



# Revised National Tuberculosis Control Programme

## DOTS-Plus Guidelines



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

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## Abbreviations and Acronyms

AFB	Acid Fast Bacilli
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
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
MDR-TB	Multidrug-resistant Tuberculosis
MIC	Minimal Inhibitory Concentration
MO	Medical Officer
MO-PHI	Medical Officer – Peripheral Health Institute
MO-TC	Medical Officer – TB Control
NaCl	Sodium Chloride
NGO	Non-Governmental Organisation
NRL	National Reference Laboratory
NTI	National TB Institute, Bangalore
PAS	<i>p</i> -aminosalicylic acid
NTM	Non-tuberculous Mycobacteria
Ofx	Ofloxacin
PNB	<i>p</i> -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.

Traditionally, DOTS-Plus refers to DOTS programmes that add components for MDR-TB diagnosis, management and treatment. These guidelines promote full integration of DOTS and DOTS-Plus activities under the RNTCP, so that patients with MDR-TB are both correctly identified and properly managed under the recommendations set out in this document.

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 DOTS Plus activities and will play an important role in shaping future policies and recommendations.

# **CHAPTER 1: BACKGROUND**

## **1.1 Chapter objectives**

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.

## **1.2 Recent developments**

### ***1.2.1 Prevention of MDR-TB***

It is well known that resistance levels are higher in areas with a poorly performing DOTS programmes. Use of inadequate regimens and inappropriate directly observed treatment (DOT) leads to increase in drug resistance levels in the community. 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. DOTS-Plus services, for management of MDR-TB, are supplementary services under the expanded framework of the DOTS package. Therefore in every DOTS implementing unit of the country, DOTS would be prioritised above DOTS-Plus with the view that DOTS reduces the emergence of MDR-TB, and therefore the need for DOTS Plus over time.

### ***1.2.2 Expansion of the DOTS package***

Over the past few years, the basic package of DOTS for TB control has been expanded in many areas to include components that address additional challenges such as TB/HIV co-infection, multidrug-resistant TB, contributing to health system strengthening, engaging all care providers, empowering patients and communities, and enabling and promoting research. Emphasis on expanding laboratory capacity (smear microscopy first, then culture/drug sensitivity testing) and the use of quality assured drugs, are important parts of this more comprehensive approach to TB control.

### ***1.2.3 Introduction of DOTS-Plus***

The first WHO endorsed DOTS-Plus programmes 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. DOTS-Plus 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, DOTS-Plus projects have multiplied rapidly. By the end of 2007, 67 projects in 52 countries approved by the GLC, with a cumulative total of over 30,000 MDR-TB patients, had been launched worldwide, many of them with financial support from the GFATM. Based on data and experience from these projects, practices and further scientific evidence have emerged regarding services for MDR-TB. DOTS-Plus programmes can and should strengthen the basic DOTS strategy.

#### 1.2.4 Integration of TB 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 DOTS-Plus 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 <sup>1</sup>**

<b>Providers/Programmes:</b>	<b>Drugs:</b>	<b>Patients:</b>
<b>Inadequate regimens</b>	<b>Inadequate supply/quality</b>	<b>Inadequate drug intake</b>
<ul style="list-style-type: none"> <li>-Absence of guidelines or inappropriate guidelines</li> <li>-Non-compliance with guidelines</li> <li>-Inadequate training of health staff</li> <li>-No monitoring of treatment</li> <li>-Poorly organized or funded TB control programmes</li> </ul>	<ul style="list-style-type: none"> <li>-Non-availability of certain drugs (stock-outs or delivery disruptions)</li> <li>-Poor quality</li> <li>-Poor storage conditions</li> <li>-Wrong dosages or combination</li> </ul>	<ul style="list-style-type: none"> <li>-Poor adherence (or poor DOT)</li> <li>-Lack of information</li> <li>-Non-availability of free drugs</li> <li>-Adverse drug reactions</li> <li>-Social and economic barriers</li> <li>-Malabsorption</li> <li>-Substance abuse disorders</li> </ul>

Use of standardized short course chemotherapy in patients diseased with multidrug-resistant TB strains fails to cure a significant proportion of such cases and can create even more resistance to the drugs in use. This has



been termed the “amplifier effect of short course therapy” and it implies that the resistant strains in the bacterial population are selected repeatedly when a regimen is used continuously over a long period in a given community, and these become the dominant strains.

Ongoing transmission of established drug-resistant strains in a population is also a significant 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 DOTS Plus 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 Category IV regimens are essential to stop primary transmission. DOTS/DOTS-Plus integration works synergistically to shut down all the potential sources of TB transmission.

## **1.5 Magnitude of the MDR-TB problem in India**

### ***1.5.1 Drug resistance***

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.

The prevalence of **multi-drug resistant TB (MDR-TB)**, defined as resistance to isoniazid and rifampicin with or without resistance to other drugs, is found to be at a low level in most of the regions. Data from studies conducted by TRC and NTI, have found MDR-TB levels of less than 1% to 3% in new cases and around 12% in re-treatment cases.<sup>3,4</sup> 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.<sup>5</sup> 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 two community based state level drug resistance surveillance (DRS) studies in Gujarat and Maharashtra. 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.<sup>6</sup> 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 Andhra Pradesh, Orissa and Western Uttar Pradesh. It is also proposed to repeat these DRS surveys periodically to study the trend of prevalence of MDR-TB.

A major limiting factor in making available state representative data on drug resistance is, as stated earlier, the lack of quality assured culture and DST laboratory facilities. It also needs to be recognized that the diagnosis of MDR-TB is a laboratory based diagnosis. For RNTCP to provide diagnostic and treatment services to MDR-TB patients, in addition to having the capacity to undertake DRS surveys, the programme is in the process of establishing, in a phased manner, a nation-wide network of quality assured culture and DST laboratory facilities. RNTCP aims to have at least one such laboratory, known as the Intermediate Reference Laboratory (IRL), for culture and DST in each large state by 2009-10. The State level laboratory could be in a STDC, a Medical college or a State public health laboratory. Besides the IRLs the programme is also involving the existing Medical College and Private sector Laboratories to support the diagnostic and follow up services. Any laboratory that wishes to be included in the network will need to undergo an assessment and accreditation process under RNTCP.

### ***1.5.2 Multi-drug resistant tuberculosis and DOTS-Plus***

Although the standardized drug regimens used by RNTCP are highly effective, with low failure rates of around 2% and 6% amongst Category I and II cases respectively, the issue of the treatment of those pulmonary tuberculosis patients who remain smear-positive following a fully supervised Cat I, II or III treatment regimen, has previously not been well addressed by the RNTCP. Although these cases represent a small minority of the overall caseload of TB patients in India, they are an important group from epidemiological and human rights viewpoint. Also, although small in relation to percentages and proportions, these rates translate into large absolute numbers. Moreover, MDR-TB patients often live a number of years before succumbing to the disease. Therefore MDR-TB prevalence may be three times greater than its incidence.<sup>7</sup> After successfully establishing the DOTS services across the country RNTCP is now introducing the DOTS Plus services to address the needs of this group of patients.

The 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

DOTS-Plus guidelines and will be done in designated RNTCP DOTS-Plus sites. These sites will be in highly specialized centres (e.g. Medical College hospitals, Chest and respiratory disease institutes etc.) which will have ready access to an RNTCP accredited culture and DST laboratory, with qualified staff available to manage patients using standardized second-line drug regimens given under daily DOT and standardized follow-up protocols, have systems in place for an initial short period of in-patient care to stabilise the patient on the second-line drug regimen followed by ambulatory DOT and with a logistics system and standardized information system in place. Each DOTS Plus site will cater to approximately 10 million population. However this norm is neither limiting nor restrictive and will be reviewed and revised periodically. The DOTS-Plus sites will be initiated in a phased manner similar to that for the establishment of the culture and DST laboratory network.

### ***1.5.3 RNTCP DOTS Plus vision***

It is envisioned that by the year 2010 the DOTS Plus services will be introduced in all the states across the country. By 2012, it is aimed to extend these services to all smear positive retreatment cases and new cases who have failed an initial first line drug treatment. And by 2015, these services will be made available to all smear positive pulmonary TB cases registered under the programme. It is intended to treat at least 30,000 MDR cases annually by 2012-13.

## **1.6 Special considerations for DOTS-Plus**

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

- Quality-assured laboratory capacity (smear, culture and DST);
- Treatment design;
- Adherence to difficult-to-take regimens for long periods;
- Side-effect management;
- Drug procurement;
- Recording and reporting; and
- Human and financial resource constraints.

The method of case finding is designed taking into consideration the resources and technical capacity available to the RNTCP at this time. Also the DOTS-Plus treatment regimen for MDR-TB has been tailored to the Indian setting. Many health care providers have little or no experience with second-line drugs and their side effects,

especially in combinations of 4 to 6 at a time. The framework presented in this document is designed to address the challenges faced by RNTCP in relation to MDR-TB in India.

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## **CHAPTER 2: FRAMEWORK FOR EFFECTIVE CONTROL OF MULTIDRUG-RESISTANT TUBERCULOSIS**

### **2.1 Chapter objectives**

The objective of this chapter is to describe the framework approach to DOTS-Plus, the five essential components of the DOTS-Plus strategy, and the need to tailor these components to the local situation, within the context of the RNTCP.

