Advice on the importance of taking prescribed treatment regularly without interruption is of utmost importance for they must clearly understand that non adherence to treatment will result in treatment failure and this is their last chance of achieving a cure. They also should be instructed on the importance of providing a satisfactory sputum sample for culture and direct smear.

CHAPTER 7

TREATMENT OF MONO AND POLY DRUG RESISTANT TB

This chapter describes the recommended treatment strategies for patients with DR-TB other than MDR-TB. Mono-drug resistance refers to resistance to a single first line drug and poly-drug resistance tuberculosis (PDR-TB) refers to resistance to two or more first line drugs but not to both rifampicin and isoniazid.

Cases of mono- or poly-drug resistance will be identified during the course of case finding for MDR-TB.

7.1 Consequences for reporting

Patients who require adjustments to treatment due to mono- or poly-drug resistance should be recorded in the District Tuberculosis Register. These changes are considered as modifications of first line treatment. They are not classified as second-line treatment.

The adjustments should be noted in the comments section of the register and the adjusted treatment continue for the indicated length of time.

7.2 Treatment of patients with mono and PDR-TB

Table 7.1 gives suggested regimens for different DST patterns. In practicing recommendation in the Table, following points should be taken in to consideration.

- Further resistance should be suspected if the patient was on functional equivalent of only one drug for a significant period of time (usually considered as one month or more but even periods of less than one month inadequate therapy can lead to resistance). Sometimes resistance may develop if the patient was on functional equivalent of two drugs depending on the drugs concerned. For example, Z is not considered a good companion drug to prevent resistance. If a patient is receiving functionally only R and Z in the

initial phase (because of resistance to H and E), resistance to R may develop. Thus it is crucial to consider which functional drugs the patient received between the time of DST specimen collection and the time of new regimen designed.

- The DST result that prompts a change in treatment may not accurately reflect the bacterial population at the time it is reported since it reflects the bacterial population at the time the sputum was collected. The regimens in Table 7.1 are based on the assumption that the pattern of drug resistance has not changed during this interval. Table 7.1 should therefore not be used if further resistance to any of the agents in the suggested regimen is suspected. It is also important to note that a high level of confidence in the laboratory is needed for effective use of the recommendations in this Table. It should be noted that DST of E and Z is not highly reproducible. Currently, NTRL does not do DST for Z. Therefore, Z cannot be depended upon as being an effective drug in the regimen. However, a significant percentage of patients would benefit by addition of Z, although it could not be counted upon as a core drug in the regimen.
- CRP should take the decision on the treatment regimen. DTCO/ a designated MO should follow up the patient who should seek the advice of CRP as and when necessary.

Table 7.1: Suggested regimens for mono and poly drug resistance (when further acquired resistance is not a factor and laboratory results are reliable)

Pattern of drug resistance	Regimen	Minimum duration of treatment (months)	Comments
H only	R, Z, S and E	6–9	Use Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found switch to full MDR-TB treatment.
H + S	R, Z and E +FQ	6–9	Use Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found switch to full MDR-TB treatment.
H and E (+/-S)	R, Z, and FQ	9–12	Use Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found switch to full MDR-TB treatment. Some experts recommend using a second-line injectable agent for the first three months
H, E, Z, (± S)	R, FQ, plus Ethionamide, plus a second- line injectable agent for the first 2–3 months. (+/- Z)	18	A longer course (6 months) of the second-line injectable may strengthen the regimen for patients with extensive disease. Z should be added if resistance is uncertain. Use Xpert MTB/RIF at month 0, 2 and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to second-line anti-TB drugs. If culture positive after month 2, repeat DST to first- and second-line anti-TB drugs.
Confirmed R mono- or poly-drug resistance	Full MDR-TB regimen.	20	Add H if resistance to H is not established

CHAPTER 8

TREATMENT OF DRUG RESISTANT TB UNDER SPECIAL SITUATIONS

This chapter outlines the management of drug resistant TB in special conditions and situations.

8.1 Pregnancy

All female patients of childbearing age are tested for pregnancy on initial evaluation. Pregnancy is not a contraindication for treatment of DR-TB which poses a risk to the lives of both foetus and mother. However, contraception is recommended for all non-pregnant female patients of child bearing age receiving treatment of DR-TB because of consequences of the infection and adverse reactions to drugs which can affect both mother and child. Pregnant patients are carefully evaluated, taking into consideration gestational age and severity of the DR-TB. The risks and benefits of treatment are carefully evaluated, with the primary goal of achieving smear conversion and to protect the health of the mother and child, before and after birth.

The following are some general guidelines:

- As majority of teratogenic effects occur in the first trimester, treatment may be delayed until the second trimester. Such decision is primarily based on the analysis of life threatening signs & symptoms and severity/aggressiveness of the disease and should be agreed by both patient and the doctor. If continuing pregnancy poses a great threat to the life of the mother medical termination of pregnancy may be considered after detailed counselling of the patient.
- Aminoglycosides should not be used during the whole duration of pregnancy because they are toxic to foetal ear. Where an injectable agent cannot be avoided capreomycin is an alternative though that too carries a risk of ototoxicity.

- Ethionamide has shown teratogenic effects on animal studies and can increase the risk of nausea and vomiting during pregnancy. Therefore ethionamide should be avoided at least during the first trimester of the pregnancy.

8.2 Breastfeeding

Breastfeeding women with active drug-resistant TB will receive a full course of anti-tuberculosis treatment. Mother and the baby should not be separated completely. If the mother is sputum positive, she will be provided with masks, preferably a surgical mask and care of the infant will be given to a caregiver until she converts, if this is feasible. In such a situation infant formula may be recommended as an alternative to breast feeding. When mother and the baby are together, that common time should be spent in well ventilated areas or outdoors.

8.3 Children

Every effort should be made to confirm DR-TB by the use of DST to avoid exposing children unnecessarily to toxic second-line drugs. Frank discussion with parents is essential at the outset of treatment. No anti-TB drug is absolutely contraindicated in children. However risks and benefits of each drug should be carefully evaluated in designing a regimen. Anti-TB drugs should be dosed according to body weight. Monthly monitoring of body weight is important to adjust doses as children gain weight.

8.4 Diabetes mellitus

Diabetic patients with MDR-TB are at risk of poor outcomes. Furthermore, the presence of diabetes may potentiate the adverse effects of anti-TB drugs particularly renal dysfunction and peripheral neuropathy. Optimal control of diabetes throughout the treatment of DR-TB is of utmost importance to cure the latter. Creatinine and potassium levels should be monitored more frequently (weekly during the first month and at least monthly thereafter).

8.5 Renal insufficiency

Renal insufficiency should be assessed initially and monitored subsequently. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency and the dose and/or the interval between dosing should be adjusted according to the Table 8.1.

Table 8.1: Adjustment of anti-tuberculosis medication in renal insufficiency[a]

Drug	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	15–25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity
Rifapentine	No adjustment necessary
Streptomycin	12–15 mg/kg per dose two or three times per week (not daily)[b]
Capreomycin	12–15 mg/kg per dose two or three times per week (not daily)[b]
Kanamycin	12–15 mg/kg per dose two or three times per week (not daily)[b]
Amikacin	12–15 mg/kg per dose two or three times per week (not daily)[b]
Ofloxacin	600–800 mg per dose three times per week (not daily)
Levofloxacin	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Gatifloxacin	400 mg three times a week
Cycloserine	250 mg once daily, or 500 mg/dose three times per week[c]
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid	4 g/dose, twice daily maximum dose[d]
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Delamanid	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10–30 ml/min, dose 1000 mg as amoxicillin component twice daily; for creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily
Imipenem/cilastin	For creatinine clearance 20–40 ml/min dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20–40 ml/min dose 750 mg every 12 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours

High dose isoniazid	Recommendations not available
Clarithromycin	500 mg daily

[a] Adapted from Companion Handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis 2014

[b] Caution should be used with injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. If on dialysis, dose after dialysis.

[c] The appropriateness of 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible measure serum concentrations and adjust accordingly).

[d] Sodium salt formulations of PAS may result in an excessive sodium load and should be avoided in patients with renal insufficiency. Formulations of PAS that do not use the sodium salt can be used without the hazard of sodium retention and are the preferred formulation in patients with renal insufficiency.

BOX 8.1 Calculating creatinine clearance[a]

Estimated glomerular filtration rate = $\frac{\text{weight (kg) x (140 – age) x (constant)}}{\text{serum creatinine (µmol/L)}}$

The creatinine is measured in the serum

The constant in the formula is = 1.23 for men and 1.04 for women

If creatinine is reported in conventional units (mg/dl) from the laboratory, it can be converted it to a SI Unit (µmol/l) by multiplying by 88.4.

(For example, a creatinine = 1.2 mg/dl is equivalent to (88.4 x 1.2) = 106.1 µmol/l.) Normal values for creatinine clearance are:

Men: 97 to 137 ml/min

Women: 88 to 128 ml/min

Example: If a female patient (age = 46 years, weight = 50 kg) has serum creatinine = 212 µmol/l, what is the creatinine clearance?

Calculation of creatinine clearance:

Weight (kg) x (140 – age) x (constant) **/** serum creatinine =

50 x (140 – 46) x (1.04 for women)/ 212 =

23.0 ml/min

The creatinine clearance is below 30; every drug in the regimen should be examined and adjusted if necessary according to Table 8.1.

Note: Creatinine clearance can also be calculated with a 24 hour urine and serum creatinine, but that is usually more cumbersome.

[a] Adapted from Companion Handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis 2014

8.6 Liver disorders

In the second-line drug regimen, pyrazinamide is the drug which is most likely to cause hepato-toxicity. Ethionamide and PAS may cause hepato-toxicity less commonly while fluoroquinolones can be rarely hepato-toxic. Pyrazinamide is best avoided in patients with MDR- TB whose baseline liver function tests are abnormal. Such patients can be commenced on other second-line drugs while monitoring liver function tests closely. Reader is referred to General Manual on Treatment of Tuberculosis for further details on hepatitis and first line drugs.

8.7 Seizure disorders

Patient with MDR-TB and having history of seizure disorder will be evaluated with regard to control of seizures. If the seizures are not well under control, anti-seizure medication should be adjusted and optimized so that good seizure control is achieved prior to treatment of drug resistant tuberculosis. In addition, any underlying correctable cause of seizures should be corrected. Cycloserine should be avoided in patients with active seizure disorders that are not well under control with medication. Seizures that occur after initiation of anti-TB treatment could be due to adverse drug reactions (this can be due to first or second-line drugs). It should also be remembered that such seizures could be due to neurological involvement of tuberculosis whether it is drug resistant or sensitive.

