Revised National Tuberculosis Control Programme

Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India

Central TB Division, Directorate General of Health Services,
Ministry of Health & Family Welfare, Nirman Bhavan, New Delhi – 110011

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May 2012

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Annexure

I. RNTCP Request for Culture and Drug Sensitivity Testing
II. LPA Certification Mechanism
III. RNTCP PMDT Referral for Culture-DST Register for Diagnosis and Follow-up Cultures (held at the DTC)
IV. RNTCP Laboratory Culture and DST Register
V. RNTCP PMDT Referral for Treatment Form
VI. Follow-up schedule during MDR TB treatment
VII. Checklist for initial evaluation and treatment surveillance
VIII. RNTCP PMDT Treatment Card
IX. RNTCP PMDT Treatment Register
X. RNTCP PMDT TB Identity Card
XI. RNTCP PMDT Quarterly report on Case Finding
XII. RNTCP PMDT Six Month Interim Report
XIII. RNTCP PMDT Twelve Month Culture Conversion Report
XIV. RNTCP PMDT Report on Result of Treatment of M/XDR-TB patients
XV. Evaluation at Completion of M/XDR TB Treatment
XVI. Specifications of Monthly PWB for M/XDR TB Patients
XVII. Formats for Drug Logistics Management of 2nd line drugs under PMDT
XVIII. Composition and Terms of Reference of the various administrative structures under RNTCP PMDT
XIX. Job responsibilities of various categories of staff under PMDT
XX. Guidelines for PMDT Training Plan
XXI. PMDT appraisal format for State, DR-TB Centre, C-DST Laboratories, State Drug Store (SDS) and Districts
XXII. Summary of recommendations for Airborne Infection Control in M/XDR-TB Wards
XXIII. Second Line anti-TB drugs information sheets

Abbreviations and Acronyms

AFB	Acid Fast Bacilli
Category IV	Regimen for MDR TB
Category V	Regimen for XDR TB
CP	Continuation Phase
CPC	Cetyl Pyridinium Chloride
CNS	Central Nervous System
Cs	Cycloserine
CTD	Central TB Division
DMC	Designated Microscopy Centre
DOT	Directly Observed Treatment
DRS	Drug Resistance Surveillance
DR-TB	Drug resistant tuberculosis
DST	Drug Sensitivity Testing
DTC	District TB Centre
DTO	District TB Officer
E	Ethambutol
EQA	External Quality Assessment
Eto	Ethionamide
GFATM	Global Fund to fight AIDS, TB and Malaria
GLC	Green Light Committee
GoI	Government of India
GMSD	Government Medical Store Depot
H	Isoniazid
HAART	Highly Active Anti-Retroviral Therapy
HCW	Health Care Worker
HIV	Human Immunodeficiency Virus
HRD	Human Resource Development
IP	Intensive Phase
IRL	Intermediate Reference Laboratory
Km	Kanamycin
Lfx	Levofloxacin
LJ	Lowenstein-Jensen
LRS	Lala Ram Sarup TB Institute, Delhi
LT	Laboratory Technician
LPA	Line Probe Assay
MDR-TB	Multidrug-resistant Tuberculosis
MGIT	Mycobacterium Growth Inhibitory Testing
MIC	Minimal Inhibitory Concentration
MO	Medical Officer
MO-PHI	Medical Officer – Peripheral Health Institute
MO-TC	Medical Officer – TB Control
NaCl	Sodium Chloride
NIRT	National Institute for Research in Tuberculosis (erstwhile TRC)
NGO	Non-Governmental Organisation
NRL	National Reference Laboratory
NTI	National TB Institute, Bangalore
PAS	*p*-aminosalicylic acid
NTM	Non-tuberculous Mycobacteria

Ofx	Ofloxacin
PNB	*p*-nitrobenzoic acid
R	Rifampicin
RNTCP	Revised National TB Control Programme
S	Streptomycin
SEARO	WHO South-East Asia Regional Office
SNRL	Supra-National Reference Laboratory
SOP	Standard Operating Procedures
STDC	State TB Training and Demonstration Centre
STLS	Senior TB laboratory Supervisor
STO	State TB Officer
STR	Standardized Treatment Regimen
STS	Senior TB Treatment Supervisor
TB	Tuberculosis
TRC	TB Research Centre, Chennai
VCTC	Voluntary Counselling and Testing Centre
WHO	World Health Organization
Z	Pyrazinamide
ZN	Ziehl-Neelsen

INTRODUCTION

The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multidrug-resistant TB (MDR-TB), has become a significant public health problem in a number of countries and an obstacle to effective TB control. In India, the available information from the several drug resistance surveillance studies conducted in the past suggest that the rate of MDR-TB is relatively low in India. However this translates into a large absolute number of cases and as yet the management of patients with MDR-TB is inadequate. Specific measures are being taken within the Revised National Tuberculosis Control Programme (RNTCP) to address the MDR-TB problem through appropriate management of patients and strategies to prevent the propagation and dissemination of MDR-TB.

The term "Programmatic Management of Drug Resistant TB" (PMDT) (erstwhile DOTS Plus), refers to programme based MDR-TB diagnosis, management and treatment. These guidelines promote full integration of basic TB control and PMDT activities under the RNTCP, so that patients with TB are evaluated for drug-resistance and placed on the appropriate treatment regimen and properly managed from the outset of treatment, or as early as possible. These guidelines also integrate the identification and treatment of more severe forms of drug resistance, such as extensively drug resistant TB (XDR-TB, defined later)

Finally, the guideline introduces new standards for registering, monitoring and reporting outcomes of multidrug-resistant TB cases. This uniform information management system will allow systematic, consistent data collection and analysis which will facilitate appropriate supervision and monitoring of the PMDT activities and will play an important role in shaping future policies and recommendations.

CHAPTER 1: BACKGROUND & FRAMEWORK FOR EFFECTIVE CONTROL OF MULTI DRUG-RESISTANT TUBERCULOSIS

1.1 Chapter objective

The chapter summarizes key information on the emergence of drug-resistant TB, its public health impact, experience gained in patient management, and strategies for addressing drug resistance within RNTCP. The objective of this chapter is also to describe the framework approach to PMDT, the five essential components of the PMDT strategy, and the need to tailor these components to local situation, within the context of RNTCP.

1.2 Prevention of MDR TB

It is well known that poor treatment practices breed drug resistance. Areas with a poor TB control tend to have higher rates of drug resistant TB. It has been acknowledged that good treatment is a pre-requisite to the prevention of emergence of resistance. **RNTCP recognises that implementation of a good quality DOTS programme is the first priority for TB control in the country.** Prevention of emergence of MDR-TB in the community is more imperative rather than its treatment. It is impossible to tackle the problem of drug-resistant TB through treatment alone; each MDR TB case costs more than 20 times the cost of a simple drug-susceptible TB case. **Therefore basic TB diagnostic and treatment services would be prioritised with the view that DOTS reduces the emergence of MDR-TB, and therefore the need for PMDT over time.** PMDT services, for management of MDR-TB, are supplementary services under the expanded framework of the DOTS package.

The first WHO endorsed PMDT services began in 2000. At that time, the Green Light Committee (GLC) was established to promote access to high quality second-line drugs for appropriate use in TB control programmes. PMDT pilot projects have demonstrated the feasibility and effectiveness of MDR-TB treatment in less affluent countries. In 2002, the Global Fund to fight AIDS, TB, and Malaria (GFATM) started financing TB control programmes, including MDR-TB, thus greatly reducing the economic barrier to MDR-TB control. Since then, PMDT projects have multiplied rapidly. Based on data and experience from these projects, practices and further scientific evidence have emerged regarding services for MDR-TB. PMDT services can and should strengthen basic TB control services.

Detection and treatment of all forms of TB, including multidrug-resistant forms, should be integrated into national TB control programmes. Improperly treated patients with resistant

strains of TB are a source of ongoing transmission of resistant strains, resulting in added future costs. The framework for PMDT treatment of MDR-TB cases presented in this document is to be integrated into the RNTCP DOTS strategy.

1.3 Causes of drug-resistant tuberculosis

Drug-resistant TB has microbial, clinical, and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB. Table 1.1 summarizes the common causes of inadequate treatment. However it should be stressed that MDR-TB is a man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of MDR-TB.

Table 1.1 Causes of inadequate treatment [1]

Providers/Programmes: Inadequate regimens	**Drugs: Inadequate supply/quality**	**Patients: Inadequate drug intake**
-Absence of guidelines or inappropriate guidelines -Non-compliance with guidelines -Inadequate training of health staff -No monitoring of treatment -Poorly organized or funded TB control programmes	-Non-availability of certain drugs (stock-outs or delivery disruptions) -Poor quality -Poor storage conditions -Wrong dosages or combination	-Poor adherence (or poor DOT) -Lack of information -Non-availability of free drugs -Adverse drug reactions -Social and economic barriers -Mal-absorption -Substance abuse disorders

Use of inadequate treatment in patients with drug-resistant TB strains will fail to cure a significant proportion of such cases, and can create even more resistance to the drugs in use. Ongoing transmission of established drug-resistant strains in health care facilities is also believed to be a major source of new drug resistant cases.

1.4 Addressing the sources of MDR-TB

The framework approach described in these guidelines, including the integration of PMDT into DOTS can help identify and curtail possible sources of drug-resistant TB.

The factors that may be contributing to the development of new cases of MDR-TB should be reviewed (see Table 1.1 for list of possible factors). Well administered first-line treatment for susceptible cases is the best method to prevent the development of resistance in such cases. Timely identification of MDR-TB cases and adequately administered treatment regimens are

essential to stop primary transmission. DOTS - PMDT integration works synergistically to shut down all the potential sources of TB transmission.

1.5 Magnitude of the MDR-TB problem in India

Drug resistant tuberculosis has frequently been encountered in India and its presence has been known virtually from the time anti-tuberculosis drugs were introduced for the treatment of TB. There have been a number of reports on drug resistance in India in the past, but most studies used non-standardized methodologies and biased or small samples, usually from tertiary level care facilities.

Multi-drug resistant TB (MDR-TB) is **defined as *M. tuberculosis* resistant to isoniazid and rifampicin with or without resistance to other drugs**. The prevalence is found to be at a low level in most of the country where it has been studied. Data from studies conducted by NIRT (erstwhile TRC) and NTI, have found MDR-TB levels of 1% to 3% in new cases and around 12% in re-treatment cases.[3,4] A retrospective analysis of various randomized clinical trials conducted by the TRC with various rifampicin containing regimens in the initial intensive phase, and with and without rifampicin in the continuation phase, revealed an overall emergence of resistance to rifampicin in only 2% of patients, despite a high level (18%) of initial resistance to isoniazid, either alone or in combination with other anti-TB drugs.[5] With a rapid increase in coverage of the RNTCP and the high cure rate observed in most regions, a similar trend of low emergence of resistance is expected across the country.

RNTCP has recently undertaken three community-based state level drug resistance surveillance (DRS) studies in Gujarat, Maharashtra and Andhra Pradesh. These surveys have been conducted as per a common generic protocol based on internationally accepted methodology and have estimated the prevalence of MDR-TB to be about 3% in new cases and 12-17% in re-treatment cases.[6] The data from the recent studies also indicates that there has been no clear evidence of an increase in prevalence of drug resistance over the past several years. DRS surveys are also being undertaken in Western Uttar Pradesh. DRS Surveys are also initiated in Tamil Nadu in 2011 and planned in Rajasthan, Madhya Pradesh and West Bengal in 2012.

Although the proportion is small, the number of persons with MDR TB is sizeable in numbers. WHO has estimated that in 2009, 99,000 cases of MDR TB emerged in the country including those outside RNTCP. Among these, 64,000 were estimated to have emerged from TB cases notified to RNTCP. If left undiagnosed or poorly treated, MDR-TB patients often

live and suffer for months to years before succumbing to the disease; hence transmission of MDR can continue, amplifying MDR in the community.

1.6 Special considerations for PMDT

After successfully establishing the DOTS services across the country in 2006, RNTCP introduced the PMDT services since 2007 to address the needs of this group of patients and is now rapidly scaling up services across the country while also expanding services towards universal access.

RNTCP views the treatment of MDR-TB patients as a "standard of care" issue. Recognizing that the treatment of MDR-TB cases is very complex, the treatment will follow the internationally recommended PMDT guidelines.

PMDT is more complex than the basic DOTS strategy. For PMDT to be successful, special attention is needed for the following:

- Efficient and timely identification of patients who require DST;
- Quality-assured laboratory capacity (Smear, Culture-DST, rapid molecular test);
- Efficient drug procurement and supply chain management;
- Adherence to difficult-to-take regimens for long periods;
- Prompt identification and management of side-effects;
- Recording and reporting; and
- Human and financial resources.

The method of case finding is designed using a gradually expanding approach towards universal access taking into consideration the resources and technical capacity available to the RNTCP at different points in time. The framework presented in this document is designed to address the challenges faced by RNTCP in relation to MDR-TB in India.

1.7 The PMDT framework for the management of multidrug-resistant TB

The framework is organized around the same five components of the DOTS strategy, as the underlying principles are the same. The core components are comprehensive, ensuring that all essential elements of the PMDT strategy are included, and are:

1. Sustained political and administrative commitment;
2. Accurate, timely diagnosis through quality assured culture and drug susceptibility testing;
3. Appropriate treatment utilizing second-line drugs under strict supervision;
4. Uninterrupted supply of quality assured anti-TB drugs; and

5. Standardized recording and reporting system.

Each of these components involves more complex and costly operations than those for controlling drug sensitive TB. However addressing multidrug-resistant TB will strengthen the existing TB control programme.

1.7.1 Sustained political and administrative commitment

Sustained political and administrative commitment is essential to establish and maintain the other four components. It requires both long term investment and leadership in ensuring an appropriate environment for integrating the management of MDR-TB into the basic RNTCP. An appropriate PMDT environment includes adequate infrastructure, development and retention of human resources, inter-agency cooperation, TB control policies enabling rational PMDT implementation, and facilitation of the procurement of quality-assured second-line anti-TB drugs. In addition, the existing RNTCP activities must be strengthened to prevent the emergence of more MDR-TB cases.

The RNTCP budget must be sufficient for the development and retention of an adequate work force with interest and expertise in MDR-TB without weakening the workforce of the TB programme as a whole. The patient should have no financial barrier to appropriate care for MDR-TB.

1.7.2 Diagnosis of drug-resistant TB through quality assured, timely culture and DST

Accurate and timely diagnosis is the backbone of the PMDT activities. MDR-TB must be diagnosed correctly before commencement of treatment. Quality assured culture and DST is thus indispensable. Non-viable cultures, culture contamination, and unreliable DST results have major consequences for both individual patients and the TB control programme as a whole. Therefore, internal quality control and external quality assurance will be in place, including a link for proficiency testing with a recognized reference laboratory such as one of the RNTCP National Reference laboratories.

1.7.3 Appropriate treatment strategies utilizing second-line anti-TB drugs under appropriate management conditions

RNTCP will be using a standardized second-line drug regimen for treating MDR-TB cases. The choice between hospitalization and ambulatory treatment depends on several factors in addition to the severity of the disease. Such factors include the availability of hospital beds; the availability of trained personnel at hospitals and clinics to administer treatment and manage adverse drug reactions; the availability of a DOT provider and social support

network to facilitate adherence to ambulatory treatment; and the presence of other clinical or social-economic conditions in patients. This is further discussed in Chapter 9 “Treatment delivery and adherence”.

1.7.4 Uninterrupted supply of quality-assured second-line drugs

Management of treatment with second-line anti-TB drugs is complex. Most second-line drugs have a short shelf life, global production of quality-assured drugs is limited, and drug registration may be a lengthy and costly process that is not always attractive to drug manufacturers. In addition, drugs may need to be changed due to side effects, delayed DST results, and poor response to treatment. To ensure uninterrupted drug supply, projected drug needs will be estimated as accurately as possible and procurement will begin well in advance of the anticipated need.

1.7.5 A recording and reporting system designed for PMDT

The specific characteristics of a PMDT service require a recording system, culture and DST results, and monitoring treatment delivery and treatment response for 24 to 27 months. Cohort analysis in PMDT includes interim indicators and treatment outcomes after 2 or more years. Case definitions and treatment outcome definitions for MDR-TB used in RNTCP PMDT are given in Chapter 4, and will be used for conducting cohort analyses under the RNTCP PMDT activities. The developed recording and reporting system (Chapter 12) is essential for evaluating programme performance and treatment effectiveness.

1.8 Summary

The framework approach to PMDT, summarized in Figure 1.1, includes five essential components which form the basis for every TB control programme that includes detection and treatment of multidrug-resistant TB.

FIGURE 1.1 FIVE COMPONENTS OF PMDT

1. **Sustained political and administrative commitment**
   - A well functioning DOTS programme
   - Long term investment of staff and resources
   - Coordination efforts between community, local governments, and international agencies
   - Addressing the factors leading to the emergence of MDR-TB

2. **Diagnosis of MDR-TB through quality-assured culture and drug susceptibility testing**
   - Proper triage of patients for C-DST testing and management under PMDT
   - Co-ordination with National and Supra-National Reference Laboratories

3. **Appropriate treatment strategies that utilize second-line drugs under proper management conditions**
   - Rational standardized treatment design (evidence-based)
   - Directly observed therapy (DOT) ensuring long-term adherence
   - Monitoring and management of adverse drug reactions
   - Adequate human resources**.**

4. **Uninterrupted supply of quality assured Second line anti-TB drugs.**

5. **Recording and reporting system designed for PMDT services that enable performance monitoring and evaluation of treatment outcome**

References

1. Lambregts-van Wezenbeek CSB, Veen J. Control of drug-resistant tuberculosis. *Tubercle and Lung Disease* 1995: **76**; 455-458.
2. CN Paramasivan, P Venkataraman. Drug resistance in tuberculosis in India. *Indian J Med Res* 2004: 120; 377-386.
3. B Mahadev, P Kumar, SP Agarwal, LS Chauhan, N Srikantaramu. Surveillance of drug resistance to anti-tuberculosis drugs in districts of Hoogli in West Bengal and Mayurbhanj in Orissa. *Indian J Tuberc* 2005: 52 (1); 5-10.
4. CN Paramasivan, P Venkataraman, V Chandrasekaran, S Bhat, PR Narayanan. Surveillance of drug resistance in tuberculosis in two districts of South India. *Int J Tuberc Lung Dis* 2002: 6 (6); 479-484.
5. Tuberculosis Research Centre, Indian Council of Medical Research, Chennai, India. Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. *Int J Tuberc Lung Dis* 2001: 5(1); 40-45.
6. Ramachandran R, Nalini S, Chandrasekar V, Dave PV, Sanghvi AS, Wares F, Paramasivan CN, Narayanan PR, Sahu S, Parmar M, Chadha S, Dewan P, Chauhan LS. Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. *Int J Tuberc Lung Dis* 2009: 13(9); 1154-1160.
7. Blower SM, Chou T. Modelling the emergence of the "hot zones": tuberculosis and the amplification dynamics of drug resistance. *Nat Med* 2004: **10** (10); 1111-1116.

CHAPTER 2: STRUCTURE AND RESPONSIBILITES

2.1 Chapter Objectives

This chapter describes the structure and responsibilities for PMDT at the State level and DR-TB Centre

2.2 State-level structure and responsibilities

While a national expert technical working group has developed national policies, technical and operational guidelines, the State level is where the majority of planning activities, implementation and monitoring occur. The overall structures and roles are summarized in the figure below.

State PMDT Committee are responsible for developing plan of action for implementation, expansion, maintenance, supervision, monitoring and quality enhancement of PMDT services in the respective state. The composition and terms of reference of the State PMDT Committee is detailed in ***Annexure XVIII.***

2.3 DR-TB Centres:

Treatment is decentralized, but the complicated clinical care needs require a clinical expert resource centre. This is the DR-TB Centre. These DR-TB Centres is utilized to initiate treatment, follow-up case management, and manage complications. One DR-TB Centre is expected per 10 million populations roughly, and these sites are being scaled up nationwide in a phased manner. The requirements to be fulfilled by an institute to be selected and the provisions under RNTCP to upgrade them to function as a RNTCP designated DR-TB Centre are enlisted below:

Requirements from Institute and Provision from RNTCP

A. Requirements from the Institute:

1. It should be preferably a Tertiary Care Hospital
2. Separate Ward for Male & Female should be available
3. All the PMDT services (beds, investigations and ancillary drugs for management of adverse drug reactions) to be provided free of cost to the patient
4. Relevant specialties like Pulmonologist, Physician, Psychiatrist, Dermatologist & Gynecologist etc. should be available or linkages for these services are established
5. DR-TB Centre Committee to be formed
6. National Training of DR-TB Centre committee doctors (including Chairperson)

7. National Air Borne Infection Control Guidelines to be implemented in MDR ward. ***(Annexure XXII)***
8. Routine clinical laboratory investigation facility to be made available for pre-treatment evaluation and monitoring
9. Ancillary drugs to be provided as per DR-TB Centre Committee`s advise
10. Management of adverse drug reactions (ADRs) as per PMDT Guidelines
11. Doctors and Nursing staff should be available from the institute
12. Records and Reports to be maintained for PMDT
13. Quarterly reports to be submitted electronically

B. Provision under RNTCP:

1. Remuneration of Sr. Medical Officer & Statistical Assistant – DR-TB Centre
2. Training, formats and registers for PMDT
3. Second Line Anti TB Drugs
4. Computer and Internet Facility

All the locations where the state proposes to have a DR-TB Centre; the site must be established in the Government Medical College Hospital under the auspices of Department of Pulmonary Medicine or Department of Medicine (if the former department does not exist). The requirements from the institute listed above must be provided by the Government Medical College / Institutes including free laboratory investigations and ancillary drug supply as part of their commitment for which no reimbursement will be available from the programme. However, the government medical colleges / institutes will be eligible for all the provisions from RNTCP listed above along with one-time provision of up to Rs.10 lacs for up-gradation of the ward to incorporate airborne infection control measures.

Private Hospitals and NGO Hospitals may be considered to serve as DR-TB Centre at places where a government medical college is not available. A scheme is under approval; till such scheme is available under the programme guidelines, any state aspiring to engage private / NGO institutes as DR-TB Centres due to non availability of a suitable government institute; may work out their own MoU with terms and conditions as agreed upon by the respective state health societies and the concerned institute under consultation with CTD.

DR-TB Centre Committee needs to be established with an expert group of clinicians from the institute and local programme managers at every DR-TB Centre. The composition and terms of reference of the DR-TB Centre Committee is detailed in ***Annexure XVIII.***

2.4 Coordination

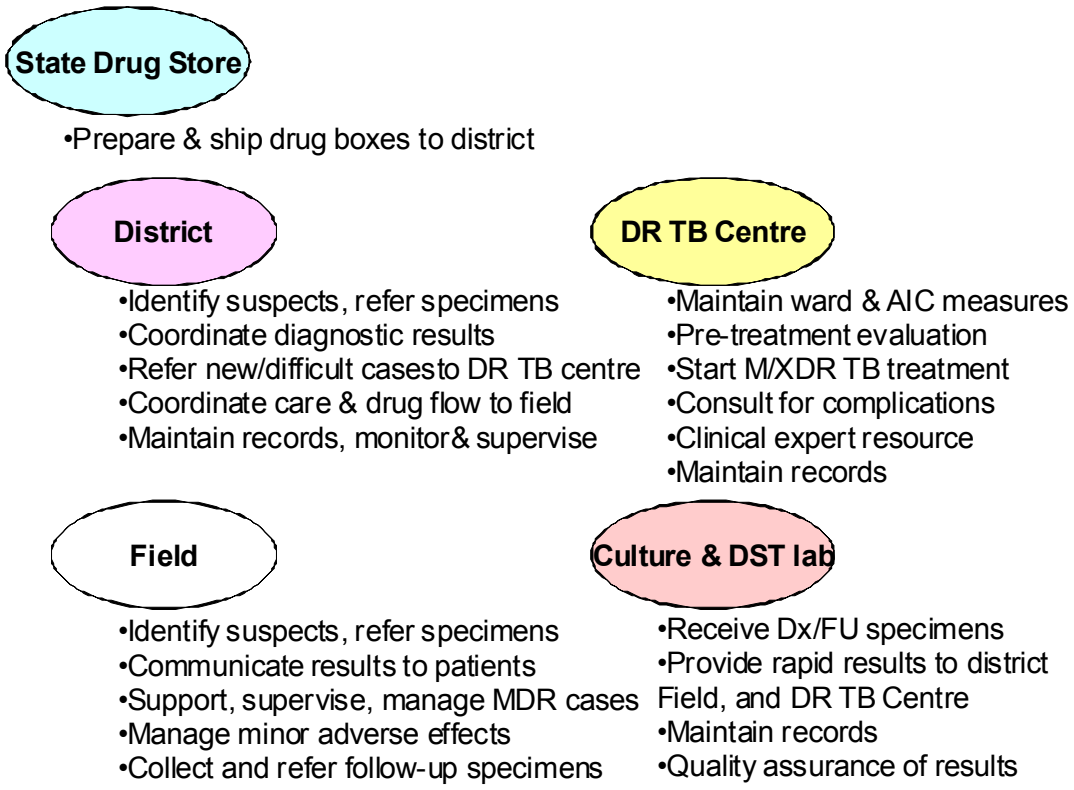
As RNTCP embarks on PMDT activities for the management of MDR-TB, coordination of activities at all levels is critical. Co-ordination needs to include the contribution of all the key stakeholders, organizations and external partners, as considered below:

- **Central TB Division (CTD), Ministry of Health and Family Welfare, Government of India.** The CTD is the central coordinating body for the activities described in the framework. Commitment of the necessary resources, particularly towards a strong central management team, ensures that all aspects are in place from the procurement of second line anti-TB drugs to the appropriate implementation and monitoring of the PMDT service. As needed, partnerships with all relevant health care providers can be built. The CTD is supported by a National PMDT Committee, comprised of members from CTD, the three central TB institutes (NTI, NIRT and LRS), medical colleges and WHO. The terms of reference of National PMDT Committee is detailed in ***Annexure XVIII.***
- **Local Health System.** RNTCP PMDT activities will be tailored to fit into the respective state and district levels infrastructure. The exact organizational structure of the RNTCP PMDT services may vary between the different settings depending on how the local health care is provided. Transfer between hospitals to outpatient settings or between DOT centres requires great care, advance planning, good communication. Given the type of care required in the treatment of MDR-TB, a team of health workers including physicians, nurses, and social workers (wherever available) should be used.
- **Community Level.** Community involvement and communication with the community leaders can greatly facilitate implementation of PMDT, and may respond to needs that cannot be met by the medical services alone. Community education, involvement, and organization around TB issues can encourage a feeling of community ownership of TB programmes and reduce stigma. In some circumstances, communities can also help address the patient's interim needs including the provision of DOT, food and/or housing, vocational support etc.

2.5 Overview of model of care

Integration of PMDT services will require multiple care levels to work in coordination. No longer can the field level unit be totally self-sufficient as in basic DOTS. The care at the field level is supported by the laboratory and the DR-TB centre, coordinated by the district, and supported by State. This is depicted in the Figure 2:

Figure 2: Overview of model of care in RNTCP PMDT



CHAPTER 3: NATIONAL PLANNING FOR UNIVERSAL ACCESS TO QUALITY DIAGNOSIS AND TREATMENT OF MDR TB.

3.1 Chapter Objectives

This chapter provides a brief overview of the RNTCP PMDT Vision; the strategy for prevention and control of MDR TB; strategy to strengthen laboratory capacity and treatment services; the development of national PMDT scale up plan.

3.2 RNTCP PMDT Vision

The RNTCP PMDT Vision is to promptly diagnose and effectively treat all TB patients with drug-resistant TB, through decentralized DST and PMDT treatment services integrated into RNTCP. Given the complexity, scale and cost, a phased approach has been developed, focusing first on those most likely to have drug-resistant TB. Realizing this vision will require more laboratory capacity, more second-line drugs, infrastructure and manpower.

Specific objectives are to:

- By end 2012, complete nationwide geographical coverage of access to basic MDR TB diagnostic and treatment services;
- By 2012-13, expanded access to MDR-TB diagnosis and treatment for
    - all smear positive re-treatment TB cases and
    - new cases who have failed an initial first-line drug treatment
- By 2015, nationwide access to MDR-TB diagnosis and treatment for all smear positive TB (re-treatment or new*) cases registered under RNTCP before or early during their treatment*

RNTCP expects to treat about 1,60,000 MDR-TB and 4,100 XDR-TB cases over the next 5 years (2012-2017).