### **2.2 The DOTS-Plus 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 DOTS-Plus strategy are included, and are:

1. Sustained government 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.

#### ***2.2.1 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 DOTS-Plus environment includes adequate infrastructure, development and retention of human resources, inter-agency cooperation, TB control policies enabling rational DOTS-Plus 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.

#### ***2.2.2 Diagnosis of drug-resistant TB through quality assured, timely culture and DST***

Accurate and timely diagnosis is the backbone of the DOTS-Plus 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.

Under RNTCP, any patient who fails a Cat I or III treatment regimen or any Cat II patient who remains smear positive at the end of the fourth month of treatment or later or contacts of MDR cases will be identified as “MDR-TB suspect” and will be tested by culture and DST. (This is elaborated in Chapter 4: Case finding and definitions).

### ***2.2.3 Appropriate treatment strategies utilizing second-line anti-TB drugs under appropriate management conditions***

RNCTP 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 and social support network to facilitate adherence to ambulatory treatment; and the presence of other clinical or social conditions in patients. This is further discussed in Chapter 10 “Treatment delivery and adherence”.

### ***2.2.4 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.

### ***2.2.5 A recording and reporting system designed for DOTS-Plus***

The specific characteristics of a DOTS-Plus programme require a recording system, culture and DST results, and monitoring treatment delivery and treatment response for 24 to 27 months. Cohort analysis in DOTS-Plus includes interim indicators and treatment outcomes after 2 or more years. Case definitions and treatment outcome definitions for MDR-TB used in RNTCP DOTS-Plus are given in Chapter 4, and will be used for conducting cohort analyses under the RNTCP DOTS-Plus activities. The developed recording and reporting system (Chapter 13) is essential for evaluating programme performance and treatment effectiveness.

## 2.3 Summary

The framework approach to DOTS-Plus, summarized in Figure 2.1, includes five essential components which form the basis for every TB control programme that includes detection and treatment of multidrug-resistant TB.

### **FIGURE 2.1 FIVE COMPONENTS OF DOTS-PLUS**

- 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 Culture & DST testing and management under DOTS-Plus
  - 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 anti-TB drugs.**
- 5. Recording and reporting system designed for DOTS-Plus programmes that enable performance monitoring and evaluation of treatment outcome**

## **CHAPTER 3: GOVERNMENT COMMITMENT & COORDINATION**

### **3.1 Chapter Objectives**

Sustained administrative commitment is a prerequisite for control of multidrug-resistant TB. This chapter considers how administrative commitment needs to be translated into practical measures to support all aspects of the framework for control of MDR-TB and the practical implications for RNTCP. The main elements are described and a check-list is included to aid managers of the RNTCP DOTS-Plus activities.

### **3.2 General considerations**

Sustained administrative commitment and leadership are the foundation for any sound TB control programme. In India, the TB services under public services throughout the country are being provided under the Government of India's national programme, the RNTCP. Administrative commitment is expressed through adequate financial support and appropriate infrastructure, including facilities and trained human resources. Sufficient training and retention of medical and public health personnel depend on long range administrative planning and support.

### **3.3 Political Commitment**

Administrative commitment must be expressed at all stages of the health intervention process, from planning and implementation to monitoring and evaluation. Political support needs to be garnered from many sources including government ministries (central and state), non-governmental organizations (NGOs) and the private sector, the pharmaceutical industry, academic and research institutions, professional medical societies and the donor community. This commitment comes in the form of financial and human resources, training, legal and regulatory documents, infrastructure, and coordination of all stakeholders. In short, there should be a strong commitment to apply all aspects of the framework described in Chapter 2.

#### ***3.3.1 Sufficient Economic Support***

The RNTCP's 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 necessary financial resources needed to support the framework described in Chapter 2, should be provided. The patient should have no financial barrier to appropriate care for MDR-TB.

To tackle MDR-TB, the RNTCP will need physicians, managers, nurses, engineers, microbiologists, information technology specialists, pharmacists, and other specialists with expertise in managing MDR-TB. These human resource issues are discussed in Chapter 11.



### **3.3.2 Regulatory and operational documents**

Before embarking on a DOTS-Plus programme, policies need to be developed by the central government to provide the foundation for any subsequent legal, administrative and technical support necessary for the initiation, implementation, and monitoring of the MDR-TB programme. Regulatory document(s) should consider how the programme will integrate with the basic DOTS programme. Following steps have been taken by RNTCP in this regards.

- Instructions/orders issued to assure proper registration, availability, use, and distribution of second-line drugs.
- A national expert DOTS-Plus Committee formed to develop policies, technical and operational guidelines.
- State DOTS-Plus committee responsible for developing plan of action for implementation, expansion, maintenance and supervision of DOTS Plus services in the respective state.
- DOTS Plus site committee will be formed which will be responsible for initiating the MDR patients on treatment and providing follow up and emergency services on an ongoing basis in addition to addressing programme problems.
- RNTCP DOTS-Plus training modules for the Medical Officers and Paramedical staff have been developed for disseminating operational and clinical protocols to ensure consistency. These have been officially endorsed by the national DOTS Plus Committee and the Central TB Division, Ministry of Health and Family Welfare, Government of India. The module not only describes treatment protocols but defines responsibilities for different health care providers and delineates the human resources that will be needed. These specifically describe how patients will be diagnosed, registered, reported, treated, and followed, in addition to programme monitoring and evaluation.

## **3.4 Coordination**

As RNTCP embarks on DOTS-Plus 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 DOTS-Plus programme. As needed, partnerships with all relevant health care

providers can be built. The CTD is supported by a National DOTS-Plus Committee, comprised of members from CTD, the three central TB institutes (NTI, TRC and LRS), medical colleges and WHO.

- **Local Health System.** RNTCP DOTS-Plus activities will be tailored to fit into the respective state and district levels infrastructure. The exact organizational structure of the RNTCP DOTS-Plus programme 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 DOTS-Plus, 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.
- **International Level.** CTD is supported in its DOTS Plus activities by international technical support through WHO, GLC, and other technical agencies. The collaboration between such entities requires effective coordination and communication on an ongoing basis.

### 3.5 Summary and a check list

From the earliest planning stage, the full range of issues encompassed in administrative commitment needs to be addressed. These include adequate financial support, an enabling regulatory environment, sufficient human resources, physical infrastructure, and effective coordination. In addition, a communication strategy should be established to ensure effective dissemination of information from the central level to the periphery, and that reports from the peripheral level are received centrally. Box 3.2 on page 24 provides a checklist for programme managers to make the process easier by summarizing the key aspects of a DOTS-Plus programme.

## **BOX 3.2 Summary check list for Programme Managers**

### ***Political Commitment:***

- Clear definition of the roles and responsibilities of each stakeholder/ organization
- DOTS-Plus manual approved by CTD
- Overall budget secured (including budget for all the components below)

### ***Human Resources:***

- Estimation of human resources calculated
- Organizational structure and management system of human resources
- Workforce in post

### ***Training:***

- Training Curriculum
- Training schedule in place
- Refresher courses in place
- Separate training activities for general medical community

### ***Data Gathering, Analysis, and Application:***

- Surveillance Systems
- Accurate reporting systems to identify and track MDR-TB patients (treatment cards, registers, forms for ordering and reporting lab results)

### ***Laboratory:***

- Specimen collection system for smears and cultures
- Dedicated culture and DST laboratory space
- Adequate staffing and training
- Testing and maintenance of equipment
- Biosafety measures in place
- Reagents supply
- Supervision and quality assurance system (relationship with a WHO Supra-National Reference Laboratory established)
- Results reporting system to treatment care centre
- Laboratory for the free monitoring of electrolytes, creatinine, thyroid function, and liver enzymes in place.
- HIV testing, counselling and referral available
- Pregnancy testing

### ***Patient Care***

- DOTS-Plus site committee set up
- Adequate capacity and trained staff at the health centre for DOT and patient support
- Adequate DOT in place and plan to assure case holding
- System to detect and treat adverse effects including appropriate medications
- Patient and family support to increase adherence to treatment, including support group, psychotherapy, transportation subsidy,
- Patient, family, and community education, including stigma reduction

### ***Programme strategy:***

- DOTS-Plus activities fully integrated within DOTS programme
- DOTS-Plus manual published and disseminated (and understood)
- Location of care defined and functional (ambulatory and in-door)

### ***Prevention:***

- Training of all health care workers to identify, refer, and diagnose possible TB cases and individuals at high risk
- Maintain high case detection and cure rates under DOTS programme to prevent emergence of MDR-TB
- MDR-TB case finding and treatment amongst Category II cases as per RNTCP guidelines
- Screening of household contacts of MDR-TB cases as per RNTCP guidelines

### ***Drug and supply procurement:***

- Projected needs
- Ordering with long lead times to receive second line drugs
- Adequate budget for drug procurement
- Adequate budget for consumable items (sputum cups, laboratory reagents...etc)
- Drugs to treat side effects available

### ***Logistics:***

- Inventory and expiration date management
- Transportation and distribution
- Adequate national, state, and local drug storage facilities

## **CHAPTER 4: CASE-FINDING AND DEFINITIONS**

### **4.1 Chapter Objectives**

This chapter describes the RNTCP strategy for case-finding and diagnosis of patients with suspected MDR-TB. The RNTCP DOTS-Plus 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. RNTCP has undertaken state representative DRS surveys in order to obtain data for new and re-treatment patients, to further inform programme planning and drug procurement.