8.8 Psychiatric disorders

Prior to MDR-TB Treatment, patients with pre-existing psychiatric disorders should be evaluated by a psychiatrist and condition documented. Such documentation will be helpful for comparison if new psychiatric symptoms which develop while on treatment. Advice regarding further management of such pre-existing psychiatric disorders should be obtained. Psychiatric manifestations which occur after initiation of MDR-TB treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with MDR-TB due to the chronicity

and socioeconomic factors related to the disease. Psychiatric symptoms can also manifest as a result of MDR-TB medication particularly cycloserine. The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders. The PMDT site committee may consider substituting Cs with Na PAS in cases where psychiatric issues are a cause of concern and cannot be dealt with using standard management procedures. Treatment with psychiatric medication, individual counselling and/or group therapy may be necessary to manage patients suffering from pre-existing psychiatric disorders or adverse psychiatric effects caused by medication. Psychiatric emergencies should be anticipated. These include psychosis, suicidal ideas and patients being a danger to themselves or to the others. Strategy to tackle such situations should be in place.

8.9 Substance dependence

Patients with substance dependence disorders will be offered treatment for their addiction. Complete abstinence from alcohol and other substances is strongly encouraged. If the treatment is frequently interrupted because of patient's dependence, MDR-TB treatment should be suspended until successful measures to ensure adherence have been established. They will be counselled for complete abstinence from alcohol or other substances and treatment adherence will be ensured.

8.10 Management of contacts of RR/MDR-TB

Close contacts of RR/MDR-TB patients should receive careful clinical follow-up for a period of at least two years. Symptom screening of all contacts initially, and at 6-monthly interval for at least 24-months. If symptomatic, follow the diagnostic algorithm for symptomatics irrespective of the duration of symptoms using rapid diagnostic techniques, where

available. If diagnosed to have RR/MDR-TB, further management will be as per the standard line of management, as described earlier.

There are no definite chemo-prophylactic recommendations for contacts of MDR-TB patients.

New-born children of MDR-TB mothers should be vaccinated with BCG after excluding congenital TB.

CHAPTER 9

DR-TB AND HIV INFECTION

TB / HIV co-infection is a significant challenge for prevention, diagnosis and treatment of DR-TB, especially in the case of MDR-TB and XDR-TB. Reports have shown high mortality rates among HIV infected patients with DR-TB and alarming mortality rates in patients with XDR-TB and HIV. Early diagnosis of DR-TB and HIV, prompt treatment with adequate regimens, intense monitoring of treatment, sound patient support and strong infection control measures are all essential components in the management of DR-TB in HIV infected patients. HIV is a powerful risk factor for all forms of TB and MDR and XDR-TB outbreaks in HIV infected patients appear to be common. DR-TB is often associated with higher mortality rates in the HIV infected compared with the non-infected. However the use of Antiretroviral Treatment (ART) in addition to treatment of DR-TB has been reported to improve outcomes of DR-TB in the HIV infected.

9.1 Diagnosis of HIV in patients with DR-TB

All patients who are diagnosed to have DR-TB should be screened for HIV infection. Similar to the case of drug sensitive TB, provider initiated HIV testing and counselling should be offered to all DR-TB patients on diagnosis.

9.2 Diagnosis of DR-TB in HIV infected.

The diagnosis of TB, whether drug sensitive or resistant, is more difficult and can be confused with other pulmonary or systemic infections. The presentation is more likely to be sputum negative or extra-pulmonary than in HIV negative patients, especially when immuno-suppression advances. This can result in either delay in diagnosis or misdiagnosis. All HIV infected patients are presumptive DR-TB (more importantly MDR-TB) cases. Therefore molecular tests using the GeneXpert and cultures of sputum or

other fluids and tissues are recommended to help the diagnosis of sputum negative PTB and extra-pulmonary TB. Drug sensitivity tests should be performed on positive cultures to detect drug resistance. The heavy reliance on smear microscopy has significant limitations and is insufficient to reliably diagnose a significant proportion of HIV co-infected patients especially as the degree of immuno-suppression advances.

9.3 Treatment of DR-TB in HIV infected

Prompt initiation of appropriate anti-TB treatment and subsequent early initiation of ART can reduce mortality among HIV/ DR-TB co infection. The treatment of DR-TB in patients with HIV is very similar to that of patients without HIV. Treatment for DR-TB should be commenced promptly followed by ART as soon as possible and within first two weeks. Initiating ART with second-line anti-TB drugs may be challenging because many second-line anti-TB drugs can produce serious side-effects, but a well-trained clinical team can usually initiate ART within 2–4 weeks of starting MDR-TB treatment.

The team of care providers should be familiar with treatment of both DR-TB and HIV, close monitoring of adverse effects of drugs, assessment of nutritional status and periodic assessment of therapeutic response of both infections to treatment and preventive measures. Where possible patients with DR-TB/HIV should be offered and provided with socio-economic and nutritional support. A common first-line ART regimen used in MDR-TB treatment is AZT + 3TC + EFV. TDF is generally avoided because of the possibility of overlapping renal toxicity with the injectables, but AZT (anaemia) and d4T (peripheral neuropathy) have even more common side-effects that may make them unsuitable for some MDR- and XDR-TB patients. If TDF is used, additional monitoring of renal function and electrolytes is indicated.

(AZT - Zidovudine; 3TC - Lamivudine; EFV – Efavirenz; TDF - Tenofovir; d4T – Stavudine; DDI - Didanosine)

Co-trimoxazole prophylactic treatment should be given for all patients with HIV/TB co-infection. As mentioned earlier, adverse effects are more common in patients with HIV. It is well known that drug toxicity is more with second-line anti-TB drugs. These drugs when combined with ART can result in high incidence of adverse effects in HIV patients who are more prone to drug toxicity. Some ADRs are common to both anti-TB drugs and anti-retrovirals which can result in increased rate of adverse effects.

Immune Reconstitution Inflammatory Syndrome (IRIS) can complicate treatment (See Chapter 05 of TB/HIV Manual).

Protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) other than efavirenz cannot be given with rifampicin containing anti-TB regimens as the latter induce liver enzymes which increase the breakdown of PIs and NNRTIs. Since rifampicin is not included in second-line treatment regimens for MDR-TB, there is more flexibility in selecting ART regimens in patients on second-line treatment.

Buffered didanosine contains aluminium/magnesium based antacids which can reduce the absorption of quinolones. If these two drugs are given together, they should be given two hours apart. However the enteric coated didanosine can be given together with a quinolone without this precaution.

In newly diagnosed DR-TB patients who are already on ART there are two issues one has to consider. a) Whether ART needs modifications to reduce the potential of overlapping drug toxicities. b) Whether development of DR-TB means failure of ART.

ADRs common to both antiretroviral and anti TB drugs should try to avoid the use when it is possible. However, the benefits of using drugs that have same adverse effects often outweigh the risks of toxicity.

CHAPTER 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 child bearing 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 ethionamide / prothionamide and/or PAS; monitor for hepatitis while receiving pyrazinamide
Psychological assessment by psychiatrist	If indicated during treatment
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
Serum creatinine	At baseline, then monthly while receiving an injectable drug
Serum potassium	At baseline, then monthly while receiving an injectable drug
Thyroid stimulating hormone (TSH)	At baseline and every 6 months if receiving ethionamide and/or PAS
SGPT (ALT) and serum bilirubin	At baseline and when indicated during treatment
HIV screening	At baseline, repeat if clinically indicated
Pregnancy tests	At baseline for women of childbearing age, repeat if indicated
Audiometry	Should ideally be done at baseline
Visual acuity	Should ideally be done at baseline

Table 10.2: Recommended schedule for monitoring

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 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:

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

CHAPTER 11

ADVERSE DRUG REACTIONS (ADRs) AND MANAGEMENT

DOT provider, nurses in the hospital and clinicians will monitor and record all the adverse effects routinely using a checklist and laboratory screening tests will be done 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.

11.1 Training of medical staff on close monitoring and management of ADRs

Training of health staffs 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 the chest wards in the district, if this facility is available or in the 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.

11.2 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 available at Table 11.2.

Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen and when to notify DOT provider or the DCC. Proper management of adverse effects begin with pre-treatment patient education. Depending on the severity of ADR the following actions may be indicated. If the ADR is mild and not serious treatment can be continued with the help of ancillary drugs if needed. The adverse effects of a number of second-line drugs are dose-dependent. Reducing the dosage of the offending drug or terminating the offending drug is another method of managing adverse effects.

Psychosocial support is an important component of the management of adverse effects. This may be provided through patient education and motivation by DOT provider, patient support groups like patients' association/organization or through group discussions while in the hospital.

The recommended schedule for ADR management is as given below:

Table 11.1: Common adverse effects, the likely responsible agents and the suggested management strategies

Side Effects	Suspected Agent/s	Suggested Management Strategies	Comments
Psychotic symptoms	Cs, H	1. Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control 2. Initiate antipsychotic therapy 3. Lower dose of suspected agent if this can be done without compromising regimen 4. Discontinue suspected agent if above measures fail, provided that this can be done without compromising regimen	1. Some patients will need to continue antipsychotic throughout MDR-TB therapy 2. Previous history of psychiatric disease is not a contra-in the use of agents listed here but may increase the lik psychotic symptoms developing during treatment 3. Psychotic symptoms are generally reversible upon cor MDR-TB treatment or cessation of the offending agent 4. Depression is particularly important as it can be caused r drugs but also by the chronicity of the disease and socio factors related to the disease. An attempt should be made the socio-economic status. Group or individual counse important as pharmacological treatment
Rash, allergic reaction and anaphylaxis	Any drug	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 reactions (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include • Antihistamines • Hydrocortisone cream for localized rash • Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful • Phototoxicity may respond to sunscreens, but these can also cause rash • Dry skin may cause itching (especially in diabetics), liberal use of moisturizing lotion is recommended. Dry	1. History of previous drug allergies should be carefully revi known drug allergies should be noted on the treatment ca 2. Flushing reaction to rifampicin or pyrazinamide is usuall resolves with time. Antihistamines can be used. Hot flush palpitations can be caused with isoniazid and tyramine- foods (cheese, red wine). If this occurs advise patients to a that precipitate the reaction. 3. Any of the drugs can cause hives (urticaria). To identify introduce the drugs one at a time. In the case o desensitization attempt can be made. 4. Any drug that resulted in anaphylaxis or Stevens– syndrome should never be reintroduced, not even as a ch