3.3 RNTCP Strategy for Prevention and Control of MDR TB

The RNTCP response to MDR TB revolves around strategy to prevent drug resistant TB and strategy to stop transmission of MDR TB. These are enumerated below:

Prevention of MDR TB

- Sustained high-quality DOTS implementation
- Promote rational use of anti-TB drugs
- Implement infection control measures

Stopping transmission of MDR TB

- *Improve laboratory capacity for Rapid diagnosis of MDR-TB (expanded below)*
- *Initiation and rapid scale up of MDR-TB services (expanded below)*
- Effective treatment of MDR-TB patients
- Evaluate the extent of second-line anti-TB drug resistance and management strategies

3.4 Improving laboratory capacity for rapid diagnosis of M/XDR TB

RNTCP has developed a National Laboratory Scale up Plan, integrating contributions from national resources with donor resources under UNITAID and Global Fund R9, with the following set of activities:

- Enhanced sputum processing capacity (staff, centrifuges, Bio-Safety Cabinets)
- Nationwide availability of rapid DST to meet MDR TB diagnosis and treatment requirements
- Nationwide availability of sufficient culture capacity (solid + liquid) to meet part of follow-up culture requirements, given treatment scale-up plan
- Engage with laboratories from other sectors like NGOs, Private Labs, Medical Colleges, ICMR labs, to meet demands beyond public sector service availability
- Strengthened human resource capacity at select laboratories
    - Microbiologist, Sr. Lab technician and Data Entry Operator at every state-level culture and DST laboratory
    - Additionally, Technical Officer, Microbiologists and LTs under Global Fund project to strengthen selected public sector labs

According to the plan, the annual DST capacity is expected to scale-up to examine >1,44,000 MDR TB Suspects for diagnosis annually. Including other sectors, there exists now a consolidated list of > 60 labs that can contribute to PMDT scale-up (including the 43 labs identified the national lab scale up plan).

In addition, RNTCP is planning to develop and scale-up the availability of some second-line anti-TB drug DST, necessary for diagnosis of XDR TB among those identified as MDR TB.

3.5 Initiation and rapid-scale-up of effective treatment services for MDR TB:

The scaling up of PMDT services is also based on a graded expansion of MDR TB suspects criteria (indication for testing) to enable the districts / states start slow, overcome the teething challenges in system adaptation for effective service delivery without compromising the quality of basic DOTS services and gradually scale up to move towards universal access.

RNTCP plans to gradually scale up treatment services to reach as stage that the programme can initiate at least 30,000 MDR cases on treatment annually by 2013.

To that end, quality assured second line drugs are being procured in adequate quantities by the programme and distributed to States. DR-TB Centres are being scaled up nationwide to establish 120 DR-TB Centres across the country (about 1 per 10 million pop). Programme treatment infrastructures are provided additional human resource capacity for management and supervision including:

- Pharmacist and Store Assistant at State Drug Store
- Sr. Medical Officer and SA at DR-TB Centres
- Sr. DR-TB and TB HIV Coordinator in every district
- Additional HR – Counsellor at all DR-TB Centres to promote treatment adherence

Moreover, the following interventions are also being undertaken to enable system strengthening to effectively scale up treatment services of MDR TB:

- Advocate with Indian Drug Manufacturers with Global Drug Facility (GDF) support
  - Adhere to WHO Prequalification and GDF Quality Assurance systems,
  - Develop second-line drug production plans to meet national drug demand,
- Integrated national on-line electronic recording and reporting system,
- Advocate rational use of anti-TB drugs (FQ in respiratory cases) with all professional associations and practitioners,
- Procurement of rapid automated Cartridge-based Nucleic Acid Amplification Testing (CB-NAAT) for decentralized DST in districts, starting with difficult/inaccessible locations without sufficient laboratory capacity,
- Procurement of second line anti-TB drugs for management of MDR TB cases scaled up to 38,000 courses annually by 2017 including drugs for management of Extensively Drug Resistant TB (XDR TB).

3.3 National PMDT Scale up Plan (2011-12)

The National PMDT Scale up Plan for 2011-2012, an operational plan, was developed by consolidating the state wise PMDT micro-plans developed during the series of meetings with 35 states organized by CTD at LRS Institute, New Delhi in November 2010. The plan was developed with the objective to align the RNTCP vision for PMDT scale with state plans, second line drugs, laboratory capacity. Outputs include clarity and transparency on national

training and district appraisal needs, laboratory scale-up requirements, and national/state/district responsibilities understood by all.

In development, careful consideration was made of all preparatory activities like civil work up-gradations, appointments and training of staff, procurement and plan for sample collection and transport and drug logistic management, trainings and appraisals. The timelines were set by the states for scale up of services by districts (i.e. geographical expansion), and by gradually expanding MDR TB suspect criteria.

As per the consolidated state plans, it is planned to test 1,31,516 MDR TB suspects and initiate treatment for 24,326 MDR TB cases cumulatively over a period of 2 years (2011-2012) with an exponential increase over 8 quarters. The enrolment plan of MDR TB Suspects to be tested and MDR TB Cases to be put on treatment is matched with the available laboratory capacity and the drug envelops (cases that can be started on treatment with 15 month working stock per case) available over the next 8 quarters. This operation plan laid down the baseline for monitoring the progress made by every state against their respective state plans over 2011 and 2012. Every state and district must strive to achieve the planned introduction and scale up of services by geography and by suspect criteria over the two years to realise the nationwide PMDT scale up 2012-13. The National PMDT Scale up Plan - 2011-12, with detailed state wise plans, is available for reference at www.tbcindia.nic.in.

CHAPTER 4: LABORATORY SERVICES FOR PROGAMMATIC MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS

4.1 Chapter Objectives

This chapter introduces the concept of certification of laboratories for quality-assured results, introduces the case definitions for MDR TB and XDR TB, describes the laboratory services needed to diagnose and treat MDR-TB cases, job responsibilities of the State TB Officer, STDC Director, IRL Microbiologist and liaising with the NRL for setting up laboratory services and certification process for Solid, Liquid Culture DST and LPA for drug resistance for the State level IRL and Culture and DST laboratories of the Medical Colleges and Private sector that have been identified for providing support to RNTCP PMDT services.

4.2 Laboratory services required for introduction of PMDT

Optimal management of MDR-TB requires both mycobacterial and clinical laboratory services. At a minimum, the State level Intermediate Reference Laboratory (IRL) or any other RNTCP-certified Culture & DST laboratory should provide:

- diagnostic culture on solid and/or liquid media,
- confirmation of resistance to rifampicin by either molecular tests (Line probe assay or other RNTCP-approved technology);
- confirmation of the species as M. tuberculosis or non- tuberculous mycobacteria (NTM); and
- testing for susceptibility to at least isoniazid and rifampicin by solid or liquid culture.

Clinical laboratory services are required for the proper evaluation and monitoring of patients, including basic hematology, biochemistry, serology, and urine analysis as would be available at the DR-TB Centres identified by the state.

4.3 Definition of accreditation and certification:

Laboratory Accreditation means third-party certification by an authorized agency using internationally approved standards for evaluating the competence of laboratories to perform specific type(s) of testing and is a formal recognition of competent laboratories. It includes all aspects of the laboratory including physical infrastructure, biosafety, competencies of staff, processes, procedures and quality system elements (QSE) enumerated in the system i.e (ISO, CAP, NABL etc)

Certification is a process by which a specific procedure being performed in the laboratory i.e DST in TB labs is being quality assured by means such as standard EQA system (retesting and panel testing) by a higher level laboratory to ensure quality of that service.

RNTCP previously used the terminology of accreditation for quality assurance of its laboratory network. However though most aspects of the QSE are being used in this exercise, it does not fulfil the criteria of being an authorized agency like ISO, NABL etc. for providing accreditation. Henceforth the term certification will be used to describe the quality assurance process for maintenance of TB DST EQA in its network of laboratories.

4.4 Definitions

RNTCP is in the process of scaling up laboratory services for drug-susceptibility testing nationwide. In that process, the eligibility for DST will expand in a phased manner. Therefore the definition of an MDR TB suspect must be flexible for that expansion of services.

- **MDR TB suspect:** A patient suspected of drug-resistant tuberculosis, based on RNTCP criteria for submission of specimens for drug-susceptibility testing (described in chapter 5, case finding).

A patient is confirmed to have MDR or XDR TB only when the results are from a RNTCP quality-assured Culture & DST Laboratory and by a RNTCP-endorsed testing method.

Such patients are classified according to the following definition:

- **MDR-TB case:** A TB patient whose sputum is culture positive for *Mycobacterium tuberculosis* and is resistant *in-vitro* to isoniazid and rifampicin with or without other anti-tubercular drugs based on DST results from an RNTCP-certified Culture & DST Laboratory
- **XDR TB case:** An MDR TB case whose recovered *M. tuberculosis* isolate is resistant to at least isoniazid, rifampicin, a fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and a second-line injectable antiTB drug (kanamycin, amikacin, or capreomycin) at a RNTCP-certified Culture & DST Laboratory.

It is to be noted that rifampicin resistance is quite rare without isoniazid resistance. The great majority of DST results with rifampicin resistance will also be isoniazid resistance, i.e. MDR TB. Therefore RNTCP has taken the programmatic decision that patients who have any Rifampicin resistance, should also be managed as if they are an MDR TB case, even if they do not formally qualify as an MDR-TB case as per the above definition. Therefore

programme and clinical actions will be driven primarily by rifampicin DST results. This is detailed in subsequent chapters.

4.4 Methods for drug susceptibility testing

Presently, 3 technologies are available for diagnosis of MDR TB viz. the conventional solid egg-based Lowenstein-Jensen (LJ) media, the liquid culture (MGIT), and the rapid molecular assays such as Line Probe Assay (LPA) and similar Nucleic Acid Amplification Tests like Xpert MTB/Rif. Conventional DST evaluates if M. tuberculosis grows in the presence of drug-containing media, and is also known as *phenotypic DST*. Molecular DST evaluates for the presence of genetic mutations that are highly associated with phenotypic resistance, and is also known as *genotypic DST*.

The differences between the tests should be understood. Phenotypic DST is available for more drugs, and is considered very reliable for isoniazid (H), rifampicin (R), and streptomycin (S), and somewhat less reliable for other drugs such as ethambutol (E). Molecular/genotypic DST is highly reliable for rifampicin, but has limited sensitivity for detection of isoniazid resistance. Results from any RNTCP-approved tests are considered equivalent, and can be the basis of clinical action, though in some settings additional testing will be done.

Molecular/genotypic tests are much faster than phenotypic tests, as molecular tests don't require growth of the organism, and M. tuberculosis is notoriously slow growing. The turnaround time for C-DST results by Solid LJ media is around 84 days, by Liquid Culture (MGIT) is around 42 days, by LPA is around 72 hours and by CB-NAAT is around 2 hours.

DST for Ofloxacin (O) and Kanamycin (Km) and Pyrazinamide (Z) will be introduced and gradually scaled up to all RNTCP-certified C-DST Laboratory in the near future.

4.5 Organization and development of the laboratory network

RNTCP has a three tier laboratory network. The first is the designated microscopy centres (DMCs) covering 1 lakh population and providing sputum smear microscopy services. The second tier are the Intermediate Reference Laboratories (IRL) that have 2 main functions (1) Training of State level laboratory for smear microscopy services and external quality assessment [EQA] of sputum smear microscopy network in the districts and DMCs and on-site evaluation of the laboratory network in the State. (2) Culture and DST for first line drugs for M. tuberculosis by solid/ liquid culture, Line Probe Assay for rapid diagnosis of MDR

TB. The third-tier is the National Reference Laboratories (NRL). The overall quality assurance of the IRL and any other culture and DST laboratories (Medical colleges, NGO, Private etc.) is the responsibility of the designated NRL to which the State is linked. NRLs are also responsible for all training activities and EQA for culture and DST and molecular diagnostics (LPA & CB-NAAT) for state level staff.

4.6 Choice of Diagnostic Technology:

Currently, the programme is scaling up the laboratory capacity of various Culture and DST laboratories at state level IRLs and other laboratories. The choice of technology to be used for diagnosis of MDR TB has been determined as per recommendations of the National Laboratory Committee. Thus, for DST at certified laboratory, **wherever available Molecular DST (e.g. Line Probe Assay (LPA)) is preferred diagnostic method** because of the rapid and highly-accurate rifampicin results, followed in preference by Liquid C-DST and then Solid C-DST.

MDR Diagnostic Technology	**Choice**
Molecular DST (e.g. LPA DST)	First
Liquid culture isolation and LPA DST	Second
Solid culture isolation and LPA DST	Third
Liquid culture isolation and Liquid DST	Fourth
Solid culture isolation and DST	Fifth

Similarly for follow up cultures, wherever available, Liquid Culture will be preferred over solid culture. However, this will be liquid cultures for at least the crucial months of follow-up (IP-3,4,5,6 and CP-18,21,24) and over and beyond this, it will be determined by the workload of individual laboratories.

Laboratories who have become functional should first achieve proficiency in culture recovery by solid or liquid culture. In parallel they can be trained for LPA technology and get proficiency tested for LPA. This will allow for expediting the process of laboratory support for initiating PMDT services, while the laboratory can continue efforts to get certified for DST in solid or liquid culture in the stipulated time required for such certification.

Laboratories performing solid / liquid culture and under process of proficiency testing of solid / liquid DST with the NRLs; but have achieved LPA certification ahead in time; can start service using LPA for diagnosis and solid / liquid culture for follow up.

States with laboratories yet to be certified can be linked to another certified lab as an interim arrangement. CTD has finalized the laboratory back up for all the states that are not likely to have their own state laboratory certified in 2011-12 by linking them to the RNTCP-certified laboratories at NRLs or adjoining state IRLs or private laboratories under NGO-PP C-DST Scheme.

4.7 New technology - Cartridge-Based Nucleic Acid Amplification Testing (CB-NAAT)

The general principle is that new technology for DST may be accepted by RNTCP as per the latest advice of the relevant National Technical Working Group that can be referred from www.tbcindia.nic.in for the latest information.

The cartridge based nucleic acid amplification test (CB-NAAT, e.g. the Xpert MTB/RIF assay) will be increasingly available at district, sub-district, medical colleges or private sector in the future. The major advantages are that this highly-automated system requires only a minimally trained staff to generate DST results, can be applied to any pulmonary specimen (irrespective of smear status), results are free of cross-contamination risk and are internally quality-assured, and results are available within 2 hours. Where RNTCP has deployed CBNAAT for TB/MDR-TB detection, results can be used for patient management as per the latest available guidance from the programme.

4.8 Specimen Collection

An often-overlooked problem is that of obtaining adequate good quality specimens at the peripheral laboratories. Unless specimens are collected with care and promptly transported to the laboratory under temperature control, diagnosis may be missed, and the patient could miss the chance to be detected and put on the correct treatment. A good sputum specimen may literally make the difference between life and death, and allow containment of the disease and prevent spread to others in the family and community.

The Laboratory technician needs to explain the process of collecting “a good quality sputum specimen” and avoid using vernacular terminologies that convey the meaning as saliva instead of sputum. In addition though the general guideline for collection of sputa is one spot and one morning, this does not preclude from collecting 2 spot specimens that need to be collected with a gap of at least one hour (60 minutes) if the patient is coming from a long distance or there is a likelihood that the patient may default to give a second specimen.

A good sputum specimen consists of recently discharged material from the bronchial tree, with minimum amounts of oral or nasopharyngeal material. Satisfactory quality implies the

presence of mucoid or mucopurulent material. Ideally, a sputum specimen should have a volume of 3-5ml. The patient must be advised to collect the specimen in a sterile container (falcon tube) after through rinsing of the oral cavity with clean water.

Specimens should be transported to the laboratory as soon as possible after collection. If delay is unavoidable, the specimens should be refrigerated up to 1 week to inhibit the growth of unwanted micro-organisms.

4.9 Specimen transportation to culture-DST laboratories

Fresh sputum samples will need to be transported from the DMC to the RNTCP-certified C-DST laboratory in cold chain within 72 hours. Ideally an agency (courier / speed post) with a pan district presence should be identified for this purpose. Two innovative models for specimen collection and transport using fresh samples in falcon tubes to be transported in cold chain using gel packs and their technical specifications have been developed by Gujarat (from peripheral DMCs) and Andhra Pradesh (from high burden DMCs at TUs/DTCs).The Technical Specification of these Transport Boxes for Sputum Samples transportation in Cold Chain are detailed in Figure 4.1 below.

All states and districts should establish sample transport system in cold chain irrespective of the time taken for transport considering the hot climatic conditions in most of the states during most of the year. An appropriate courier / speed post service with pan district presence should be identified and contracted by the DTO of every district for prompt transport of the specimen cold box on the same day from the DMC linked to the courier / speed post office in the locality to the assigned RNTCP-certified C-DST laboratory.

Figure 4.1: Technical Specification of Transport Box for Sputum Samples transportation in Cold Chain

A: Gujarat Model: Total capacity up to 4 Falcon Tubes (from peripheral DMCs)

Thermacol Box: Outer dimension (Cm): 18.5 X 12.5 X 13 Inner dimension (Cm): 14.25 X8.25 X 10.25

No. of gel packs required: 2 Weight of fully packed consignment box: 400 grams.

Approximate cost of courier charge: 60-70 Rupee per box

Gel packs maintain a temperature between 12 - 20 Deg Celsius for up to approximately +48 hours in tightly packed thermocol boxes (average outside temperature 35°C)

If conditioned in the deep freezer (temperature between -20 to C to -15 o C) for a minimum of 48 hours to a maximum of 72 hours before use

{This is a onetime use box. Thermocol boxes and gel packs are not reused.}

B: Andhra Pradesh Model: Total capacity up to 8 Falcon Tubes (from high burden TU/DTC DMCs)

Thermacol Box: Outer dimension (inches): 11 X 9 X 9 Inner dimension (inches): 8 X 6.5 X 6.5

A cardboard /thermocol sheet also to hold the falcon tubes upright

No. of gel packs required: 2 Weight of fully packed consignment box: 1.5 kg.

Approximate cost of courier charge: 200-300 Rupee per box

Gel packs maintain a temperature between 12 - 20 Deg Celsius for up to approximately +48 hours in tightly packed thermocol boxes (average outside temperature 35°C)

If conditioned in the deep freezer (temperature between -20 to C to -15 o C) for a minimum of 48 hours to a maximum of 72 hours before use

{This is a onetime use box. Thermocol boxes and gel packs are not reused.}

The following points are critical for the collection of fresh sputum samples at DMCs:

- The falcon tubes and the 3 layer packing materials like thermocol box, ice gel pack (pre-freezed at -20 degree for 48 hours), request for C-DST forms, polythene bags, tissue paper roll as absorbent, parafilm tapes, brown tape for packaging box, permanent marker pen, labels, bio-hazard sticker, scissors, spirit swab etc. should be supplied to the DMCs for collection of sputum through the DTO.

- The falcon tubes should carry a label indicating the date of collection of the samples and the patient's details like name, date of sample collection, name of DMC/DTC, Lab. No:- XYZ, specimen A or B
- The Lab technicians at DMCs should be trained to carefully pack the sputum samples in the cold box to avoid spillage of the samples.
- The LT of DMC issuing the falcon tubes to the patients should also give clear instructions to the patients on correct technique of collection of the sputum. Also the date of issue of the falcon tubes to the patient should be recorded.
- The LT of the DMC should ensure that the request for C-DST form is packed in a separate plastic zip pouch and placed in the cold box before sealing the lid of the box. Also, the bio-hazard symbol should be pasted on the external side of the cold box along with the label indicating the postal address of the RNTCP-certified C-DST Lab assigned.
- The LT of the DMC should promptly inform the sample transport agency like a courier / speed post service, speed post or a human carrier to collect and transport the samples

As per the national guidelines for Biomedical waste management the containers used for transporting sputum samples to the RNTCP-certified laboratory should be labeled with a "BIO-HAZARD" sticker.

For every MDR TB suspect referred by the MO-DMC, the date of referral and transport of sputa samples to the Culture & DST laboratory should be entered in the "Remarks" column of the respective DMC Lab register and the TB Register in which the patient is registered for RNTCP DOTS treatment and in the Referral for Culture and DST Register held at the DTC ***(See Annexure I and III).*** Alternatively the MDR-TB suspect referred to nearby DMC selected for sample collection and transport for C-DST may be provided two falcon tubes by the concerned DMC LT/MO and instructed on collecting two samples (one early morning and one supervised spot). These samples will be taken by the patient / relative to the DMC selected for sample collection for C-DST from where these will be packed in cold boxes and transported to the RNTCP-certified laboratory for culture and DST. Once the sputum has been transported to the RNTCP-certified laboratory, the MDR suspect should return to continue their RNTCP DOTS treatment.

4.10 Quality Assurance for culture and DST

Quality assurance with regard to tuberculosis bacteriology is a system designed to continuously improve the reliability, efficiency and use of the tuberculosis laboratory services. In order to achieve the required technical quality in laboratory diagnosis, a continuous system of quality assurance needs to be established. The national reference laboratory should supervise the laboratory network periodically.

It consists of two sets of activities, one which is called a retesting exercise which is undertaken when a new laboratory starts its services or whenever there is a new activity (DRS, prevalence survey) and another which is called regular panel testing (annual) which is undertaken by the NRL that supervises the IRL or C-DST labs. Certification is usually provided for a 2 year term with annual panel testing for proficiency.

The actual setting up of the laboratory, layout, design for LPA and negative pressure environment is available on www.tbcindia.nic.in including a detailed checklist for certification in a separate document on 'Certification Procedure for Mycobacteriology Units of RNTCP Intermediate Reference Laboratories' and this covers the minimum required information for laboratory pre-assessment, supply of necessary equipment and consumables, training and proficiency testing of Culture and DST laboratory and assessments for certification. RNTCP has developed and disseminated a guidance document for certification of C-DST laboratories in Medical Colleges that is available on the programme website.

Briefly, the certification process of a Culture and DST laboratory has the following components:

1. Assessment of infrastructure, including HR, good laboratory practices and quality control procedures, SOPs etc, which is performed using the "IRL Mycobacteriology Certification Pre-Assessment Tool" (RNTCP IRL APAT) for preliminary assessment of requirements for an IRL/other C-DST labs before it is subjected to the full certification procedures. Based on the data provided, the CTD identifies laboratories that could fulfil the requirement for PMDT activities. This procedure may take a maximum of one month. A similar tool is also available for the C-DST laboratories functional in Medical Colleges and other sectors.
2. Training of Microbiologists and LTs on the laboratory culture and DST manual including EQA procedures.

3. Supply and installation of equipment in the lab, will be done after a review of the requirement of the respective lab, based on the "IRL Mycobacteriology Certification Pre-Assessment Tool" (RNTCP IRL APAT) by CTD.
4. Proficiency testing of the lab's culture and DST procedures by the SNRL/NRL will follow once the respective lab starts performing culture and DST examinations at the lab. The SNRL/NRL will receive the results of 100 cultures and DST done by lab in the past three months, randomly select 10 cultures from the lab's list for performance of DST at the SNRL/NRL, and will review all results. Also, the SNRL/NRL will send a panel of 20 cultures for DST by the respective lab, and review the subsequent results. Identification of causes for any error, will lead to the required corrective action being taken. Panel testing will be conducted on an annual basis. **An overall sensitivity and specificity of ≥90% for H and R,** would entitle the lab to submit their application to CTD for RNTCP certification.
5. Issue of RNTCP certification by CTD, will be done immediately after receipt of a favourable assessment report from the RNTCP assessment team. Certification will be reviewed annually by CTD after the first 2 years.

Certification for liquid culture DST is undertaken by the NRLs on similar lines as mentioned for solid cultures. The procedures for certification LPA is summarised in ***Annexure II***.

References

1. Laboratory Services in Tuberculosis Control. Part III – culture. WHO/TB/98.258, 1998
2. IUATLD. The Public Health Service National Tuberculosis reference laboratory and The National Laboratory Network, 1998
3. PAHO/WHO Advisory Committee on Tuberculosis Bacteriology. Manual of technical standards and procedures for tuberculosis bacteriology. Part II: The Culture of Mycobacterium Tuberculosis. PAHO, Marlinez, Argentina,1998
4. Jensen, K.A. Towards a standardisation of Laboratory methods. Second report of the Sub-Committee of Laboratory Methods of the IUAT. Bull Int. Union Tuberc. 1995, 25 (1-2): 89-104
5. Canetti, G, Fox W, Khomenko A, Mahler, H.T., Menon, N.K., Mitchison.D.A *et al* Advances in techniques of testing mycobacterial drug sensitivity and the use of sensitivity tests in tuberculosis control programmes. Bull WHO, 1969; 41, 21-43
6. IUATLD. The public health service national tuberculosis reference laboratory and the national laboratory network, 1998
7. Public health mycobacteriology –A guide for the level III laboratory. CDC, Atlanta, Georgia, 1985
8. PAHO/WHO Advisory committee on Tuberculosis Bacteriology. Manual of technical standards and procedures for tuberculosis bacteriology. Part III Sensitivity of *M. tuberculosis* to anti-TB drugs. PAHO, Marlinez, Argentina, 1998.
8. Sulochana S, Venkataraman P and Paramasivan CN. Evaluation of various methods of susceptibility to ofloxacin in strains of *M.tuberculosis.* Indian J Med Res 1999,110, 186-188.

10. NCCLS. Susceptibility testing of Mycobacteria, Nocardia & Other Aerobic Actinomycetes. NCCLS document 2003; M24-A 23: No.18.
11. Sulochana S, Paramasivan CN. Susceptibility of *Mycobacterium tuberculosis* strains to Gatifloxacin and Moxifloxacin by different methods. Chemotherapy, 2006.
12. Sulochana S, Rahman F, Paramasivan CN. *In Vitro* activity of fluoroquinolones against *Mycobacterium tuberculosis* Journal of Chemotherapy, 2005, 17, 169-173.
13. Laboratory services in tuberculosis control. Part I, II and III. WHO/ TB/98. 258, 1998.
14. The public health service national tuberculosis reference laboratory and the national laboratory network. IUATLD, 1998
15. Quality assurance in bacteriology and immunology: WHO regional publication, SEA series No. 28, 1998.

CHAPTER 5: CASE-FINDING

5.1 Chapter objectives

This chapter describes the RNTCP strategy for case-finding and confirmation of diagnosis in patients suspected of MDR-TB. The RNTCP PMDT strategy strives to identify and initiate adequate treatment for MDR-TB in a timely manner for confirmed cases of MDR-TB. Timely identification and prompt initiation of treatment prevent the patient from spreading the disease to others, developing a resistant strain to more drugs, and progressing to chronic state of permanent lung damage.

5.2 MDR suspect policies and definitions

The programme will use a strategy that screens patients with initially a very high risk of MDR-TB using DST. As laboratory and treatment capacity builds, the programme will scale up to achieve universal access to quality assured DST.

During scale-up, the criteria for referral of a specimen for DST will by necessity differ and advance among the districts. The graded criteria for suspecting MDR TB are as follows:

Table 5.1: MDR Suspect Criteria

Criteria A – • All failures of new TB cases • Smear +ve previously treated cases who remain smear +ve at 4th month onwards • *All pulmonary TB cases* who are contacts of known MDR TB case
Criteria B – *in addition to Criteria A:* • All smear +ve previously treated pulmonary TB cases at diagnosis • Any smear +ve follow up result in new or previously treated cases
Criteria C – *in addition to Criteria B* • All smear -ve previously treated pulmonary TB cases at diagnosis, • HIV TB co-infected cases at diagnosis

In other words, for districts implementing MDR Suspect Criteria B, any smear-positive diagnostic (except in a new patient) or any smear-positive follow-up result, should prompt a referral for DST.

For districts implementing MDR TB Suspect Criteria C, all patients should be referred for DST at diagnosis of TB, except new patients (smear positive and smear negative) at diagnosis without HIV infection.

It is not necessary for districts to start with MDR Suspect Criteria A; small states (e.g. like Goa, all North East states (except Assam) and all Union Territories) are expected to initiate services with Criteria B and move to Criteria C as soon as services are established on ground. It is expected that all districts in the country would be implementing Criteria B by 2012-2013, and Criteria C by 2015.

5.3 Case finding strategy

In districts implementing services with MDR TB Suspect Criteria A, after a TB patient has been declared as a failure of an RNTCP regimen for new or previously treated case, the first priority is to ensure that the patient is initiated on an RNTCP regimen for previously treated case and is re-registered in the appropriate TB Register as type "failure" patient. Similarly, close contacts of MDR-TB patients should be screened and tested for TB as per RNTCP guidelines and if found to be pulmonary TB, such patients should be started on RNTCP DOTS treatment based on whether they are new or re-treatment cases.