This chapter also provides case definitions and outcome definitions for patients that will enter the RNTCP Category IV regimen. The purposes of the definitions are to:

- Facilitate proper patient registration and case notification;
- Facilitate case evaluation according to site, bacteriology, and treatment history; and
- Facilitate cohort analysis of registered MDR-TB patients and MDR-TB treatment outcomes.

### **4.2 Case finding strategy**

At present, RNTCP does not have sufficient quality assured laboratory capacity to do culture and DST in all TB patients. Hence the programme will use a strategy that enrolls patients with a very high risk of MDR-TB into RNTCP DOTS-Plus activities and treatment with the RNTCP Category IV regimen. Patients who are defined as an “MDR-TB suspect” should be identified and investigated further for MDR-TB.

MDR-TB Suspect can be any of the following:

- Any TB patient who fails an RNTCP Category I or III treatment regimen;
- Any RNTCP Category II patient who is sputum smear positive at the end of the fourth month of treatment or later; or
- Close contacts of MDR-TB patients who are found to have smear positive pulmonary TB (PTB) disease

After a TB patient has been declared as a failure of an RNTCP Category I or III treatment, the initial priority is to ensure that the patient is initiated on an RNTCP Category II regimen and is re-registered in the appropriate TB Register as a Category II type “failure” patient. Similarly close contacts of MDR-TB patients should be screened as per RNTCP guidelines and if found to be smear positive PTB, such patients should be started on Category I or II based on whether they are new or re-treatment cases.

A patient who is an “MDR TB Suspect” should be referred by the respective medical officer – peripheral health institute (MO-PHI) to the District TB Officer (DTO) for confirmation. **It should be ensured that the MDR suspects are identified and referred to the DTO for confirmation at the earliest i.e. within 2 weeks of failing a Category I or III regimen, and in case of Category II patients (who have taken at least 4 months of treatment) and close contacts of MDR-TB cases as soon as the sputum results are available. 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.**

The MDR suspect is referred to the DTO with a copy of their Cat I/II/III treatment cards and request for culture and DST form (*See Annex I on page 86*) and the drug-o-gram (*See Annexure II on page 87*).

The drug-o-gram will be used to record the patient’s anti-TB drug (*Annex II on page 87*). Since fluoroquinolones are used widely for diseases other than TB, patients should be carefully questioned about possible treatment with these drugs. It is also important to record if the patient has ever received *second-line anti-tubercular drugs*<sup>\*</sup> and for how long they received such drugs. The drug history will be further verified by the DTO and any additional information elicited will be recorded in the drug-o-gram.

Once the DTO 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 accredited Culture and DST facility along with the RNTCP culture and DST request form (*Annex I*). For sputa to be collected and sent from the District TB Centre (DTC), all necessary materials, e.g. sample bottles, referral forms etc, need to be made available at the DTC. The samples will need to be transported in Cetyl Pyridinium Chloride (CPC) solution if the delay in transportation is likely to exceed 72 hours. A note of this referral to the Culture & DST laboratory should be entered in the “Remarks” column of the respective TB Register in which the patient is registered for Cat II treatment and in the Referral for Culture and DST Register held at the DTC (*See Annex III page 88*). Alternatively the MDR-TB suspect referred to DTC may be provided two sample bottles with CPC by the concerned DMC and instructed on collecting two samples (one early morning and one supervised spot). These samples will be taken by the patient to the DTC from where they will be transported to the laboratory for culture and DST. Once the sputum has been transported to the RNTCP accredited laboratory by the DTO the MDR suspect should return to continue their Category II/Category I treatment.

The following points are critical for the collection of sputum in CPC bottle at DMCs.

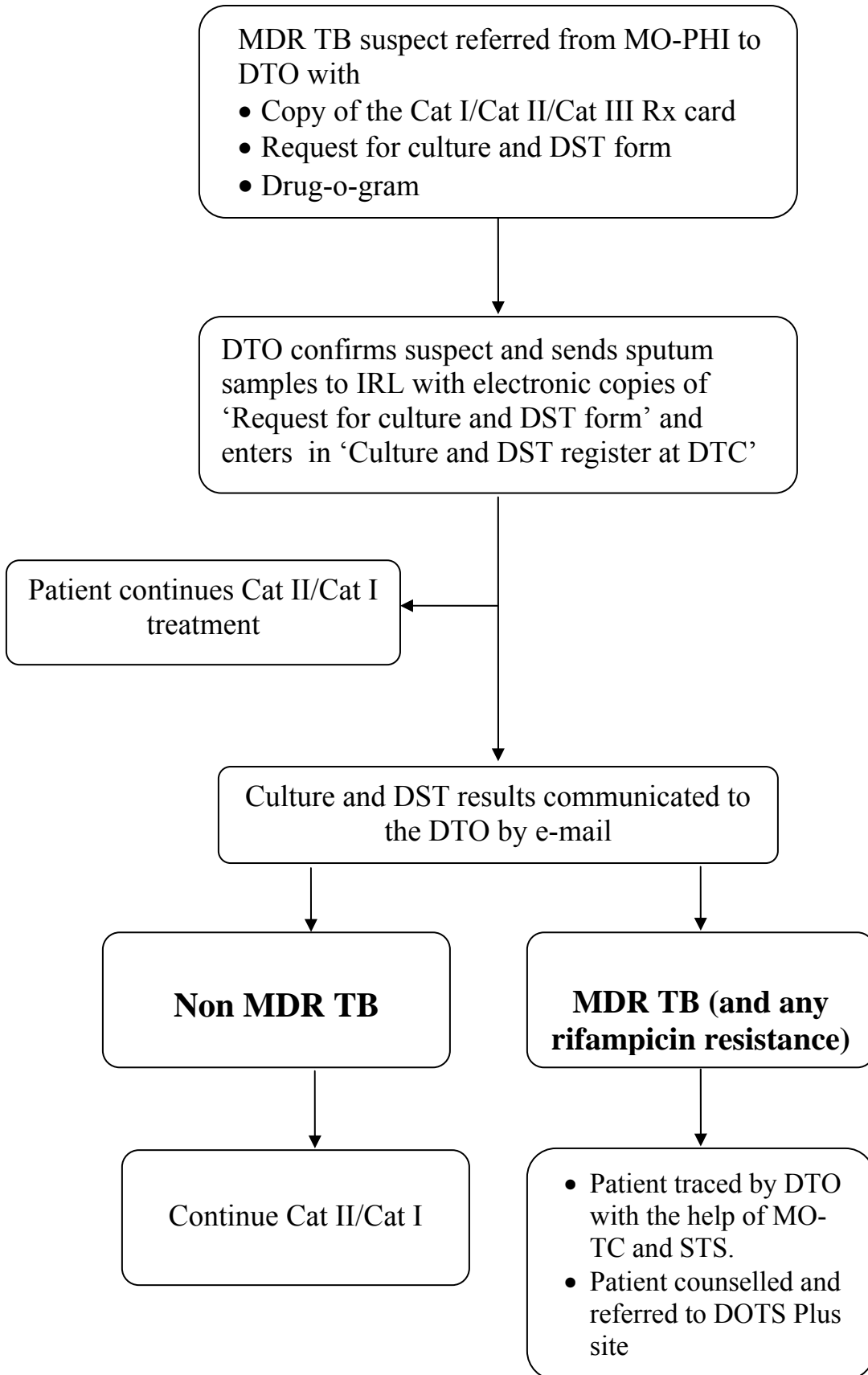
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\* *The second line drugs include: All Fluoroquinolones (Ciprofloxacin, Ofloxacin, Pefloxacin, Levofloxacin, Gatifloxacin, Sparfloxacin, Moxifloxacin, Perulifloxacin, Gemifloxacin), Kanamycin, Amikacin, Capreomycin, Cycloserine, Ethionamide Prothionamide, PAS.*

- CPC solution should be prepared at the DTC and the CPC containing bottles should be supplied to the DMCs for collection of sputum.
- The CPC bottles should carry a label indicating the date of preparation and expiry. Date of expiry should not be beyond 30 days from the date of preparation.
- The Lab technicians at DMCs should be instructed to carefully examine the CPC bottles prior to issuing them to patients for sputum collection. Bottles found containing expired/decolorized CPC or contaminants should not be used and these should be sent back to the DTC.
- The LT of DMC issuing the CPC bottles 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 CPC bottle to the patient should be recorded.

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

**Figure 1 : Patient Flow .....Diagnosis**



## 4.3 Case Definitions

### 4.3.1 Drug Resistant Cases

A patient is confirmed to have multi-drug resistant TB only by an RNTCP quality assured culture and DST laboratory. Such patients are classified according to the following definition:

- **Confirmed MDR-TB case: An MDR-TB suspect who is sputum culture positive and whose TB is due to *Mycobacterium tuberculosis* that are resistant *in-vitro* to at least isoniazid and rifampicin (the culture and DST result being from an RNTCP accredited laboratory).**

**Patients with are not MDR but have any Rifampicin resistance will also be treated with Cat IV regimen.**

Internal quality control and external quality assurance of the laboratory are required. Mishandling of a specimen or cross-contamination in the laboratory can result in erroneous reports.