Side Effects	Suspected Agent/s	Suggested Management Strategies	Comments
		skin is a common and significant problem with clofazimine. 4. Once the rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause. 5. Suspend permanently any drug identified to be the cause of a serious reaction	
Nausea and vomiting without liver function test (s. bilirubin SGPT) abnormality	Eto, PAS, Z, H, E, Z, Amx/Clv, Cfz	1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis. Initiate rehydration therapy if indicated and correct any electrolyte disturbances. If there is blood in the vomit, check haemoglobin and treat for possible bleeding ulcers. 2. Initiate a stepwise approach to manage nausea and vomiting. **Phase 1:** Adjust medications and conditions without lowering the overall dose: – Give 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 two hours after other anti-TB drugs. **Phase 2:** Start antiemetic(s): – Metoclopramide/domperidone 10 mg, 30 minutes before anti-TB medications. – Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used.) For refractory nausea give 24 mg, 30 minutes before the dose can be tried.	1. Nausea and vomiting is universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy 2. Electrolytes should be monitored and may be replete if vomiting is severe 3. Reversible upon discontinuation of suspected agent

Side Effects	Suspected Agent/s	Suggested Management Strategies	Comments
		Phase 3: Decrease dose of the suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.	
Seizures	Cs, H, FQ	1. Suspend suspected agent pending resolution of seizures 2. Initiate anticonvulsant therapy (e.g. phenytoin, valproate) and titrate the dose to achieve optimal seizure control 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride. 5. Restart suspected agent in full dose or at a lower dose, if it is essential to the regimen 6. Discontinue suspected agent if above measure fail	1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued. 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. If the patient is receiving anti-convulsant treatment, this should be continued. 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy
Peripheral neuropathy	Cs, H, Lzd, S,Km, Amk, Cm, H, FQ, rarely Pto/Eto, E	1. Correct any vitamin or nutritional deficiencies. Increase pyridoxine to maximum daily dose (200 mg per day) 2. Lower dose of suspected agent, if this can be done without compromising regimen 3. Discontinue suspected agent if this can be done without compromising regimen 4. Initiate medical therapy: 5. Nonsteroidal anti-inflammatory drugs or paracetamol may help alleviate symptoms. 6. Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime, the dose may be increased to a maximum of 150 mg) can be tried. Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors and other anti-depressant drugs. 7. Carbamazepine, an anticonvulsant, at 100 to 400 mg twice daily can be tried. 8. Gabapentin (used off-label) at 300 mg thrice a day; it can be used at a maximum dose of 3600 mg/day in three or four divided doses.	1. 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 2. Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended

Side Effects	Suspected Agent/s	Suggested Management Strategies	Comments
		9. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised	
Hearing loss	Aminoglycosides, Cm, Clr	1. Assess hearing loss by audiometry and compare with baseline audiometry if available 2. Decrease frequency and/or lower the dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week) 3. Discontinue suspected agent if above measures fail.	1. Patients may have baseline hearing loss either due to previous use of aminoglycoside or other factors such as advanced age. 2. In such patients, audiometry will be helpful at the start of MDR-TB therapy 3. Hearing loss is generally not reversible 4. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen.
Hypothyroidism	Eto/ Pto. PAS	1. Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner: • Young healthy adults can be started on 75–100 mcg daily • Older patients should begin treatment with 50 mcg daily • Patients with significant cardiovascular disease should start at 25 mcg daily. 2. Monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions.	1. Baseline thyroid function tests should be done and repeated every six months. 2. Completely reversible upon discontinuation of PAS or ethionamide The combination of ethionamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug
Gastritis and abdominal pain	PAS, Eto, Pto, Cfz, FQs, H, E, and Z	1. Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent. 2. If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) initiate medical therapy with the use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg	1. Severe gastritis, as manifested by haematemesis, or melena is rare 2. Dosing of antacids should be carefully timed so as not to interfere with the absorption of anti-TB drugs (take 2 hours before or 3 hours after anti-TB medications)

Side Effects	Suspected Agent/s	Suggested Management Strategies	Comments
		twice daily). Avoid the use of antacids as they decrease absorption of fluoroquinolones. 3. For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days). 4. Lower the dose of the suspected agent, if this can be done without compromising the regimen. 5. Discontinue the suspected agent if this can be done without compromising the regimen.	
Hepatitis	R, H, Z, , occasionally to Pto / Eto, and PAS	1. Eliminate other potential causes of hepatitis like viral hepatitis, alcohol induced hepatitis and other potential hepato-toxic drugs which patient may be on for other conditions. 2. If enzymes are more than three times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non-hepatotoxic medications. 3. Once liver functions returned to normal, restart. Offending drugs one by one starting with a lower dose gradually increasing the dose to the recommended dose. In doing so liver functions should be monitored closely and drugs which are unlikely to cause hepatitis can be continued. If a drug is found to cause repeated hepatitis, it should be discontinued.	1. Hepatotoxicity is usually caused by first line drugs R, H, and Z. Of these, only Z is used in second-line treatment (RR/ MDR-TB treatment). Occasionally Eto and PAS may also be responsible for hepatitis 2. History of previous hepatitis should be carefully analyzed to determine whether any drug had to be discontinued in the past because of hepatitis. Such drugs should be avoided. Generally drugs which can cause hepatitis can be recommenced.
Renal toxicity	Aminoglycosides	1. Consider dosing 2 to 3 times a week while monitoring blood urea, serum creatinine and serum electrolytes closely. If there is evidence of progressive deterioration of renal function, aminoglycoside will have to be discontinued.	1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure 2. Renal impairment may be permanent

Side Effects	Suspected Agent/s	Suggested Management Strategies	Comments
Electrolyte disturbances (hypokalaemia and hypomagnesaemia)	Cm,Km, Am, S	1. Check potassium. 2. If potassium is low, also check for magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalaemia). 3. Replace electrolytes as needed. Dose oral electrolytes apart from fluoroquinolone as they can interfere with fluoroquinolone absorption	1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride, 5–10 mg daily, or spironolactone, 25 mg daily, may decrease potassium and magnesium wasting, and thus useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.
Arthralgia	Z, E, Bdq, Flouroquinolones	1. Initiate therapy with non-steroidal anti-inflammatory drugs. (NSAIDs) 2. Check blood uric acid levels if arthritic symptoms do not respond to NSAIDs. 3. Lowering the dose or discontinuation of suspected agent, may be needed if reassurance and NSAIDs fail to alleviate symptoms.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated. However, allopurinol appears not to correct the uric acid levels in such cases. There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present it should be used. 3. If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc

11.4 Drugs used in the management of ADRs

Management of ADRs often requires the use of ancillary medications to eliminate or to lessen the adverse effects. All PMDT sites should have a stock of these drugs and they should be available free of charge to the patient. Table 11.2 describes commonly used ancillary medications.

Table 11.2: Commonly used ancillary medications

Indication	Drug/s
Nausea, vomiting, upset stomach	Metoclopramide, domperidone, prochlorperazine, promethazine
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, famotidine, etc.), proton pump inhibitors (omeprazole, pantaprazole, esomeprazole etc.). Avoid antacids because they can decrease absorption of fluoroquinolone
Oral candidiasis	Fluconazole, clotrimazole lozenges, nystatin suspension
Diarrhoea	Loperamide
Depression	Selective serotonin re-uptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam
Insomnia	Diazepam
Psychosis	Haloperidol, trifluoperazine, chlopromazine (Also include stocks of benzhexol to prevent extrapyramidal effects.)
Seizures	Phenytoinsodium, carbamazepine, sodiumvalproate, phenobarbiton
Prophylaxis of neurological complications of cycloserine and isoniazid	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline, gabapentin, carbamazepine
Vestibular symptoms	Cinnarizine betahistine, prochlorperazine,
Musculoskeletal pain, arthralgia, headaches	Ibuprofen,diclofenac sodium, paracetamol,
Cutaneous reactions, itching	Hydrocortisone cream, betamethasone cream, calamine lotion,
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, cetrizine, loratidine, desloratidine), corticosteroids (prednisolone,)
Bronchospasm	Inhaled/oral bronchodilators (salbutamol, theophylline etc.) inhaled corticosteroids (beclomethasone, fluticasone etc. with or without long acting beta 2 agonistst), oral steroids (prednisolone), injectable steroids (hydrocortisone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium, magnesium and calcium replacement therapy (oral and intravenous formulations)

11.5 Summary

Early detection and prompt appropriate management of ADRs is the key to get good results in PMDT programme. Ward nurses and DOT providers should be familiar with the common adverse effects of DR/MDR-TB therapy. Patients reporting adverse effects should be referred to doctors who are in charge of patient's treatment unless the ADRs are trivial. It is rarely necessary to suspend anti-TB drugs completely. Ancillary drugs for the management of adverse effects should be available to the patient free of charge.

Intensive monitoring and timely management of, adverse effects caused by second-line drugs are essential components of DR-TB control programmes. Poor management of adverse effects increases the risk of default or irregular treatment, and may result in death or permanent morbidity.

CHAPTER 12

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.

12.1 Education and counselling of patients and their families

All patients and their families should receive education and counselling about MDR-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 and should be culturally sensitive.

12.2 Treatment delivery settings

In PMDT projects in other countries, multiple strategies have been used for the delivery of MDR-TB treatment, including hospitalization, clinic-based, and community-based care. Regardless of the mode of delivery, key in the management of MDR-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.

12.2.1 Initial in-patient care

When a presumptive MDR-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 their 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 undertaken. 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 would be intimated 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 to the prolonged treatment.

12.2.2 Ambulatory care-Training?

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 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 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 PMDT referral for treatment form.

12.3 Adherence

Adherence with 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 with 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, 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 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.

12.4 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.

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

MDR-TB patients are likely to be hospitalized during initial part of the IP. In the event of a patient getting discharged early, the DTCO should ensure to identify a DOT provider who can administer injection kanamycin during the intensive phase. 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.

12.4.2 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.

12.5 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 assess the need for appropriate socioeconomic interventions and monitor their delivery.

12.6 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.

12.7 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.

There is no separate nutrition support programme for MDR-TB patients in the country. While being admitted to a hospital, a high protein diet is arranged through the hospital services. It is planned that nutrition support through the government Thriposha scheme will be arranged for patients once they are discharged from the hospital. Such support is also expected to help treatment adherence.

12.8 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 patient and family to ensure treatment continuation.

12.9 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. Management of adverse drug reactions are addressed in detail in Chapter 11.

12.10 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 death audit would be discussed by PMDT site committee as well as central PMDT committee to improve management of other patients and prevent deaths, wherever possible.

12.11 Adherence promotion strategies for second-line treatment

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

Chapter 13

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.

13.1 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.

13.1.1 Administrative controls

The administrative controls include policies and procedures intended to promptly identify and treat infectious cases so that additional precautions can be taken. An important aspect of administrative control measures is the physical separation of patients known or suspected of having TB or MDR-TB (especially smear-positive cases) from other patients.