In districts implementing services with MDR TB Suspect Criteria B, the DMC LT will trigger the identification of MDR TB suspect for every smear-positive TB case diagnosed in the DMC and will take a detailed history of past anti TB treatment to classify the case as new case (not exposed to more than 1 month of anti-TB treatment) or previously treated case (exposed to more than 1 month of anti-TB treatment). If the patient is found to be a previously treated case, the patient will be indentified as an MDR TB suspect. The DMC LT will also trigger the identification of MDR TB suspect if any TB patient (new or previously treated) under RNTCP who is found to the smear positive during any follow up sputum examination. In either case, the DMC LT will mention the reason of suspecting the case as MDR TB in the remarks column of the DMC lab register.

In districts implementing services with MDR TB Suspect Criteria C, in addition to the above, the MO PHI will also identify any smear-negative previously treated pulmonary TB case or any TB patient who is HIV positive as an MDR TB suspect.

A patient who is an "MDR TB Suspect" should be referred by the respective medical officer – peripheral health institute (MO-PHI) to the nearby DMC that has been developed for sample collection for C-DST at the earliest i.e. as soon as the sputum results are available.

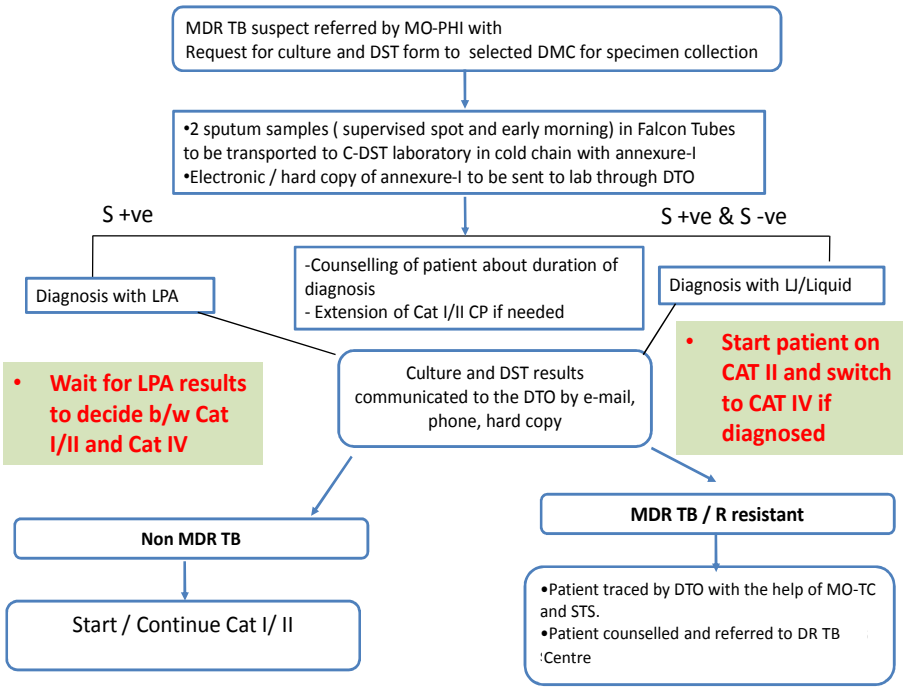
If the diagnosis is based on Line Probe Assay (LPA), the patient's results will be available within 48 hours and the decision of starting the patient on the appropriate regimen can be taken after results are available.

5.4 Operational process of specimen referral

Once the MO PHI confirms that the patient is an MDR-TB suspect, he/she should arrange for sending two sputa samples, one of which is an early morning sample and the other a "supervised" spot sample, from the patient to the RNTCP certified C-DST laboratory along with the RNTCP Culture and DST request form. For samples to be collected and transported from the DMC, all necessary materials for sample collection and transport need to be made available at the DMC identified by the DTO as sample collection centre for C-DST.

Empty falcon tubes can be provided by the LT / MO to the patient with guidance to collect fresh sputum sample on the next day early morning and go with the early morning sample and records to the nearest DMC identified for sample collection for C-DST by the DTO. The spot sample can be collected in such cases when the patient arrives to submit the early morning sample. Alternatively, samples can be collected at such DMCs and PHIs and transported in vaccine carriers by the staff on the same day to the nearest DMC identified as sample collection centre for C-DST for packing in cold boxes and further transport to through courier or speed post. If there is likely to be a delay in transporting the samples, the samples should be stored in a refrigerator at the peripheral DMC / PHI with bio-safety precautions.

Flow of specimen from periphery to C-DST laboratory



All women of child bearing age identified as MDR TB suspects should be advised to use a reliable and appropriate contraceptive method till the C-DST results are available.

5.4 Programme preparation to advance MDR Suspect Criteria

Any district planning to roll out Criteria B should complete all additional preparatory activities as per the table below and intimate the status of preparation to CTD through the STO office.

Table 5.2: Checklist for Preparation to introduce Criteria B with LPA

DR-TB Centre	– Sensitization of RNTCP Key staff (DR-TB Centre – MO,SA, Nurses) – Availability of additional beds / adequate number of DR-TB Centres – Availability of loose drugs – Logistics (Treatment cards, I cards)
IRL	– **Availability of Certified Lab for LPA** – Communication to LAB about shifting the criteria – Workload at C and DST Lab – Prompt Communication of results to the District (SMS from IRL to the District and sub district level)
SDS	– Availability of drugs – Availability of PP and loose SM injections
District Level	– Sensitization of RNTCP Key staff (DTO, DMC LT & MO, Senior DR-TB TB-HIV Coordinator, STS, STLS, TBHV) – Availability of C-DST forms, Falcon tubes, Sputum transportation boxes & packing materials, courier / speed post agency – Micro-planning for sputum collection and transportation linked to courier pick-up points – Availability of drugs – Availability of PP and loose SM injections

The key difference from prior RNTCP activities is the role of the DMC laboratory technician in MDR suspect identification. The DMC LT is expected to evaluate whether or not each TB case will require specimen referral for C-DST for smear positive cases while the MO-PHI is expected to do so for smear negative and HIV associated cases.

If the S+ve result is from a follow-up specimen, then referral for C-DST should be automatic.

If the S+ve result is from a diagnostic specimen, only previously-treated patients are eligible for C-DST. The DMC LT should enquire from the patient or relative about any history of consuming anti-TB drugs for more than a month from any source in the past and indicate the same of the lab request form for smear microscopy as well as mention in the remarks column of the DMC lab register if the patient is a previously treated case. The DMC LT will then take the patient to the Medical Officer for referral for C-DST. The MO will fill the request for

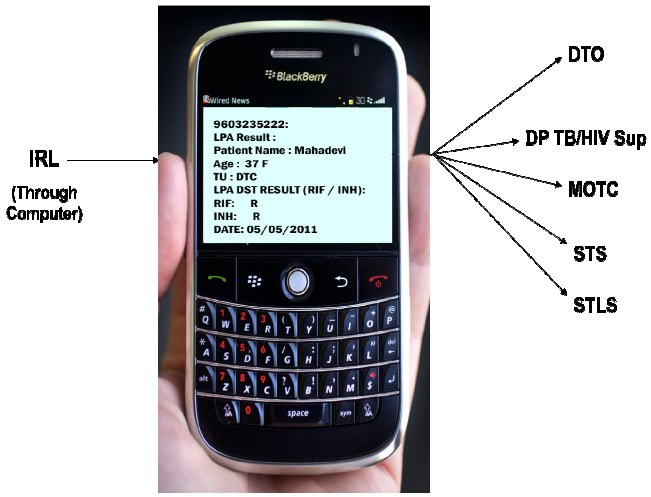
C-DST form after confirmation of the past history of anti-TB drugs in case of diagnosis. In the remarks column of the lab register, the DMC LT should indicate if specimen indicates DST (i.e. previously treated or follow-up); the Date of sending sample for C-DST; and after getting result, specify TB registration number).

Table 5.3: Opportunities to detect an MDR Suspect (in Criteria B)

At referral	Referring provider should indicate need for DST, and what makes that patient eligible (e.g. prior treatment, MDR suspect)
At time of specimen submission	LT should assess history of prior anti TB treatment, smear results
At time of sputum results	LT should ensure that each patient with smear-positive results is considered for DST: i.e. all patients with follow-up s+ve results, and all patients with diagnostic s+ve results *unless patient is 'new'*. MO-PHI should routinely consider if DST is required for each patient
At categorization	MO-PHI should routinely consider if DST is required for each patient (i.e. previously treated, smear-positive)
At registration or recording of follow-up results	STS/STLS should check for DST results for all registered smear-positive re-treatment patients STS/STLS should check DST results for all patients with smear-positive follow-up results
During routine supervision	STS/STLS should review smear-positive results for DST submission

5.5. Communication of results between C-DST laboratory and providers

All attempts must be made to communicate the DST results to the district as soon as available, so that patient treatment decisions can be smoothly managed. The C-DST Laboratory can use available computer software to send the results as SMS to the concerned districts as shown in the figure below followed immediately by an email.



After the referral or transportation of sputa samples of an MDR-TB suspect to the RNTCP-certified laboratory, the results of the smear, Culture and DST / LPA are entered in the Culture and DST Register ***(Annexure IV)*** held at the laboratory. The culture results are communicated to the DTO immediately by e-mail. In case the culture result is positive, this would be followed by the DST result when available. If the patient is confirmed as a case of MDR-TB, the culture and DST or LPA results are also communicated to the respective DR-TB Centre using the later part of ***Annexure I.*** If the culture result shows contamination, the same is informed to the DTO within 24 hours and s/he should arrange to send a repeat sample (one early morning and one spot) to the laboratory within 3 days.

If LPA is found to be invalid or the sputum is smear negative, the sputum sample is inoculated on Solid or Liquid Culture immediately. If the culture result is found to be positive, the culture isolate is subjected to LPA test for confirming MDR TB / Rif resistance.

5.6 Management of patient treatment while results are awaited

The approach to initiation on treatment will depend on the efficiency of laboratory services and results reporting available locally.

If the LPA results are available within 7 days of sample collection, in S+ve previously treated cases suspected as MDR TB at the time of diagnosis, the patient may be directly placed on the appropriate DST-driven regimen, i.e.

- For RIF-sensitive patients, place on the Regimen for previously treated cases and
- For RIF-resistant patients, referral for pre-treatment evaluation for consideration of RNTCP Regimen for MDR TB.

If results may be delayed more than 7 days of sample collection, the patient should be initiated on RNTCP DOTS treatment till the results are available.

- If solid/liquid culture and DST used for diagnosis, a routine PWB of RNTCP regimen for previously treated cases should be used, as it will be 2-4 months before a DST result is available.
- If LPA is used for diagnosis in such cases, the patients should be initiated on RNTCP regimen for previously treated cases using prolongation pouches and Inj SM for 1 month and registered in the TB register[‡].

[‡] Exception: in case of MDR-TB suspects who are contacts of MDR-TB cases and have no prior history of TB treatment in the past, use Regimen for New patients.

- If RIF resistance is not detected, the patient should continue treatment with Re-treatment regimen.
- If RIF resistance is detected, treatment should be stopped and the patient immediately referred for pre-treatment evaluation for Regimen for MDR TB

- In case of any delay in laboratory results, treatment would continue till results are available. For example, if LPA results are invalid or the sample is found to be smear negative at the C-DST Lab, the sample should be inoculated on liquid / solid culture; and if found to be culture positive, the culture isolates must be promptly subjected to LPA at the RNTCP C-DST Lab to complete the diagnosis.
- In case of follow-up results where sometimes the MDR-TB suspect completes the treatment before DST results are available, the patient should be continued on continuation phase treatment till the time the results are obtained. This situation will become less and less common as all DST switches to rapid methods.

5.7 Recording treatment outcomes

The treatment outcome will depend on the duration of the treatment completed at the time of confirmation as MDR TB cases. The outcome will be as follows:

- "Switched to Regimen for MDR TB" if the patient has completed less than 5 months of RNTCP DOTS treatment
- "Failure" if the patient has completed more than 5 months of RNTCP DOTS treatment

However some patients may have other outcomes e.g. died or defaulted prior to the DST results being available. Those would be left unchanged.

CHAPTER 6: PRE-TREATMENT EVALUATION

6.1 Chapter objectives

The chapter provides the process of referral for pre-treatment evaluation, and the pre-treatment evaluation process.

6.2 Referral for pre-treatment evaluation

It is crucial that patients with Rifampicin resistance be referred for treatment as soon as possible. If Rifampicin resistance – with or without INH resistance – is confirmed, the DTO will trace the patient, with help of the Medical Officer – TB control (MO-TC) and Senior Treatment Supervisor (STS) and bring them to the DTC where they will be counselled by the DTO. Counselling should include (1) information on the lab results, and the reliability of lab results from RNTCP certified C-DST laboratories, (2) the need for additional treatment, (3) the importance of rapid initiation of treatment, (4) the services RNTCP offers for PMDT, (5) what patients should do next, and (6) infection control precautions that are necessary, and re-assurance to the family against panic or unnecessary stigmatization of the patient.

After counselling, the patient is referred to the concerned DR-TB Centre with their DST result and PMDT referral for treatment form ***(See Annexure V)***, for pre-treatment evaluation and initiation of Regimen for MDR TB. **In addition to those patients diagnosed as MDR-TB, patients who are found to be resistant to Rifampicin but sensitive to Isoniazid, will also be referred to the DR-TB Centre for pre-treatment assessment. Patients who are not MDR, but have any Rifampicin resistance, will also be treated with Regimen for MDR TB.**

While the MDR-TB case is undergoing pre-treatment evaluation, the DTO should ensure an initial home visit to verify the address and meet the family members. A DOT provider (who can either be a health care worker, a community worker or a community volunteer or a private practitioner), should be identified in consultation with the patient. The DOT centre can be either at the sub-centre of the health system or in the community. The DOT provider should be given training for drug administration, identification of adverse effects during treatment, the frequency of follow up and record keeping.

6.3 Pre-treatment Evaluation

The patient should be hospitalised (at the DR-TB Centre) for pre-treatment evaluation and treatment initiation. Pre-treatment evaluation should include a thorough clinical evaluation

by a physician, chest radiograph, and relevant haematological and bio-chemical tests detailed below. Since the drugs used for the treatment of MDR-TB are known to produce adverse effects, a proper pre-treatment evaluation is essential to identify patients who are at increased risk of developing such adverse effects. A thorough clinical examination should be done during the pre-treatment evaluation. The pre-treatment evaluation will include the following:

1. Detailed history (including screening for mental illness, drug/alcohol abuse etc.)
2. Weight
3. Height
4. Complete Blood Count with platelets count
5. Blood sugar to screen for Diabetes Mellitus
6. Liver Function Tests
7. Blood Urea and S. Creatinine to assess the Kidney function
8. TSH levels to assess the thyroid function
9. Urine examination – Routine and Microscopic
10. Pregnancy test (for all women in the child bearing age group)
11. Chest X-Ray

All MDR-TB cases will be offered referral for HIV counselling and testing at the nearest centre if the HIV status is not known or the HIV test is found negative with results more than 6 months old. TSH levels alone are usually sufficient to assess the thyroid function of the patient.

In case of pre-treatment evaluation for XDR TB, an ECG, serum electrolytes, and surgical evaluation should be added to the pre-treatment evaluation.

Patients should receive counselling on 1) the nature and duration of treatment, 2) need for regular treatment, 3) possible side effects of these drugs and 4) 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 any side effects experienced by them**. Female patients should receive special counselling on family planning.**

At the DR-TB Centre in-door facility, the DR-TB Centre committee will consider all the clinical and biochemical results before starting the patient on an RNTCP Regimen for MDR TB. The patient will then be counselled and their treatment card opened. If clinically appropriate the patient may be discharged 7 days after the treatment is initiated, or later if appropriate.

6.4 Management of patients who refuse treatment initiation or inpatient admission in DR-TB Centre

DST results from an RNTCP-certified laboratory can be considered actionable for 12 months. In case of a patient who refuses to initiate treatment, all efforts should be made to convince him/her, including involving the patient's family and community. If the patient continues to refuse treatment initiation, infection control counselling for family and periodic follow-up is recommended, as the patient may change their mind at a later date. If the patient returns for treatment initiation within 12 months of diagnosis, they can be immediately registered and started on treatment based on the original laboratory result. After 12 months, microbiologic confirmation is recommended before initiation of treatment.

In case a patient is unable to get hospitalized, all efforts should be made to convince him/her. However, if despite all efforts the patient is still unwilling for hospitalization, treatment should not be denied and alternative local arrangements should be made for pre-treatment evaluation. The results of the pre-treatment evaluation are communicated to the DR-TB Centre Committee and, if approved, the regimen for MDR TB can be initiated at the DTC.

Table 6: Management differences when patients not admitted at DR TB Centre

Admitted at DR-TB Centre	Not admitted at DR TB Centre
Pre-treatment evaluation done at DR-TB centre	Pre-treatment evaluation conducted locally and the patient/ results sent to the DR-TB Centre committee
DR-TB Centre committee decides to initiate MDR TB treatment. DTO informed through e mail as soon as decision taken, so district level preparations can be ready.	DTO initiates Regimen for MDR TB with concurrence of DR-TB Centre committee
Treatment card opened and patient registered in the RNTCP PMDT Register at DR-TB Centre. Patient discharged after at least one week post treatment initiation with maximum 7 days drug supply for the transit.	Treatment card opened by DTO and registered in District RNTCP PMDT Register. Treatment initiated by DTO and the first dose given under supervision at the DTC. Copy sent to DR-TB Centre for recording in RNTCP PMDT Register at the DR-TB Centre. The PMDT TB number of such patients will be provided by the concerned DR TB Centre.

In both the scenario, DTO then refers the patient to the identified DOT Provider with information to MO-PHI. Drugs and patient records sent to the identified DOT Provider

6.5 Providing Counselling to Patient and Family Members

Providing counselling and health education to the MDR-TB patient and their family members about the disease and about the necessity of taking regular and adequate treatment is of utmost importance. Health education and counselling is provided to all patients and family members at different levels of health care, right from one at the periphery to those at the DR-TB Centre facility. It is started at the initial point of contact and carried on a continuous basis at all visits by the patient to a health facility. The counselling and motivation is required to be done not only of the patient but also of the family members.

CHAPTER 7: TREATMENT OF MDR & XDR TB

7.1 Chapter Overview

An "MDR-TB suspect" confirmed by an RNTCP-certified C-DST laboratory to have MDR-TB, or any rifampicin resistance, will be treated with the RNTCP Regimen for MDR TB. Similarly, a patient confirmed as XDR TB by an RNTCP-certified C-DST laboratory for second line DST, will be treated with the RNTCP Regimen for XDR TB. The chapter provides guidance on the treatment of such patients under RNTCP and deals with:

- Drugs and doses for MDR and XDR TB
- Initiation of treatment regimen for MDR TB and XDR TB
- Establishing drug dosages and administration
- Providing health education
- Treatment of patients with baseline second-line drug resistance, who do not respond to treatment

7.2 Classes of anti-TB drugs

The anti-TB drugs can be grouped based on efficacy, experience of use, and drug class.

Table 7.1: Grouping of anti-TB drugs

Grouping	Drugs
Group 1: First-line oral anti-TB agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2: Injectable anti-TB agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vm).
Group 3: Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lvx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
Group 4: Oral second-line anti-TB agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizadone (Trd); *para*-aminosalicylic acid (PAS)
Group 5: Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/Clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); Clarithromycin (Clr)

7.3 RNTCP integrated algorithm for DR-TB treatment (MDR TB, XDR TB, second-line drug resistance, and poor treatment response)

RNTCP recommends a standard treatment, but treatment of DR-TB is more complicated than standard TB. Firstly, baseline resistance to crucial drugs (fluoroquinolone or injectables) can compromise the effectiveness of the Regimen for MDR TB. Secondly, drug intolerance more frequently leads to discontinuation than in first-line anti-TB treatment. Thirdly, poor response to treatment should prompt an examination for programmatic, clinical, and microbiologic reasons for poor treatment response, including non-adherence and additional drug resistance. Based on the accumulated experience and evidence of RNTCP PMDT efforts, the following integrated treatment algorithm should be followed. All patients should initially start a regimen for MDR TB.

As indicated in the "Integrated DR-TB treatment algorithm" isolates would be subject to second-line DST at certain time points. Those indications for second-line DST are:

Indication	Specimen	Source of second-line DST
*Baseline	Diagnostic specimen	Local laboratory certified for second-line DST, if available
Persistent culture-positivity as of six-month isolate results	Latest follow-up culture isolate available	DST from local laboratory if RNTCP-certified for second-line DST; else from NRL
Culture-reversion at any time	Latest follow-up culture available	DST from local laboratory if RNTCP-certified for second-line DST; else from NRL

*Baseline isolates *ideally* should be examined for second-line drug resistance, and the regimen appropriately modified. This is subject to locally-available laboratory capacity. If the RNTCP-certified second-line DST is not locally available, baseline second-line DST will not be possible to immediately implement. NRLs do not have the capacity for baseline second-line DST for all cases in the nation. Hence *in the case where baseline second-line DST is not locally-available, this baseline test would simply not be done*. The capacity of the existing national laboratory network is being augmented for second-line DST.

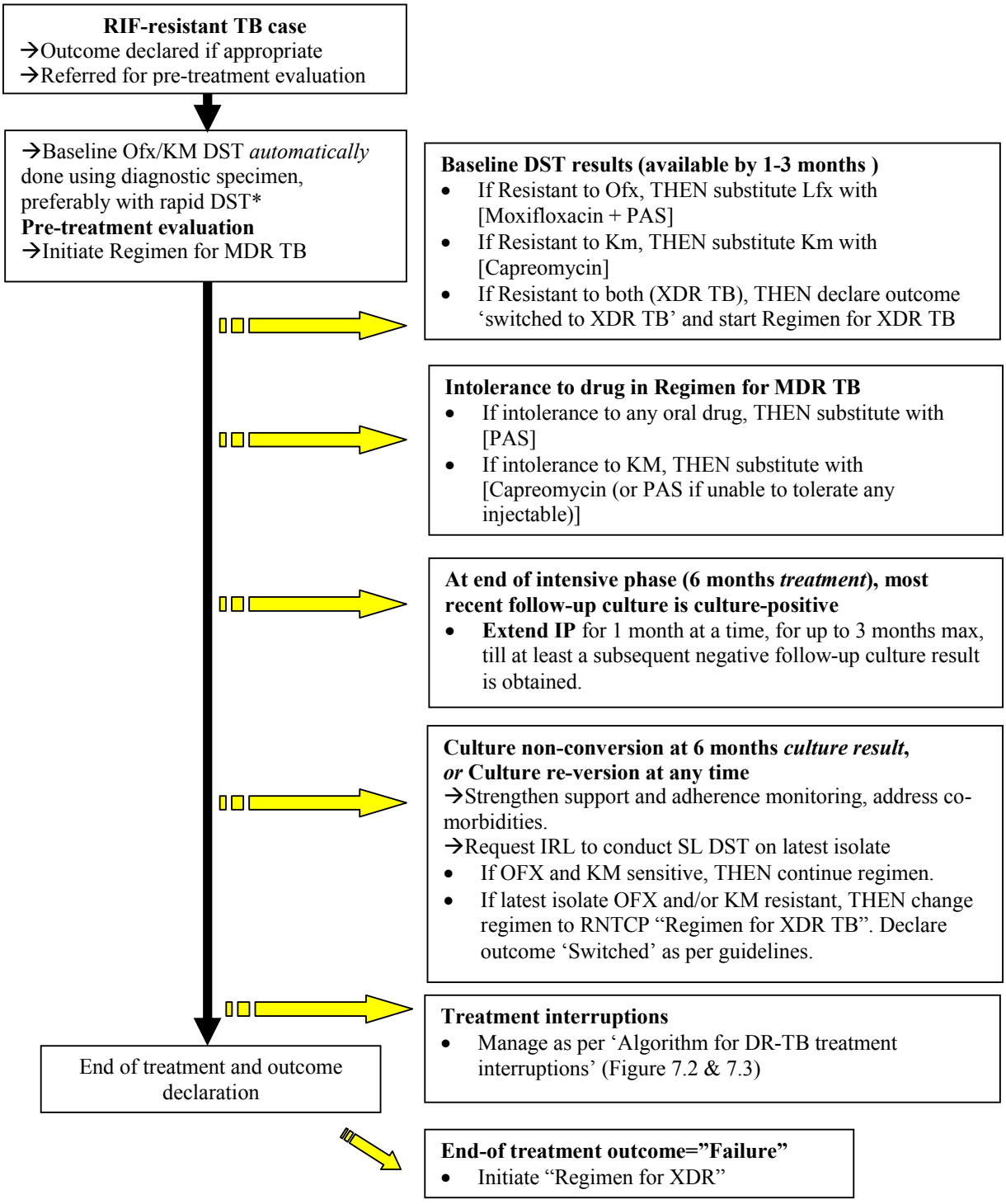
In any case, patients who by the end of 6 months of treatment remain culture-positive should be evaluated in detail for reasons for poor response to treatment. At the end of intensive-phase, if the latest culture result is positive, then extension of the Intensive phase (IP) is indicated, i.e. extended use of injectable drug (kanamycin usually) and PZA. The IP is to be extended for 1 month at a time, till at least one subsequent negative follow-up culture result is obtained, for up to 3 months max (i.e. total 9 months max duration of IP of treatment).

For patients who have *not* achieved culture conversion as of the 6 month culture result, or experience Culture re-version at any time, this is considered as poor treatment response requiring evaluation and second-line DST. If RNTCP-certified second-line DST is not locally available, latest follow-up culture isolates should be sent to the designated NRL. The decision to test or refer for testing an isolate for second-line DST should be implemented automatically by the laboratory based on the isolate history from that patient, and does not require a separate request from the district or DR-TB Centre. The laboratory should inform the concerned DR TB Centre and DTO that second-line DST is pending.

Latest follow-up culture isolates will be subjected to drug susceptibility testing for at least Kanamycin and Ofloxacin, which will diagnose the majority of XDR TB cases, with capreomycin to be added as capacity permits. In-vitro resistance to the fluoroquinolones

clinically used by RNTCP (levofloxacin, moxifloxacin) is not known to occur without ofloxacin resistance.

Figure7.1: Integrated algorithm for DR-TB treatment



7.4 Regimen for MDR-TB

This regimen comprises of 6 drugs - Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol and Cycloserine during 6-9 months of the Intensive Phase and 4 drugs- Levofloxacin, Ethionamide, Ethambutol and Cycloserine during the 18 months of the Continuation Phase.

RNTCP Regimen for MDR TB: 6 (9) Km Lvx Eto Cs Z E / 18 Lvx Eto Cs E
[Reserve/Substitute drugs: PAS, Mfx, Cm]

Special adjustments to the standard Regimen for MDR TB are as follows:

- In case of intolerance to Kanamycin, then Capreomycin (or PAS if injectable agent not feasible) is the available substitute drug.
- In case of intolerance leading to discontinuation of other oral second-line drug, p-aminosalicylic acid (PAS) is the available substitute drug.
- Baseline Kanamycin mono - resistance should lead to substitution of Kanamycin with Capreomycin.
- Baseline Ofloxacin mono - resistance should lead to substitution of Levofloxacin with the combination of Moxifloxacin and PAS.
- Baseline Ofloxacin and Kanamycin resistance (i.e. XDR TB) should lead to declaration of outcome, referral to DR-TB Centre for pre-treatment evaluation for Regimen for XDR TB.

All drugs should be given in a single daily dosage under directly observed treatment (DOT) by a DOT Provider. All patients will receive drugs under direct observation on 6 days of the week. On Sunday, the oral drugs will be administered unsupervised whereas injection Kanamycin will be omitted. If intolerance occurs to the drugs, Ethionamide, Cycloserine and PAS may be split into two dosages and the morning dose administered under DOT. The evening dose will be self-administered. The empty blister packs of the self-administered doses will be checked the next morning during DOT. Pyridoxine should be administered to all patients on Regimen for MDR TB.