Once a patient has been confirmed as having MDR-TB or any rifampicin resistance, the Cat II/Cat I<sup>‡</sup> treatment will be stopped and the patient will be placed on an RNTCP Category IV treatment regimen after pre-treatment evaluation. These patients will have to be given a treatment outcome under Cat II/I. 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:

- “Failure” if the patient has completed more than 5 months of Cat I/II treatment
- “Switched to Cat IV” if the patient has completed less than 5 months of Cat I/II treatment

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

### 4.3.2 Bacteriology

With respect to drug-resistant TB, bacteriology includes both sputum smear microscopy and culture examination. Smear microscopy and culture should be performed and results reported according to international standards. These techniques should be used at the initiation of treatment to confirm cases and identify those that are most infectious (smear positive). Both bacteriological techniques are used to monitor patients throughout therapy and should be performed as per the schedule given in Chapter 5. Bacteriological testing is also useful to record, report and evaluate programme performance:

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<sup>‡</sup> *Category I in case of MDR-TB suspects who are contacts of MDR-TB cases and have no prior history of TB treatment in the past.*



## 4.4 Cohort analysis

All patients that are identified with MDR-TB and are to be treated with an RNTCP Category IV regimen, should be entered into the RNTCP DOTS-Plus Register maintained at the DOTS Plus site (*See Annex IX on page 97*). An MDR-TB cohort is defined as a group of patients registered for Cat IV treatment during a specified time period (e.g., one quarter of the year). The date of registration for category IV treatment 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.

### Reference

1. World Health Organization (WHO). Treatment of Tuberculosis: Guidelines for National Programmes, 3rd edition. WHO/CDS/TB 2003.313 Geneva, Switzerland: WHO, 2003.

## CHAPTER 5: DIAGNOSIS AND EVALUATIONS

### 5.1 Objectives

The chapter provides the definitions of MDR-TB diagnosis, pre-treatment evaluations, drug susceptibility testing, MDR-TB suspects' flow for diagnosis, the various forms and registers used in the process.

### 5.2 Patient flow (refer to flowchart on page 18)

After the referral or transportation of sputa samples of an MDR-TB suspect to the RNTCP accredited laboratory, the results of the smear, Culture and DST are entered in the Culture and DST Register (*See Annexure IV on page 89*) 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 results are also communicated to the respective DOTS-Plus site using *Annexure I*. If the culture result shows contamination, the same is informed to the DTO at the earliest and s/he should arrange to send a repeat sample (one early morning and one spot) to the laboratory. The results of culture and DST and further action to be taken is summarised in Figure 2 on page 25.

If the patient is confirmed as a non-MDR-TB case, he/she will be continued on the Category II/Category I regimen. If MDR-TB 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. After counselling, the MDR-TB patient is referred to the state DOTS-Plus site with their DST result and DOTS-Plus referral for treatment form (*See Annexure V on page 90*) and the drug-ogram, for pre-treatment evaluation and initiation of Category IV treatment. In case the MDR-TB suspect completes the Category II treatment before the culture and DST results are available, the patient should be continued on Category II CP till the time the results are obtained. **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 DOTS-Plus site for pre-treatment assessment and initiation of Category IV treatment.**

**MDR-TB Case: An MDR-TB suspect who is sputum culture positive and has *M. tuberculosis* resistant to isoniazid and rifampicin, with or without resistance to other anti-tubercular drugs based on DST results from an RNTCP accredited laboratory.**

## 5.3 Culture and DST

### 5.3.1 Diagnostic examination

Presently conventional solid egg-based Lowenstein-Jensen (LJ) media will be used for primary culture at the RNTCP accredited laboratory. DST will be performed for streptomycin (S), isoniazid (H), rifampicin (R) and ethambutol (E) only. Pyrazinamide (Z) sensitivity testing may be included at a later period of DOTS-Plus implementation.

### 5.3.2 Follow up smear and culture schedule during treatment

For follow up examination four sputum specimens will be collected and examined by smear and culture at least 30 days apart from the 3<sup>rd</sup> to 7<sup>th</sup> month of treatment (i.e. at the end of the months 3, 4, 5, 6 and 7) and at 3-monthly intervals from the 9<sup>th</sup> month onwards till the completion of treatment (i.e. at the end of the months 9, 12, 15, 18, 21 and 24). Of the four specimens, two specimens for AFB (one early morning and one supervised spot) will be collected and examined at the respective DMC/DTC (at the end of the months 3, 4, 5, 6, 7, 9, 12, 15, 18, 21 and 24). The other two specimens for culture (one early morning and one supervised spot) will be collected and transported in CPC bottles from the respective DTC to the RNTCP accredited laboratory (at the end of the months 3, 4, 5, 6, 7, 9, 12, 15, 18, 21 and 24). If any of the cultures in the last three quarters becomes positive, it will be followed up by monthly cultures in the following 3 months (*See Annexure VI on page 91*).

The importance of the sputum examination during treatment needs to be emphasized, since the most important objective evidence of improvement is the conversion of sputum smear and culture to negative. 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). Similarly patients will be considered **smear converted** after having two consecutive negative smears taken at least one month apart. Two separate indicators, one based on sputum smears and the other on cultures will be calculated and interim reports will be given by the state level DOTS Plus site for smear and culture after completing 6 months and 12 months of treatment.

Though smear conversion can be taken as an indicator, culture conversion which reflects viability of tubercle bacilli, is more sensitive and is necessary to monitor progress in MDR-TB patients. Good quality sputum is essential to get proper results.

## 5.4 Pre-treatment Evaluation

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. 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
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 (*See Annexure VII on page 92*).

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

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), 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 and the frequency of follow up.

At the DOTS-Plus site in-door facility, the DOTS-Plus site committee will consider all the clinical and biochemical results before starting the patient on an RNTCP Category IV treatment. 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. The details of the treatment are given in Chapter 7.

As mentioned above the MDR-TB case will require to be hospitalised (at the DOTS Plus site) for pre-treatment evaluation and treatment initiation. In case a patient refuses for hospitalization 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 DOTS Plus site Committee and, if approved, the Cat IV treatment is initiated at the DTC.

## **5.5 Monitoring progress during treatment**

### ***5.5.1 Clinical monitoring***

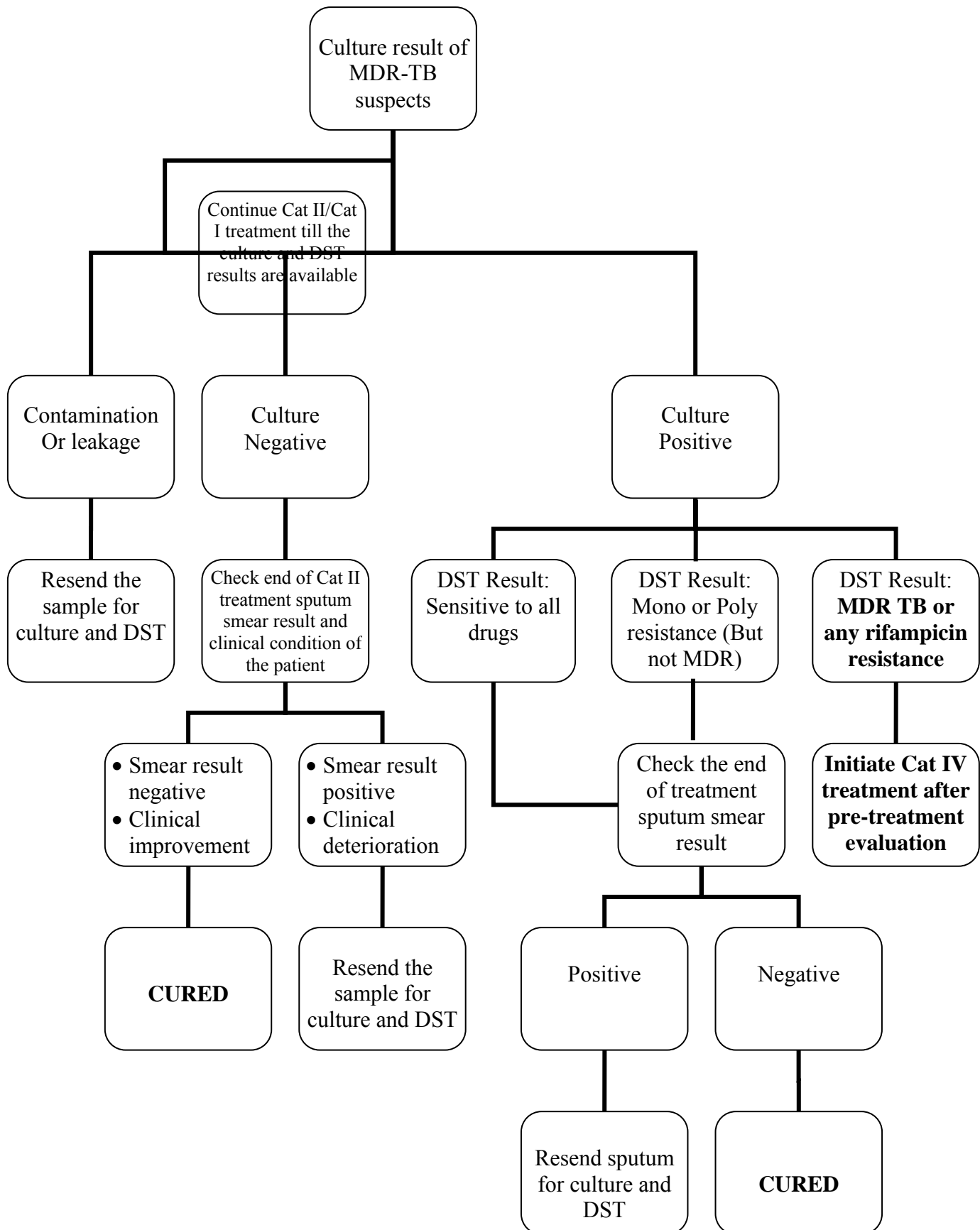
Patients should be seen by the respective DTO for clinical evaluation at monthly intervals during the IP, after discharge from the state DOTS-Plus site, and at 3-monthly intervals during the CP until the end of treatment. The DTO should screen patients for clinical improvement and possible adverse reactions. Body weight should be monitored by the DTO at every visit. The patient may need to be hospitalized during treatment for medical or sociological reasons.