Administrative measures proposed to be undertaken:

a. General airborne infection control measures at all places managing chest symptomatics
b. As far as possible the waiting areas for chest symptomatics would have adequate natural ventilation and access to the consultation rooms will be from open space rather than closed corridors
c. Early detection of patients and commencement of treatment
d. Isolation of diagnosed MDR-TB patients in ward in the intensive phase
e. Health education for patients and the families
f. Proper disposal of sputum specimens via incineration

13.1.2 Environmental controls

In warm climates, infection control can be assured most effectively by strong natural ventilation (i.e. open windows in opposite walls).
Design of rooms, patient waiting areas and airflow needs will be considered. In addition to the above, basic infection control measures will be taught to patients such as covering the nose and mouth during coughing and sneezing and to discard used tissue into covered bins.

Environmental measures proposed to be undertaken:

a. Educating patients on cough hygiene
b. Ensuring proper cross ventilation in the ward.
c. Ensuring proper sputum disposal methods by patients

13.1.3 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 N-95 masks 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 symptomatics and referral of those

like to have TB/MDR-TB when TB management facilities are not available within the health facility.

13.2 Essential actions for effective TB infection control safety without stigma

13.2.1 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.

13.2.2 Develop an infection control plan

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

13.2.3 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

13.2.4 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 bended forearm (near elbow), cloth such as handkerchief or clean rag, paper tissues, or paper masks.

13.2.5 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 of having 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.

13.2.6 Assure rapid 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. Sputum collection should be done away from other people. Sputum specimens are sent to a quality-assured laboratory for AFB smear. A patient-tracking system assures that presumptive TB cases who are AFB smear-negative receive additional procedures (e.g. chest x-ray and referral visits) or treatment as quickly as possible. DOTS treatment for TB begins immediately when a diagnosis of TB is made.

13.2.7 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.

13.2.8 Protect HCWs

HCWs should know the symptoms of TB and should be regularly screened for TB. 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.

13.2.9 Capacity building

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

13.2.10 Monitor infection control practices

Infection control committees should be established at all DCCs and functioning of these will be monitored by the central infection control committee of NPTCCD. 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.

CHAPTER 14

TRAINING ON MDR-TB MANAGEMENT

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

The full curricula of the training courses on MDR-TB control include the following topics:

- MDR-TB Definitions: case registration, bacteriology and treatment outcomes
- Specific case-finding strategies
- Laboratory service for essential laboratory exams and MDR-TB
- Treatment strategies for MDR-TB
- Treatment of drug-resistant tuberculosis in special conditions
- HIV infection and MDR-TB
- Monitoring of treatment
- Management of adverse effects
- Treatment adherence and missed-dose and defaulter tracing
- Counselling
- Management of patients after MDR-TB treatment failure
- Management of contacts of MDR-TB patients
- Recording and reporting system

However, according to 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.

14.1 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. irregular drug intake.
- Schedule for follow up.
- Procedures for sputum collection and transportation of specimens to the appropriate laboratory with molecular testing facility, NTRL at Welisara or to intermediate culture laboratories for culture for *Mycobacterium tuberculosis* and drug susceptibility testing.
- Filling of the request form for bacteriological examination in the special request form which will be colour coded (to be filled in duplicate, one to be maintained at the referral centre).
- Tracing of patients reported to have RR/ MDR-TB.
- Counselling of patient and family.
- Need for hospitalization of patients for the intensive phase of treatment
- Organizing DOT for 18 months after discharge from the hospital at the district. Identifying and management of adverse drug reactions.
- Periodic evaluation of patients on treatment as per guidelines.
- Infection control measures.
- Recording and reporting for PMDT.

14.3 Laboratory staff

14.3.1: The laboratory technicians at the microscopy centres will be trained to:

- Identify presumptive DR-TB cases and refer them to the Medical Officer.
- The laboratory technician at the DCC will be trained to collect two sputum samples of good quality in sterile McCartney bottles supplied to the DCC by the NTRL for diagnosis and follow up.
- Educating patients on sputum disposal and respiratory hygiene.

14.3.2: The laboratory staff at the central laboratory will be trained on:

- Procedures for receiving sputum specimens.
- Maintaining the register of presumptive MDR-TB cases.
- Handling of specimens, processing for molecular tests and/or culture and DST as per the available services at the laboratory.
- Reading results.
- Recording and reporting to the respective DCCs.
- Maintaining of the Laboratory Register for PMDT.
- Schedule for follow up.
- Culture and DST quality assurance with SNRL.
- Newer diagnostics.
- Infection control and bio-safety procedures.

14.4 Basic health staff

On-the-job training has then do be regularly delivered by the DTCO/CRP of the DCCs. They are also responsible to train the health staff that will be newly recruited.

Table 14.1: Tentative training schedule

Activity	Time frame	No Of Programmes	Participants
Training for DTCOs & MOOs	Annually	Two	Twenty
Training for NOOs in Chest Clinics	Annually	Two	Twenty
Training for Health Assistants	Annually	Two	Twenty

CHAPTER 15

DRUG MANAGEMENT

15.1 Management of second-line drugs

The PMDT coordinator will provide estimates of the drug requirement to the Global Drug Facility (GDF) who will procure and supply the same to Director NPTCCD. The drugs will be supplied to the CDS at Welisara. When a patient is to be initiated on MDR-TB treatment, the PMDT coordinator will inform the pharmacist at the CDS to send two months' supply of second-line drugs to the PMDT site and replenish the stock at monthly interval on the request of the PMDT coordinator.

One week prior to discharge from the hospital, the PMDT coordinator will inform the pharmacist of the Central Drug Stores 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 PMDT site to cover for the period of travel. The patient will report to the DTCO who in turn will refer him to the peripheral DOT provider after counselling.

The DTCO will request drugs from the CDS on a quarterly basis based on the estimated requirement, buffer stock for one month and stock in hand. The DTCO will replenish the stock at the periphery on a monthly basis. 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 left drugs.

Procurement of SLDs: The programme will continue to procure quality assured second-line drugs through reliable sources. The quantities needed for a year will be calculated based on the number of patients that are likely

to be put on treatment along with those that are continuing treatment from the previous year. The available stocks will be deducted after consideration of lead time for procurement from the date of calculation. Cm and Na PAS will be purchased for 10% of MDR-TB patients as back-up for any reactions to drugs in the standard regimen.

For XDR-TB, drugs will be purchased for approximately 9%[5] of MDR-TB cases

15.2 Supervision

It is necessary that every dose of treatment is given under DOT and supervision is needed at all levels. Supervision should also include ensuring availability of drugs and providing necessary support to the patients and the health worker. The treatment cards need to be updated from the provider level to health facility and all adverse drug reactions entered. A good supervisor will motivate the patient and also the DOT provider, since the treatment for MDR is prolonged and adequate motivation ensures treatment compliance.

[5]Since the country does not have data on SLD resistance, the current global average of 9% XDR-TB cases among the MDR-TB cases is being used

CHAPTER 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 public health system.

To overcome these challenges, the programme with actively seek the cooperation of all non-governmental organisations (NGOs) and civil society organisations (CSOs) that have 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 grassroots. Counselling support will also become important in case of treatment interruption where the community organisations can support patient in overcoming barriers to treatment adherence.
- Mobilising economic support – Financial support of Rs 5,000/- per month for first six months of treatment has recently been announced through the provincial social service department. However the patients may face procedural challenges to access these funds. Further, some patients may need additional economic support after the first six months as the MDR-TB treatment will continue for at least 20 months. The NGOs and CSOs can provide support to the patients by coordinating with responsible officers for easy access to available money. These organisations can also

mobilise funding support for such patients or undertake rehabilitation services, as described below.

- Rehabilitation services – Many of the patients on MDR-TB treatment lose jobs or face reduced earnings. Such patients will need support to enter back in 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 the PMDT services like up gradation of wards in remote areas for possible admission of the MDR-TB patients.
- Advocacy/ awareness campaigns - The NGO and CSO which have members with technical background can support NTP or collaborate with other agencies in organising awareness campaign for various associations so as to sensitise them to needs for screening drug resistance as well as proper treatment of TB as well DR-TB.
- Palliative care – the number of MDR-TB patients in the country is small and so far there have been no instances where treatment options were exhausted. However, as the programme expands, there could be instances where the patient has to be taken off treatment and the only option of care is palliative. The Government has not yet established any palliative care mechanism for such drug resistant TB cases. NGOs and CSOs can provide palliative care at home or in an institutionalised manner.

- As members of the PMDT committees at various levels, provide operational inputs for making the services more accessible and convenient for the patients.

CHAPTER 17

RECORDING AND REPORTING

This chapter describes the information system for patients who are entered in the second-line treatment register, with the objective of recording information needed to monitor programme performance and treatment outcomes.

The aims of the information system are twofold:

1. To allow managers of national TB control programmes at different levels to monitor overall programme performance to provide the basis for programme and policy developments. Performance indicators include:
   - The outcome of patients with drug-resistant TB, including MDR-TB,
   - The results of second-line treatment and the results in subgroups.
2. To aid staff in treatment units to provide adequate management of individual patients.

17.1 Scope of the information system

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

All recording and reporting systems will be followed as per the WHO guideline and separate register will be developed for recording at all treatment centres.

17.2 Description of the recording and reporting system

(See Annexes I-a to I-l)

17.2.1 Request for bacteriological examination (Annexure I-a)

This form has to be used when bacteriological examination is requested including GeneXpert test, LPA test, and/or culture and DST.

17.2.2 Register of Referral for bacteriological examination (Annexure I-b)

This register has to be kept at office of DTCO. All the presumptive MDR-TB cases whose sputa collected and transported to the GeneXpert performing lab, NTRL or regional TB culture laboratories with the bacteriological examination request form have to be appropriately recorded in this register.

17.2.3 PMDT referral for treatment (Annexure I-c)

This form is to be filled in triplicate with one copy sent to the respective DCC receiving the patient, one copy sent through the patient and the third is filed at the facility. The form gives the details of sputum culture and DST which are to be filled by the DCC when the patient is referred to the PMDT site for hospitalization and treatment. The lower part of the form contains the details of second-line treatment received by the patient at the PMDT site and is to be filled up at the PMDT site when the patient is referred back to the DCC for continuation of the treatment.

17.2.4 Checklist for initial evaluation and treatment surveillance (Annexure I-d)

This is filled up at the PMDT site and should be scrutinized by the PMDT site committee prior to initiation of treatment. The PMDT site coordinator would ensure completion of this checklist and also monitor that relevant investigations are done at the prescribed time intervals.