Table 7.2: Regimen for MDR TB dosage and weight band recommendations

S.No	Drugs	16-25 Kgs	26-45 Kgs	46-70 Kgs
1	Kanamycin	500 mg	500 mg	750 mg
2	Levofloxacin	250 mg	750 mg	1000 mg
3	Ethionamide	375 mg	500 mg	750 mg
4	Ethambutol	400 mg	800 mg	1200 mg
5	Pyrazinamide	500 mg	1250 mg	1500 mg
6	Cycloserine	250 mg	500 mg	750 mg
7	Pyridoxine	50 mg	100mg	100mg
	Na-PAS (80% weight/vol)[2]	5 gm	10 gm	12 gm
	Moxifloxacin (Mfx)	200 mg	400 mg	400 mg
	Capreomycin (Cm)	500 mg	750 mg	1000 mg

Table 7.3: Regimen for MDR TB drug formulation and packaging

Drugs	16-25 Kg	26-45 Kg	46-70 Kg
Kanamycin	1x 0.5 gm vial	1x 0.5 gm vial	1 x 0.75 gm vial
Levofloxacin	1x 250 mg tab	1x500 mg + 1x250 mg tab	2 x 500 mg tabs
Ethionamide	1 x 250 mg + 1x125 mg tab	2 x 250 mg tabs	3 x 250 mg tabs
Ethambutol	1 x 400 mg tab	1 x 800 mg tab	1x800 mg + 1x400mg tabs
Pyrazinamide	1 x 500 mg tab	1x500 mg + 1x750mg tabs	2 x 750 mg tabs
Cycloserine	1 x 250 mg caps	2 x 250 mg caps	3 x 250 mg caps
Pyridoxine	1 x 50 mg tab	1 x 100mg tab	1 x 100mg tab
Na PAS	100 gm box	100 gm box	100 gm box
Moxifloxacin	0.5 x 400 mg tab	1 x 400 mg tab	1 x 400 mg tab
Capreomycin	1x 0.5 gm vial	1x 0.75 gm vial	1x 1.0 gm vial

If a patient gains 5 kgs or more in weight during treatment and crosses the weight-band range, the DR-TB Centre committee may consider moving the patient to the higher weight-band drug dosages. Similarly if a patient loses 5 kgs or more in weight during treatment and crosses the weight band the DR-TB Centre committee may consider moving the patient to the lower weight band. The new higher/lower dosages are provided whenever the patient is due for the next supply of drugs in the normal course of treatment and not as soon as change of weight is noted.

[2] *In case of PAS with 60% weight/volume the dose will be increased to 7 gm (16-25 Kg); 14 gm (26-45 Kg) and 16 gm (> 45 Kg)*

Large majority of the patients will fall into one of the above weight bands. However, there have been reports of some cases weighing less than 16 kg and more than 70 kg who may require some alteration in the dosage of the drugs in the MDR TB regimen as follows:

- The dosages of 2nd line drugs for MDR TB cases in paediatric age group weighing < 16 kg as per the table below:

Table 7.4: Dosage of Regimen for MDR TB for paediatric age group <16 kg

Drug	Daily Dose – mg/kg body weight
Kanamycin / Capreomycin	15-20 mg/kg
Levofloxacin / Moxifloxacin	7.5-10 mg/kg
Ethionamide	15-20 mg/kg
Cycloserine	15-20 mg/kg
Ethambutol	25 mg/kg
Pyrazinamide	30-40 mg/kg
(Na-PAS)	150 mg/kg

- The dosages for higher weight patients include use additional dosages of some 2nd line drugs for MDR TB cases in patients weighing > 70 kg taking the dosage to Kanamycin/Capreomycin (1 gm), Ethionamide (1 gm), Cycloserin (1 gm), Ethambutol (1.6 gm) and Pyrazinamide (2 gm). Other drugs dosages would remain the same. All these are well within the maximum permissible dosage for each drug as per the WHO guidelines.

7.5 Treatment Duration for Regimen for MDR TB

The treatment is given in two phases, the Intensive phase (IP) and the Continuation phase (CP). The total duration of treatment for Regimen for MDR TB is 24 – 27 months, depending on the IP duration. IP should be given for at least six months. After 6 months of treatment, the patient will be reviewed and the treatment changed to CP if the 4^{th} or 5^{th} month culture result in solid or liquid culture is negative respectively. If the 4^{th} or 5^{th} month culture result remains positive, the treatment is extended by 1 month. Extension of IP beyond 1 month will be decided on the results of sputum culture of 5^{th} or 6^{th} and 6^{th} or 7^{th} months. If the result of the 4^{th} month culture is still awaited after 6 months of treatment, the IP is extended until the result is available, with further treatment being decided according to the culture result. The IP can be extended up to a maximum of 3 months after which the patient will be initiated on the CP irrespective of the culture result. The recommended duration for CP is 18 months.

7.6 Discharge from DR-TB Centres and transition to decentralized supervised treatment

Patients admitted at the DR-TB Centre, if clinically appropriate, may be discharged 7 days after treatment initiation to their district of residence with a maximum of 7 day supply of drugs and arrangement for injections in transit. The respective DTO should be informed of the patients discharge three days prior to the actual time of discharge. The DTO will inform the respective MO-PHI and the identified DOT provider about the expected discharge of the patient. The monthly drug box and the patient records will be passed on to the identified DOT Provider from the respective TU. The details of the drug logistics will be dealt in Chapter 13. Local arrangements will need to be made for daily injections during the intensive phase.

7.7 Regimen for XDR TB

All XDR-TB patients should also be subject to a repeat full pre-treatment evaluation, but also including consultation by a thoracic surgeon for consideration of surgery. Identification must be done for the site (tertiary centres) with such surgical facilities.

MDR TB patients diagnosed as XDR-TB would be given an outcome of "Switched to Regimen for XDR TB". The decision and initiation of Regimen for XDR TB is to be taken by the concerned DR-TB Centre Committee. Drugs will be centrally procured (though till the time of availability, drugs are to be procured by the state as per the technical specifications given by CTD).

The **Intensive Phase** (6-12 months) will consist of 7 drugs – Capreomycin (Cm), PAS, Moxifloxacin (Mfx), High dose-INH, Clofazimine, Linezolid, and Amoxyclav
The **Continuation Phase** (18 months) will consist of 6 drugs – PAS, Moxifloxacin (Mfx), High dose-INH, Clofazimine, Linezolid, and Amoxyclav

RNTCP Regimen for XDR TB: 6-12 Cm, PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv / 18 PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv [Reserve/Substitute drugs: Clarithromycin, Thiacetazone]

The dosage of the drugs would vary as per the weight of the patient (≤ 45Kg or > 45Kg). All drugs are to be given on a daily basis. Injections of Capreomycin will be given for 6 days/week (not on Sundays). All morning doses are to be supervised by the DOT Provider except on Sundays. After taking DOT for morning doses on Saturday, next day medicines

would be given to the patient to be taken at home on Sunday. Empty blisters of medicines taken unsupervised in evening and on Sundays are to be collected by DOT Provider.

Table 7.5: Regimen for XDR TB dosage and weight band recommendations

Drugs	Dosage/day	
	≤ 45 Kgs	**> 45 Kgs**
Inj. Capreomycin (Cm)	750 mg	1000 mg
PAS	10 gm	12 gm
Moxifloxacin (Mfx)	400 mg	400 mg
High dose INH (High dose-H)	600 mg	900 mg
Clofazimine (Cfz)	200 mg	200 mg
Linezolid (Lzd)	600 mg	600 mg
Amoxyclav(Amx/Clv)	875/125 mg BD	875/125 mg BD
Pyridoxine	100 mg	100 mg
Reserve/Substitute drugs		
Clarithromycin (Clr)	500 mg BD	500 mg BD
Thiacetazone (Thz)#	150 mg	150 mg

Depending on availability, not to be given to HIV positive cases

Technical Specifications of drugs for treatment of XDR TB under RNTCP (meant for local purchase of drugs for XDR-TB patients when centrally-procured supplies are not available) are available at the programme website www.tbcindia.nic.in.

The reserve/substitute drugs would be used in the following conditions:

- In case the patient was on PAS, PAS will be replaced with one of the reserve drugs in the regimen for XDR TB
- If the patient is unable to tolerate one or more of the drugs
- If the patient is found to be resistant to Capreomycin

7.8 Duration of Regimen for XDR TB

The Regimen for XDR TB would be of 24-30 months duration, with 6-12 months Intensive Phase (IP) and 18 months Continuation Phase (CP). **The change from IP to CP will be done only after achievement of culture conversion i.e. 2 consecutive negative cultures taken at**

least one month apart. In case of delay in culture conversion, the IP can be extended from 6 months up to a maximum of 12 months. In case of extension, the DR-TR Centre Committee, which will be responsible for initiating and monitoring the Regimen for XDR TB, can decide on administering Capreomycin injection intermittently (3 times/week) for the months 7 to 12.

7.9 Differences in management of XDR TB, compared to MDR TB

Pre-treatment evaluation and inpatient hospitalization

Patients would be admitted at the DR-TB Centre, preferably for at least one month, for pre-treatment evaluation and XDR-TB treatment initiation. This applies to patients who are already on treatment with a regimen for MDR TB (including those diagnosed with Rif resistance); they should again return to the DR-TB Centre for a new pre-treatment evaluation, and new laboratory baseline examinations. Pre-treatment evaluation is largely identical, with the addition of ECG, serum electrolyte testing, and surgical consultation to assess the feasibility of segmental or lobar resection. The duration of admission is flexible, but at least a week is expected, longer if clinically indicated. The patient will be discharged thereafter to continue ambulatory treatment under strict direct observation.

Treatment

While the regimen itself is obviously different, the IP to CP change signal is also different. For regimen for XDR TB, the change from IP to CP will be done only after achievement of culture conversion i.e. 2 consecutive negative cultures taken at least one month apart.

Follow-up monitoring (discussed in Chapter 8)

Direct observation of treatment remains even more crucial, as this is the last chance at successful treatment that these patients will have. Because of the use of drugs with different toxicity profiles, XDR TB requires more intensive monitoring during follow-up.

- Complete Blood Count with Platelets Count: weekly in first month, then monthly to rule out bone marrow suppression and anaemia as a side effect of Linezolid
- Kidney Function Test- monthly creatinine and addition of monthly serum electrolytes to the monthly creatinine during the period that Inj Capreomycin is being administered
- Liver Function Tests: monthly in IP and 3 monthly during CP
- CXR every 6 months

No difference to follow-up Sputum Smear and Culture for patients on regimen for MDR TB and XDR TB.

7.10 Management of treatment interruptions and default for M/XDR TB patients

All efforts should be made to ensure that M/XDR TB patients do not interrupt treatment or default. Action should be taken to promptly retrieve patient who fail to come for DOT, discussed in detail in Chapter 9. The following situations may be seen in case of treatment interruption.

- **Patients in IP/CP who miss doses:**

  All the missed doses during IP must be completed prior to switching the patient to CP. Similarly all missed doses during CP must be administered prior to ending treatment.

- **Patients who interrupt treatment for less than 2 months during IP:**

  When the patient returns to resume treatment the IP will be continued, however the duration of treatment will be extended to complete IP. The follow up cultures will be done as per the revised schedule.

- **Patients who interrupt treatment for less than 2 months during CP:**

  When the patient returns to resume treatment, the CP will be continued, however the duration of treatment will be extended to complete the CP. The follow up cultures will be done as per the revised schedule.

- **Patients who default (interrupt treatment for 2 or more months) and return back for treatment:**

  Such patients will be given an outcome of “default” and then will be re-registered for further treatment which is based on the duration of default as per the flow charts given in on the next page. Re-registration of patients will be done by the DR-TB Centre.

Figure 7.2: Algorithm for management of M/XDR patients who default and return for treatment within 6 months of discontinuing Regimen for M/XDR TB

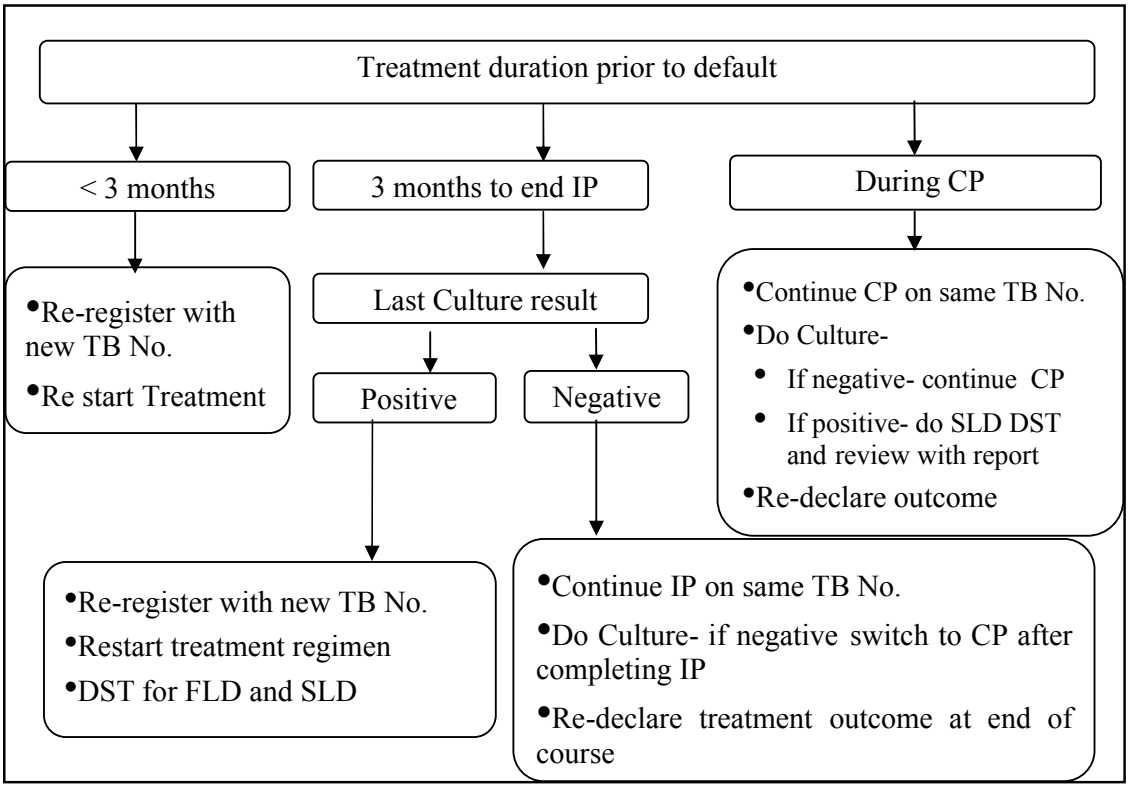
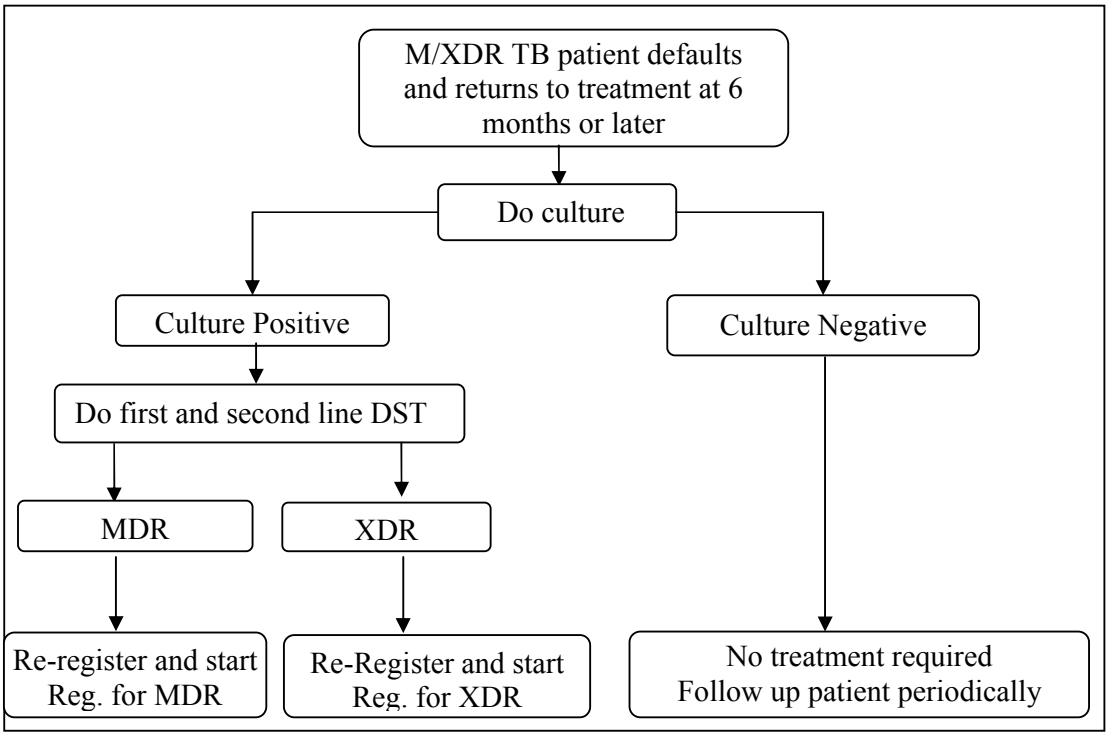


Figure 7.3: Algorithm for management of M/XDR patients who default and return for treatment after 6 months



7.11 Transfers of M/XDR TB patients

Till such time that PMDT services are available in all districts of India, all efforts must be taken at the time of pre-treatment evaluation and treatment initiation to counsel the patient to avoid any kind of migration during the long course of treatment and intimate the concerned DOT provider and TU staff about their plans to migrate due to any reason. It is important to note the address of the current residence, native place, the place of work and occupation of the patients to get a fair idea about the possible places that the patient can move and also whether PMDT services are available at those places.

However, in spite of all efforts, if an M/XDR TB patient on treatment decides to migrate and informs the health care worker, the patient can be transferred out to the district where he/she wishes to migrate, provided that district is implementing PMDT services, else the patient may run a high risk of default. Transfer out should be brought to the notice of the DR-TB Centre by the concerned DTO.

If the patient is migrating to an adjoining district being served by the same DR-TB Centre as the current district of residence, then the patient may be shifted with 7 days of drugs for transit period to a suitable DOT provider at that place where he/she proposes to move in consultation with the DTO of that district and under intimation of the DR-TB Centre. This patient will continue treatment on the same PMDT TB number and the same patient records including the referral for treatment form (Annexure V), the copies of the PMDT treatment cards with a transfer note will be sent to the district receiving the patient. The details of the patient will be updated in the PMDT treatment register at the DR-TB Centre.

If the patient is migrating to any other district that is not being served by the same DR-TB Centre; then the patient may be formally transferred out with 7 days of drugs for transit period to a suitable DOT provider at that place where he/she proposes to move in consultation with the DTO of that district and under intimation of the DR-TB Centre. This patient will be registered at the DR-TB Centre catering to the receiving district with a new PMDT TB number mentioning the old PMDT TB number in the remarks column for future reference. The patient will be continued on the same treatment on the new PMDT TB number. The patient records including the referral for treatment form, the copies of the PMDT treatment cards with a transfer note as well as a copy of the clinical information booklet from the DR-TB Centre will be sent to the district and the DR-TB Centre receiving the patient by the DTO who initiated the transfer out process. The details of the patient will be updated in the PMDT treatment register at the DR-TB Centre for future reference. It is the

responsibility of the receiving DTO and DR-TB Centre to send a feedback about the patient with the new PMDT TB number to the former district and DR-TB Centre to establish a link for future exchange of information about the interim reports, culture conversion and treatment outcomes of the patient.

7.12 Managing referrals from other sectors of patients for MDR TB evaluation and treatment

As happened during RNTCP DOTS expansion, RNTCP PMDT services are scaling up into an existing situation of widespread availability in the open market of anti-TB drugs and DST from private laboratory. It is therefore anticipated that some patients with previous diagnosis of M/XDR TB and/or treatment with second-line anti-TB drugs will wish to avail RNTCP services. RNTCP will offer treatment to all confirmed cases.

RNTCP has a policy against empirical treatment of M/XDR TB without microbiological confirmation from an RNTCP-certified laboratory. Microbiological confirmation from an RNTCP-certified laboratory is required before initiation for treatment of M/XDR TB. If second-line DST capacity is locally available under RNTCP, then that would be offered to all patients at baseline. If not locally available, then the regimen for MDR TB applies irrespective of prior second-line DST results from laboratories not certified for second-line DST under RNTCP.

Similarly, even though some patients may have consumed variable amounts of second-line anti-TB drugs, such prior anti-TB treatment is not likely to be uniformly reliable in quality of drugs, or quantity and duration consumed. Given that uncertainty, the basic principle is that duration of the Regimen for M/XDR TB offered under RNTCP will not be reduced. There may be exceptional circumstances that the DR-TB Centre may consider where prior treatment is very well-documented, adequate, and effective. The local DR-TB Centre committee can exceptionally adjust the duration after detailed case review, approval, and documentation of decisions taken.

Table 7.6: Recommended management strategy for patients with history of past or current treatment with second-line anti-TB drugs, and those with DST results from a laboratory that is not RNTCP-certified.

RNTCP certification status of laboratory	Patients not being treated with second-line anti-TB drugs	Patients being treated with second-line anti-TB drugs
RIF-resistant results, lab certified for first-line DST **Also certified for second-line DST**	Register and initiate treatment as per guidelines, using 'Integrated algorithm for DR-TB treatment'. Use Ofx, KM SL DST results in case management	Register and initiate treatment as per guidelines. No 'credit' prior anti-TB treatment, without detailed review and exceptional approval of DR-TB Centre committee.
RIF-resistant results, lab certified for first-line DST ***not* certified for SL DST**	Register and initiate treatment as per guidelines, using 'Integrated algorithm for DR-TB treatment'. Do not use SL DST results in case management	Register and initiate treatment as per guidelines. No 'credit' for prior anti-TB treatment, without detailed review and exceptional approval of DR-TB Centre committee.
RIF-resistant results, lab *not* certified for first-line DST	Treat case as 'MDR TB suspect', and refer specimens for rapid DST at RNTCP-certified laboratory.	Treat case as 'MDR TB suspect', and refer specimens for rapid DST at RNTCP-certified laboratory. No 'credit' for prior anti-TB treatment, without detailed review and exceptional approval of DR-TB Centre committee.

CHAPTER 8: MONITORING & OUTCOME DEFINITIONS

8.1 Chapter objective:

This chapter provides information on the clinical and laboratory monitoring for patients on treatment for M/XDR TB. It also provides the treatment outcome definitions to be used.

8.2 Clinical monitoring

Patients should be seen by a medical officer trained in RNTCP PMDT guidelines for clinical evaluation after discharge from the DR-TB Centre, at monthly intervals during the IP, and at 3-monthly intervals during the CP until the end of treatment. The responsible medical officer should assess clinical, microbiologic, and radiologic response to treatment, measure weight, assess possible adverse reactions, and encourage the patient to continue treatment. The follow-up visit should result in updation of treatment cards.

Close monitoring of patients is necessary to ensure that the adverse effects are recognized early by the DOT provider. DOT makes it possible to closely monitor patients. Patients should be encouraged to volunteer if they experience any adverse effects, though patients should not be asked any leading question to elicit any adverse reaction.[1] However, if the patient makes any complaint, s/he should be interrogated in detail and the necessary action taken. The DOT provider should be trained to recognize adverse reactions like nausea, vomiting, diarrhoea, skin rash, loss of hearing, reduced sensation, psychiatric symptoms and jaundice.[2-5] Training should also be provided on the management of minor reactions and when the patients should be referred to the medical officer.

Severe adverse reactions should be referred to an appropriate clinical facility, which may include the DR-TB Centre coordinating care for the patient. Other relevant investigations may be done as and when clinically indicated. **These investigations can be done at the DR-TB Centre or district hospitals/medical colleges as per the arrangement, however patients should not be charged for these investigations.** Patients may need to be hospitalized during treatment for medical or psychosocial reasons.

8.3 Follow-up investigations during treatment

Chest radiograph

A baseline chest radiograph should be available from the pre-treatment evaluation. Follow-up chest radiograph will be done at the end of the IP, end of treatment, and whenever clinically indicated.

Serum creatinine

In addition to clinical monitoring, certain laboratory investigations may be required to detect certain occult adverse effects. Serum creatinine is to be done every month for the first 3 months and every three months thereafter whilst the patient is receiving kanamycin.

Thyroid testing

Thyroid testing after the baseline would be conducted as and when required.

The checklist for initial evaluation and treatment surveillance is available at ***Annexure VII.***

8.4 Follow up smear and culture examination during treatment

The importance of the sputum examination during treatment

The most important objective evidence of response to M/XDR treatment is the conversion of sputum culture to negative. Smear conversion is less reliable than culture conversion, which reflects viability of tubercle bacilli and is a more accurate reflection of response to treatment. Good quality sputum is essential to get proper results.

- Patients will be considered **culture converted** after having two consecutive negative cultures taken at least one month apart.
- Time to culture conversion is calculated as the interval between the date of MDR-TB treatment initiation and the date of the first of these two negative consecutive cultures (the date that the sputum specimens are collected for culture should be used).
- Patients will be considered **smear converted** after having two consecutive negative smears taken at least one month apart.

Logistics of follow-up examinations

Arrangements can be made to collect the sputum samples at the respective DMC which will then be transported to the RNTCP-certified Culture and DST laboratory, along with intimation of DTC. Necessary arrangements for the supply of falcon tubes for follow up sputum culture examination should be ensured.

Schedule for follow-up sputum examinations

For follow up examination the required number of sputum specimens will be collected and examined by smear and culture at least 30 days apart from the 3rd to 7th month of treatment (i.e. at the end of the months 3, 4, 5, 6 and 7) and at 3-monthly intervals from the 9th month onwards till the completion of treatment (i.e. at the end of the months 9, 12, 15, 18, 21 and 24). The specimens for smear and culture at the RNTCP certified laboratory will be collected

and transported in falcon tubes with cold chain from the respective DTC to the RNTCP-certified laboratory (at the end of the months 3, 4, 5, 6, 7, 9, 12, 15, 18, 21 and 24).

Wherever available, as per the laboratory decision based on resources available, follow-up sputum culture should be done using liquid culture for *all IP follow-up cultures* and for the last 6 months of CP. For the rest of the follow up cultures and wherever liquid culture is not available, solid media will be used for follow up.

In case of extension of IP, the follow up culture months will shift by every month of extension of IP ***(Annexure VI).***

8.5 Action based on follow-up sputum examination results

Districts are the key responsible party for promptly recording results of sputum examinations in treatment cards and registers, communicating results to patients, and taking the appropriate management actions on results, as per the integrated treatment algorithm above. Results of evaluations should be communicated to the concerned DR-TB Centre committee.

- Baseline DST results shows resistance to fluoroquinolone or injectable drug: adjust treatment regimen as shown in "Integrated algorithm for DR TB treatment".
- Culture conversion: Record date of conversion in the register and inform patient.
- Positive culture results during IP: Conduct a detailed review of patient treatment (adherence, regimen, baseline DST for second-line drugs, dosing), IP extension till the first negative culture result is available.
- Persistent culture positivity at 6 months: Conduct a detailed review of patient treatment (adherence, dosing), evaluate patient response to treatment (clinical exam and radiograph), confirm with IRL that second-line DST in process for evaluation of XDR TB.
- Culture reversion: Conduct a detailed review of patient treatment (adherence, dosing), evaluate patient response to treatment (clinical exam and radiograph), confirm with IRL that second-line DST in process for evaluation of XDR TB.

Sending patients back to DR-TB Centre

After discharge, the patient goes to DR-TB Centre facility for management of severe adverse reactions; change of regimen or dosage and at the end of treatment.

It is not essential to send the patient to DR-TB Centre for change from IP to CP. The respective DTO/medical officer can switch the patient to CP after obtaining the approval of the DR-TB Centre Committee by e mail. Decision of shifting from IP to CP should be based

on the latest (4^{th} or 5^{th}) month culture results available at 4th month or beyond considering the lower turnaround time (TAT) likely wherever liquid culture follow up examination is considered.

8.6 M/XDR TB Treatment Outcome definitions

Standardised treatment outcome definitions are to be used following treatment of an MDR-TB case. These definitions apply to patients with rifampicin resistance (who are taken to be MDR TB for management purposes), and XDR TB cases as well:

- **Cure:** A patient who has completed treatment and has been consistently culture negative (with at least 5 consecutive negative results in the last 12 to 15 months). If one follow-up positive culture is reported during the last three quarters, patient will still be considered cured provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, provided that there is clinical evidence of improvement.
- **Treatment completed:** A patient who has completed treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of bacteriological results.
- **Treatment failure:** Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12-15 months are positive, or if any of the final three cultures are positive.
- **Death:** A patient who dies for any reason during the course of M/XDR-TB treatment
- **Treatment default:** A patient whose treatment was interrupted for two or more consecutive months for any reasons.
- **Transfer out:** A patient who has been transferred to another reporting unit (DR-TB Centre in this case) and for whom the treatment outcome is not known. Till the time the PMDT services are available across the country, the M/XDR TB patients can be transferred out only to those districts, within or outside the state, where these services are available. If a patient moves from one district to another, both of which are covered by the same DR-TB Centre, transfer out will not be required.
- **Treatment stopped due to adverse drug reactions:** A patient who develops severe adverse reactions and could not continue the M/XDR-TB treatment in spite of the management of the adverse reactions as per the defined protocols and decision has been taken by the DR-TB Centre committee to stop treatment

- **Treatment stopped due to other reasons:** A patient who could not continue the M/XDR-TB treatment for any other medical reason (than adverse drug reactions), and a decision has been taken by the DR-TB Centre committee to stop treatment.
- **Switched to Regimen for XDR TB:** A MDR-TB patient who is found to have XDR-TB by an RNTCP certified C-DST laboratory, who subsequently switched to a regimen for XDR TB treatment initiated.
- **Still on treatment:** An M/XDR-TB patient who, for any reason, is still receiving their treatment at the time of the submission of the Treatment Outcome Report.