### ***5.5.2 Investigations during treatment***

Chest radiograph will be done during the pre-treatment evaluation, at the end of the IP, end of treatment and when clinically indicated.

Serum creatinine is to be done every month for the first 3 months and every three months thereafter whilst the patient is receiving kanamycin. Other relevant investigations may be done as and when clinically indicated. **These investigations can be done at the DOTS-Plus site or district hospitals/medical colleges as per the arrangement, however patients should not be charged for these investigations.**

**Figure 2. Culture and DST results and further action**



## CHAPTER 6: LABORATORY ASPECTS

### 6.1 Chapter Objectives

This chapter describes the laboratory services needed to diagnose and treat MDR-TB cases, job responsibilities of the NRL and IRL laboratory personnel, and provides the standard operating procedures for bacteriological aspects of DOTS-Plus.

### 6.2 General considerations

A patient is confirmed to have drug resistant TB only by an RNTCP quality assured Culture & DST Laboratory. Such patients are classified according to the following definition:

- **Drug-resistant case:** A patient whose TB is due to tubercle bacilli that are resistant *in vitro* to at least one *anti*-TB drug according to accepted laboratory methods in an RNTCP accredited laboratory.
- **Mono-resistance:** A patient whose TB is due to tubercle bacilli that are resistant *in vitro* to exactly one anti-TB drug in an RNTCP accredited laboratory.
- **Poly-resistance:** A patient whose TB is due to tubercle bacilli that are resistant *in-vitro* to more than one anti-TB drug, except not both isoniazid and rifampicin in an RNTCP accredited laboratory.
- **MDR-TB case:** An MDR-TB suspect who is sputum culture positive and whose TB is due to *Mycobacterium tuberculosis* that are resistant *in-vitro* to isoniazid and rifampicin with or without other anti-tubercular drugs based on DST results from an RNTCP accredited Culture & DST Laboratory.

Optimal management of MDR-TB requires both mycobacterial and clinical laboratory services. The mycobacteriology reference laboratory, which at the state level is an intermediate reference laboratory (IRL) or any other RNTCP accredited Culture & DST laboratory, should provide: culture; confirmation of the species as *M. tuberculosis* or non- tuberculous mycobacteria (NTM); and testing for susceptibility to at least isoniazid and rifampicin. 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 DOTS Plus sites identified by the state (see Chapters 5 and 9). A comprehensive, routine system of internal quality control and external quality assurance is mandatory. For the national reference laboratories, formal links should be made with the WHO network of Supra-National Reference Laboratories for provision of quality assurance through validation of drug susceptibility data. Quality assurance goes beyond the relationship with the SNRL and includes good infection control measures and internal quality assurance methods to document that the results are valid. These aspects are discussed below.

### 6.3 Organization and development of the laboratory network

RNTCP has a three tier laboratory network based on the designated microscopy centres (DMCs) covering 1 lakh populations and providing sputum smear microscopy services, and IRLs (undertaking training, external quality assessment [EQA] of sputum smear microscopy network in the districts and DMCs, and culture and DST for first line drugs for *M. tuberculosis*), and NRLs (undertaking training, EQA of sputum smear microscopy network in the states allotted to them, and culture and DST for first and second line drugs for *M. tuberculosis*).

### 6.4 Job Responsibilities under DOTS-Plus

	Level	Job responsibilities
1	<b>National Reference Laboratory</b>	<ol style="list-style-type: none"> <li>1. To train IRL Microbiologist, IRL key staff and LTs in TB bacteriology.</li> <li>2. To review the results of pilot testing of forms etc in DMC (s) selected for DOTS-Plus.</li> <li>3. To conduct on-site evaluation of IRL for smear microscopy, culture and DST as per RNTCP Mycobacteriology Laboratory Accreditation Guidelines.</li> <li>4. Re-check at least 10 randomly selected cultures, at the time of accreditation, from IRL for identification and DST and communicate the results with suggestions to IRL, STO and CTD.</li> <li>5. Send a panel of 20 cultures to IRL once a year to perform identification and DST for proficiency testing and receive the results and communicate the proficiency of DST to IRL, STO and CTD.</li> <li>6. Review the results of IRL on culture and DST once in a year.</li> <li>7. Conduct annual review of DOTS-Plus and reports to include;               <ol style="list-style-type: none"> <li>a. Information on field work, such as enrolment of patients, transport or logistic problems, and</li> <li>b. EQA of smear microscopy (as per EQA Guidelines), contamination of samples, number of specimens negative by culture, and insufficient growth for susceptibility testing, logistics, laboratory procedures, quality control results, DST results etc as per RNTCP Mycobacteriology Laboratory Accreditation Guidelines.</li> <li>c. If the data or comments suggest that a significant problem has occurred, the NRL will analyze the situation and develop a plan of action in</li> </ol> </li> </ol>



		<p>consultation with the investigators.</p> <p>8. To attend the National level meetings on DOTS-plus and discuss the DST results and reports and develop a plan of action in consultation with the IRL Microbiologist, STDC Director and STO.</p>
2	<b>Intermediate Reference Laboratory and State TB Training and Demonstration Centre</b>	<ol style="list-style-type: none"> <li>1. To prepare a map of selected DMCs and treatment centres for DOTS-plus</li> <li>2. To open and maintain a Culture and DST Register for DOTS-Plus for referred patients (Annexure IV).</li> <li>3. Arrange for a courier agency for transport of specimens to IRL.</li> <li>4. Identify and train the trainers of DTOs, MO-TCs, STS, STLS, MOs and LTs.</li> <li>5. Arrange the venue, time and duration for training of other personnel based on the geographical area and the number of personnel to be trained;</li> <li>6. Train the following personnel; <ol style="list-style-type: none"> <li>a. All IRL / concerned technical staff, <ol style="list-style-type: none"> <li>i. In DOTS-Plus methodology,</li> <li>ii. In TB bacteriology,</li> <li>iii. In EQA of smear microscopy,</li> <li>iv. As trainers,</li> <li>v. As Supervisors.</li> </ol> </li> <li>b. All MO-TCs of the districts of the selected DOTS-Plus sites, <ol style="list-style-type: none"> <li>i. In DOTS-Plus methodology</li> <li>ii. As trainers of STS, STLS, MOs and LT</li> </ol> </li> <li>c. All STS of the districts of the selected DOTS-Plus sites, <ol style="list-style-type: none"> <li>i. In DOTS-Plus methodology, particularly tracing of patients after DST results are available,</li> <li>ii. Identification of DOT providers who can give injectables</li> <li>iii. Training of DOT providers.</li> </ol> </li> <li>d. All STLS of the districts of the selected DOTS-Plus sites, <ol style="list-style-type: none"> <li>i. Specimen collection &amp; transportation for DOTS-Plus</li> <li>ii. As trainers of LTs.</li> </ol> </li> <li>e. All MOs of selected DMCs, <ol style="list-style-type: none"> <li>i. In enrolment and regular follow up of patients</li> <li>ii. Management of minor side effects of</li> </ol> </li> </ol> </li> </ol>

		<p>drugs etc</p> <p>f. All LTs of selected DMCs in,</p> <ol style="list-style-type: none"> <li>i. Proper collection of samples,</li> <li>ii. Transportation of samples,</li> <li>iii. Recording.</li> </ol> <p>7. Receive the laboratory forms for Culture and DST from Category II patients with smear positive results after 4 months or later, along with their two specimens from MOs and ensure that the data is entered in computer.</p> <p>8. Communicate the results of Culture and DST to DOTS-Plus site committee and the concerned DTO.</p> <p>9. Receive a set of 20 panel cultures once in a year from NRL, perform and send results of identification and DST for proficiency tests to NRL.</p> <p>10. Identify IRL Microbiologist as a member of the state level DOTS-Plus committee and the DOTS-Plus site committee, and perform the duties allotted to the respective committees.</p>
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6.3.3 Human Resources Required for DOTS Plus: At NRLs and IRLs: One Microbiologist, four LTs, and four Lab Assistants.

## 6.4 CULTURE OF SPUTUM SPECIMENS

### 6.4.1 SPECIMEN COLLECTION

In tuberculosis bacteriology an often-overlooked problem is that of obtaining adequate good quality specimens. The advantages of decontamination techniques, obtaining maximum yield by cultures, sensitive culture media and simple identification schemes will not be complete unless specimens are collected with care and promptly transported to the laboratory.

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.

Specimens should be transported to the laboratory as soon as possible after collection. If delay is unavoidable, the specimens should be refrigerated to inhibit the growth of unwanted micro-organisms. If refrigeration is not possible and a delay of more than 3 days is anticipated, a suitable preservative viz., an equal volume of a mixture of 1% CPC and 2 % sodium chloride (NaCl) solution is recommended to be used.