17.2.5 Second-line treatment Card (PMDT treatment card; Annexure I-e)

This card is a key instrument for health staff who administers drugs to patients on a daily basis. When decision is taken to initiate second-line treatment, a MDR-TB Treatment Card is filled up by the MO 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 MDR-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.
- **MDR-TB Registration Number.** This is a new unique patient identification number. Previous district TB registration number can be recorded in the appropriate column.
- **The registration group of patient according to previous treatment:** The relevant registration group will be entered in the relevant space.
- **Previous anti-TB Treatment Episodes.** This section lists and describes any previous treatment with details of drugs received and outcomes. Start with the most distant treatment and label it as “Number 1”. The “source of previous treatment” indicates from where the patient received the respective previous treatment. The outcome of any past treatments is also noted here (cure, completed, failure, defaulted or unknown).
- **PMDT site meetings.** There should be periodic meetings of the PMDT site committee, with the caregivers involved with the patients on SLD, in which the progress of the individual patient is reviewed.

This section provides a space to record any major changes by the committee.

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 lead 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:

- **Drug regimen:** The second-line regimen and appropriate weight band is recorded on the treatment card.
- **Drug regimen change:** Details on any change to the drug regimen, its details and date of the change made.
- **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.
- **Weight, laboratory and X-ray monitoring:** These items can be recorded on the treatment card in the monthly drug administration section in the last column. Requirements regarding the schedule for monitoring these parameters are given in Table 10.1.
- **Default retrieval actions:** Record any details on default retrieval activities.

Page 4 of the Treatment Card

- **Record of daily observed administration of drugs:** This is continued over the page 4.
- **Adverse drug reactions:** Record any ADRs and action taken.
- **Treatment outcome:** At the end of the treatment, record the

treatment outcome. The outcome definitions are given in Chapter 4: Section 4.7.

17.2.6 Second-line treatment register (PMDT register; Annexure I-f)

The register is filled by the DTCO/ PMDT coordinator on the basis of the information contained in the individual patient's second-line treatment card. Information as smear, molecular test and culture results can be updated on 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 start and regimen used)
- Date of bacteriological examinations and results
- Treatment outcome
- Whether HIV testing 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 PMDT patient identity card (Annexure I-g)

This card include all the general information related to the MDR-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 by the patient.

17.2.8 Quarterly report on RR/ MDR-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 2013 will be filled and submitted in April 2013. The PMDT coordinator is responsible for submission of the report in a timely manner.

17.2.9 Six month quarterly interim report of RR/ MDR-TB patients (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 day 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 2013 should have the preliminary six month interim report filled out in January 2014. 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 Culture conversion quarterly report of MDR-TB patients (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 day 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 first quarter of 2013 should have the Culture Conversion Report filled out in July 2014.

17.2.11 Quarterly report on the result of second-line treatment (treatment outcome; Annexure I-k)

This report is prepared by the PMDT coordinator. It shows final result of treatment by year of treatment start. It is first completed at 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.

17.2.12 Evaluation at Completion of second-line treatment (Annexure I-l)

This form is maintained by the PMDT coordinator and contains the smear and culture results for the patient who has completed its treatment. It also contains information on whether the patient was clinically evaluated at the completion of treatment and the specific complaints with action taken in such situations.

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ANNEXURE

Annexure I

FORMATS OF RECORDING AND REPORTING SYSTEM

a. Request form for TB Culture, Drug Susceptibility and Molecular Testing

b. Register of Referral for Culture and DST

c. PMDT Referral for Treatment

d. Checklist for Initial Evaluation and Treatment Surveillance

e. Second-line Treatment Card

f. Second-line treatment register

g. PMDT Patient Identity Card

h. Quarterly Report on RR/MDR-TB Case Finding

i. Six Month Quarterly Interim Report of RR/MDR-TB Patients

j. Culture Conversion Quarterly Report of RR/MDR-TB Patients

k. Quarterly Report on the Results of Second-line Treatment

l. Evaluation of Completion 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		
Sputum	Other (Specify)	dd	mm	Yy

Lab Use Only		Serial No		
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			Sex	
yyyy	mm	dd	M	F

Contact Number	NIC/ID of Patient/Parent/Guardian

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

Patients Address:		Residential District:	

Test/s Requested	Culture & DST		Xpert (MTB/RIF)	

Indication	For Diagnosis		Follow Up CAT I		Follow Up CAT II		Follow Up CAT IV		Other (Specify)	

Probable Diagnosis	PTB Smear positive		PTB Smear negative		EPTB		Site/s	

Treatment History	New		Previously Treated		Known MDR		Known MOTT		History Unknown	

If Previously Treated	First Relapse		>1 Relapse		Rx After Failure		Rx After Loss to Follow Up		Other (Specify)	

Details of Treatment

Past ATT (Indicate periods of treatment)	Cat I/Cat II/Cat IV
Present ATT (on the date of specimen collection)	Not on ATT / On ATT (indicate regime & starting date) Cat I /Cat II /Cat IV

Current Sputum Smear Status of Follow Up Patients	
Positive	Negative

Duration of Treatment

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

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

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: Register of Referral for Culture and DST

Serial No.	Name of patient	Sex	Age	Treatment unit[a]	*DTB / Standard Card / BHT No*	Presumtive DR-TB case[b]	If presumptive case, reason[c]	Date of referral	Laboratory result[d]				Results of DST for positive cultures[e]				Remarks
									Microscopy	WRD	LPA	Culture	S	H	R	E	

[a] Treatment Unit: District Chest Clinic/ Name of Hospital and Ward No/ Name of Private Hospital/ Name of other units
[b] Presumptive DR-TB Suspect: **Yes/ No**; If already diagnosed MDR-TB patient, write **MDR**
[c] If presumptive DR-TB, reason: **Re**= Retreatment, **SP**= sputum not converted; **Pr**= Prisoner; **HCW**= Healthcare worker; **Contact**=Contact of MDR-TB patient; **HIV**=HIV Positive; **D**=drug addict; **Abroad**=returning from overseas; **Outside**= TB patient treated outside; **Other**=Other reasons
[d] Culture results: **Neg**=Negative; **Pos**=Positive; **Con**=Contaminated; **Decom**=Decomposed
GX – GeneXpert ; LPA – Line Probe Assay
[e] Results of DST: **R**= Resistance; **S**= Sensitive; **MS**= Moderately sensitive

4. Xpert MTB/RIF results reported as follows:

T	= MTB detected, rifampicin resistance not detected
RR	= MTB detected, rifampicin resistance detected
TI	= MTB detected, rifampicin resistance indeterminate
N	= MTB not detected
I	= invalid / no result / error

Annexure I-c: PMDT Referral for Treatment

(Fill in triplicate. Send one copy to the respective facility receiving the patient, one copy sent through patient and keep the third copy in file)

Name and address of the District Chest Clinic				
Email address of referring unit				
Name of patient		Age		Sex: M/ F
Complete Address				

laboratory test results

Date of sputum collection:	Date of GeneXpert results	Date of LPA results	Date of culture result	Date of DST result:
DST result (resistance pattern only): (specify RR or MDR-TB)				

Details of Second-line treatment

RR/MDR-TB Registration Number		Date Second-line regimen started		
Second-line treatment regimen				
Number of doses taken	Intensive Phase		Continuation Phase	
Referred for	In-door treatment		Ambulatory treatment	
Remarks				
Date				

Signature		Designation	

Reminder for the health facility where the patient has been referred:
Please send an email to the referring unit, informing the referring doctor of the date that the above-named patient reported at the receiving health facility

Annexure I-d: Checklist for Initial Evaluation and Treatment Surveillance

Initial Evaluation

Parameter	Done	Not done
Initial physician evaluation		
Smear for AFB		
Culture		
Susceptibility testing		
Chest radiograph		
Laboratory analysis (includes liver function tests, creatinine, potassium, blood urea, complete blood count, TSH, HIV)		
ß-HCG for women		
Home visit		
Family planning		
Contact screening (as per PMDT guidelines)		

Routine Surveillance During treatment

- AFB smear and culture at months 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24
- Monthly weight for 1st 6 months and 2-monthly afterwards
- Chest radiograph at end of IP, six monthly interval and as clinically indicated
- Physician evaluation every month for six months, then every two months
- Creatinine and urea monthly during IP
- TSH every six months

Annexure I-e: Second-line Treatment Card

Patient's Name:.....

DOT-provider:.....

MDR-TB Registration Number	
District TB Registration Number	

Date of MDR-TB Registration:.....

District:.....

Address:.....

.....

Contact Telephone Numbers:.....

Sex: Male ☐ Age:..... Date of Birth:..... NID No:.....

Female ☐

Site: Pulmonary ☐ Extra Pulmonary ☐

(If patient has both, report as Pulmonary)

If Extra pulmonary, site:.....

Last sputum result:.....

Lab number:..... Date:.....

HIV testing done: Yes ☐ No ☐ Unknown ☐

Registration Group (Choose one only)	
New	
Relapse	
Treatment after loss to follow-up	
Tr. after failure of Cat I treatment	
Tr. After failure of Cat II treatment	
Transfer in	
Other	

Previous anti-TB Treatment Episodes

No	Source	Start Date (If unknown put Year)	Regimen (Write regimen in drug abbreviations)	Outcome

Drug Abbreviations: H= Isoniazid, R= Rifampicin, E= Ethambutol, Z= Pyrazinamide, S= Streptomycin Am= Amikacin, Km= Kanamycin, Cfx= cifrofloxacin, Cfm= Capreomycin, Ofx= Ofloxacin, Lfx= Levofloxacin, Mfx= moxifloxacin, Gati= Gatifloxacin, Pto= protionamide, Eto= Ethionamide, Cs= Cycloserine, PAS= *p*-aminosalicylic acid

Review Panel Meetings: dates and decisions

Date	Decision	Next date		Date	Decision	Next date

Month of treatment	Sputum smear microscopy		
	Date*	Sample No	Result
Prior**			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			

Month of treatment	Culture		
	Date*	Sample No	Result
Prior**			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			

Drug Susceptibility testing (DST) results

Date*	Date DST results	S	H	R	E	K m	Lf x	

Notation method for DST:

R= Resistant S= Sensitive C= Contaminated Unk = Unknown

Notes

* Date: Date sputum collected from the patient

** Prior: The date the sputum was collected that led to the patient being registered with MDR-TB

Notation method for recording smears

No AFB	0
1-9 AFB per 100 HPF	Scanty (report number of AFB
10-99 AFB per 100 HPF	+
1-10 AFB per HPF	++
>10 AFB per HPF	+++

Notation method for recording cultures

No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

Notation Method for Recording Xpert MTB/RIF results

T	MTB detected, rifampicin resistance not detected
RR	MTB detected, rifampicin resistance detected
TI	MTB detected, rifampicin resistance indeterminate
N	MTB not detected
I	invalid / no result / error
T	MTB detected, rifampicin resistance not detected

Intensive Phase								
Date started:.....								
Drugs (Tick as appropriate) with dose								
Km	Eto	Cs	Lfx	E	Z			

Continuation Phase						
Date Started:.....						
Drugs (Tick as appropriate) with dose						
Eto	Cs	Lfx	Z			

Initial Weight (Kg)	