CHAPTER 9: TREATMENT DELIVERY AND ADHERENCE

9.1 Chapter objectives

This chapter outlines the treatment delivery strategies that will improve patient adherence in the patients receiving treatment for MDR-TB.

9.2 Education of patients and their families

All patients and their families should receive health education and information about MDR-TB, its treatment, potential adverse drug reactions and the need for adherence with therapy. Educational interventions should commence at the start of therapy and continue throughout the course of treatment. Education can be provided by the attending doctors, nurses, community health workers, and other health care workers. Materials need to be appropriate to the literacy levels of the population and should be culturally sensitive.

9.3 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.[1,2] 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. Although early in the history of MDR-TB treatment, strict hospitalization of patients for the complete treatment was felt to be necessary, studies have demonstrated that home-based care provided by trained lay and community health workers can achieve comparable results and theoretically may result in decreased rates of nosocomial spread of the disease.[1] Whatever the setting, care should be delivered by a multidisciplinary team of providers including physicians, nurses, social workers, and community health workers or volunteers.

Initial in-patient care

When an MDR-TB suspect is confirmed to have MDR-TB by the RNTCP-certified Culture and DST laboratory, the respective DTO will be informed of the DST result by the laboratory. The DTO and MO-TC will confirm the address of the patient and will arrange for the patient's referral and admission to the designated DR-TB Centre in-door facility, with their DST result and the RNTCP "PMDT referral for treatment form" ***(Annexure V)***. Once the DR-TB Centre committee decides upon RNTCP Regimen for MDR TB for the patient, the patient is counselled, an RNTCP PMDT treatment card opened, a PMDT patient Identity Card issued to

the patient, Regimen for MDR TB initiated and patient is registered in PMDT treatment register with a unique PMDT TB number issued.

The patient will be admitted in the designated DR-TB Centre in-door facility for at least seven days post- treatment initiation. This period of admission will allow for

- All necessary investigations to be undertaken;
- Initiation of the Regimen for MDR TB;
- Monitoring of patient tolerance of the Regimen for MDR TB;
- Motivation, counselling and providing health education to the patient and their families;
- Developing linkages with the services in the respective district where the patient resides (including identification and training of a local DOT provider and family treatment supporter);
- Contact assessment.

The hospital should provide comfortable living conditions, adequate food, proper ventilation and sufficient activities to keep the patients occupied. Further admission may be necessary during ambulatory treatment for management of severe adverse drug reactions, complications, to assess need and fitness for surgical intervention; social reasons, etc.

After admission at the DR-TB Centre for at least seven days post treatment initiation, the patient can be discharged to the residence district with up to a maximum of one week's supply of drugs, arrangements for injections in transit, and a copy of the treatment card and referral form. The respective DTO should be informed by the attending physician of the patient's planned discharge 3 days prior to the actual date of discharge, by means of the RNTCP PMDT referral for treatment form *(Annexure V)* which can be sent by email. Drugs provided to the patients to cover for transit period may be counted as unsupervised doses. However, as far as possible efforts should be made by the district staff to restrict these transit doses

For patients who are unwilling for admission at the DR-TB Centre, the DTO will locally arrange for the pre-treatment evaluation. The results of the pre-treatment evaluation will be communicated to the DR-TB Centre committee for a decision to initiate the patient on treatment. On receiving an affirmation from the DR-TB Centre committee the DTO will open the treatment card and start the patient on treatment. A copy of the treatment card will be sent to the DR-TB Centre for their record and registration in the PMDT register. On registration the DR-TB Centre will inform the PMDT TB number to the DTO.

Ambulatory care

The DTO arranges for availability of the monthly IP drug box (from the TU) and the patient records at the identified DOT Centre with information to the respective MO-PHI. This MO-PHI is responsible for supplying the treatment records and the drugs to the designated DOT Plus provider. The MO-PHI will need to make suitable arrangements during the intensive phase of the treatment for daily injections.

The DTO will ensure that an updated copy of the treatment card is sent to the designated DR-TB Centre, preferably electronically, every month for updating the MDR-TB Register. For collection of the follow-up samples for culture and DST, the patient will need to go to their respective DTC, where the DTO will arrange for the samples to be collected and transported to the respective RNTCP-certified Culture and DST laboratory. Alternatively arrangements can be made to collect the sputum samples at the respective DMC which will then be sent to the DTC to be transported to the RNTCP-certified Culture and DST laboratory. Necessary arrangements for the supply of falcon tubes for follow up sputum culture examination should be ensured. The patient will need to return to the DR-TB Centre for the decision to end treatment, for managing severe adverse drug reactions, and for any change of regimen or dosage. All referrals from the DTC to the DR-TB Centre or vice versa should be made on Referral for Treatment Form *(Annexure V)*. The receiving health facility should communicate the receipt of patient to the referring centre through an e mail.

9.4 Adherence

Patients with MDR-TB may be more likely to have had problems with non-adherence in the past.[3] In addition, adherence with MDR-TB therapy is made more difficult by its prolonged treatment regimens, with larger numbers of drugs that have more serious adverse effects.[4] Thus, MDR-TB patients are at risk of not being able to adhere to treatment, an essential element to prevent the generation of pan-resistant strains with the potential for community-wide spread and virtually no chance of cure for the patient .[5]

MDR-TB treatment can be successful with high overall rates of adherence when adequate support measures are provided.[1] 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 DTC and designated DR-TB Centre
- Emotional support and counselling to the patient and family members and education on MDR-TB treatment;

- Early and effective management of adverse drug reactions;
- Honorarium to the non salaried DOT providers.

9.5 Directly observed therapy

Because MDR-TB treatment is the last therapeutic chance for patients and there is a high public health consequence if a patient with MDR-TB fails therapy, it is recommended that all patients receiving RNTCP Regimen for MDR TB receive daily DOT wherever they are receiving the treatment, be it either in the community, at health centres, or within the hospital setting i.e. every dose of RNTCP Regimen for MDR TB is to be given under DOT by an appropriate, acceptable and accountable 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 accessing services may all contribute to a decreased efficacy of DOT.

Who can deliver DOT for MDR-TB patients?

Since the treatment of MDR TB requires administration of Injection Kanamycin during the intensive phase, the identified DOT provider should be someone, maybe a health worker or someone from the community, who is able to give injections. If required, a second DOT provider may be utilised for delivering the CP. Therefore the patient can have two different DOT providers during the course of treatment, one for IP and the other for CP. Needless to say, 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 patients. A family member should **not** deliver DOT. Family dynamics are often complicated for the MDR-TB patient, and a family observer could be subject to subtle manipulation by the patient, relatives, etc.

9.6 Socioeconomic 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 and Health Care Workers (HCW), to adhere to the treatment. 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 and HCWs to adhere to therapy. The programme is also engaging with appropriate NGOs/agencies to provide linkages for appropriate socioeconomic interventions.

There have been examples of supporting patients through skills based vocational rehabilitation by NGOs e.g. provision of sewing machine to female MDR TB cases who have the stitching skills, that enable them resume earning their livelihood and regain interest in life. Some donors and NGOs support patient's relocation with family to the main town clubbed with vocational rehabilitation that has been successful in some countries with hilly terrains.

9.7 Social and emotional support

Having MDR-TB can be an emotionally devastating experience for patients and their families; there may be stigma attached to the disease and this may interfere with adherence to therapy. In addition, the long nature of MDR-TB therapy combined with the medications' adverse effects 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. Ideally a multidisciplinary team, comprising of a social worker, nurse, health educators, companions, and doctors, should be set up to act as a "support to adherence" team to the patient. Linking up these cases with the available social welfare schemes through active engagement with the civil society partners and NGOs is another option the programme officer must explore to promote treatment adherence.

9.8 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 visit the patient's home on the same day to find out why the patient has not appeared for his/her 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 and to resolve the specific reason identified.

9.9 Early and effective management of adverse drug reactions

Minor adverse reactions are extremely common in MDR TB treatment, and should be expected and built into patient counselling from the beginning; most such side effects are manageable with reassurance and symptomatic treatment. 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[6]. Adverse reactions are discussed in details in Chapter 11.

9.10 Death Audit

The DTOs should conduct an in-depth audit of all the deaths occurring amongst the MDR patients prior to initiation of treatment and 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.

Table 9: Summary of adherence promotion strategies for PMDT

- Directly observed therapy
- Social support
- Support to adherence team approach
- Effective management of adverse drug reactions

References

1. Mitnick, CD, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. New England Journal of Medicine 2003; 348(2):119-28.
2. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, Laserson KF, Wells CD. Clinical outcome of individualised treatment of multi-drug resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005; 365:318-26.
3. Mitchison, D. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. International Journal of Tuberculosis and Lung Disease 1998; 2(1): 10-15.
4. Chaulk, C., Chaisson R., Lewis, J., et al. Treating multidrug-resistant tuberculosis: compliance and side effects. Journal of the American Medical Association 1994; 271(2): 103-104.
5. Espinal M., Dye, C., Raviglione, M., et al. A rational "DOTS-Plus" for the control of MDR-TB. International Journal of Tuberculosis and Lung Disease 1999; 3(7): 561-563.
6. Furin, JJ, Mitnick, CD, Shin, SS, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. International Journal of Tuberculosis and Lung Disease 2001; 5(7): 648-55

CHAPTER 10: MDR-TB in special situations

10.1 Chapter objectives

Compared to drug sensitive TB, MDR-TB is more demanding in terms of cost of treatment, duration of treatment, higher adverse reactions to second line drugs, resources required by the treatment providers, and the prolonged adherence required by the patients. To add to these issues certain associated special situations make the treatment of MDR-TB more difficult.[1, 2]

This chapter outlines the management of MDR-TB in the following special situations and conditions:

1. MDR-TB in pregnancy
2. MDR-TB with co-infected HIV infection
3. MDR-TB requiring surgery
4. MDR-TB in patients with renal impairment
5. MDR-TB in patients with pre-existing liver disease
6. MDR-TB with seizure disorders
7. MDR-TB with psychiatric illnesses
8. MDR-TB in Extra-Pulmonary TB patients
9. Management of contacts of MDR-TB

10.2 MDR-TB in pregnancy [(3-7)]

There is a lack of experience in treating pregnant women with MDR-TB. Teratogenicity has been demonstrated with only some of the drugs used to treat MDR-TB. It is prudent to solicit the opinion of an experienced gynaecologist/obstetrician while treating such patients.

All women of childbearing age who are receiving MDR-TB therapy should be advised to use birth control measures because of the potential risk to both mother and foetus It should be remembered that oral contraceptives might have decreased efficacy due to vomiting and drug interactions with MDR-TB drugs. Thus for prevention of pregnancy the use of barrier methods (Condoms/diaphragms), IUDs (CuT) or depot-medroxyprogesterone (Depo-provera) are recommended based on individual preference and eligibility. Similarly all women of child bearing age identified as MDR TB suspects should be advised to use a reliable and appropriate contraceptive method till the results of culture and DST are available.

All female MDR suspects and MDR patients of childbearing age should be counselled intensively in relation to the use of contraceptive methods. All women of childbearing age should be tested for pregnancy as part of the pre-treatment evaluation and whilst on treatment if there is a history of amenorrhea of any duration. MDR-TB patients found to be pregnant prior to treatment initiation or whilst on treatment are evaluated in consultation with a Gynaecologist/Obstetrician taking into consideration the following factors:

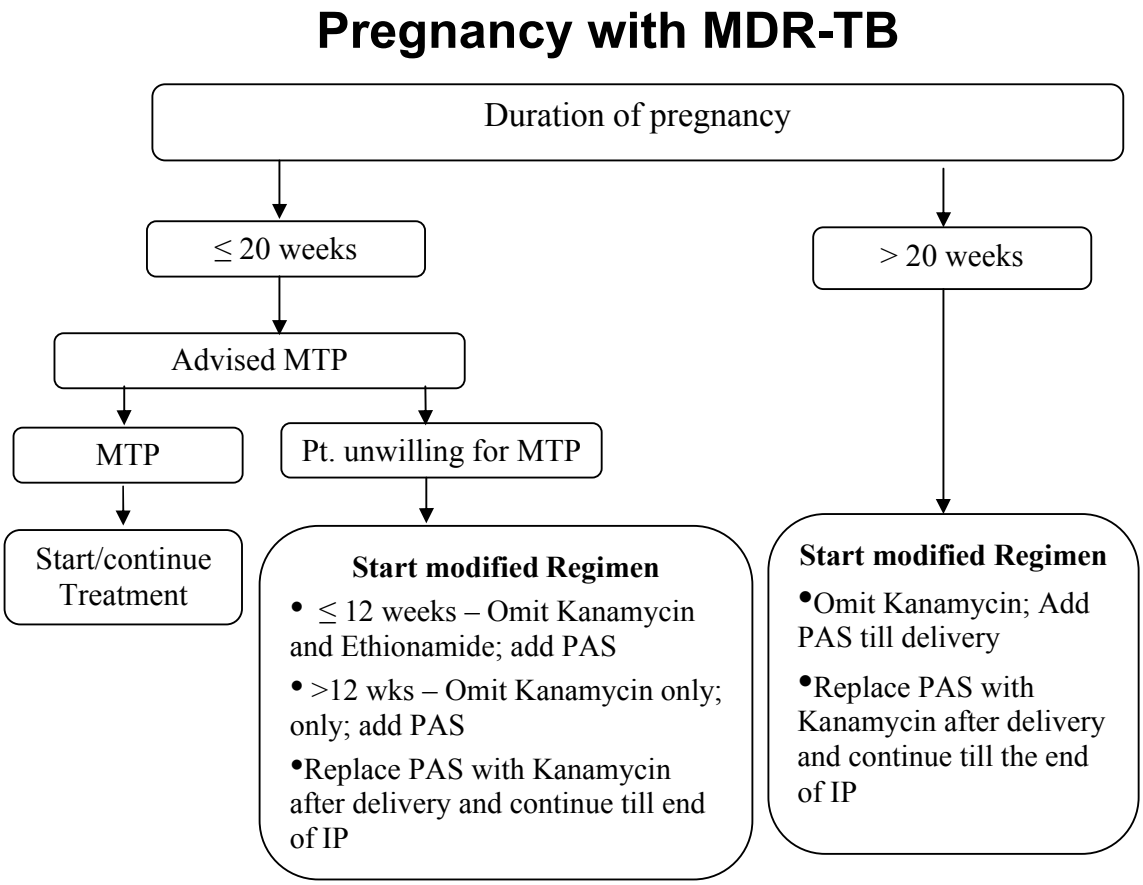
- Risks and benefits of MDR-TB treatment
- Severity of the MDR-TB
- Gestational age
- Potential risk to the foetus

Further management of MDR-TB patients who are pregnant prior to initiation of treatment or whilst on treatment are based on the duration of pregnancy.

- If the duration of pregnancy is <20 weeks, the patient should be advised to opt for a Medical Termination of Pregnancy (MTP) in view of the potential severe risk to both the mother and foetus. If the patient is willing, she should be referred to a Gynaecologist/Obstetrician for MTP following which treatment can be initiated (if the patient has not started treatment) or continued (if the patient is already on treatment) by the DR-TB Centre Committee.
- For patients who are unwilling for MTP or have pregnancy of >20 weeks (making them ineligible for MTP), the risk to the mother and foetus needs to be explained clearly and a modified Regimen for MDR TB should be started as detailed below:
  - For patients in the first trimester (≤ 12 weeks), Kanamycin and Ethionamide are omitted from the regimen and PAS is added.
  - For patients who have completed the first trimester (>12 weeks), Kanamycin is replaced with PAS. Post partum, PAS may be replaced with Kanamycin and continued until the end of the Intensive Phase.

Pregnant MDR-TB patients need to be monitored carefully both in relation to the treatment and the progress of the pregnancy. This approach should lead to good results, since the patient should be smear-negative at the time of parturition, and mother and infant do not need to be separated. Breast-feeding should be encouraged as long as the patient is sputum negative.

The management of MDR-TB patients with pregnancy is summarised in the flow chart on the next page:



10.3 MDR-TB with HIV co-infection [8-13]

The presentation of MDR-TB in the HIV-infected patient does not differ from that of drug-sensitive tuberculosis in the HIV-infected patient. However the diagnosis of TB in HIV-positive persons can be more difficult and may be confused with other pulmonary or systemic infections. As the HIV disease progresses and the individual become more immune-compromised, the clinical presentation is proportionately more likely to be extra-pulmonary or smear-negative than in HIV-uninfected TB patients. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality. With the nation wide scale up of Intensified TB HIV Package, it is expected that more and more numbers of TB patients have know HIV status and if found to be HIV positive, they must be linked to ART Centres and provided Co-trimoxazole preventive therapy (CPT).

The treatment of HIV positive individual with MDR-TB is the same as for HIV negative patients. However treatment is more difficult and adverse events more common. Deaths during treatment, partly due to TB itself and partly due to other HIV-related diseases, are more frequent in HIV-infected patients, particularly in the advanced stages of immunodeficiency. Due to the increased frequency of adverse drug events, rigorous monitoring in this particular group of patients is required in order to ensure adherence to treatment, early identification and treatment of adverse events and reduce default

Initiating ART (Anti-Retroviral Therapy) in patients with MDR- TB

The use of ART in HIV infected patients with TB improves survival for both drug resistant and susceptible disease. However HIV infected MDR patients without the benefit of ART may experience mortality rates exceeding 90%. The likelihood of adverse effects could compromise the treatment of HIV or MDR TB if both treatments are started simultaneously. On the other hand undue delay in starting ART could result in significant risk of HIV related death amongst MDR patients.

Based on the WHO Guidelines on Antiretroviral therapy for HIV infection in adults and adolescents - Recommendations for a public health approach- 2010 revision; Irrespective of CD4 cell counts, patients co-infected with HIV and TB should be started on ART as soon as possible after starting TB treatment. ART should be initiated as soon as possible in all HIV/TB-co-infected patients with active TB (within 8 weeks after the start of TB treatment).

For patients who are already on ART at the time of MDR-TB diagnosis be continued on ART when MDR-TB therapy is initiated. Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs or radiographic manifestations of TB after beginning TB treatment. This paradoxical reaction occurs in HIV-infected patients with active TB and is thought to be a result of immune restitution due to the simultaneous administration of antiretroviral and tuberculosis medication (IRIS Syndrome). Symptoms and signs may include high fever, lymphadenopathy, expanding intra-thoracic lesions and worsening of chest radiographic findings. The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other aetiologies, particularly TB treatment failure. For severe paradoxical reactions prednisone (1-2 mg/kg for 1-2 weeks, then gradually decreasing doses) may be used.

10.4 Role of surgery in management of MDR-TB [14-17]

In MDR-TB patients with localized disease, surgery, as an adjunct to chemotherapy, can improve outcomes provided skilled thoracic surgeons and excellent post-operative care are available. When unilateral resectable disease is present, surgery should be considered for the following cases:

- Absence of clinical or bacteriological response to chemotherapy despite six to nine months of treatment with effective anti-tuberculosis drugs;
- High risk of failure or relapse due to high degree of resistance or extensive parenchymal involvement;
- Morbid complications of parenchymal disease e.g. haemoptysis, bronchiectasis, bronchopleural fistula, or empyema;
- Recurrence of positive culture status during course of treatment; and
- Relapse after completion of anti-tuberculosis treatment.

If surgical option is under consideration at least six to nine months of chemotherapy is recommended prior to surgery.

10.5 MDR-TB in patients with renal impairment [18]

Renal insufficiency due to longstanding TB disease itself, previous use of aminoglycosides or concurrent renal disease is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal impairment. Consideration needs to be taken that MDR-TB patients require aminoglycosides for 6 months or more. Other drugs, which also might require dose or interval adjustment in presence of mild to moderate renal impairment, are: Ethambutol, Quinolones, Cycloserine and PAS. In the presence of severe renal impairment many other drugs may also require adjustments (Table 10.1).

In MDR-TB patients, blood urea and serum creatinine should be monitored prior to treatment initiation, monthly for three months after treatment initiation and then every three months whilst injection Kanamycin is being administered. In patients with mild renal impairment, the dose of aminoglycosides may be reduced. In the presence of severe renal failure, the aminoglycoside therapy should be discontinued and replaced with other potent non-nephrotoxic antituberculosis drugs.

Table 10.1: Dose adjustment of anti-TB drugs in presence of renal impairment

Drug	Method of modification	Glomerular filtration rate, ml/min		
		> 50	10-50	<10
Kanamycin	D, I	7.5-15mg /Kg /24 hr	4-7.5mg/Kg/24 hr	3mg /Kg /48 hr
Ethambutol	I	20mg /Kg /24 hr	20mg/Kg/24–36 hr	20mg /Kg /48 hr
Pyrazinamide	D	30mg /Kg /24 hr	30 mg/Kg/24 hr	15-30 mg/Kg/ 24 hr
Ofloxacin	D	100% *	50 – 75% *	50% *
Ethionamide	D	100% *	100% *	50% *
Cycloserine	D	100% *	50-100% *	50% *
PAS	D	100% *	50-75% *	50% *

D = dose adjustment I = interval adjustment

* Percentage of recommended dose to be given

10.6 MDR-TB in patients with pre-existing liver disease [19]

In the RNTCP Regimen for MDR TB, Pyrazinamide, PAS and Ethionamide are potentially hepatotoxic drugs. Hepatitis occurs rarely with the fluoroquinolones. The potential for hepatotoxicity is increased in elderly, alcoholics and in patients with pre-existing liver disease. In general, most of second line drugs can be safely used in presence of mild hepatic impairment, as they are relatively less hepatotoxic than the first-line drugs. However Pyrazinamide should be avoided in such patients.

Once a patient on second line drugs develops hepatitis, other aetiologies should also be excluded such as viral hepatitis, alcoholic hepatitis, drug induced hepatitis by non-TB drugs etc. The further management should be on the same guidelines as in non- MDR-TB patients. **MDR patients having deranged liver function test (LFT) during pre-treatment evaluation should be strictly monitored through monthly LFTs while on treatment**. **However routine LFT is not recommended in all cases**.

10.7 MDR-TB in patients with seizure disorders [19,20]

Some patients requiring treatment for MDR-TB will have a past or present medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking anti-seizure medication to control the disorder. If the seizures are not under control, initiation or adjustment of anti-seizure medications will be needed prior to the start of MDR-TB therapy. In addition, if other underlying conditions or causes for seizures exist, they should be corrected.

Among second line drugs, Cycloserine, Ethionamide and fluoroquinolones have been associated with seizures, and hence should be used carefully amongst MDR-TB patients with history of seizures. Pyridoxine should be given with Cycloserine to prevent seizures. Cycloserine should however be avoided in patients with active seizure disorders that are not well controlled with medication. In cases where no other drug is appropriate, Cycloserine can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. The risk and benefits of using Cycloserine should be discussed with the patient and the decision on whether to use Cycloserine are made together with the patient.

Antiepileptic drugs may have drug interactions with Cycloserine and fluoroquinolones. Hence close monitoring of serum levels of anti-epileptic drugs should be done. One should remember that TB might itself involve central nervous system and may cause seizures. However when seizures present for the first time during anti-TB therapy, they are likely to be the result of an adverse effect of one of the anti-TB drugs.

10.8 MDR-TB in patients with psychosis [21,22]

For MDR-TB patients with a concurrent psychiatric illness, it is advisable to have an evaluation carried out by a psychiatrist before the start of treatment for MDR-TB. The initial evaluation documents any pre-existing psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any identified psychiatric illness at the start or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease. If a health care worker with psychiatric training is not available, the treating healthcare provider should document any psychiatric conditions the patient may have at the initial evaluation.

Treatment with psychiatric medication, individual counselling, and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or adverse psychiatric effect due to medication. Group therapy has been very successful in providing a supportive environment for MDR-TB patients and may be helpful for patients with or without psychiatric conditions (adequate measures to prevent infection risk should be in place for the group therapy).

Fluoroquinolones and Ethionomide have been associated with psychosis. Pyridoxine prophylaxis may minimize risk of neurologic and psychiatric adverse reactions.

Cycloserine may cause severe psychosis and depression leading to suicidal tendencies. However the use of Cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects of Cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug often outweigh the potential higher risk of adverse effects. Close monitoring is recommended if Cycloserine is used in patients with psychiatric disorders.

If patient on Cycloserine therapy develops psychosis, anti-psychotic treatment should be started and Cycloserine therapy should be temporarily suspended. Once symptoms resolve and patient is stabilized Cycloserine therapy may be resumed. Such patients may require anti-psychotic treatment till anti-TB treatment is completed. When any patient on MDR-TB treatment develops psychosis, other aetiologies such as psycho- social stresses, depression, hypothyroidism, illicit drug and alcohol use, should also be looked for.

All healthcare workers treating drug-resistant TB should closely work with a psychiatrist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation, and any situation involving the patient's being a danger to him/her self or others. Mechanisms to deal with psychiatric emergencies (often inpatient psychiatric hospital admissions) should be available twenty-four hours per day. Proper infection-control measures must be taken for the smear-positive patient who requires any hospitalization.

10.9 Management of MDR TB in Extra Pulmonary TB cases

Management of bacteriologically confirmed Extra-Pulmonary MDR-TB patients will be considered by the programme provided the diagnosis is made by an RNTCP C-DST Laboratory. Treatment regimen and schedule for EP MDR TB cases will remain the same as for pulmonary MDR TB. Patients must be registered in the PMDT Register and the treatment outcome of treatment completed will be considered.

Investigations and pre-treatment evaluation

Patients would be admitted at the DR-TB Centre, preferably for at least one week, for pre-treatment evaluation and Cat-IV treatment initiation. **EP MDR-TB** patients will undergo all those pre-treatment investigations as done for pulmonary MDR-TB patients as a part of the pre-treatment evaluation prior to initiating Regimen for MDR TB.

In addition, ultrasound of abdomen of the patient will also be done, if necessary, to rule out involvement of other organs and abdominal nodes.

Initiation of Treatment

After pre-treatment evaluation, treatment for Extra-pulmonary MDR-TB should be initiated based on weight of the patient. Treatment regimen, weight band and schedule for EP MDR TB cases will remain the same as for pulmonary MDR TB. Treatment for Extra pulmonary MDR tuberculosis should be given for 24 months strictly

Monitoring progress during treatment and follow-up

Clinical monitoring is the most important criteria for the follow up of patients with Extra-pulmonary MDR tuberculosis. Regular patient monitoring and periodic follow up of nodes and other extra-pulmonary symptoms with culture from the discharging node/sinus is the key in monitoring of treatment in Extra-pulmonary Lymph Nodal MDR-TB.

1) Bacteriological monitoring:

Two specimens from the discharging sinus /pus in the lymph node should be collected, one for smear and one for culture. The sample should be taken at the end of 3rd month of treatment and then every month (at least 30 days apart) in IP till there is pus /discharge from sinus (in the node). Unlike sputum smear and culture, culture from the node can be given only till the pus/discharging sinus is present from the node. The follow up is mainly based on clinical parameters.

2) ***Clinical monitoring:***

This is important in case of Extra-pulmonary MDR tuberculosis. Monitoring and follow up can be done clinically based on the following:

1. Weight Gain
2. Decrease or increase in symptoms (e.g. healing of ulcer/scrofuloderma)
3. Increase or Regression in size of nodes {**possibility of Immune Reconstitution Inflammatory Syndrome (IRIS) should be considered and differentiated from disease progression**}
4. Appearance of new nodes
5. If chest symptomatic, monthly sputum for AFB and chest X-ray (to rule out pulmonary involvement)
6. Other Extra-pulmonary sites should be monitored (USG abdomen if necessary)
7. Serum Creatinine – monthly for the first three months of treatment and then quarterly till the patient receives Kanamycin and further when clinically indicated
8. Liver function test – as clinically indicated
9. USG-abdomen – if necessary

10. Monitoring for drug adverse reactions

Same outcome definitions would be used as for Pulmonary MDR TB patients. Treatment outcome will depend on availability of culture reports of specimens taken from discharging sinuses, treatment completion and clinical improvement of the patient.