#### **6.4.2 HOMOGENISATION AND DECONTAMINATION**

*M. tuberculosis* requires special media not used for other organisms and grows slowly, taking three to six weeks or longer to give visible colonies. Cultures are usually made in bottles rather than in petri dishes because of the long incubation time required. The bottles are tightly stoppered to prevent drying of the cultures.

The majority of clinical specimens received at the tuberculosis culture laboratory are contaminated to varying degrees with more rapidly growing normal flora. These would rapidly overgrow the entire surface of the medium and digest it before the tubercle bacilli start to grow. Most specimens must, therefore, be subjected to a harsh digestion and decontamination procedure that liquefies the organic debris and eliminates the unwanted normal flora. All currently available digesting/decontaminating agents are to some extent toxic to tubercle bacilli and therefore, to ensure the survival of the maximum number of bacilli in the specimen, the digestion/decontamination procedure must be precisely followed. For tubercle bacilli to survive to give a confirmatory diagnosis, it is inevitable that a small proportion of cultures may be contaminated by other organisms of the respiratory tract. As a general rule, a contamination rate of 2%-3% is acceptable in laboratories that receive fresh specimens. If specimen transportation (especially sputum) takes several days to reach the laboratory then losses due to contamination may be as high as 5%. It is also important to note that a laboratory which experiences no contamination is probably using a harsher method that kills too many of the tubercle bacilli.

When culturing tubercle bacilli, the following aspects should be borne in mind:

- Specimens must be homogenized to free the bacilli from the mucus, cells or tissue in which they may be embedded. The milder this homogenisation the better would be the results
- Neither homogenisation nor decontamination should unnecessarily reduce the viability of tubercle bacilli
- The success of homogenisation and decontamination depends on:
  - The greater resistance of tubercle bacilli to strongly alkaline or acidic digesting solutions
  - The length of exposure time to these agents
  - The temperature build-up in the specimen during centrifugation
  - The efficiency of the centrifuge used to sediment the tubercle bacilli

Many different methods of homogenisation and decontamination of sputum specimens for culturing have been described but there is no universally recognised best technique. The choice of a suitable method is to a large extent determined by the technical capability and availability of staff in a laboratory, as well as the quality and type of equipment available, and cost. Each method has its limitations and advantages and it is recommended

that laboratories standardise on one method only. Methods which consistently yield the highest percentage of positive cultures are those which require:

- Well trained staff
- Relatively expensive equipment (e.g. centrifuges) and related supplies
- Continued maintenance of equipment and of good staff performance.

#### **6.4.3 DIGESTION AND DECONTAMINATION PROCEDURES**

Since the exposure time to digestants/decontaminants has to be strictly controlled it is best to work in sets equivalent to one centrifuge load (e.g. eight or twelve specimens at a time).

Always digest/decontaminate the whole specimen, i.e., do not attempt to select portions of the specimen as is done for direct microscopy. Since sputum specimens are the most common clinical specimens submitted for tuberculosis culture, homogenisation and decontamination procedures have been largely targeted towards their processing. Specimens other than sputum require even more care during processing because of the low numbers of tubercle bacilli present in positive specimens.

#### **PROCESSING OF SPUTUM SPECIMENS CONTAINING CPC and NaCl**

If delay of more than 48-72 hours between collection of sputum samples and processing of the same by culture is anticipated, the sputum sample should be collected in a container with 1% CPC and 2% NaCl. CPC, a quaternary ammonium compound, is used to decontaminate the specimen while NaCl effects liquefaction. The use of this method not only decreases the number of cultures lost by contamination as a result of prolonged transit time but also decreases significantly the laboratory time required for processing the specimens.

### **6.5 INOCULATION AND INCUBATION**

Two slopes per specimen are inoculated each with one 5 mm loopful of the centrifuged sediment, distributed over the surface. An additional slope containing sodium pyruvate is commonly used to identify *M. bovis* but is not required to be included as a routine in India since available evidence does not indicate prevalence of widespread disease due to *M.bovis*. Bottle caps should be tightened to minimize evaporation and drying of media. Care should be taken to avoid using red hot loop and loop should be cooled sufficiently before inoculation.

All cultures should be incubated at 35-37°C until growth is observed or discarded as negative after eight weeks. Slopes that are grossly contaminated are also discarded.

## 6.6 CULTURE EXAMINATION AND IDENTIFICATION

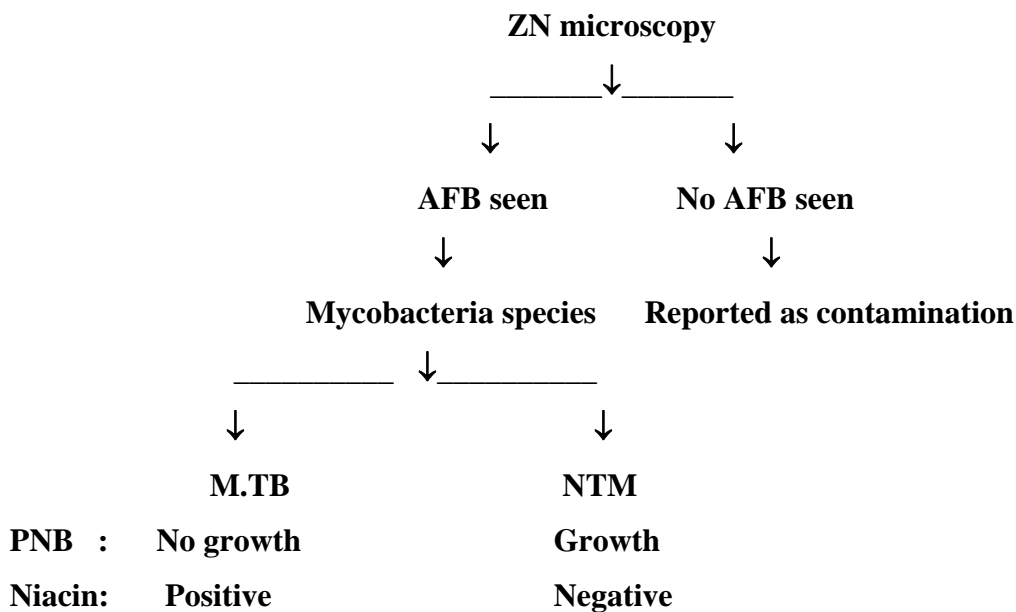
### 6.6.1 EXAMINATION SCHEDULE

All cultures should be examined 48-72 hours after inoculation to detect gross contaminants. Thereafter cultures are examined weekly, up to 8 weeks on a specified day of the week. It is useful to label containers with cultures with the dates of inoculation and to place containers in the incubator in chronological order. If contaminated cultures are found during examination, those where the surface has been completely contaminated or where medium has been liquefied or discoloured, they should be discarded.

### 6.6.2 READING OF CULTURES

Typical colonies of *M. tuberculosis* are rough, crumbly, waxy, non-pigmented (buff coloured) and slow-growers, i.e., only appearing two to three weeks after inoculation.

The colony with doubtful morphology, the acid-fastness should be confirmed by Ziehl-Neelsen (ZN) staining. A very small amount of growth is removed from the culture using a loop and gently rubbed into one drop of sterile saline on a slide. At this point the ease with which the organisms emulsify in the liquid should be noted: Tubercle bacilli do not form smooth suspensions, unlike some other mycobacteria. The smear is allowed to dry, fixed by heat and stained by the ZN method. If no AFB seen in the smear it is reported as contamination.



## 6.7 RECORDING AND REPORTING OF LABORATORY RESULTS

Tuberculosis laboratories must establish a uniform procedure for reporting culture results. If laboratory findings are to be useful, they must be communicated in ways that make sense to the different authorities.

Culture procedures for tuberculosis bacteriology are notoriously time-consuming, often taking 8-9 weeks to complete. For this reason, interim reports should be issued. The following schedule is recommended:

- If the cultures are contaminated, a report should be sent out immediately.
- At eight weeks a final report should be issued for culture negative specimens.
- If cultures are positive and growth has been identified as *M. tuberculosis*, a report should have drug susceptibility test results for patients of DOTS-Plus.
- If the colony count is less than 20 or faint growth in the first or second week, incubation is continued up to 4<sup>th</sup> week to obtain a colony count of at least more than 50 colonies or more than one loopful of growth (3mm).
- If the growth is still insufficient at the end of 4<sup>th</sup> week, a subculture should be done on a fresh LJ by touching all the colonies. The exact number of colony count in primary growth should be recorded before doing subculture and incubated at 37<sup>0</sup>C not exceeding three weeks. During this period when sufficient growth is obtained DST is done.

### Note :

- If increased negative results observed in specimens received, the following could be the reasons and should be rectified :
  - Increased concentration of malachite green used for LJ media preparation:
  - Increased temperature of incubation of cultures or
  - Increased time and temperature of inspissation.
- If increased negative results along with contamination is seen,
  - the decontamination or the liquefaction is not complete,
  - ambient temperature less than 25<sup>0</sup>C.

A detailed list of equipment and consumables has been prepared by CTD, and they will be provided by CTD to the concerned IRL involved in DOTS-Plus.