Interruption retrieval action

Drug regimen change: Date and details

Date	

Administration of drugs

Month	Day																														Weight (kg), lab, X-ray
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Administration of drugs

	Day																															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Mark in the boxes: ✓ = directly observed, N = Not supervised, Ø = drugs not taken Split cell diagonally to record two administrations in one day																																

Adverse drug reactions (ADR)			**Treatment outcome (Tick one)**	Date reporting	
Date	Details of adverse drug reactions and action taken		Cured		
			Treatment completed		
			Died		
			Failed		
			Loss to follow-up		
			Not evaluated		

Annexure I-f: Second-Line Treatment Register

Date registered	MDR-TB No	Previous District TB No	Name in full	Sex (M/F) / Age	Complete address	Treatment unit/ DOT Centre	Site of disease (P/EP)	Registration Group*	Previous history of treatment with second line drug	Results of DST						Second line treatment regimen
										S	H	R	E	Km	Lfx	Date started

Reason for starting second line treatment		Smear (S) and Culture (C) results during treatment																																							Outcome	HIV testing (Y/N/unknown)	Remarks
Confirmed RR/ MDR-TB case	Presumptive RR/MDR-TB case	Start of treatment M0		M 1		M 2		M 3		M 4		M 5		M 6		M 7		M 8		M 9/10		M 11/12		M 13/14		M 15/16		M 17/18		M 19/20		M 21/22		M 23/24		M 25/26		M 27/28		M 29/30		Date outcome given	Result	
		S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date	S / C	Date			

Notation method for recording smear

No AFB	0
1-9 AFB per 100 HPF	Scanty (report number of AFB
10-99 AFB per 100 HPF	+
1-10 AFB per HPF	++
>10 AFB per HPF	+++

Notation method for recording cultures

No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

Drug Abbreviation:

H= isoniazid, R=refampicin, E=Ethambutol, Z=pyrazinamide, S=Streptomycin

Km= kanamycin, Lfx=Levofloxacin, Eto=Ethionamide, Cs=Cycloserine, PAS=*p*-amino salicylic acid

Treatment Outcome:

Cured/ Tr. Completed/ Failed/ Died/ Lost to follow up/ Transferred out

Annexure I-g: PMDT Patient Identity Card

Name	
Complete Address	
Sex	Male ☐ Female ☐ Age:
RR/MDR-TB Number	
District TB Number (previous)	
District	
DOT Centre	
DOT Provider	

Treatment regimen:

Date treatment started	Date culture conversion	Date tr. outcome given

Treatment outcome:

Intensive Phase	Continuation Phase

Continuation Phase		REMEMBER	
		1.	Take care of your card
		2.	You can be cured if you follow your treatment regimen by taking your prescribed drugs regularly
		3.	Tuberculosis can spread to other people if you do not take your medications
		4.	Report any side effects to your DOT provider immediately
		5.	Remember to attend the clinic on the date given to you

Annexure I-h: Quarterly Report on RR/MDR-TB Case Finding

Patients registered in the Second-line register during: Quarter ☐ Year ☐

Name of PMDT coordinator :.....

Date of completion of the report :.....

Signature :.....

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

Presumptive DR-TB patients tested	
RR cases detected	
MDR-TB cases detected	
RR/ MDR-TB cases registered and started on Second-line treatment	

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

Category I positive at Month 2/3	Category II pre - treatment	Category II positive at Month 3/4	High risk group	New	Other

Comments**:**

Annexure I-i: Six Month Quarterly Interim Report of RR/MDR-TB Patients

(To be filled 9 months after treatment initiation)

Patients registered in the Second-line treatment register during: Quarter [ ] Year [ ]

Name of PMDT coordinator :.....

Date of completion of the report :.....

Signature :.....

Number of RR/MDR-TB cases registered on CAT IV regimen	Smear and culture results after 6 months of treatment (of patients still on treatment)									Outcomes of other patients in the cohort			
	Smear Negative			Smear Positive			Smear Unknown			Died	Lost to Follow up	Treatment Stopped due to	
												Adverse Reactions	Other Reasons
	Cul Neg	Cul Pos	Cul NK	Cul Neg	Cul Pos	Cul NK	Cul Neg	Cul Pos	Cul NK				

Comments:

Annexure 1-j: Culture Conversion Quarterly Report of RR/MDR-TB Patients

(To be filled out 15-months after treatment initiation)

Patients registered in the Second-line treatment register during: Quarter [ ] Year [ ]

Name of PMDT coordinator :.....

Date of completion of the report :.....

Signature :.....

Number of RR/MDR-TB cases registered on CAT IV regimen in the quarter	Culture Negative	Culture Positive	Culture Unknown	Died	Lost to Follow up	Treatment stopped due to	
						Adverse Reactions	Other Reasons

Comments:

Annexure I-k: Quarterly Report on the Result of Second-Line Treatment

(RR/MDR-TB patients registered 24-26 months earlier)

Patients registered in the Second-line treatment register during: Quarter ☐ Year ☐

Name of PMDT coordinator :.....

Date of completion of the report :.....

Signature :.....

Category of RR/MDR-TB patients	Number registered on second-line regimen	Cured	Treatment completed	Died	Failure	Lost to Follow up	Treatment stopped due to		Still on treatment	Total
							Adverse* Reactions	other reasons		
New										
Previously treated with 1st -line drugs only										
Preciously treated with both 1st& 2nd line drugs										
Total										

Comments:

*This number should be included in the number in the failure column (see definition of failure)

Annexure I-l: Evaluation of Completion of Second-Line Treatment

(To be maintained by the PMDT coordinator)

Patient's Name:.....

RR/MDR-TB Number

Date Second-Line Treatment Completed

Follow-up bacteriological result

	Quarter				Month		
Smear results of last three quarters				Smear results of last three months (if positive in any of the last three quarters)			
Culture results of last three quarters				Culture results of last three months (if positive in any of the last three months			

Was patient evaluated by CRP after completion of treatment? Yes ☐ No ☐

If Yes:

Comments by CRP:

Signature of PMDT coordinator: ..... Date: .....

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										
19	Loose Motion										
20	Tenesmus										
21	Numbness										
22	Change in vision/ double vision										
23	Photophobia										
24	Breast enlargement in males (Gynaecomastia)										
25	Chest Pain										
26	Palpitation										

Month		M____	M____	M____	M____	M____	M____	M____	M____	M____	M____
Date		__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Sputum	Smear										
	Culture										
	DST 1st line										
	DST 2nd 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										
Serology	Glucose (Urine)										
	Protein										
	Pregnancy test										
	Cr. clearance										
Others	TSH										
	T3										
	T4										
Investigations	CXR										
	Audiogram										
	Psychology										
	ECG										
Weight											

Annexure IV

SECOND-LINE ANTI-TB DRUG INFORMATION SHEETS

1. Amikacin
2. Capreomycin
3. Cycloserine
4. Ethionamide
5. Kanamycin
6. Levofloxacin
7. Moxifloxacin
8. Ofloxacin
9. Para-aminosalicylic acid (PAS)
10. Pyrazinamide

Amikacin (Am)	
Drug class	Aminoglycoside
Activity against TB, mechanism of action and metabolism	**Bactericidal:** Inhibits protein synthesis. Cross-resistance with kanamycin is considered complete and some data suggesting cross-resistance with capreomycin can occur. Primarily excreted unchanged through the kidney by glomerular filtration.
Dose	**Adults:** 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram). 15 mg/kg/dose, 3 times per week can be used after culture conversion is documented after initial period of daily administration. **>59 years of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week. **Children:** 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 3 days per week after initial period daily.
Preparation and administration	**Given intravenous (IV) or intramuscular (IM).** Not absorbed orally. For IV solution, mix with D5W or other solutions (in at least 100 ml of fluid for adults or 5 mg/ml for children). IM absorption can be delayed if same site is used consistently.

Amikacin (Am)	
	For IV administration, infuse over 30–60 minutes for adults; 1–2 hours for children; IM absorption is complete within 4 hours
Storage	Solution is stable at room temperature (15–25 °C); diluted solution is stable at room temperature for at least 3 weeks or in the refrigerator for at least 60 days.
CSF penetration	Variable penetration; appears to penetrate inflamed meninges better.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided during pregnancy due to congenital deafness seen with streptomycin and kanamycin. Can be used while breastfeeding. **Use in renal disease:** Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. 12–15 mg/kg/dose after dialysis 2–3 times weekly (not daily). The drug is variably cleared by haemodialysis. **Use in hepatic disease:** Drug concentrations not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution in patients with severe liver disease as it may progress rapidly to hepato-renal syndrome.
Adverse reactions	**Common:** Local pain with intramuscular injections. Proteinuria. **Occasional:** Nephrotoxicity, ototoxicity (hearing loss), vestibular toxicity (vertigo, ataxia, dizziness). All increases with advanced age and prolonged use. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia, and hypomagnesaemia. **Rare:** Neuropathy, rash.
Contraindications	**Pregnancy —** relative contraindication (congenital deafness). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular or auditory impairment.
Drug interactions	Co-administration of loop diuretics (furosemide) and aminoglycoside antibiotics carries an increased risk of ototoxicity.

Amikacin (Am)	
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Patient instructions and alerting symptoms	**Instruct patients to inform their health care provider right away if any of the following occurs:** • Problems with hearing, dizziness or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Swelling, pain or redness at your IV site • Muscle twitching or weakness.

Capreomycin (Cm)	
Drug class	Cyclic polypeptide
Activity against TB, mechanism of action and metabolism	**Bactericidal:** has strong anti-TB activity; inhibits protein synthesis. Some data suggest cross-resistance with amikacin and kanamycin
Dose	**Adults:** 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 g, but a large, muscular person could receive more and should have the concentrations monitored). 15 mg/kg/dose, 2–3 times per week after an initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations). **>59 years of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after the initial period. Alternatively, 15 mg/kg/dose, 3 times per week. **Children:** 15–30 mg/kg/day (max 1 g), 5–7 days per week.