10.10 Management of contacts of MDR-TB [23-27]

All close contacts of MDR-TB cases should be identified through contact tracing and evaluated for active TB disease as per RNTCP guidelines. If the contact is found to be suffering from pulmonary TB disease irrespective of the Smear results, he/she will be identified as an "MDR-TB suspect". The patient will be initiated on Regimen for new or previously treated case based on their history of previous anti-TB treatment. Simultaneously two sputum samples will be transported for culture and DST to a RNTCP-certified C&DST laboratory. If the patient is confirmed to have MDR-TB, the patient will be admitted to the DR-TB Centre ward for pre-treatment assessment and initiation of Regimen for MDR TB.

Among contacts of patients with MDR-TB, the use of Isoniazid may reasonably be questioned. Although alternative prophylaxis treatments have been suggested, there is no consensus regarding the choice of the drug(s) and the duration of treatment. Prompt treatment of MDR-TB is the most effective way of preventing the spread of infection to others. The following measures should be taken to prevent spread of MDR-TB infection:

1. Early diagnosis and appropriate treatment of MDR-TB cases;
2. Screening of contacts as per RNTCP guidelines
3. Further research into effective and non-toxic chemoprophylaxis in areas of high MDR-TB prevalence.

References

1. WHO/IUATLD. Global Project on Anti-tuberculosis Drug Resistance Surveillance. Anti-tuberculosis drug resistance in the world. Report No.2. HO/CDS/TB/2000.278.
2. World Health Organization. The WHO/IUATLD. Global Project on Antituberculosis Drug Resistance Surveillance: Antituberculosis drug resistance in the world. Report No.3.Geneva: Switzerland; 2004. WHO/CDS/TB/2004.
3. Drobac PC, del Castillo H, Sweetland A, Anca G, Joseph JK, Furin J, Shin S. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. Clin Infect Dis. 2005;40:1689-92.
4. Shin S, Guerra D, Rich M, Seung KJ, Mukherjee J, Joseph K, Hurtado R, Alcantara F, Bayona J, Bonilla C, Farmer P, Furin J. Treatment of multidrug-resistant tuberculosis during pregnancy: a report of 7 cases. Clin Infect Dis. 2003;36:996-1003.

5. Duff P. Antibiotic selection in obstetric patients. Infect Dis Clin North Am. 1997;11:1-12.
6. Valleho JG, Surke Jr. Tuberculosis and pregnancy Clinic Chest Med. 1992; 13(4):693-707.
7. Hamadeh MA, Glassroth J. Tuberculosis and Pregnancy: Chest 1992;101:1114-20.
8. Li J, Burzynski JN, Lee YA, Berg D, Driver CR, Ridzon R, Munsiff SS. Use of therapeutic drug monitoring for multidrug-resistant tuberculosis patients. Chest 2004;126:1722-4.
9. Dlodlo RA, Fujiwara, and Enarson DA. Controversial issues in tuberculosis: Should tuberculosis treatment and control be addressed differently in HIV-infected and -uninfected individuals? Eur Respir J 2005; 25: 751–757.
10. World Health Organization. Strategic framework to decrease the burden of TB/HIV. WHO/CDS/TB/2002.296, WHO/HIV_AIDS/2002.2).
11. Grant AD, Djomand G, De Cock KM. Natural history and spectrum of disease in adults with HIV/AIDS in Africa. AIDS 1997; 11 (suppl B): S43-S54.
12. Safe and effective use of antiretroviral treatments in adults, with particular reference to resource limited settings. Geneva, World Health Organization, 2000 (document WHO/HIS/2000.04).
13. World Health Organization. Preventive therapy against tuberculosis in people living with HIV. Weekly Epidemiological Record 1999; 74: 385-398.
14. Takeda S, Maeda H, Hayakawa M, Sawabata N, Maekura R. Current surgical intervention for pulmonary tuberculosis**.** Ann Thorac Surg 2005; 79: 959-63.
15. Pomerantz BJ, Cleveland JC, Olson HK, Pomerantz M. Pulmonary resection for multi-drug resistant tuberculosis. J Thorac Cardiovasc Surg 2001;121:448-453.
16. Pomerantz M, Madsen LA, Goble M. Iseman MD, Surgical management of resistant mycobacterial pulmonary infection. Ann Thorac Surg 1991;52:1108-12.
17. Teasure RL. Seaworth B. Current role of surgery on Mycobacterium Tuberulosis Am Thorax Surg 1995;59:1405-7.
18. Ruckenstein MI. Vertigo and disequilibrium with associated hearing loss. Otolaryngol Clin North Am 2000; 33:535-62.
19. Braunwald E. Harrison's Principal of Internal Medicine. 15th edition. New York: McGraw-Hill, 2001.
20. WHO. Treatment of tuberculosis: guidelines for national programmes. WHO/CDS/TB 2003.313. Geneva: WHO 2003.
21. Lansdown FS, Beran M, Litwak T., Psychotoxic reaction during ethionamide therapy: Am Rev Resp Dis 1967;95:1053-5.
22. Patel AM, McKeon J. Avoidance and management of adverse reactions to antituberculosis drugs. Drugs Saf 1995;12:1-25.
23. Passannante MR, Gallagher CT, Reichman LB. Preventive therapy for contacts of multidrug – resistant tuberculosis: a Delphi survey. Chest 1994; 106: 431-434.
24. Centers for Disease Control and Prevention. Management of persons expose to multidrug-resistant tuberculosis. MMWR1992;41:61-71.
25. Stevens JP, Daniel TM. Chemoprophylaxis of multidurg-resistant tuberculosis infection in HIV uninfected individuals using ciprofloxacin and pyrazinamide. A decision analysis. Chest 1995; 108:712-717.
26. Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-47.
27. Lou HX, Shullo MA, McKaveney TP. Limited tolerability of levofloxacin and pyrazinamide for multidrug-resistant tuberculosis prophylaxis in a solid organ transplant population. Pharmacotherapy 2002;22:701-4.

CHAPTER 11: ADVERSE REACTIONS

11.1 Chapter Objectives

This section provides information on identification and management of adverse drug reactions when patients are treated for M/XDR TB. It addresses the following:

- Monitoring for early detection of ADR
- Commonly encountered ADRs with the regimen used
- Strategies for managing ADRs

The timely and intensive monitoring for, and 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 adherence to treatment, and may result in death or permanent morbidity

11.2 Notable adverse reactions to the drugs used

Injectables – Kanamycin / Capreomycin

- Ototoxicity [6,7]
- Nephrotoxicity
- Vertigo
- Electrolyte imbalance

Quinolones – Ofloxacin, Levofloxicin, Moxifloxacin [8,9]

- Gastro Intestinal symptoms: diarrhoea, vomiting, and abdominal pain
- Central nervous system (CNS): dizziness and convulsions
- Phototoxicity and photosensitivity
- Tendinopathy and tendinitis
- Skin rash
- Cardiotoxicity – QT prolongation
- Arthralgia

Ethambutol

- Visual disturbance

Pyrazinamide

- Arthralgia
- Hyperuricaemia
- Hepatitis
- Pruritis with or without rash

Ethionamide

- Gastro-intestinal: epigastric discomfort, anorexia, nausea, metallic taste, vomiting, excessive salivation, and sulfurous belching
- Psychiatric: hallucination and depression
- Hepatitis
- Hypothyroidism and goitre with prolonged administration
- Gynaecomastia, menstrual disturbances, impotence, acne, headache, and peripheral neuropathy

Cycloserine [10]

- CNS: dizziness, slurred speech, convulsions, headache, tremor, and insomnia
- Psychiatric: confusion, depression, altered behaviour, and suicidal tendency
- Hypersensitivity reaction

PAS

- Gastro-intestinal: anorexia, nausea, vomiting, and abdominal discomfort
- Skin rash
- Hepatic dysfunction
- Hypokalemia
- Hypothyroidism and goitre with prolonged administration

11.3 Management of adverse drug reactions

DOT worker, nurses in the hospital and clinician will monitor and record all the adverse events routinely and laboratory screening tests will be done on a routine basis as per the national guidelines. The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects or poor outcomes. Laboratory screening is invaluable for detecting certain adverse effects that are more occult, and before serious harm is done.

Training of all the health staffs will be done to identify and manage ADRs. Close monitoring of patients is necessary to ensure that the adverse effects of the 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 treatment. The majority of adverse effects are easy to recognize. Commonly, patients will volunteer that they are experiencing adverse effects. It is important to have a systematic method of patient monitoring since some patients may be reticent about reporting even severe adverse effects. DOT workers should be

trained to screen patients regularly for symptoms of common adverse effects: rashes, toxic epidermal necrolysis, gastrointestinal symptoms (nausea, vomiting, diarrhoea), psychiatric symptoms (psychosis, depression, anxiety) jaundice, ototoxicity, peripheral neuropathy, symptoms of electrolyte wasting (muscle cramping, palpitations), and convulsions. DOT workers should also be trained to identify ADRs and refer the patient to the MO PHI for minor ADRs and to the DTO for major ADRs. Most of the ADRs could be managed by the DTO/chest physician of the district hospital. If required, hospitalisation could be done at the districts where inpatient facility is available or referred to a referral hospital for admission. The DR-TB Centre Committee would be consulted to take decisions regarding reduction/termination of any drug. If any drug is withheld / terminated due to ADR, it would be replaced with the appropriate substitute drug as per the DR-TB Centre Committee.

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 if and when they occur, to notify a health-care provider. Proper management of adverse effects begins with pre-treatment patient education. Depending on the severity of ADRs the following actions may be indicated: If the adverse effect is mild and not serious, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option. Most of 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 workers, patient support groups like patients' association/organization or through group discussions while in the hospital. The recommended schedule for ADR management is detailed in the below.

11.3.1 Gastro-intestinal symptoms (nausea and vomiting)

This may be due to the bulk of drugs and/or due to Ethionamide, PAS, Pyrazinamide and Ethambutol. Patients who complain of nausea or vomiting can be advised to take the drugs embedded in a banana. If vomiting persists, drugs will be administered one hour after one tablet of Domperidone and/or a course of proton pump inhibitor (Omeprazole) or H2 receptor inhibitor (Famotidine, Ranitidine). **Other antacids are not usually given since they interfere with absorption of fluoroquinolones.** In case of severe vomiting the hydration status of the patient should be monitored and rehydration therapy initiated if required. If the offending drug is Ethionamide, the drug is more acceptable if it is administered with milk, or

after milk, or at bed-time to avoid nausea. If vomiting is severe, drugs can be withheld temporarily and tests should be conducted to rule out other causes of vomiting like hepatitis.

11.3.2 Giddiness

Giddiness could be due to Aminoglycosides, Ethionamide, Fluoroquinolone and/or Pyrazinamide. Whenever a patient complains of giddiness, over sleepiness or poor concentration, patients need to be counselled. If severe, the patient the offending drug should be identified by giving the drugs individually and observing the response. The dose of the offending drug identified may be adjusted or the offending drug terminated if required.

11.3.3 Ocular toxicity

Whenever a patient complains of blurring of vision or disturbance in colour vision, Ethambutol should be withheld, and the patient referred to an ophthalmologist for opinion.

11.3.4 Renal toxicity

Prior to starting treatment, all patients will have renal function evaluated. During treatment of MDR-TB, if the patients presents with symptoms and/or signs of renal impairment (oliguria, anuria, puffiness of face, pedal oedema), all the drugs should be withheld, renal function tests should be done and, if required, opinion of nephrologist should be sought. Re-introduction of drugs will be undertaken by the DR-TB Centre committee in consultation with a nephrologist, along with frequent monitoring of renal parameters. Common offending drug is an aminoglycoside.

During treatment, blood urea and serum creatinine should be done every month for the first three months after treatment initiation and then every three months thereafter whilst injection Kanamycin is being administered. Silent renal toxicity may be picked up by these routine follow-up biochemical examinations. If at any time, the blood urea or serum creatinine becomes abnormal, treatment should be withheld and further management decided upon in consultation with the DR-TB Centre committee.

11.3.5 Arthralgia

The offending drugs are likely to be Pyrazinamide and/or Fluoroquinolone. Patients who complain of arthralgia will be prescribed Paracetamol 500mg three times a day or aspirin 300mg three times a day. If there is no improvement after one week, a non-steroidal anti-inflammatory drug will be prescribed (e.g. Ibuprofen or Diclofenac Sodium), and uric acid checked if indicated. If there is still no improvement, or if the arthralgia worsens, the dosage of Pyrazinamide and/or Levofloxacin should be reduced or the drug withheld temporarily.

11.3.6 Cutaneous reactions

Hypersensitivity reactions such as pruritis or rash, can occur with any of the drugs used, and are commonly managed with anti-histamines. For severe reactions which do not respond to anti-histamines, an attempt will be made to identify the offending drug by challenging with individual drugs. The dose of the offending drug may be reduced or the drug terminated if required. For severe hypersensitivity reactions the offending drug may need to be stopped.

If there is a generalized erythematous rash, especially if it is associated with fever and/or mucous membrane involvement, all drugs should be withheld immediately. When the rashes subside, the medications can be restarted one by one, at intervals of 2-3 days. The order of reintroduction will be Ethambutol, Cycloserine, Ethionamide, Fluoroquinolone, Kanamycin and lastly Pyrazinamide. After identification, the offending drug will be terminated.

11.3.7 Hepatitis

This could be due to the combined effect of potentially hepatotoxic drugs such as Pyrazinamide and Ethionamide. If a patient presents with symptoms/signs of hepatitis (anorexia, nausea, vomiting, abdominal discomfort, and/or dark coloured urine), he/she will be examined for clinical jaundice and liver enlargement. Blood will be drawn for liver function tests. Patients will be questioned carefully regarding symptoms suggestive of biliary tract disease and exposures to other potential hepatotoxins, including alcohol and hepatotoxic medications.

If there is icterus, anti-TB drugs will be withheld and the patient reviewed with the results of the liver function tests. If the results are abnormal, Ethionamide and Pyrazinamide are to be withheld, and the other drugs continued. If the results of the liver function tests are normal, the treatment will be resumed. Patients with abnormal liver function will be reviewed at weekly intervals and liver function repeated when jaundice subsides clinically. The regimen will be resumed after the liver function become normal.

If the jaundice recurs after reintroduction of the allocated regimen, further management of the patient will be decided by the DR-TB Centre committee.

11.3.8 Neurological symptoms

Peripheral neuropathy

The common offending drugs are Cycloserine and Ethionamide. To prevent the occurrence of such adverse reaction, all patients on an RNTCP Regimen for MDR TB should receive daily Pyridoxine 100mg. If peripheral neuropathy develops, an additional 100mg Pyridoxine

will be given. If there is no improvement or symptoms worsen, Amitriptylline 25mg will be added and if still there is no improvement, patient should be referred to a neurologist.

Seizures

The offending drug could be either Fluoroquinolone and/or Cycloserine. If a patient develops seizures these drugs will be withheld and the patient will be referred to a neurologist for opinion. The physician will decide on the further management including use of anti-convulsants, based on the neurologist's opinion.

11.3.9 Psychiatric disturbances [11]

The common offending drugs are Cycloserine, Fluoroquinolone and/or Ethionamide. In cases of suicidal tendencies and other psychiatric disturbances, the first offending drug is Cycloserine, followed by Ethionamide and Fluoroquinolone. These drugs will be withheld and further management of the patient will be done in consultation with the psychiatrist.

11.3.10 Vestibulo-auditory disturbances

Offending drug is usually the Aminoglycosides. Patient may present with tinnitus, unsteady gait or loss of hearing. Aminoglycoside will be withheld and patient referred for a specialist opinion.

11.3.11 Hypothyroidism

The offending drugs are usually PAS and/or Ethionamide and the combination of these drugs may increase the possibility for the same. Patients may present with slowing of activities, puffiness of face and/or thyroid swelling. Patients need to be evaluated for hypothyroidism and if present, may be treated with Thyroxine. The dosage of Thyroxine need to be adjusted based on clinical status and laboratory results at the DR-TB Centre facility.

Table 11.1: Drugs used in the management of ADRs

ADRs	Suggest Drugs to manage the ADR
Nausea, vomiting, upset Stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate, donperidone
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), Proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of flouroquinolone eg. alumnium hydroxide
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges, Nystatin suspension, itroconazole liquid
Diarrhoea	Loperamide

Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Any hypnotic
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal Effects), Buromazine, thioridazine
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, Promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine, diclofenac
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity Reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement

All the drugs listed in the table are available in the local market.

11.4 Role of DR-TB Centre committee in the management of adverse reactions

Whenever a patient has serious adverse reactions to any of the second-line anti-TB drugs, he/she is ideally admitted at the DR-TB Centre and the committee decides on further management of the patient. This may require withholding or discontinuing the offending drug in the treatment regimen. The committee will be responsible for arranging the drugs to be given for managing these reactions.

Timely and intensive monitoring for identifying and management of adverse reactions are essential components of the PMDT services. This will help to improve patient adherence to treatment, reduce mortality and obtain better treatment outcomes. Ancillary drugs for the management of adverse reaction should be made available to the patient free of cost. Proper training of staff and support to the patient are other important activities that are required.

References

1. Furin JJ, Mitnick CD, Shin SS et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2001; 5(7): 648-55.
2. Chaulk C, Chaisson R, Lewis J et al. Treating multidrug-resistant tuberculosis: compliance and side effects. JAMA 1994; 271(2): 103-104.
3. Chan E D, Laurel V, Strand M J et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2004; 169: 1103–1108.
4. Torun T, Gungor G, Ozmen Y, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005; 9(12):1373-1377.
5. Iseman MD. Treatment of multidrug-resistant tuberculosis. NEJM 1993; 329: 784–791.
6. Moore RD, Smith CR, Lietman PS. Risk factors for the development of auditory toxicity in patients receiving aminoglycosides. J Infect Dis 1984; 149: 23–30.
7. de Jager P, van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. Int J Tuberc Lung Dis 2002; 6: 622–627.
8. Arora VK, Tumbanatham A. Severe arthropathy with ofloxacin in two cases of MDR tuberculosis. Int J Tuberc Lung Dis 1998; 2(11): 941-3.
8. Yew WW, Chan CK, Chau CH et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest 2000; 117: 744–751.
10. Akula SK, Aruna, AS et al. Cycloserine-induced Stevens-Johnson syndrome in an AIDS patient with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 1997; 1(2): 187-90.
11. Vega P, Sweetland A, Acha J, et al. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2004; 8: 749–758.

Table 11.2: Common adverse effects, the likely responsible agents and the suggested management strategies

SIDE EFFECTS	SUSPECTED AGENT (S)	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Gastrointestinal			
Nausea and vomiting	*Ethionamide* *Sodium PAS* *Pyrazinamide* Isoniazid Moxifloxacin Linezolid Clofazamine Amoxyclav Clarithromycin Thioacetazone	– Assess for dehydration; initiate dehydration if indicated – Patients who complain of nausea or vomiting can be advised to take the drugs embedded in a banana. – Initiate anti-emetic therapy – If vomiting persists, drugs will be administered one hour after one tablet of domperidone and/or a course of proton pump inhibitor or H2 receptor inhibitor (omeprazole, famotidine, ranitidine). – **Other antacids are not to be given since they interfere with absorption of fluoroquinolones.** – Lower dose of suspected agent, if this can be done without compromising regimen	– Nausea and vomiting universal in early weeks of therapy due to the bulk of drugs and usually abate with time on treatment and adjunctive therapy – Electrolytes should be monitored and repleted if vomiting is severe – Reversible upon discontinuation of suspected agent – Severe abdominal distress and acute abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended

		– Discontinue suspected agent if this can be done without compromising regimen – rarely necessary	
Gastritis	Ethionamide Sodium PAS Pyrazinamide Levofloxacin Moxifloxacin Isoniazid Linezolid Clofazamine Amoxiclav Clarothromycin Thioacetazone	– H2-blockers, proton-pump inhibitors; NO OTHER ANTACIDS – Stop suspected agent(s) for short periods of time (e.g, one to seven days) – Patients can be advised to take the drugs embedded in a banana. – Lower dose of suspected agent, if this can be done without compromising regimen – Discontinue suspected agent if this can be done without compromising regimen	– Severe gastritis, as manifested by haematemesis, melaena or haematechezia, is rare – Dosing of any medications should be carefully timed so as to not interfere with the absorption of antituberculosis drugs (take 2 hours before or 3 hours after anti-tuberculosis medications) – Reversible upon discontinuation of suspected agent(s)
Hepatitis	Pyrazinamide Ethionamide Isoniazid *Sodium PAS* Moxifloxacin Linezolid	– Stop all therapy pending resolution of hepatitis – Eliminate other potential causes of hepatitis – Consider suspending most likely agent permanently. Reintroduce remaining drugs,	– History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens – Generally reversible upon discontinuation of suspected agent.

	Clofazamin	one at a time with the most hepatotoxic agents first, while monitoring liver function	
Cutaneous and hypersensitivity reactions			
Hypersensitivity	Sodium PAS Linezolid Clofazamine Clarithromycin	– Withhold all drugs and treat symptomatically with antihistamines/ steroids till the reaction subsides. – Identify offending drug in severe forms – Attempt desensitisation of the offending drug – Discontinue suspected agent and substitute with the reserve drug	– Hypersensitivity reactions could range from mild itching/rashes to rare forms like toxic epidermal necrolysis or exfoliative dermatitis necessitating termination of the offending drug
Cutaneous	Linezolid Clofazamine	– Treat symptomatically with antihistamines till the reaction subsides. – Patient should be counselled on the skin discoloration with long term use of clofazamine	– Cutaneous reaction could range from rashes, pruritis, alopecia to bullous skin eruptions rarely
Psychiatric			
Depression	Socio-economic circumstances Chronic disease	– Improve socioeconomic conditions – Group or individual counseling – Initiate antidepressant therapy	– Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression.

	Moxifloxcin Isoniazid	– Lower dose of suspected agent if this can be done without compromising the regimen – Discontinue suspected agent if this can be done without compromising regimen	– Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated – History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment
Neurological			
Peripheral neuropathy	Isoniazid linezolid	– Increase pyridoxine to maximum daily dose (200 mg per day) – Initiate therapy with tricyclic antidepressants such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms – Lower dose of suspected agent, if this can be done without compromising regimen – Discontinue suspected agent if this can be done without compromising regimen	– 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 – Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended
Convulsions	Isoniazid Moxifloxacin Linezolid	– Suspend suspected agent pending resolution of convulsions – Initiate anticonvulsant therapy (e.g.	– Anticonvulsant is generally continued until treatment is completed or suspected agent discontinued.

		phenytoin, valproic acid) – Increase pyridoxine to maximum daily dose (200 mg per day). – Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen – Discontinue suspected agent if this can be done without compromising regimen	– History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant therapy – Patients with history of previous seizures may be at increased risk for development of convulsions during therapy
Hearing loss	Capreomycin Claritromycin	– Document hearing loss and compare with baseline audiometry if available – Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin – Increase frequency and/or lower dose of suspected agent if this can be done without compromising the regimen(consider administration three times per week) – Discontinue suspected agent if this can be done without compromising the regimen	– Patients with previous exposure to aminoglycosides may have baseline hearing loss – In such patients, audiometry may be helpful at the start of therapy – Hearing loss is generally not reversible – The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen.
Ocular	Linezolid Clofazamine	– In consultation with the ophthalmologist	– Periodic ocular monitoring for ocular toxicity such as optic neuropathy with linezolid, bull's eye

			reinipathy with clofazamine
Musculoskeletal			
Arthralgia	Pyrazinamide Levofloxacin Moxifloxacin	– Initiate therapy with non-steroidal anti-inflammatory drugs.	– Symptoms of arthralgia generally diminish over time, even without intervention. – Caution should be taken with non-steroidal agents to avoid exacerbating gastritis
Musculoskeletal	Levofloxacin Moxifloxacin Clofazamine	– In consultation with the orthopedician	– Rarely, Tendon rupture occur with levo/moxifloxacin – Can produce bone pain
Haematological			
Haematalogic	Linezolid Clarithromycin Capreomycin Sodium PAS	– Monitor for anemia, bleeding tendency and cell counts	– May present with thrombocytopenia, reduced haemobglobn, pancytopenia, or leucopenia – Elevation of prothrombin time
Renal			
Renal toxicity	Kanamycin Capreomycin Linezolid Clarithromycin	– Discontinue suspected agent – Use capreomycin if an aminoglycoside had been the prior injectable in regimen – Consider dosing 2 to 3 times a week if	– 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

		drug is essential to the regimen and patient can tolerate (close monitoring of creatinine) – Adjust all TB medications according to the creatinine clearance	– Renal impairment may be permanent
Metabolic and Electrolytes			
Metabolic and electrolyte	Capreomycin Linezolid Clofazamine moxifloxacin	– Periodic monitoring of serum electrolytes and blood sugar	– Reduction in magnesium Potassium and calcium with capreomycin – Hyper lactacemia, reduction in potassium, increase in CPK and SAP with linezolid – Imcrease in fasting glucose and reduction in serum potassium – Dysglycemia with moxifloxacin
Endocrine			
Thyroid dysfunction	Sodium PAS	– Supplement with thyroxine	– Monitor clinically and T3,4 and TSH if required
Cardiovascular			
QT prolongation Thromboembolism	Moxifloxacin Clarithromycin Clofazamine	– Monitor for QT prolongation with Moxi and clarithromycin Monitor platelet count, bleding tendencies – In consultation with cardiologist	– Rare reactions, bit still needs to be monitored

CHAPTER 12: RNTCP PMDT RECORDING AND REPORTING SYSTEM

12.1 Chapter objectives

This chapter describes the information system for patients that fall under RNTCP PMDT, with the objective of recording information needed to monitor resistance trends and programme performance.

12.2 Aims of the information system

The aims of the information system are:

1. To allow the managers at the different levels in the RNTCP to follow overall programme performance through following:
   - the distribution and trends in M/XDR-TB notification;
   - the response to treatment in M/XDR-TB patients treated with RNTCP Regimen for M/XDR TB.
2. To aid the staff in the treatment units in providing adequate management of the individual patient.

12.3 Scope of the information system

The information system for RNCTP PMDT is based upon, and is an extension of, the basic RNTCP information system. The forms are therefore made as similar as possible to the existing forms in the RNTCP.

The chapter defines the minimum instruments and variables of the information system, necessary to satisfactorily implement and monitor treatment with the RNTCP Regimen for M/XDR TB. This information system does not include all of the detailed information that the treatment units may need to manage the individual patient: this is contained in the clinical record and other special forms used in the wards or clinics and depends on the local requirements and practices.

12.4 Records, reports and flow of information

The following describes the forms, registers and reports that will be used for RNTCP PMDT to enable proper recording of diagnosis, monitoring, and care, in addition to the reporting of outcomes. The case registration and outcome definitions are defined in Chapters 4, 5 and 8 above.

12.4.1 RNTCP Request for Culture and DST form (Annexure I)

All individuals who are suspected of having TB are required to have a sputum smear examination. When only requesting smear, the regular RNTCP request form for sputum examination can be used. When requesting culture and/or DST, the RNTCP Culture and DST form should be used. The left side of form is for information about the patient and referring facility, and the reason for testing. The right side of the form is for reporting the molecular test or solid / liquid culture and DST results by the laboratory. The same form is sent back to the treating unit with the results. MO-PHI/DMC will initiate three copies of this form, one copy to be sent to DTO and one copy to the laboratory along with the sample. Similarly, MO-PHI will initiate 2 copies for follow up and send 1 copy to the Culture & DST laboratory which will send the results electronically to the DR-TB Centre and DTO.

12.4.2 RNTCP PMDT Referral for Culture-DST Register for Diagnosis and Follow-up Cultures (Annexure III)

The RNTCP PMDT referral for C-DST register is used to record the details of all individuals whose samples are collected and transported to the RNTCP-certified C-DST laboratory from the district. This register is to be maintained at the DTC. If the collection and transport system is decentralized, the Sr. DR-TB and TB-HIV coordinator of the district must liaise with the STLSs of the districts to periodically update this information. The utility of this register is to keep a track and closely monitor the sample collection and transport from every suspect of MDR TB for diagnosis and the follow up samples of every MDR TB case, monitor timely availability of the results from the laboratory and ensure that every diagnosed M/XDR TB patient in the district is promptly traced and referred for treatment to the DR-TB Centre as soon as the results are available. The PMDT TB number allotted by the DR-TB Centre or reason for not initiating the patient on treatment may be entered in the remarks column.