## 6.8 IDENTIFICATION TESTS

Although a presumptive diagnosis of tuberculosis may be made by an experienced laboratory technologist on the basis of the morphological characteristics of tubercle bacilli described before, it is best to do confirmatory tests. Unfortunately there is no completely reliable single test that will differentiate *M. tuberculosis* from other mycobacteria. Nevertheless, the following tests, when used in combination with the characteristics described below will enable the precise identification of >95% of *M.tuberculosis* strains:

- 1) susceptibility to *p*-nitrobenzoic acid (PNB); and
- 2) niacin test.

Of these, the PNB test can be included along with the drug susceptibility test.

*M. tuberculosis* does not grow on medium containing 500µg/ml of PNB. All other mycobacteria are mostly resistant to PNB and hence grow on medium containing 500µg/ml of PNB.

## 6.9 DRUG SUSCEPTIBILITY TESTS

Drug susceptibility testing is one of the most difficult procedures to perform and standardize in the Mycobacteriology laboratory. Proficiency in susceptibility tests demands an understanding of :

- The origin of drug resistance
- The variation in stability of drugs subjected to different conditions of filtration, heat or storage
- The alteration in the activity of certain drugs when incorporated into different kinds of media
- The type of susceptibility test performed
- The reading and reporting of test results
- The criteria of resistance

Drug susceptibility tests should be performed in the following instances:

- For re-treatment smear positive patients who are smear positive after four or more months of Category II treatment.
- To change the drug regimen to DOTS-Plus regimen when MDR-TB is confirmed.
- Undertaking drug resistance surveillance studies in a state.

There are three commonly applicable and internationally recommended methods used for determining drug susceptibility of mycobacteria: (1) the absolute concentration method; (2) the resistance ratio method; and (3)

the proportion method. When properly standardized and performed, all three methods have been shown to be equally satisfactory.

## 6.8.1 DST METHODS

### *6.8.1.1 Absolute Concentration Method:*

This method uses a standardized inoculum grown on drug-free media and media containing graded concentrations of the drug(s) to be tested. Several concentrations of each drug are tested, and resistance is expressed in terms of the lowest concentration of the drug that inhibits growth; i.e., minimal inhibitory concentration (MIC). This method is greatly affected by inoculum size and the viability of the organisms.

### *6.8.1.2 The Resistance Ratio Method*

It compares the resistance of unknown strains of tubercle bacilli with that of a standard laboratory strain. Parallel sets of media, containing twofold dilutions of the drug, are inoculated with a standard inoculum prepared from both the unknown and standard strains of tubercle bacilli. Resistance is expressed as the ratio of the MIC of the test strain divided by the MIC for the standard strain in the same set.

### *6.8.1.3 Proportion Method*

This is the method recommended for DOTS-Plus sites in India.

It enables precise estimation of the proportion of mutants resistant to a given drug. Several 10-fold dilutions of inoculum are planted on to both control and drug –containing media; at least one dilution should yield isolated countable (50 -100) colonies. When these numbers are corrected by multiplying by the dilution of inoculum used, the total number of viable colonies observed on the control medium, and the number of mutant colonies resistant to the drug concentrations tested may be determined. The proportion of bacilli resistant to a given drug is then determined by expressing the resistant portion as a percentage of the total population tested. **The proportion method is currently the method of choice.** The economic variant of proportion method is used for DOTS-plus.

## 6.8.2 CRITERIA OF RESISTANCE

Any strain with 1% (the critical proportion) of bacilli resistant to any of the four drugs – rifampicin, isoniazid, ethambutol, and streptomycin – is classified as resistant to that drug. For calculating the proportion of resistant bacilli, the highest count obtained on the drug free and on the drug-containing medium should be taken (*regardless of whether both counts are obtained on the 28<sup>th</sup> day, both on the 42<sup>nd</sup> day, or one on the 28<sup>th</sup> day and the other on the 42<sup>nd</sup> day.*)



## 6.10 QUALITY ASSURANCE PROGRAMME

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 reference laboratory should supervise the laboratory network.

The components of a quality assurance programme are:

- Quality control
- Quality improvement
- Proficiency testing

The detailed description of Quality Assurance Programme is available in DOTS-Plus TB Bacteriology Manual.

### *Proficiency testing*

Proficiency testing, which is called External Quality Assessment (EQA) by WHO standards refers to a system of retrospectively and objectively compared results from different laboratories by means of programs organized by external agency, such as a reference laboratory. The main objective is to establish between – laboratory comparability, in agreement with a reference standard. For this purpose, material for testing is prepared by a reference laboratory and distributed to lower level laboratories. The recipients perform the necessary procedures and report their results to the reference laboratory which then can be assessed. Detection of deficiency through this indirect system will then determine the need for quality improvement.

Proficiency testing is highly desirable but not easy to achieve. In order to be successful they must run in the form of continuous assessments, and they require skilled and dedicated staff.

Although quality improvement is the quickest and most effective form of (external) quality assurance, it is often difficult to perform on a regular basis owing to limitation of time and travel. Indirect technical and administrative control through proficiency testing programs (also called “external quality assessment” or “inter-laboratory test comparison”) should therefore become an essential component of quality assurance.

EQA of the NRLs will be conducted by WHO Supra-National Reference Laboratories.

Proficiency testing of DST by the Culture and DST laboratories is conducted at the time of accreditation by the respective designated NRL. The Culture and DST laboratories should send a list of all cultures to NRLs, who would randomly select ten cultures for proficiency testing. These cultures would be then sent to NRLs by

Culture and DST laboratories and the result of NRLs will be communicated to the laboratories with corrective actions, if required.

In addition, NRLs will send a set of 20 cultures to the laboratories at the time of accreditation and annually thereafter, and the results will be compared and suggestions for improvement would be provided, if required.

### **6.11 Accreditation of Laboratories for Culture and DST under RNTCP**

A standardized assessment of the organization and function of the existing laboratory network will serve as a basis for strengthening the laboratory component of the RNTCP. A Mycobacteriology Laboratory, which is accredited for the purposes of culture and DST, is a pre-requisite for implementing DOTS-Plus activities in the respective state.

A detailed checklist for accreditation is given in a separate document on ‘Accreditation 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 accreditation.

Briefly, the accreditation 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 Accreditation Pre-Assessment Tool” (RNTCP IRL APAT) for preliminary assessment of requirements for an IRL before the IRL is subjected to the full accreditation procedures. Based on the data provided, the CTD identifies laboratories that could fulfil the requirement for DOTS-Plus activities. This procedure may take a maximum of one month.
2. Training of Microbiologists and LTs on the DOTS-Plus TB Bacteriology Training module, including EQA procedures. The DOTS-Plus is an extension of the existing RNTCP TB Bacteriology Training modules, and includes testing and quality control for DST for second line drugs. The training will be at the identified supra national reference laboratory (TRC) or national reference laboratory (NTI and LRS). However, as DST for second line drugs is performed only at the NRLs, the training in TB Bacteriology will concentrate on DST of first line drugs (SHREZ) only. The duration will be for three weeks for new IRL staff and one week for IRL Lab staff already trained in DRS methodology.
3. Supply and installation of equipment in the IRL, will be done after a review of the requirement of the respective IRL, based on the “IRL Mycobacteriology Accreditation Pre-Assessment Tool” (RNTCP IRL APAT) by CTD. This will be followed by supply and installation of equipment(s) at the respective IRL by the concerned agency. The whole procedure should take about eight to twelve weeks after receipt of the pre-assessment report by the SNRL/NRL team. Use of equipment by IRL staff will result

in identification and fine tuning of errors. The expected duration for these activities may take a minimum of three weeks for new IRLs and two weeks for those IRLs where the laboratory staff has already been trained in DRS methodology.

4. Proficiency testing of the IRL's culture and DST procedures by the SNRL/NRL will follow once the respective IRL starts performing culture and DST examinations at the IRL. The SNRL/NRL will receive the results of 100 cultures and DST done by IRL in the past three months, randomly select 10 cultures from the IRL'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 IRL, 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  $\geq 90\%$  for H and R, and  $\geq 80\%$  for S and E, would entitle the IRL to submit their application to CTD for RNTCP accreditation.
5. An accreditation application of an IRL (using the "RNTCP Mycobacteriology Laboratory Application for Accreditation" form [RNTCP IRL AMLA], or application for renewal of accreditation, will be reviewed by the SNRL/NRLs. The process of review should be completed within two weeks of submission of the application, and the concerned IRL will be informed of the results of the review, and the expected date and duration of assessment of the respective IRL for accreditation.
6. An assessment report will be submitted by the RNTCP assessment team after a visit to the respective IRL, within two weeks of receipt of a valid application form by an IRL. The assessment will be performed, using the "Checklists RNTCP-AML-1, 2 & 3" contained in RNTCP IRL AG&F", by the SNRL/NRLs.
7. Issue of RNTCP accreditation by CTD, will be done immediately after receipt of a favourable assessment report from the RNTCP assessment team.
8. Accreditation will be reviewed annually by CTD, following the procedures laid out in 5, 6 and 7 above.

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## **CHAPTER 7: TREATMENT OF MULTI-DRUG RESISTANT TB**

### **7.1 Chapter Objectives**

An “MDR-TB suspect” confirmed by an RNTCP accredited C&DST laboratory to have MDR-TB, or any rifampicin resistance, will be treated with the RNTCP Category IV regimen containing second-line anti-TB drugs. The chapter provides guidance on the treatment of such patients under RNTCP and deals with:

- Initiation of treatment
- Deciding drug dosages and administration
- Deciding treatment duration
- Providing health education

### **7.2 Referral of a confirmed MDR-TB case to indoor facility at the DOTS-Plus site**

Once confirmed, the MDR-TB patients and those with any rifampicin resistance are referred to the RNTCP designated DOTS-Plus site, with their DST result and request for Category IV treatment form (*Annexure V*).