Capreomycin (Cm)	
	130 mg/kg/day (max 1 g), 2–3 days per week after initial period daily. **Renal failure/dialysis:** 12–15 mg/kg/dose, 2–3 times weekly (not daily). **Markedly obese individuals** should have an adjusted dose due to decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. **For dosing, use adjusted weight as follows:** Ideal body weight +40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft. Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft. *Serum concentrations should be followed closely when possible.*
Route of administration	IV or IM
Preparation	Capreomycin is available in vials of 1 gram for either IM or IV administration. The contents of the vial should be reconstituted with 2 ml or more of normal saline or sterile water.
Storage	Package insert indicates that reconstituted capreomycin can be stored in the refrigerator up to 24 hours prior to use. Other data suggest that it may be held for 14 days in the refrigerator or 2 days at room temperature (15–25 °C).
Oral absorption	There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.
CSF penetration	There is a paucity of data regarding capreomycin's penetration of the meninges.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided during pregnancy due to congenital deafness seen with streptomycin and kanamycin. There are case reports of its safe use in pregnancy (unaffected new-borns). Can be used while breastfeeding. **Use in renal disease:** Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in

Capreomycin (Cm)	
	severe liver disease; however, use with caution – some patients with severe liver disease may progress rapidly to hepatorenal syndrome.
Adverse reactions	Similar to the aminoglycosides. Nephrotoxicity: 20–25% including proteinuria, reduced creatinine clearance, and depletion of potassium and magnesium. Ototoxicity (hearing loss): Occurs more often among the elderly or those with pre-existing renal impairment and vestibular toxicity. Local pain with intramuscular injections. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia and hypomagnesaemia.
Contraindications	**Hypersensitivity to capreomycin.** Some experts would not use capreomycin if vestibular side-effects resulted from aminoglycoside use. **Generally avoided during pregnancy** due to congenital deafness seen with aminoglycosides and mechanism of ototoxicity may be similar with capreomycin. There are case reports of its safe use during pregnancy (unaffected new-borns).
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any other concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor capreomycin concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Patient instructions and alerting symptoms	**Instruct patients to inform their health care provider right away if any of the following occurs:** • Rash • Fever or chills • Bleeding or bruising • Problems with hearing, dizziness or balance • Bleeding or a lump where the shot is given • Decreased urination • Trouble breathing • Muscle weakness

Cycloserine (Cs)	
Drug class	Analog of D-alanine
Activity against TB, mechanism of action and metabolism	**Bacteriostatic:** inhibits cell wall synthesis.
Dose	**Adults:** 10–15 mg/kg/day usually (max. 1000 mg/day); Usually 500–750 mg/day given in two divided doses or once a day if tolerated. Some patients may require only alternate day 250 mg and 500 mg dosing to avoid toxicity. **Children:** 10–20 mg/kg/day divided every 12 hours (daily maximum 1 g). **Pyridoxine (vitamin B6):** Although supporting data are not extensive, MDR-TB experts recommend that all patients should receive vitamin B6 while taking cycloserine. Adults need 100 mg or more (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day). **Renal failure/dialysis:** 250 mg once daily or 500 mg, 3 times per week; monitor drug concentrations to keep peak concentrations <35 mcg/ml.
Route of administration:	Oral; not available parenterally.
Preparation:	250 mg capsule.
Storage	Room temperature (15–25 °C) in airtight containers.
Oral absorption	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids or orange juice.
CSF penetration	Concentrations approach those in serum.
Special circumstances	**Use in Pregnancy/breastfeeding**: Not well studied, but no teratogenicity documented. Use if there are not better choices. Can be used while breastfeeding (dose the infant with vitamin B6 if breastfed). **Use in Renal disease**: Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see above). Use with caution. **Use in Hepatic Disease:** Not associated with hepatotoxicity.

Cycloserine (Cs)	
Adverse reactions	CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis and suicidal ideation, usually occur at peak concentrations >35 mcg/ml, but may be seen in the normal therapeutic range. Other side-effects include peripheral neuropathy and skin changes. Skin problems include lichenoid eruptions and Stevens-Johnson syndrome.
Contraindications	Relative contraindications include seizure disorder, psychotic disease or alcohol abuse.
Monitoring	Peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept below 35 mcg/ml. Baseline and monthly monitoring for depression using a tool such as the Beck Depression Index should be done.
Patient instructions and alerting symptoms	If food is taken, avoid a large fatty meal. Avoid alcohol. You must also take a high-dose vitamin B6 supplement while on this drug. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Seizures • Shakiness or trouble talking • Depression or thoughts of hurting yourself • Anxiety, confusion or loss of memory • Personality changes, such as aggressive behavior • Rash or hives • Headache.

Ethionamide (Eto)	
Drug class	Carbothionamides group, derivatives of isonicotinic acid
Activity against TB, mechanism of action and metabolism	**Weakly Bacteriostatic.** blocks mycolic acid synthesis
Dose	**Adults:** 15–20 mg/kg/day frequently divided (max dose 1 gram per day); usually 500–750 mg per day in 2 divided doses or a single daily dose. **Children:** 15–20 mg/kg/day usually divided into 2–3 doses (max dose 1 gram per day). A single

Ethionamide (Eto)	
	daily dose can sometimes be given at bedtime or with the main meal. Many individuals require gradual ramping up of the dose and treatment for gastrointestinal upset. **Pyridoxine (vitamin B6):** Although there is little supporting data, most MDR-TB experts recommend that all patients should receive vitamin B6 while taking ethionamide. Suggested dose for adults is 100 mg and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day). **Renal failure/dialysis:** No change
Route of administration	Oral; not available parenterally.
Preparation	Coated 250 mg tablet.
Storage	Store at room temperature (15-25 °C)
Oral absorption	Erratic absorption, possibly due to gastrointestinal disturbances associated with the medication.
CSF penetration	Concentrations approach those in the serum; one paediatric study evaluating drug concentrations in the CSF suggests that ethionamide should be dosed on the high end of the range for patients with meningitis.
Special circumstances	**Use in Pregnancy/breastfeeding**: Generally avoided during pregnancy due to reports of teratogenicity; little data about use during breastfeeding – an estimated 20% of the infant therapeutic dose will be passed on to the baby in the breast milk (dose the infant with vitamin B6 if breastfed). **Use in Renal disease:** No precautions are required for renal impairment. **Use in Hepatic disease:** Can cause hepatotoxicity similar to that of isoniazid – use with caution in liver disease.
Adverse reactions:	Gastrointestinal upset and anorexia: sometimes intolerable (symptoms are moderated by food or taking at bedtime). Premedication with an antiemetic like ondansetron is often helpful. Low dose Ativan 0.5 mg has also been used successfully. Metallic taste. Hepatotoxicity. Endocrine effects: Gynaecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism – treat with thyroid replacement. Neurotoxicity (patients taking ethionamide should take high doses of vitamin B6). Side

Ethionamide (Eto)	
	effects may be exaggerated in patients also taking cycloserine.
Contraindications	Sensitivity to ethionamide.
Monitoring	Monitor thyroid stimulating hormone for evidence of hypothyroidism requiring replacement; therapeutic drug monitoring required if malabsorption is suspected. Monitor liver function tests.
Patient instructions and alerting symptoms	Take this medicine with food. You must also take a high-dose vitamin B6 supplement while on this drug. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Any problems with your eyes: eye pain, blurred vision, colour blindness or trouble seeing • Numbness, tingling or pain in your hands or feet • Unusual bruising or bleeding • Personality changes such as depression, confusion or aggression • Yellowing of your skin or eyes • Dark-colored urine • Nausea and vomiting • Dizziness • Swollen breasts (in men).

Kanamycin (Km)	
Drug class	Aminoglycoside
Activity against TB, mechanism of action and metabolism	**Bactericidal:** has strong anti-TB activity. Cross-resistance with amikacin and some data suggesting cross-resistance with capreomycin; inhibits protein synthesis.
Dose	**Adults:** 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram, but a large, well-built person could receive more and should have concentrations monitored). **>59 years of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose, 3 times per week. **Children:** 15–30 mg/kg/day (max 1 gram) 5–7 days per week. Renal failure/dialysis: 12–15 mg/kg/dose, 3 times weekly. Markedly obese

Kanamycin (Km)	
	individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. **For dosing, use adjusted weight as follows:** Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft *If possible, concentrations should be followed closely.*
Route of administration	IV or IM; not absorbed orally.
Preparation	250 mg/ml in vials of 500 mg or 1 gram; 1 gram in 3 ml vial; or 75 mg/vial for infants. Can be mixed with D5W or normal saline for intravenous infusion. Adult IV doses should be mixed in at least 100 ml of fluid, and paediatric IV doses should be mixed to a concentration of at least 5 mg/ml. For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children.
Storage	The product supplied by the Global Drug Facility does not need storage in in the refrigerator.
Oral absorption	Not absorbed orally; 40–80% of the dose is absorbed intramuscularly.
CSF penetration	Minimal and variable CSF penetration – slightly better with inflamed meninges.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided in pregnancy due to documented congenital deafness. Can be used while breastfeeding. **Use in renal disease:** Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. The drug is variably cleared by haemodialysis. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution because patients with severe liver disease may progress rapidly to hepatorenal syndrome.

Kanamycin (Km)	
	Diuretic use: Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Adverse reactions	Nephrotoxicity: Appears to be more nephrotoxic than streptomycin. Ototoxicity (hearing loss) and vestibular toxicity: Increases with advanced age and prolonged use; appears to occur slightly more commonly with kanamycin than with streptomycin and about the same frequency as amikacin. Kanamycin seems to have slightly less vestibular toxicity.
Contraindications	**Pregnancy** (congenital deafness seen with streptomycin and kanamycin use in pregnancy); **hypersensitivity to aminoglycosides;** caution with renal, vestibular or auditory impairment; patients with intestinal obstructions.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment is present); document creatinine clearance if there is baseline renal impairment or any other concern; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Patient instructions and alerting symptoms	**Instruct patients to inform their health care provider right away if any of the following occurs:** • Problems with hearing; dizziness or balance • Rash or swelling of face • Trouble breathing • Decreased urination • Swelling, pain, redness at injection site • Muscle twitching or weakness

Levofloxacin (Lfx)	
Drug class	Fluoroquinolone
Activity against TB, mechanism of action and metabolism	**Bactericidal:** has strong anti-TB activity. Cross-resistance with other fluoroquinolones but may not be complete. Data suggests

Levofloxacin (Lfx)	
	greater activity than ciprofloxacin or ofloxacin. Inhibits DNA gyrase.
Dose	**Adults:** For treatment of TB disease 10–15 mg/kg once daily. **Children:** 5 years and under: 15–20 mg/kg split into two doses (morning and evening). Over 5 years: 10–15 mg/kg once daily. **Renal failure/dialysis:** 750–1000 mg/dose, 3 times weekly (not daily) for creatinine clearance <30 ml/min.
Route of administration	Oral or intravenous.
Preparation	Coated tablets (250 mg, 500 mg, 750 mg); solution for injection 25 mg/ml; 250 mg in 50 ml container; 500 mg in 100 ml container; 750 mg in 150 ml container. Oral suspension is 25 mg/ml.
Storage	Oral forms, undiluted solution, and pre-mixed solutions are stored at room temperature (15–25 °C). Once diluted, the solution can be kept at room temperature for 3 days, in the refrigerator for 2 weeks, or frozen for 6 months.
Oral absorption	Excellent oral absorption. Levofloxacin in an anion and taking with divalent cations will result in bonding and not being absorbed: administrate two hours before or four hours after ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Concentrations are 65% of that in the serum.
Special circumstances	**Use in pregnancy/breastfeeding:** Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to possibility of arthropathy. However, there are a few case reports of fluoroquinolones being used safely during pregnancy. **Use in renal disease:** Dosage adjustment is recommended if creatinine clearance is <50 ml/min. The drug is not cleared by haemodialysis; supplemental doses after dialysis are not necessary. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease. Presumed to be safe in severe liver disease.
Adverse reactions	Nausea and bloating. Headache, dizziness, insomnia or tremulousness.