12.4.3 Culture and DST Register (Annexure IV)

The RNTCP laboratory register for Culture and DST is used to record culture and DST examination results. This register should be compared regularly with the RNTCP PMDT register to ensure that all MDR-TB cases to be started on RNTCP Regimen for MDR TB are entered in the PMDT register and in the quarterly reports on case finding. The lab PID number is a unique number, given to a patient first time his/her specimen comes the lab. On all subsequent specimen sent to the lab, the same PID number is retained for the patient, but the new specimen is provided with a new lab number. This gives an opportunity to easily extract the

test results of all the specimen provided by the patient and there by track his/her response to the treatment. Further this simplifies the data entry at the lab in any database.

12.4.4 RNTCP PMDT Referral for Treatment Form (Annexure V)

This form has to be filled for all confirmed MDR or XDR TB cases that are referred from one centre to another centre. The form has to be filled by the doctor of the referring centre in duplicate and one copy sent along with the copy of the current treatment card to the referred centre. This form can be used for referring the patient at various points in time during the management of the patient between the PHI, DTC and DR-TB Centre for reasons like initiation of treatment, adverse drug reaction, transfer out, ambulatory treatment or any other reason. In cases that are transferred out, a copy of the updated PMDT treatment card must also be sent along with the referral for treatment form.

12.4.5 RNTCP PMDT Treatment Card (Annexure VIII)

This card is a key instrument for the DOT Provider administrating the drugs daily to the patient. The card will be initiated at the DR-TB Centre when the patient is admitted for staring treatment. However for those patients who are not willing for admission the card will be initiated by the DTO. The card should be updated daily, ticking off the administration of drugs by the DOT provider. The card is the source to complete and periodically update the PMDT register. The original treatment card will be maintained at the DR-TB Centre and three / four copies will be kept at the DTC, at the TU/STS, at PHI and with the DOT provider (if it is other than the PHI). Accountable systems have to be developed locally for updating cards at all levels. When or if the patient moves from the DR-TB Centre to his/her district of residence a copy of the card, must follow the patient. A copy of this card may be used as a notification form and to inform about final outcome of treatment.

The card contains the following sections:

<u>Page 1 of the treatment card:</u>

- **Basic demographic information**. Name, sex, age, address, telephone number, state, DR-TB Centre, district, TU, PHI and details of the DOT Provider.
- **PMDT TB number.** This is a new unique patient identification number given to the patient at the DR-TB Centre on initiation of treatment. The PMDT TB number should include the following – S.No./Name of the DR-TB Centre code/year of initiation of treatment. E.g.

PMDT TB number of the first patient started on treatment at Nagpur DR-TB Centre in 2012 will be 1/NGP/2012. Every year the PMDT TB number will be started at 1.

- **Reason for Suspecting MDR TB.** This section lists and describes the details of the reason for suspecting the case as MDR TB suspect. This includes the various types of cases that has to be ticked as applicable under Criteria A, B and C. The latest TB No. of the patient at the time of suspecting the case also must be entered.
- **Date of Starting Monthly Box:** The date of starting the monthly patient wise drug boxes in various months of intensive and continuation phase must be entered in the blocks provided for each month in DD/MM/YY format.
- **DR-TB Centre Committee meetings.** There should be periodic meetings of the DR-TB Centre committee, with the caregivers involved with the M/XDR TB patients, in which the progress of the individual patient is reviewed. This section provides a space to record any major changes by the Committee like extension of IP; change of IP to CP; completion of treatment; severe adverse reactions; change of treatment, declaring treatment outcome etc.

Page 2 of the treatment card:

- **Monitoring of culture**. Record the date, sample number and result of the monitoring culture examinations. The culture date is the date on which the sputum was collected from the patient for these tests.
- **DST**. Record the date, type of culture test used and results of all DST performed on the treatment card. Enter 'R' for resistant and 'S' for sensitive under the drugs for which DST has been performed at the RNTCP-certified laboratory. Drugs which have not been tested will remain blank.
- **CXR:** Details of the report of Chest X rays performed should be entered in relevant section.
- **HIV Testing:** Record the date of testing, PID No of the recent result if available. Also specify the date of initiation of CPT and ART. As per the national policy, the information sharing on the HIV status of the patients should be restricted within the health care facilities based on the concept of "Shared Confidentiality". Hence, this information must not be written on the copy of the card held by the DOT Provider.

Page 3 and 4 of the treatment card:

- **Regimen.** The RNTCP Regimen for MDR TB and XDR TB, the initial weight, appropriate weight band along with the height, date of starting intensive and continuation phase are recorded on the treatment card and any changes to it are recorded in the same section. One line is used for each date on which a drug (or drugs) is changed.

- **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. The CP should be documented on new line.
- **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 Chapter 8.
- **Date and details of adverse drug reactions and action taken** should be recorded in the relevant section.
- **Date and details of the retrieval action taken** should be recorded in the relevant section
- **Outcome of treatment.** At the end of treatment, the outcome should be recorded on the treatment card. The outcome definitions are given in Chapter 8.

12.4.6 RNTCP PMDT Treatment Register (Annexure IX)

The RNTCP PMDT TB register will be used for registering and recording the details of all patients who receive RNTCP Regimen for M/XDR TB. The RNTCP PMDT treatment register is a key instrument to follow the progress of patients with MDR-TB. It will allow quick assessment of the implementation of RNTCP PMDT, facilitating quarterly reporting and analysis of case finding and treatment outcome.

The RNTCP PMDT treatment register will be held at the DR-TB Centre. A person should be identified for maintaining this register by the DR-TB Centre Committee, preferably a joint responsibility of the nodal officer and the Sr. Medical Officer DR-TB Centre. The register should be updated as soon as it is decided that an M/XDR-TB patient is to be started on treatment. The PMDT treatment register is filled in based on the information contained in the individual patient's PMDT treatment card.

The person responsible for maintaining the RNTCP PMDT treatment register at the DR-TB Centre should enter an M/XDR TB patient into this register as soon as the patient is initiated on an RNTCP Regimen for M/XDR TB. This entry in the register will define the date of registration of the M/XDR-TB patient. The patients should be entered consecutively by their date of registration. A new quarter must be started on a fresh page. Information from the treatment card, including culture results, as well as final outcome can be completed once a month during the patient review at the monthly DR-TB Centre committee meeting.

For patients who are unwilling for admission at the DR-TB Centre and are initiated on treatment at the DTC, the DTO will send the requisite information to the DR-TB Centre along with a copy

of the treatment card. The DR-TB Centre will register the patient and communicate the PMDT TB number to the DTO electronically.

Usually only the first thirteen columns, except column number 8, of the PMDT register are filled in at the time of initial registration. The rest of the registration information is filled in from the treatment card and the register is periodically updated from information on the treatment card. The following is recorded in the PMDT register:

- **PMDT TB No.** This is a unique patient identification number for patients that are initiated on treatment for M/XDR TB. It has been described earlier. Every year the PMDT TB number will be started at 1.
- **Date registered.**
- **Name, sex, age, address, RNTCP district and TU of residence and name of PHI providing DOT.**
- **HIV Status with date of CPT / ART initiation.**
- **Date and reason for MDR TB suspect:** This includes the various types of cases that coded as applicable for various reasons of suspecting MDR TB under Criteria A, B and C. The latest TB No. of the patient at the time of suspecting the case also must be entered.
- **Site of disease.** Whether Pulmonary or Extra Pulmonary is mentioned in this column.
- **Date sample taken for DST, Lab specimen No.; Name of Lab, Type of test.** These details need to be recorded here. Patients may have had more than one DST. Specify the type of test used for diagnosis of M/XDR TB viz. LPA, MGIT, LJ or any other.
- **Result of Drug Resistance Test at diagnosis.** Enter the DST that resulted in the patient being registered as an M/XDR TB patient. Enter 'R' for resistant and 'S' for sensitive under the drugs for which DST has been performed at the RNTCP-certified laboratory. Drugs which have not been tested will remain blank.
- **Regimen for M/XDR TB.** Specify whether the patient has been initiated on the regimen for MDR TB or XDR TB.
- **Drugs, (in drug initials), Weight band (<16Kg, 16-25 Kg, 26-45 Kg, 46-70Kg or >70Kg) and Date started.** The initials of the drugs prescribed under standard regimen or if altered for Ofloxacin or Kanamycin resistant cases at baseline along with the appropriate weight band, and date of treatment start are recorded here.
- **Results and date of follow up smear and cultures:** The dates and results of each and every follow up smear and culture undertaken must be recorded without delay under the specific month of follow up until the end of treatment.

- **Culture monitoring results.** Date and results of all culture examinations should be recorded in this section without any delay under the specific month of follow up until the end of treatment. For culture enter 'Neg' for Negative and 'Pos' for Positive.
- **6 months, 12 months and Final treatment outcomes.** See earlier detailed list for outcome definitions.
- **Comments.** This section is reserved for any additional information that may need to be given in the register.

A copy of the RNTCP PMDT register will also be held at every district, where the details of every patient hailing from the respective district and registered on treatment at the concerned DR-TB Centre will be registered using the PMDT TB number given from the DR-TB Centre. Due care must be taken to avoid duplication of the patients at the district level register. This district level PMDT treatment register must be regularly updated and matched with PMDT register at the DR-TB Centre while updating of the treatment cards. It will facilitate the DTO and the district team to regularly update the in close monitoring of every patient on treatment and is likely to provide better case holding opportunity. The district DR TB and TB HIV Coordinator will be most suited to be given this responsibility. Summary tables on every page of the register are available for consolidating the quarterly reports on case finding, 6 months interim report and 12 months culture conversion reports at the districts and DR TB Centers.

12.4.7 Patient Identity Card (Annexure X)

When a patient is diagnosed as having MDR-TB and is placed on a Regimen for M/XDR TB, a new RNTCP PMDT patient identity card should be filled out by the health care provider at the same time that the treatment card is filled out. The card should be kept by the patient. The card, which is wallet-sized, contains the name, age, sex, PMDT TB number, essential information about the treatment (start date, regimen, and severe adverse reactions to drugs), and the details of the health centre and DOT provider where the patient will receive treatment. Mention date of missed doses and date and result of all follow up cultures in the space under Intensive and Continuation Phase. It also has a place to write the date of the next appointment for follow up at DTC and the DR-TB Centre.

12.4.8 RNTCP PMDT Quarterly report on case finding (Annexure XI)

The RNTCP quarterly report of M/XDR TB case finding is filled in from the laboratory culture and DST Register and the PMDT treatment register held at the DR-TB Centre. From 2nd quarter

2012 onwards, this report will be filled by every implementing district from the PMDT treatment register held at the DTC and entered in epi-centre software.

Block 1 is designed to report laboratory diagnosis of M/XDR TB. The data of this block has to be prepared by each of the culture and DST laboratory for every district and share this information on email with all the linked districts and DR TB centers by the 5th of the month after the end of every quarter. The information includes the following.

- The number of M/XDR TB suspects whose sputa were received and tested by the laboratory for culture and DST in the particular quarter. Suspects whose samples were collected but were not received by the RNTCP-certified Culture and DST laboratory due to various reasons (e.g. delay in transportation etc.) should not be included. This information has to be disaggregated by the reason for testing in case of MDR TB suspects.
- Number of M/XDR cases diagnosed in the particular quarter (on the basis of the culture and DST results reported in the culture and DST register). This information also has to be disaggregated by the reason for testing in case of MDR TB suspects.
- Number of patients tested for second-line DST and of them cases diagnosed with Ofloxacin resistance and XDR TB in the particular quarter.

Block 2 is designed to report the total number of MDR and XDR TB cases registered and started on regimen for M/XDR TB in the particular quarter.

Block 3 is designed to report the status of HIV test, infection, initiation of CPT and ART among the MDR and XDR TB cases initiated on treatment. Block 3 is designed to report the distribution of various MDR TB suspect criteria under which the patient is tested for diagnosis.

The case finding report will be filled and submitted in the month following the end of the quarter (e.g. report of the 1Q 2012 will be filled and submitted in April 2011) by the DTO through epicentre and the DR-TB Centre Nodal Officer in excel. The data of block 2 and 3 is to be reported from the RNTCP PMDT Treatment Register at the district and DR TB Centers.

12.4.9 RNTCP PMDT Six Month Interim Report (Annexure XII)

Each quarterly cohort defined by the date of the start of PMDT registration should have an interim or preliminary outcome report after 6 months of treatment. This report should be developed by the DR-TB Centre Nodal Officer based on the PMDT 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. From the cohort of 2nd quarter 2012 onwards, this report will be filled by every implementing district from the PMDT treatment register held at the DTC

and entered in epi-centre software, while the DR-TB Centre will continue sending these consolidated reports of the previous cohorts up to 1st quarter 2012 in excel sheets.

The interim results will be reported 12 months past the opening day of the notified cohort reported on. Reporting at 12 months past the opening 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 1Q 2012 should have the Preliminary Six Month Interim Outcome Report filled out in January 2013 (1Q2013). The number of patients who have no positive 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 patients who are likely to go on to be cured.

12.4.10 RNTCP PMDT Twelve month Culture Conversion Report (Annexure XIII)

Each quarterly cohort defined by the date of the start of PMDT registration should have a culture conversion report submitted after 12 months of treatment. This report should be developed by the DR-TB Centre nodal officer based on the PMDT 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. From the cohort of 2nd quarter 2012 onwards, this report will be filled by every implementing district from the PMDT treatment register held at the DTC and entered in epi-centre software, while the DR-TB Centre will continue sending these consolidated reports of the previous cohorts up to 1st quarter 2012 in excel sheets.

The conversion results will be reported 18 months past the opening day of the notified cohort reported on. Reporting at 18 months past the opening date, allows culture information for the first 12 months of treatment to be included for all patients reported in the cohort. For example, MDR-TB patients registered during 1Q 2012 should have the Culture Conversion Report filled out in July 2013 (3Q 2013). Block 1 is designed to report the culture conversion status of all MDR and XDR TB cases registered in the cohort while Block 2 is designed to report the culture conversion status of HIV infected MDR and XDR TB cases registered

12.4.11 RNTCP PMDT Report on Result of Treatment of M/XDR TB Cases (Annexure XIV)

This report shows the final result of treatment by quarterly cohort since the start of treatment of all M/XDR TB cases notified in the respective cohort. Since treatment is of long duration, the results reflect retrospectively the management of treatment over a prolonged period. From the cohort of 2nd quarter 2012 onwards, this report will be filled by every implementing district from the PMDT treatment register held at the DTC and entered in epi-centre software, while the DR-TB Centre will continue sending these consolidated reports of the previous cohorts up to 1st quarter 2012 in excel sheets.

The report is submitted 31-33 months after patients in the respective cohort started treatment. For example, MDR-TB patients registered during the 1Q 2012 would have their treatment outcomes reported in October 2014 (4Q 2014). It is desirable that every patient is evaluated at the completion of Regimen for M/XDR TB at the DR-TB Centre by the Nodal Officer before the declaration of the final treatment outcome. Block 1 is designed to report the treatment outcomes of all MDR and XDR TB cases registered in the cohort while Block 2 is designed to report the treatment outcomes of HIV infected MDR and XDR TB cases registered

Quarterly PMDT Drugs and Logistics Management Report (Annexure XVII) described in the next chapter.

12.5 Computerized systems

All the reports will be available in both paper and electronic versions. To facilitate better quality of the information as well as data analysis, the PMDT quarterly reporting formats are being uploaded on Epi-center Software and every implementing district will start reporting the quarterly reports from 2nd quarter 2012 cohort onwards. The development of a case based web based data management system for real time monitoring of TB and DR TB cases is underway.

12.6 Training in Data Management:

The information system requires knowledge of the RNTCP basic information system, with additional training on the specifics of the RNTCP PMDT MIS. Regular supervisory visits by the central team to the PMDT treatment sites using the information system, are fundamental to maintaining good quality of information.

12.7 Cohort analysis

All patients that are identified with MDR-TB and are to be treated with an RNTCP Regimen for MDR TB, should be entered into the RNTCP PMDT Register maintained at the DR-TB Centre and District level. An MDR-TB cohort is defined as a group of patients registered for treatment during a specified time period (e.g., one quarter of the year). The date of registration for regimen for MDR TB determines what cohort the patient belongs.

- Cohort analysis should be performed on all registered MDR-TB patients, using the date of MDR-TB registration to define the cohort.
- Cohort analysis of treatment outcomes should also be performed on all patients who receive MDR-TB treatment, regardless of treatment duration.

- The recommended time frame for MDR-TB treatment cohort analyses reflects the long duration of MDR-TB treatment regimens. Final analysis should be performed thirty-six months after the last patient enrolment date in the cohort.
- Patients still on treatment at the end of a designated cohort treatment period must also be explicitly identified as such, and whether they were culture-positive or negative at the time of the cohort analysis; this is an interim status until a final outcome is available. Interim status should be assessed at six months and twelve months of treatment to monitor patient progress.

CHAPTER 13: LOGISTICS OF SECOND-LINE ANTI-TB DRUGS

13.1 Chapter objectives

This chapter provides information on the procedures for inventory management of the second-line drugs used in the treatment of drug-resistant TB.

13.2 Overview

All drugs used in the Regimen for M/XDR TB shall be supplied through a centralized procurement system & shall be supplied as loose drugs to the State Drug Stores (SDS) directly by the manufacturer. An advance intimation of all drug supplies shall be communicated in advance to the States for the SDS to make available requisite space in the drug store. On receipt of drugs, the SDS shall acknowledge the receipt to the supplier as well as to CTD. The SDS will then need to re-pack the loose drugs into 1 monthly boxes of Type A (core oral drugs) and Type B (IP Plus) boxes. Na PAS shall also be procured and supplied to States to deal with patients who need individual drugs substitution due to adverse drug reactions and supplied as Type C box. The three types of monthly boxes shall contain following drugs:

For Regimen of MDR TB

Type A (Core oral drug box)	**Type B (IP Plus box))**	**Type C (Common box containing Na PAS)**
	Kanamycin-500mg /1G(Km)	Box containing 1 month of Na PAS and will be common for all patients
	Pyrazinamide-500/750 mg (Z)	
Levofloxacin-250/500 mg (Lfx)		
Ethionamide-125/250 mg (Eto)		
Cycloserine-250mg (Cs)		
Ethambutol-200/800 mg (E)		
Pyridoxine-50/100mg		
Reserve/Substitute Drugs		
Moxifloxacin- 400 mg (Mfx)	Capreomycin-750mg/1G (Cm)	

For Regimen of XDR TB

Type A (Core oral drug box)	**Type B (IP Plus box))**	**Type C (Common box containing Na PAS)**
	Capreomycin-750mg /1G(Cm)	Box containing 1 month of Na PAS and will be common for all patients
Moxifloxacin-400 mg (Mfx)		
Isoniazid-300 mg (INH)		
Clofazimine-200mg (Cfz)		
Linezolid-600 mg (Lzd)		
Amoxyclav-875/125mg (Amx/Clv)		

Pyridoxine-50/100mg		
Reserve/Substitute Drugs		
Clarithromycin-500mg (Clr)		
Thiacetazone- 150 mg (Thz)**		

**** Depending on availability not to be given to HIV +ve patients**

Technical specification of patient wise box

The technical specifications of the 1 monthly patient wise box for M/XDR TB cases is detailed in ***Annexure XVI.*** The patient on Intensive Phase (IP) shall be put on Type A and Type B boxes in each month. During the Continuation Phase (CP), the patient will be put on only Type A box for the entire duration and Type C box will be issued in case of intolerance to any of the drug in the M/XDR TB Regimen, i.e.

For IP= Type A box + Type B box of same weight band

For CP= Type A box of same weight band.

For both IP and CP= Type C box containing Na PAS only

The SDS will supply drugs to the DTC in the form of 1 monthly Type A and Type B drug boxes (excluding PAS which will be supplied separately Type C box) during the Intensive and Continuous Phases. However, in case of drug boxes for < 16 kgs and > 70kgs drugs to be added or removed from the existing boxes following the recommended dosage and label the boxes accordingly. These are included in the Type of boxes category for the accountability and reporting of the drugs. These drug boxes will be prepared at the SDS and will be of eleven different types:

For Regimen of MDR TB

Type of box	**Weight Bands**
Type A	< 16 kgs
	16 - 25 kgs
	26 - 45 kgs
	46-70 kgs
	>70 kgs
Type-B	<16 kgs
	16 - 25 kgs
	26 - 45 kgs
	46-70 kgs
	>70 kgs
Type C	Containing NaPAS only (common for all wt. Bands)

For Regimen of XDR TB

Type of box	Weight Bands
Type A	< 45kgs
	>45 kgs
Type-B	< 45kgs
	>45 kgs
Type C	Containing NaPAS only (common for both wt. Bands)

The Type A box containing oral drugs shall be common in both the Intensive & the Continuation Phase for each weight band. Only Type B box containing Inj Km & Pza shall be required additionally in the Intensive Phase and Type C to be given on requirement basis.

For Regimen of MDR TB

Weight Bands	Intensive Phase (IP) Box	Continuation Phase (CP) Box	Common Box
<16kgs	Type A + Type B	Type A	**Additional box Type C containing only NaPAS**
16 - 25 Kgs	Type A + Type B	Type A	
26 - 45 Kgs	Type A + Type B	Type A	
46-70kg kgs	Type A + Type B	Type A	
>70kgs	Type A + Type B	Type A	

For Regimen of XDR TB

Weight Bands	Intensive Phase (IP) Box	Continuation Phase (CP) Box	Common Box
< 45kgs	Type A + Type B	Type A	**Additional box Type C containing only NaPAS**
> 45kgs	Type A + Type B	Type A	

The quantity of drugs required for all the five categories of body weights in IP & CP 1-monthly PWBs is given as below:

For Regimen of MDR TB

S.No	Drugs	16-25 Kg	26-45 Kg	46-70 Kg	>70kg
1	Kanamycin(500&1G) (IP)	500 mg	500 mg	750 mg	1G
2	Levofloxacin (250 & 500mg) (IP/CP)	250 mg	750 mg	1000 mg	1000mg
3	Ethionamide (250mg) (IP/CP)	375 mg	500 mg	750 mg	1000mg
4	Ethambutol (200 & 800mg) (IP/CP)	400 mg	800 mg	1200mg	1600mg
5	Pyrazinamide (500 & 750mg) (IP)	500 mg	1250 mg	1500 mg	2000mg
6	Cycloserine (250mg) (IP/CP)	250 mg	500 mg	750 mg	1000mg
7	PAS (80% Bioavailability)	5 gm	10 gm	12 gm	12gm
8	Pyridoxine (100mg) (IP/CP)	50 mg	100mg	100mg	100mg

For Regimen of XDR TB

S.No	Drugs	< 45kg	>45kg
1	Capreomycin (750&1G) (IP)	750 mg	1G
2	Moxifloxacin (400mg) (IP/CP)	200 mg	400mg
3	Isoniazid (300mg) (IP/CP)	600mg	900mg
4	Clofazimine (200 mg) (IP/CP)	200 mg	200mg
5	Linezolid (600mg) (IP/CP)	600 mg	600mg
6	Amoxyclav (875/125mg) (IP/CP)	875/125 mg (BD)	875/125 mg (BD
7	PAS (80% Bioavailability)	10 gm	12gm
8	Pyridoxine (100mg) (IP/CP)	100 mg	100mg
Reserve/Substitute Drug			
1	Clarithromycin (500mg)	500mg (BD)	500mg (BD)
2	Thiacetazone (150mg)	150mg	150mg

- *The dosages of 2nd line drugs for cases < 16 kg based on the Guidelines for Programmatic Management of Drug Resistant TB, Emergency Update-2008 will be used for treatment of MDR TB cases in paediatric age group weighing < 16 kg as per the table below:*

Drug	Daily Dose – mg/kg body weight
Kanamycin / Capreomycin	15-20 mg/kg
Levofloxacin / Moxifloxacin	7.5-10 mg/kg
Ethionamide	15-20 mg/kg
Cycloserine	15-20 mg/kg
Ethambutol	25 mg/kg
Pyrazinamide	30-40 mg/kg
(Na-PAS)	150 mg/kg

- *For cases > 70 kg, use additional drug dosages of some 2nd line drugs to treat the MDR TB cases taking the dosage to Kanamycin (1 gm), Ethionamide (1 gm), Cycloserin (1 gm), Ethambutol (1.6 gm) and Pyrazinamide (2 gm) based on the WHO Guidelines for Programmatic Management of Drug Resistant TB, Emergency Update-2008. These are well within the maximum permissible dosage for each drug as per the WHO guidelines.*

Packing Instructions

i. Packaging of loose drugs into Type A, B & C boxes should be done under guidance of the STO/Medical Officer/Drug logistics In-charge at the State level.

ii. One monthly pouch of Cap. Cycloserine & Tab. Ethambutol each should be made from plastic bag with zip lock facility in which 1 gm. pouch of silica gel desiccant should be kept. In each Type A box, one pouch of silica gel desiccant of 4 gm. weight should also be kept.

iii. Durable cardboard boxes with defined thickness, size, and material should be used for the Type A, B & C boxes. The boxes shall be made from weather resistant, triple walled, insulated, corrugated, RSC (Universal) type 4-ply Shippers, each ply having strength of minimum 150gsm. These should be fabricated from virgin quality 'A' grade Kraft paper.

iv. Each Type A, B & C box should be numbered consecutively at the SDS. The record of the serial no. of the box should be maintained at the State, District & Sub-district (TU) Drug Stores and it would be of help while tracking a particular box.

v. Instructions should be issued to the DOT provider that the drug boxes should be closed properly every time after withdrawal of drugs from them.

vi. Label on the boxes to clearly mention the following:-

   a. Item-wise name of drugs with quantity of each drug in the box.
   b. Batch No. & DOE of individual drugs.
   c. DOE of the boxes – would be the expiry date of the drug having shortest expiry.
   d. Date of Issue of the box from SDS.
   e. Serial number of the box
   f. Storage instructions on the box in English/ Hindi/ local regional language for ensuring adequate precautions in storage of the drugs, especially at the DOT provider level. Some suggested messages are:-
      - Store in a cool and dark place preferably in a clean cup board.
      - Do not expose to direct sunlight.
      - Keep away from children/unauthorized persons.
      - Box to be closed properly every time after withdrawal of drugs.

In addition to the preparation of boxes at the SDS, loose drugs shall also be issued to the DR-TB Centre for patients already put on treatment along with a buffer of a month's requirement.

Monthly Stock Statement (MSS)

The SDS Pharmacist shall prepare a Monthly Stock Statement providing details of receipts, issues, and opening/ closing balance of loose drugs as well as details of the monthly Type A, B & C boxes, as at the last day of each calendar month in the prescribed format. The MSS shall be sent to the STO by the 7th of every month, by all the SDSs, in the state. The statement shall facilitate determination of drug stocks available with SDS(s) within the state.

MSS shall thereafter be forwarded to CTD through the STO, by the 15th of every month. In the case of more than one/ multiple SDSs within the state, all the MSSs shall be forwarded to CTD within the timelines stated above.

13.3 Drug management cycle of second-line anti-TB drugs

The management cycle of second-line anti-TB drugs comprises six elements: drug selection; quantitative assessment of drug requirements; management of procurement and distribution; assurance of drug quality; and ensuring rational drug use.

A number of factors must be considered when selecting second-line anti-TB drugs, including the efficacy of the drugs, success of the treatment regimen, adherence, the treatment strategy, possible side effects, and the cost of the treatment.

Accurate demand forecasting of second-line anti-TB drugs, i.e. correct quantification of the drug needs for a specific period of time, is one of the elements that guarantees an uninterrupted drug supply.

Inventory Management

Procedures for on-going tracking and replenishment of the inventory of 2nd line anti-TB drugs at the State Drug Store (SDS) and all subordinate stocking points ensures that these are maintained at or close to the stocking norms suggested by Central TB Division (CTD).

Drug flow – distribution and supply chain management

- **DR-TB Centre-** The loose drugs supplied by the SDS to the indoor facility of the DR-TB Centre shall be based on the number of admitted MDR patients expected at the DR-TB Centre over a period of a month. Thereafter, issue of drugs shall be based on the Monthly Stock Statement submitted by the DR-TB Centre, to ensure maintenance of adequate stocks for a month of treatment plus a buffer of 1 month. On discharge of the patient, loose drugs for 7 days shall be issued by the DR-TB Centre to the patient to cover the transit period. During this time, it is expected that the patient shall reach home for the ambulatory treatment to commence on the 1-monthly IP box which has by then been issued to the respective DOTS provider as arranged by the DTO.
- **Implementing DTC-** The Patient will report to the respective DTO who will arrange for the supply of the 1 monthly drug boxes of Type A, B & C from the respective PHI to the DOT Centre. The DTO will also be responsible for:

  a) Identification of the DOT provider in consultation with the MO-PHI and the patient

b) Training or briefing of the respective MO-PHI.