Levofloxacin (Lfx)	
	Rare tendon rupture, arthralgias (can usually be treated symptomatically). QTc prolongation, hypoglycaemia.
Contraindications	Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication).
Monitoring	Side effect monitoring, but no specific laboratory monitoring required.
Patient instructions and alerting symptoms	You can take levofloxacin with food. Drink plenty of beverages. Do not take milk-based products, antacids (especially aluminum- containing), mineral supplements such as iron or magnesium, or multivitamins within 2 hours of this medication or within 4 hours after. This medicine may cause sun sensitivity; use sunscreens. Do not undertake new strenuous activities. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing or tightness in your chest • Diarrhoea • Yellow skin or eyes • Anxiety, confusion or dizziness.

Moxifloxacin (Mfx)	
Drug Class:	Fluoroquinolone
Activity against TB, mechanism of action and metabolism	**Bactericidal:** inhibits DNA gyrase; cross-resistance with other fluoroquinolones, but may be more active based on in vitro data
Dose	**Adults:** 400 mg daily (oral or IV). **Children:** No established dose. **Renal failure/dialysis:** No dose adjustment required.
Route of administration	Oral or intravenous.
Preparation	Tablets (400 mg); aqueous solution (400 mg/250 ml) for IV injection.
Storage	Store oral and IV products at room temperature (15–25 °C). Do not refrigerate.
Oral absorption	Good oral absorption (90% bioavailable). Moxifloxacin is an anion and taking with divalent cations will result in bonding and not

Moxifloxacin (Mfx)	
	being absorbed: Administrate 2 hours before or 4 hours after ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Good penetration in animal model studies.
Special circumstances	**Use in pregnancy/breastfeeding:** Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to possibility of arthropathy. However, there are a few case reports of fluoroquinolones being used safely during pregnancy. **Use in renal disease:** Excretion unchanged during renal failure; no data on effect of dialysis. **Use in hepatic disease:** Rarely associated with hepatotoxicity; use with caution. No dose adjustment required for mild or moderate liver disease.
Adverse reactions	Nausea and diarrhoea. Headache and dizziness. Rare tendon rupture; arthralgias. Rare hepatotoxicity. QTc prolongation, hypo/hyperglycaemia.
Contraindications	Fluoroquinolone intolerance, prolonged QTc.
Monitoring	Symptomatic monitoring.
Patient instructions and alerting symptoms	Moxifloxacin can be taken with food, but do not take milk-based products, antacids (especially aluminum-coating), vitamin supplements, or sucralfate within 2 hours of this medication or 4 hours after. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing or tightness in your chest • Diarrhoea • Yellow skin or eyes • Anxiety, confusion or dizziness.

Ofloxacin (Ofl)	
Drug class	Fluoroquinolones
Activity against TB, mechanism of action and metabolism	**Bactericidal**: Acts by inhibiting the A subunit of DNA gyrase (topoisomerase) which is essential in the reproduction of bacterial DNA. There is no cross-resistance with other antituberculosis agents, but complete cross-resistance between ofloxacin and ciprofloxacin. There is limited metabolism to desmethyl and N-oxide metabolites; desmethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 65 to 80% of a dose is excreted unchanged in the urine over 24 to 48 hours, resulting in high urinary concentrations.
Preparation and dose	200 or 400 mg tablets. Usual dose: 600 to 800 mg daily in one or two divided doses.
Storage	Room temperature (15-25^{o} C), airtight containers protected from light.
Oral absorption	90-98% oral absorption.
Distribution, CSF penetration	About 25% is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF, and tissue penetration is good. It crosses the placenta and is distributed into breast milk. It also appears in the bile.
Special circumstances	**Pregnancy/breastfeeding:** Usually compatible with the breastfeeding. **Renal disease:** Doses of ofloxacin should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 600 – 800 mg 3 times/week.
Adverse reactions	Generally well tolerated. **Occasional**: GI intolerance; CNS-headache, malaise, insomnia, restlessness, and dizziness. **Rare**: allergic reactions; diarrhoea; photosensitivity; increased LFTs; tendon rupture; peripheral neuropathy.
Drug interactions	Fluoroquinolones are known to inhibit hepatic drug metabolism and may interfere with the clearance of drugs, such as theophylline and caffeine that are metabolised by the liver. Cations such as aluminium, magnesium, or iron reduce the absorption of ofloxacin and related drugs when given concomitantly. Changes in the pharmacokinetics of fluoroquinolones have been reported when given with histamine H2 antagonists, possibly due to changes in gastric pH, but do not seem to be of much clinical significance.

Ofloxacin (Ofl)	
	The urinary excretion of ofloxacin and some other fluoroquinolones is reduced by probenecid; plasma concentrations are not necessarily increased.
Contraindications	Pregnancy, intolerance of fluoroquinolones
Alerting symptoms	• Pain, swelling or tearing of a tendon or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing • Diarrhoea • Yellow skin or eyes • Anxiety, confusion, or dizziness

Para-Amino Salicylic Acid (PAS)	
Drug class	Salicylic-acid. anti – folate
Activity against TB, mechanism of action and metabolism	**Bacteriostatic.**
Dose	**Adults:** 8–12 g per day divided 2–3 times per day **Children:** 200–300 mg/kg/day divided 2–4 times per day **Renal failure/dialysis:** No change
Route of administration	Oral; should be given sprinkled on or stirred into yogurt or similar food.
Preparation	4 g per packet
Storage	Packets should be kept in the refrigerator or freezer
Oral absorption	Incomplete absorption – sometimes requires increased doses to achieve therapeutic concentrations
CSF penetration	Poorly penetrates the meninges (somewhat better with inflammation)
Special circumstances	**Use during pregnancy/breastfeeding:** Not studied, but no teratogenicity known. There is little data regarding use during breastfeeding. In one patient, the milk concentration was 1 mcg/ml compared to a serum concentration of 70 mcg/ml **Use in renal disease:** Inactive metabolite is cleared by the kidneys. The package insert says to avoid with severe renal failure. Other authorities believe it can be used with caution (toxicity of metabolite not known) **Use in hepatic disease:** Use with caution; 0.5% incidence of hepatotoxicity

Para-Amino Salicylic Acid (PAS)	
Adverse reactions	Gastrointestinal distress (less with the PASER® formulation than with older preparations) Rare hepatotoxicity and coagulopathy Reversible hypothyroidism (increased risk with concomitant use of ethionamide); treat with thyroid replacement
Contraindications	Pregnancy (relative).
Monitoring	Monitor TSH, electrolytes, blood counts and liver function tests.
Patient instructions and alerting symptoms	New presentation of PASER® does not need storage in refrigerator or freezer. Sprinkle granules over apple-sauce or yogurt or swirl in acidic juices (tomato, grape, grapefruit, cranberry, apple or orange). Do not chew the granules. Take with food if desired. Do not use the packet if it is puffed up or if the granules are discoloured. Gastrointestinal discomfort and diarrhoea usually improve over time. The shells of the granules may be seen in the stool, which is normal. **Instruct patients to inform their health care provider right away if any of the following occurs** • Skin rash, severe itching or hives • Severe abdominal pain, nausea or vomiting • Unusual tiredness or loss of appetite • Black stool or bleeding

Pyrazinamide (Pza)	
Drug class	Synthetic derivative of nicotinamide.
Activity against TB, mechanism of action and metabolism	**Bactericidal** for semi-dormant *M. tuberculosis*. Mechanism unclear.
Dose	**Adults:** 25 mg/kg/day (max dose 2 g). Intermittent dosing at twice or thrice weekly up to 50 mg/kg can be given. **Children:** 30–40 mg/kg/dose. **Renal failure/dialysis:** 25 mg/kg/dose, 3 times per week (not daily). **Obesity:** Use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft

Pyrazinamide (Pza)	
Route of administration	Oral; not available parenterally.
Preparation	500 mg scored or unscored tablet.
Storage	Store the tablets at room temperature (15–25 °C).
Oral absorption	Well absorbed from the gastrointestinal tract.
CSF penetration	Concentrations equivalent to serum.
Special circumstances	**Use during pregnancy/breastfeeding:** In the United States, pyrazinamide is avoided during pregnancy for drug-susceptible disease due to lack of data regarding teratogenicity, but should be used for drug-resistant TB when the isolate is sensitive to pyrazinamide (no known teratogenicity). Can be used while breastfeeding. **Use in renal disease:** Cleared by the kidneys; dose 3 times a week and after dialysis. **Use in hepatic disease:** Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. It can be quite severe and worsen treatment progress.
Adverse reactions	Gout (hyperuricaemia) and arthralgias. Hepatotoxicity. Rash. Photosensitivity. Gastrointestinal upset
Contraindications	Allergy to pyrazinamide; severe gout.
Monitoring	Monitor transaminases and uric acid.
Patient instructions and alerting symptoms	May be taken with or without food; this medicine may cause a rash after sun exposure, so limit sun exposure **Instruct patients to inform their health care provider right away if any of the following occurs** • Skin rash, severe itching or hives • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual tiredness or loss of appetite.

Annexure V

INSTRUCTIONS FOR COLLECTION & TRANSPORT OF SPECIMENS FOR TB CULTURE AND XPERT MTB/RIF TEST

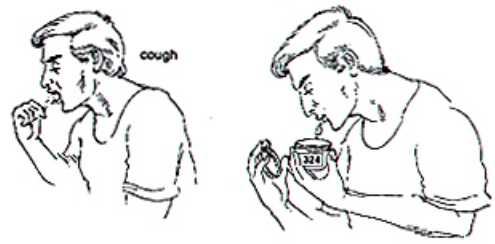
1. Container

Sterile Universal bottle, which is a heavy glass, screw-capped bottle with a wide neck
Use the bottles within the expiry date, mentioned on the bottle by the laboratory issuing the bottle.

2. Sputum Collection

If a patient has a productive cough, the patient is given a container on his first attendance. He should be instructed, 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,

o 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 conditions do not permit collection of outdoor, 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, refrigerated or kept in as cool as possible 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. Universal containers must be packaged to Cool Boxes which should be robust and leak proof.
2. Pack Universal containers with enough absorbent material so that if they are damaged or leak, the fluids will be absorbed.

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