The first time, SDS shall send some Type A, B & C boxes of the middle three weight bands (i.e 16-25kg, 26-45kg and 46-70kg) and for XDR (<45kg and > 45kg) to the implementing DTC, based on the number of admitted MDR patients at the DR-TB Centre for that district. Subsequently, the flow of Type A, B & C boxes shall be monitored through the District Quarterly Programme Management Report. The DTC shall send the boxes to its implementing TU in a similar manner on an quarter basis & then monitor through the TU Quarterly PMR. Buffer stocks of both Type A & B boxes of all weight bands may be held at all levels as per stocking norms as defined for the 1st Line Anti TB Drugs i.e. for 7 months at the district level. Type C boxes will be supplied on need based only as this is a substitute drug.

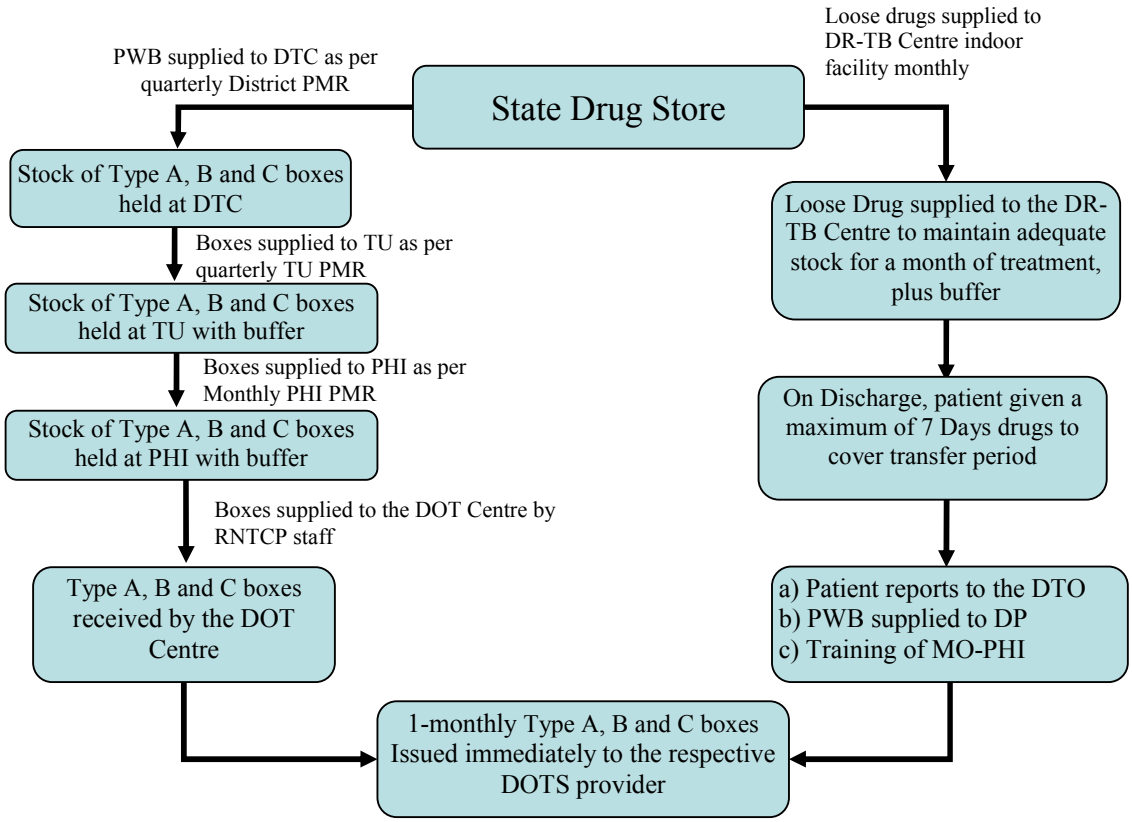
- **TB Unit - Buffer** stock equivalent to 4 months will be kept at the TU at the beginning of each quarter as in 1st Line Anti TB Drug management. The drug boxes will be supplied from the TU to the PHI. The drug box will be transferred from the TU to the respective PHI on instruction of the DTO for a new patient who has been discharged from the DR-TB Centre after initiation of treatment.

- **PHI -** Buffer stock equivalent to 2 months will be kept at the PHI at the beginning of each month as in 1st Line Anti TB Drug management. The drug boxes will be supplied from the PHI to the DOT Centre / DOT Provider.

If the IP of the patient is required to be extended, the respective DR-TB Centre Committee shall inform the DTO who will intimate the same to the MO-PHI and the respective TU. The PHI will release 1 Type A, Type B and Type C box (if needed) to the respective DOT Centre from where the patient is taking treatment. When the patient is switched to CP, the DTO shall intimate the same to the MO-PHI and the respective TU. On instruction of the DTO, the PHI will release 1 Type A box only to the respective DOT Centre from where the patient is taking treatment. During the period between when the DTO has been notified of the decision to change over to CP and the delivery of drug box from the PHI to the DOT centre, the patient's IP shall be continued. All patients who are given an extended IP must complete a full month of extension i.e. patient must have either 7, 8 or 9 months of IP.

The drug distribution flow may be depicted as follows:

Figure 13: Distribution of 2nd line drugs



Repackaging and use of partially used IP/CP boxes

In case of default/death/transferred out/treatment stopped cases, the unconsumed boxes shall be brought back from DOT Centre to PHI to TU to DTC to SDS within the shortest possible time. All loose drugs remaining in the boxes received back shall be accounted for in the Stock Register at the SDS & issued as per FEFO principles to either the DR-TB Centre or be used for repackaging into the monthly Type A or B boxes.

Reconstitution at DTC in following situations -

In a few situations where small quantities of drugs are found in the boxes returned, the DTC may reconstitute the monthly boxes from the available drugs.

Situation 1: If complete strips of loose drugs are available in the box - then these can be used as such for reconstitution of monthly boxes at the DTC and the left over strips should be immediately sent back to SDS and from there to the DR-TB Centre.

Situation 2: If incomplete strips of loose drugs are available in the box - then the same may be sent back to SDS and from there to the DR-TB Centre.

13.4 Guidelines for storage of 2nd line anti TB drugs for State and District Drug Store

1. **Storage Space:-**
   i. Requirements of space for various levels of drug stores should be based on the estimated number of MDR TB patients likely to be placed on treatment in the concerned State for whom the maximum quantity of drug stocks are to be maintained at the concerned stocking unit. As per the current guidelines of RNTCP, number of MDR TB patients who are to be placed on 2nd Line treatment are estimated as follows:-
      a. 3% of new cases of TB.
      b. 12-17% of re-treatment cases.
   ii. Based on above, storage space will need to be worked out separately for each State Drug store.
2. **Specifications for drug stores:-**
   i. The Drug Store should preferably comprise one large room. Where multiple rooms already exist, they should be contiguous or proximate to each other
   ii. Preferably separate space for storage, handling and re-packing into Type A, B & C boxes.
   iii. Ceiling to have a height of at least 3 metres.
   iv. A lockable door.
   v. At least one window with grill.
   vi. Proper lighting.
   vii. An even-level, 'pukka' floor.
   viii. Plastered walls and ceiling with whitewash without any kind of seepage in the room.
   ix. In case of a situation where separate room for storing 2nd line drugs is not possible, an attempt to demarcate and enclose a specified area for storing 2nd line drugs should be made within the larger store to ensure required temperature control for 2nd line drugs.
   x. Architects should be consulted for suitable modifications in the existing drug store/construction of a new drug store for the same.
   xi. A signage board with instructions in local language should to be put near the entrance of the store to remind the concerned officials regarding good storage practices.
   xii. Ideally, Vacuum de watered flooring (VDF) should be used for the Drug Stores. However depending on the feasibility, such flooring may be done at the State Drug Store level.

xiii. In case it is feasible at the State Drug Store level, separate areas should be demarcated for receiving and dispatching the drugs.

xiv. Contract for Pest Control should be entered into by the State to ensure drug stores free from pests, rodents etc.

3. Shelves, Racks & Storage Arrangements:-

i. If sufficient space is available on the existing storage shelves in the State Drug Store (SDS), these shelves made of 40 mm. bore medium quality (external diameter - 48.3 mm.) mild steel pipes should continue to be used as per the existing RNTCP guidelines. New shelves, if required, are to be made from pre-fabricated slotted angles ensuring sufficient 'gap' between cartons from the ceiling, floor and walls, facilitating ventilation and the free movement of air.

ii. Shelves to be positioned so that there is no possibility of seepage into cartons.

iii. Typically, five rows of shelves to be fabricated, one on top of the other into racks. A single rack to usually be long enough to accommodate three cartons on each shelf. Accordingly, a rack would typically accommodate fifteen cartons.

iv. In the case of a broad room, there shall be multiple rows of racks, all parallel to one another. There should be sufficient space between parallel blocks of racks and the walls, to facilitate free movement of men and trolleys for the smooth stacking and removal of cartons. In case of a long and narrow room, racks to be positioned such that there is sufficient space between them and the walls.

v. Drug cartons to rest on shelves and not on each other, to prevent eventual sagging of the cartons in the bottom row.

vi. Rows & Columns, where drugs are stored should be defined and locations to be assigned a unique identification number.

vii. In future, if the State Drug Store of a particular state has to handle large volume of drugs and occupies larger space, walkway space (between racks across the storeroom) can be of 3 metres. In such situation, material handling equipments shall be required.

4. Stacking Arrangements:-

i. Name of the Drugs along with their expiry dates be indicated on stickers pasted on the face of cartons/ drug boxes and should be written again by hand, in large easily visible characters using a coloured, permanent marker pen.

ii. As far as possible, the same drug should be stored at a single location within the store.

iii. Additionally, drugs of the same expiry should be stored together at the same location.

iv. Recognizing the above rules, drugs expiring earliest should be so stored that they are issued first. For example, in case IP (< than 45 Kgs) boxes are placed on multiple shelves in a single part of the store, boxes expiring earlier should be stored at ground level and fresher boxes (which shall expire later) on elevated shelves. This method of stacking shall ensure that drugs that shall expire first shall automatically be issued first, based on the principle of FEFO (First Expiry First Out).

v. Expired drugs should be segregated, sealed and stored in a separate part of the store eliminating the possibility of their issue to patients. Expiry dates should be highlighted in these cases.

vi. Bin cards at State Drug Store level be displayed which would provide details of Receipts, Issues, Closing balance (quantity) and expiry dates of drugs.

vii. Only Na-PAS is slow moving drug and should be stored at higher level shelves. Rest all other 2nd Line Drugs are fast moving, hence, should be stored on lower shelves.

5. Control of Humidity and Temperature:-

i. **Monitoring of Humidity & Temperature:-** Hydro thermometers are to be installed up to TU drug store levels to monitor humidity and temperature regularly. The record of both these variables should be maintained in charts properly and checked on a daily basis by the concerned Store In-charge. This should be reviewed by STO / Officer in-charge of SDS and necessary corrective measures be taken immediately.

ii. **Control of Humidity:-** In order to keep humidity levels below the maximum 60% recommended for storage of drugs, following measures may be taken.

a. **Ventilation:-** Open the windows or air vents of the store to allow air circulation. Ensure all windows have screens / wire mesh to keep out insects and birds and also should have metallic grills / iron bars. Drug Boxes/Cartons should be placed on shelves ensuring that there is sufficient space between shelves and walls of the store room.

b. **Packaging:-** The cartons/drug boxes should not be opened unless necessary.

c. **Circulation:-** Use fans to circulate fresh air from outside.

d. **Protection from Sunlight:-** To protect the drugs from sunlight, following measures may be taken:

i. Shade the windows or use curtains if they are in direct sunlight.

ii. Keep products in cartons/drug boxes.

iii. Do not store or pack products in sunlight.

iv. Maintain trees around the premises of the drug store to help provide shade and cooling. Check their condition regularly to prevent any untoward incident.

iii. **Control of temperature:-** The 2nd Line Anti-TB Drugs should preferably be stored below 25^0 C. In the area specified for storing 2nd Line Drugs, temperature of about 20^0 C should be maintained with the help of Air-Conditioners (Tonnage would depend on size of the room).

iv. **Power Supply:-** Regular power supply should be available for Air Conditioning in the State Drug Store. Arrangements for backup power supply should also be made through solar panels / fuel based power generators.

The purpose of information provided in the above sub-paras is to emphasise that the drugs should be stored in cool & dark place for proper efficacy. Experimental data/literature review also reveals that these drugs lose their efficacy beyond 6 months if exposed to stressful storage conditions of $40^0 \pm 2^0$ C temperature and humidity of 75% $\pm$ 5 % RH.

6. Quality Assurance of Drugs:-

The quality assurance component of the RNTCP drug supply system makes certain that each drug used by a patient is safe, efficacious, and has appropriate standards of quality.

As per the protocol developed by Central TB Division (CTD), samples of 2nd Line Anti TB Drugs shall be picked up on random basis from various levels in the field and sent for testing by an independent drug testing laboratory contracted by CTD to find out any change in the quality of these drugs. This should be done based on communication sent by CTD to the concerned states and districts.

7. Waste Disposal Guidelines:-

If any drug expires due to reasons beyond control, it should be disposed off as per the procedures laid down in the Rules under Drugs & Cosmetics Act and Bio-medical Waste (Management and Handling) Rules of Govt. of India.

8. Guidelines for Recording, Reporting,

The recording and reporting system for drug stock management from the State Drug Store to the DR-TB Centre and to the Districts, TB Units and PHIs have been recently revised to suit the 1 monthly patient wise boxes system. Formats for Drug Logistics Management of 2nd line drugs under PMDT are described in ***Annexure XVII***.

9. Transportation of Drugs and Fire Safety measures remain the same as for 1st Line Anti TB Drugs and the guidelines of RNTCP.

CHAPTER 14: SUPERVISION, MONITORING AND EVALUATION IN PMDT

14.1 Chapter Objectives

In this chapter, participants will learn about the guidelines for appraisals, supervision, monitoring and evaluation systems that need to be operationalized in all states and districts to ensure that the programme achieves the set timelines and targets for nationwide scale up of services at the same time identify operational challenges to improve quality of care of M/XDR TB cases enrolled under the programme. An effort has been made by the programme to standardize these mechanisms and the requisite tools to do so have been developed that are detailed in this chapter.

14.2 Introduction

India started implementing PMDT since 2007. With more districts starting PMDT services, it is of utmost importance to have clear guidelines for Supervision, monitoring and evaluation of PMDT. Preparatory districts have to fast track their activities in line with the PMDT national scale up plan while the implementing districts and states have to improve and sustain the quality of PMDT through continuous supervision, monitoring and evaluations.

14.3 Organization of SME for PMDT

The appraisals, supervision, monitoring and evaluation strategy of RNTCP for PMDT services has been updated and introduced to the states in May '11. The preparatory districts are evaluated by standard appraisals and monitored through a set of indicators for the preparatory activities and coverage against the PMDT scale up plan for each state as approved by CTD.

The implementing states/districts will have a more comprehensive SME plan for use at the state, district, sub-district and field levels. Additionally, to help each staff engaged in PMDT to supervise, monitor and evaluate the activities, a set of job aides are also developed. These job aides are ready-reference tools to aid the staff to take the appropriate action at each step of PMDT.

The organization of Appraisals, Supervision, Monitoring and Evaluation activities and the requisite tools are classified in the table below:

Table 14.1: Organization of SME in PMDT

Stage	Preparatory States / Districts	Implementing States / Districts
Supervision		• Supervisory checklists for various levels (DR-TB Centre, District, TU, DMC, and Patient)
Monitoring	• Monitoring indicators on PMDT Coverage introduced	• PMDT Quarterly Report • CF, 6m Int, 12m CC, TO • Quarterly Lab Reports • Monitoring indicators on PMDT implementation introduced • Lab Monitoring Indicators
Evaluation	• PMDT Appraisal Protocol – State & Central level • IE formats to include 1 page for preparatory states / districts	• IE formats to include section for implementing states / districts with assess progress on scale up plan, visits to DR-TB Centre, C-DST Lab, Drug Stores, Patients interview etc.

14.4 SME for preparatory districts

PMDT Appraisals

PMDT appraisals are conducted to assess the preparedness of the districts to roll out PMDT services. Two types of appraisals are designed viz, the state appraisal and the central appraisal. There are comprehensive guidelines and standard formats for the state and central appraisal. (***Annexure XXI***). Before CTD appraise a district, the state has to do the state appraisal of the district and take corrective actions if required. On satisfactory completion of corrective actions, the state has to request for central appraisal. The district will be permitted to roll out PMDT on receipt of satisfactory report on central appraisal.

The PMDT appraisal guidelines describe the objectives, selection of team members, selection of institutions to be appraised and the process of appraisal. The appraisal formats and structured appraisal reporting formats have exclusive sections for each component institution.

1. **State Level** – Profile, Implementation Status & Plan, State DP Committee, Staffing & Training of Trainers.
2. **DR-TB Centre** – Location, Districts linked, DR-TB Centre Committee, Civil works, AIC, Beds, R&R, Training
3. **C-DST Lab** (IRL, MC, Private) – Location, Certification, Capacity, MoU, R&R, Staffing & Training
4. **State Drug Store** – Capacity, Up-gradation, A/C, Storage, Packing & Transport, R&R, HR
5. **Districts (In Phases)** – Profile, Perf, Staffing, Training, DDS, Lab & DR-TB Centre link, Sample Collection & Transport, DOT Provision, R&R

During the expansion phase only the respective districts will be appraised if the state level institutions are already appraised. The state/districts have to submit the action taken report on the appraisals within the stipulated time.

Monitoring of preparatory districts

Appraisal checklists have been designed for use by States and Districts to prepare for PMDT services **(Annexure XXI)**. The same checklist will be used by the appraisal teams. Once the preparatory activities have been completed, a State level appraisal is carried out and the report sent to CTD in the prescribed formats. On receipt of an action taken report on the findings and recommendation of the State Appraisal, the State requests CTD to undertake a Central level Appraisal. The Central Team then carries out a through appraisal of the concerned district/s along with all the State level facilities involved in PMDT using standard checklists and reporting formats. The recommendations of the Central team are acted upon and the State submits a detailed action taken report to CTD within a month of the Central Appraisal. The districts can initiate services under PMDT after CTD reviews the action taken report submitted by the State and gives permission for the same.

14.5 SME for implementing States/districts

Supervision of PMDT services

RNTCP has a robust built in system for supervision. PMDT supervision will be an extension of this system. Similarly, the built in M&E system of RNTCP will be customized according to the levels of implementation and scale up plans. It is very important to remember here that supervision promotes successful implementation of the program policies and processes and

M&E ensure that the implementation progresses in the right direction to achieve the desired targets, objectives and goals.

Objectives of supervision:

The following are the objectives of supervision.

- To build capacity of the health staff to implement the PMDT procedures correctly.
- To ensure that the data recorded and reported is accurate and valid.
- To incorporate a system of analysis and review aimed at improving the quality of programme implementation.
- To increase the involvement and commitment of staff at different levels.
- To provide actionable and timely feedback
- To evaluate the impact of training on the performance of health staff.
- Assess re-training needs.
- To assess the stocks and replenishment of supplies.

Preparation for Supervisory visit:

Since PMDT is not a standalone activity within RNTCP, all the functionaries responsible for the implementation RNTCP are bound to supervise and, in turn, be supervised in PMDT. A checklist of activities to be supervised in a centre proposed to be visited is to be prepared in advance. (Refer to PMDT supervisory check-lists for various levels) Since it may not be possible to evaluate all the activities on a single visit, it is important for the supervisory team to prepare their own checklist in continuation with observations made during earlier visits. Review of previous reports is useful for identifying the priority areas to be focused during the supervision. The existing documents like RNTCP Supervisory Registers placed at all health institutions may be used for recording observations on DOTS as well as PMDT.

During field visits by State level supervisors to districts implementing PMDT, a selection of patients on Regimen for M/XDR TB and their DOT Providers are to be interviewed. In addition, the processes involved in the recording & reporting, drugs & logistics and supply chain management, suspects enlisting, transportation of sputum specimens to the C-DST Laboratory, referral of diagnosed MDR TB patients to the designated DR-TB Centre etc have to be examined in detail.

Modalities of Supervision

Though supervision of PMDT must, ideally, be linked to the supervision of DOTS, additional supervisory check points pertaining to PMDT are discussed below. The recommended modalities for supervision by different level of supervisory staff are presented in the table 15.3 on the next page.

All other RNTCP staffs are to follow their TORs ensuring that the diagnosis and care of MDR TB suspects and patients is taken care of on a priority.

Extensive checklists and monitoring tools have been developed for use by all supervisory staffs. These are to be put to use. All visits to the district and sub district levels by district and State level officials have to, mandatorily include supervision of PMDT activity (both for implementing as well as preparatory districts). All Central and State level Appraisals have to review PMDT activities using standard PMDT supervisory checklists.

Table 14.3 Recommended modalities for supervision by different level of supervisors

Supervisor	Methodology	Frequency
DTO	• Conduct interview with health staff and RNTCP key staff involved in PMDT • Interact with community and local opinion leaders and mobilize their support to help MDR TB patients with diagnosis and treatment. • Randomly interview patients on treatment, their DOT Provider, family members and community leaders. • Inspect records of the DTC, TU, DMCs, PHI and DOT Center and stock of Drugs. • Check the status of card updating and ensure that the original card at the DR-TB Centre is updated at least once monthly • Ensure prompt identification of MDR TB suspects and the transport of sputum specimens to the Lab as per guidelines maintaining cold chain • Physically verify the stock of PWBs at District, TU and PHI stores. • Ensure uninterrupted supply of medicines • Liaise with State TB Cell, DR-TB Centre and the designated CDST Lab	• Visit all TUs every month and all DMCs every quarter. • Visit all CHCs and Block PHCs in the district every quarter, one sub-centre from each Block PHC area and a proportion of treatment observation centers every quarter. • Conduct supervisory visit at least 3-5 days a week. • Visit at least three patients at their homes per visit including one MDR TB patient on treatment
MO –DTC	• Conduct interview with health staff and RNTCP key staff involved in PMDT	• Visit all TUs every month and all DMCs every quarter. • Visit all CHCs and Block PHCs in the district every

	• Interact with community and local opinion leaders and mobilize their support to help MDR TB patients with diagnosis and treatment. • Randomly interview patients on treatment, their DOT Provider, family members and community leaders. • Inspect records of the DTC, TU, DMCs, PHI and DOT Center and stock of Drugs. • Check the status of card updating at District, TU, PHI and DOT Provider	quarter, one sub-centre from each Block PHC area and a proportion of treatment observation centers every quarter. • Conduct supervisory visit at least 3-5 days a week. • Visit at least three patients at their homes per visit – including one MDR TB patient on treatment
MO-TC	• Interview the MO I/C Block PHC/CHC/PHC./Private/NGO hospitals regarding implementation of PMDT activities • Randomly interview patients, their DOT Provider, family members and community leaders. • Interact with community and local opinion leaders and mobilize their support to help MDR TB patients with diagnosis and treatment • Inspect records of the TU, DMCs, PHI and DOT Center and stock of Drugs. • Check the status of card updating	• Visit all DMCs every month. • Visit all CHCs / BPHCs / PHCs and a proportion of treatment observation centers at least once every quarter. • Conduct supervisory visits 7days a month. • Visit at least three patients at their homes per visit – including one MDR TB patient on treatment
STS	• Interview MPHS / MPWs at the PHC sub-centre regarding implementation of PMDT activities. • Interview DOT Providers of patients on MDR TB treatment	• Visit all PHIs at least once every month and all DOT centers once every quarter. • Visit all diagnosed MDR TB patients at their home

	• Help the DTO in identifying and training suitable DOT Providers for diagnosed MDR TB patients to be initiated on MDR TB treatment. • Verify records, Cards and Tuberculosis Laboratory Register. Ensure that the treatment cards at the DTC, TU and PHI are updated at least once monthly • Visit and interview all MDR TB suspects and patients on treatment. Ensure that they are diagnosed at the earliest and complete treatment as per guidelines. • Ensure drugs and logistics management for patients on treatment. • Interview health staff of identified Private/NGO/other sector health care centers • Impart hands on training and guidance to DOT Providers on proper administration of treatment, recording in treatment card and prompt identification of Adverse Drug Reactions	within one month of treatment initiation. • Conduct supervisory visits at least 5 days a week
STLS	• In consultation with the DTO and MO-TC, put systems in place to ensure that all MDR TB suspects are diagnosed at the earliest – facilitate the transport of sputum specimens of these MDR TB suspects to the designated RNTCP-certified lab for C-DST. • Visit all microscopy centers , review laboratory records, check stocks of Falcon Tubes, packing materials and specimen transport boxes and	• Visit all microscopy centers in the jurisdiction of the TU at least once a month. • Visit all sputum collection centers at least once a month.

	ensure that cold chain is maintained. • Impart hands on training and guidance to LTs on identification of MDR TB suspects and transport of their sputum samples to the Lab as per guidelines with proper documentation.	
Senior DRTB and TB HIV Coordinator (this section deals only with the PMDT responsibilities)	• Assist DTO in organizing direct observation of treatment for MDR-TB patients and MDR TB drug logistics management • Facilitate MOs, STSs, STLSs, LTs and other health system staff to subject all MDR-TB suspects to appropriate diagnostic tests for diagnosis of MDRTB at an RNTCP-certified laboratory • Identification and training of DOT providers for MDRTB patients and maintenance of a directory of such DOT providers at the TU and district levels. • Maintain the district level PMDT records and reports. • Ensure that the cards at the district level are updated regularly. • Supervise all PMDT treatment observation centers once in a quarter. • Update the treatment cards at the DR-TB Centre. • Assist the DTO for providing training to the staff of health facilities under his/ her jurisdiction to carry out PMDT related activities. • Establish liaison with private practitioners, NGOs and other sector dispensaries / hospitals to provide PMDT services as per the programme guidelines.	• Visit all TUs every month and all DMCs every quarter. • Visit all treatment observation centres in the district once in every quarter

Monitoring of PMDT in implementing districts

For the purpose of Monitoring of implementing districts, a set of monitoring indicators for coverage, case finding, interim and final outcomes was introduced in the RNTCP Annual Status Report – TB India 2011 and will be regularly published in all quarterly and annual performance report. These indicators were used for reviewing the status with the states since May '11. Apart from this, the State submits quarterly reports on Drugs and logistics management, Laboratory Activities, Case Finding, 6 month interim report, 12 month culture conversion reports and Treatment Outcome reports. Quarterly Reports on PMDT are submitted to DPQR@rntcp.org by all DR-TB Centres and in Epicentre by every implementing districts from 2nd quarter 2012 onwards. Quarterly Reports on Lab performance indicators submitted to Labreports@rntcp.org by all C-DST Labs by 24th of next month. Apart from these, newly introduced Quarterly report on programme management and logistics of C &DST Laboratory to be submitted by states

Evaluation of PMDT in implementing districts

For the purpose of Evaluation, RNTCP has a robust mechanism of Internal Evaluations wherein at least two districts are thoroughly evaluated every quarter for all the parameters of program performance using standard checklists. These checklists have been updated to include sections on PMDT which assess progress on scale up plan and quality of implementation of PMDT by visiting DR-TB Centres, C-DST Lab, Sputum collection sites, Drug Stores, DOT centres, patients' houses etc.

14.6 Job Aides for PMDT services.

Revised National Tuberculosis Control Program is keen to have a built in quality control for each and every aspect of the program implementation. To keep the quality uniformly standardized across the country, the program has developed certain job aides for each level of staff. Monitoring checklist for DM/DHS/STO, supervisory checklist for STS, STLS, 'RNTCP at a glance' for any level of staff etc. are some examples. Similarly, the following Job Aides for PMDT services have also been developed by CTD that have been pilot tested in 4 states in June 2011:

1. Patient Clinical Information Booklet – DR-TB Centre
2. Standard Counselling Tool for MDR TB Patients for all levels
3. MDRTB suspect line list – DMC, TU, DTC

4. Flow Charts - Diagnosis, Treatment, Ambulatory DOT, Recording, Reporting
5. Supervisory checklist for MDR TB - DR-TB Centre, District, TU, DMC, and Patient Interview
6. Monitoring and management of ADR

These job aides have been finalized based on the feedback from the 4 pilot states and have been hosted on the programme website www.tbcindia.nic.in.

Since supervision, monitoring and evaluation remains the most important strategy to ensure quality of implementation of PMDT, program managers at all levels have to see that the SME activities are undertaken in the respective areas as per the guidelines.