### **7.3 Deciding on treatment**

The DOTS-Plus site committee will review the patient’s details, including previous history, DST result and concurrent illnesses, and make a decision in relation to treatment under RNTCP with a Category IV regimen. If the Committee decides on treatment with an RNTCP Category IV regimen, the patient is initially admitted at the designated DOTS-Plus site, counselled in regards to their treatment, their treatment card is opened and treatment initiated. If the patient is able to tolerate the Cat IV drugs he/she can be discharged 1 week post-treatment initiation.

In case a patient refuses for hospitalization 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 and initiation of treatment.

### **7.4 Classes of anti-TB drugs**

The classes of anti-TB drugs have traditionally been divided into first- and second-line drugs with isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin being the primary first- line drugs. These drugs can also be grouped based on efficacy, experience of use, and drug class. The different groups are shown in Table 7.1.

**Table 7.1 Alternative method of grouping anti-TB agents**

<b>Grouping</b>	<b>Drugs</b>
<b>Group 1:</b> First-line oral anti-TB agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
<b>Group 2:</b> Injectable anti-TB agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vm).
<b>Group 3:</b> Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lvx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
<b>Group 4:</b> Oral second-line anti-TB agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizadone (Trd); <i>para</i> -aminosalicylic acid (PAS)
<b>Group 5:</b> 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)

#### 7.4.1 Category IV regimen

RNTCP will be using a **Standardised Treatment Regimen** (Cat IV) for the treatment of MDR-TB cases (and those with rifampicin resistance) under the programme. Cat IV regimen comprises of 6 drugs- kanamycin, ofloxacin (levofloxacin)<sup>†</sup>, ethionamide, pyrazinamide, ethambutol and cycloserine during 6-9 months of the Intensive Phase and 4 drugs- ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine during the 18 months of the Continuation Phase. *p*-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofx, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated.

<b>RNTCP CATEGORY IV REGIMEN: 6 (9) Km Ofx (Lvx) Eto Cs Z E / 18 Ofx (Lvx) Eto Cs E</b>
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#### 7.4.2 Drug dosages and administration

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 the 7<sup>th</sup> day (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 an RNTCP Category IV regimen.

Drug dosages for MDR-TB cases are decided according to the weight bands as shown in **Table 7.2**.

<sup>†</sup> Ofloxacin will be replaced by levofloxacin in the Category IV regimen during 2009-2010.

**Table 7.2 Dosage and weight band recommendations**

S.No	Drugs	16-25 Kgs	26-45 Kgs	>45 Kgs
1	Kanamycin	500 mg	500 mg	750 mg
2	Ofloxacin (Levofloxacin)	400 mg (200 mg)	600 mg (500 mg)	800 mg (750 mg)
3	Ethionamide	375 mg	500 mg	750 mg
4	Ethambutol	400 mg	800 mg	1000 mg
5	Pyrazinamide	500 mg	1250 mg	1500 mg
6	Cycloserine	250 mg	500 mg	750 mg
7	PAS (80% Bioavailability) ‡	5 gm	10 gm	12 gm
8	Pyridoxine	50 mg	100mg	100mg

If a patient gains 5 kgs or more in weight during treatment and crosses the weight-band range, the DOTS–Plus site 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 DOTS Plus site 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.

**Table 7.3 Drug formulation and packaging**

Drugs	16-25 Kg	26-45 Kg	>45 Kg
Kanamycin	1x 0.5 gm vial	1x 0.5 gm vial	1 x 0.75 gm vial
Ofloxacin (Levofloxacin)	1x 400 mg tab (1x 200 mg tab)	1x 200 mg + 1 x 400 mg tabs (1x 500mg tab)	2 x 400 mg tabs (1x500mg + 1x250 mg tab)
Ethionamide	1 x 250 mg + 1 x 125 mg tab	2 x 250 mg tabs	3 x 250 mg tabs
Ethambutol	1 x 400 mg tab	1 x 800 mg tab	1 x 800 mg + 1 x 200mg tabs
Pyrazinamide	1 x 500 mg tab	1 x 500 mg + 1 x 750 mg tabs	2 x 750 mg tabs
Cycloserine	1 x 250 mg caps	2 x 250 mg caps	3 x 250 mg caps
Na PAS	100 gm box	100 gm box	100 gm box
Pyridoxine	1 x 50 mg tab	1 x 100mg tab	1 x 100mg tab

‡ In case of PAS with 60% bioavailability the dose will be increased to 7 gm (16-25 Kg); 14 gm (26-45 Kg) and 16 gm (> 45 Kg)

In deciding about the dosages, apart from the considerations mentioned above, it is also necessary to rule out the existence of medical illnesses or organ dysfunctions in the individual by conducting routine haematological investigations like full blood count, random blood sugar, liver and kidney function tests, urine microscopy etc. Other additional investigations may be appropriately carried out as required in a particular case.

#### **7.4.4 Treatment Duration**

The treatment is given in two phases, the Intensive phase (IP) and the Continuation phase (CP). 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<sup>th</sup> month culture result is negative. If the 4<sup>th</sup> 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<sup>th</sup> and 6<sup>th</sup> months. If the result of the 4<sup>th</sup> 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.

#### **7.4.5 Treatment Initiation and follow up**

Preferably the patient should be admitted at the DOTS Plus site for pre-treatment evaluation and initiation of treatment. However patients who refuse admission should not be denied treatment and their pre-treatment evaluation should be arranged by the DTO locally. The patient and/or the results of the pre-treatment evaluation done at the district level are sent to the DOTS Plus site Committee. The committee after reviewing the results will decide on starting Cat IV treatment. The decision is communicated to the DTO who initiates the treatment with the first dose administered at the DTC. The DTO will simultaneously open the treatment card and send a copy of the same to the DOTS Plus site for registration. On registration the DOTS Plus site will convey the DOTS Plus TB number to the DTO.

Patients admitted at the DOTS Plus site, 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 3 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 12. Local arrangements will need to be made for daily injections during the intensive phase. *(See Fig 3 on page 46)*

As has been mentioned earlier the Cat IV patients are evaluated by the respective DTO at monthly intervals during the IP, after discharge from the state DOTS-Plus site, and at 3-monthly intervals during the CP until the



end of treatment. During the evaluation the DTO should screen patients for clinical improvement and possible adverse reactions. Body weight should be recorded during the evaluation and recorded on the treatment card. If the patient on Cat IV treatment gains/loses weight leading to a change in the weight band, the same should be intimated to the DOTS Plus site Committee for consideration for change in drug dosage. However the drug dosage is changed only on completion of the present 3 monthly drug box.

For follow-up culture examination, the patient may be sent to the DTC<sup>§</sup>. 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 accredited Culture and DST laboratory. Necessary arrangements for the supply of CPC bottles for follow up sputum culture examination should be ensured. After discharge, the patient goes to DOTS-Plus site 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 DOTS Plus site for change from IP to CP. The respective DTO can switch the patient to CP after obtaining the approval of the DOTS-Plus site Committee by e mail.

Patients on Category IV treatment whose 4<sup>th</sup> month culture result (available after 6 months of treatment) is positive, should be suspected of treatment failure. Such patients who are suspected of Category IV treatment failure will be considered as ‘XDR suspects’. It must be ensured that the 6<sup>th</sup> month follow-up culture of such patients is done in time and if found positive, the culture isolate should be sent by the C&DTS laboratory to the respective NRL for second line DST. In addition, any Category IV patient who has culture converted but is found subsequently to have 2 consecutive positive cultures, would also be suspected of treatment failure. In such cases, the culture isolate of the second positive culture would be sent by the C&DST laboratory to the respective NRL for second line DST. The “Request for Culture and DST Form” (*Annexure I*) will be used for requesting DST for second line drugs. The respective NRL will perform second line DST in case of an “XDR-TB suspect” for at least Kanamycin, Capreomycin and Ofloxacin, and will inform the respective C&DST laboratory of the result as soon as it is available. If a patient is found to have extensively drug resistant TB – “XDR-TB” (i.e. an MDR-TB isolate which is found to be resistant to ofloxacin and kanamycin or capreomycin), the DOTS-Plus site Committee will stop the Category IV treatment, and evaluate the patient for initiation of the RNTCP Category V treatment regimen. The respective DOTS-Plus site Committee can initiate the RNTCP Category V treatment after concurrence of the Central TB Division has been obtained.

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<sup>§</sup> As the schedule for the routine follow up visits for sputum culture examination and clinical evaluation are similar, these visits may be linked to facilitate fewer visits by the patient to the DTC. The patient during his visit to the DTC may bring his sputa samples in CPC bottles, to be transported to the C&DST laboratory.

#### **7.4.6 Treatment Interruption and default**

All efforts should be made to ensure that Cat IV patients do not interrupt treatment or default. Action should be taken to promptly retrieve patient who fail to come for DOT. This has been discussed in detail in Chapter 10.

The following situations may be seen in case of treatment interruption.

- **Cat IV 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.

- **Cat IV 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.

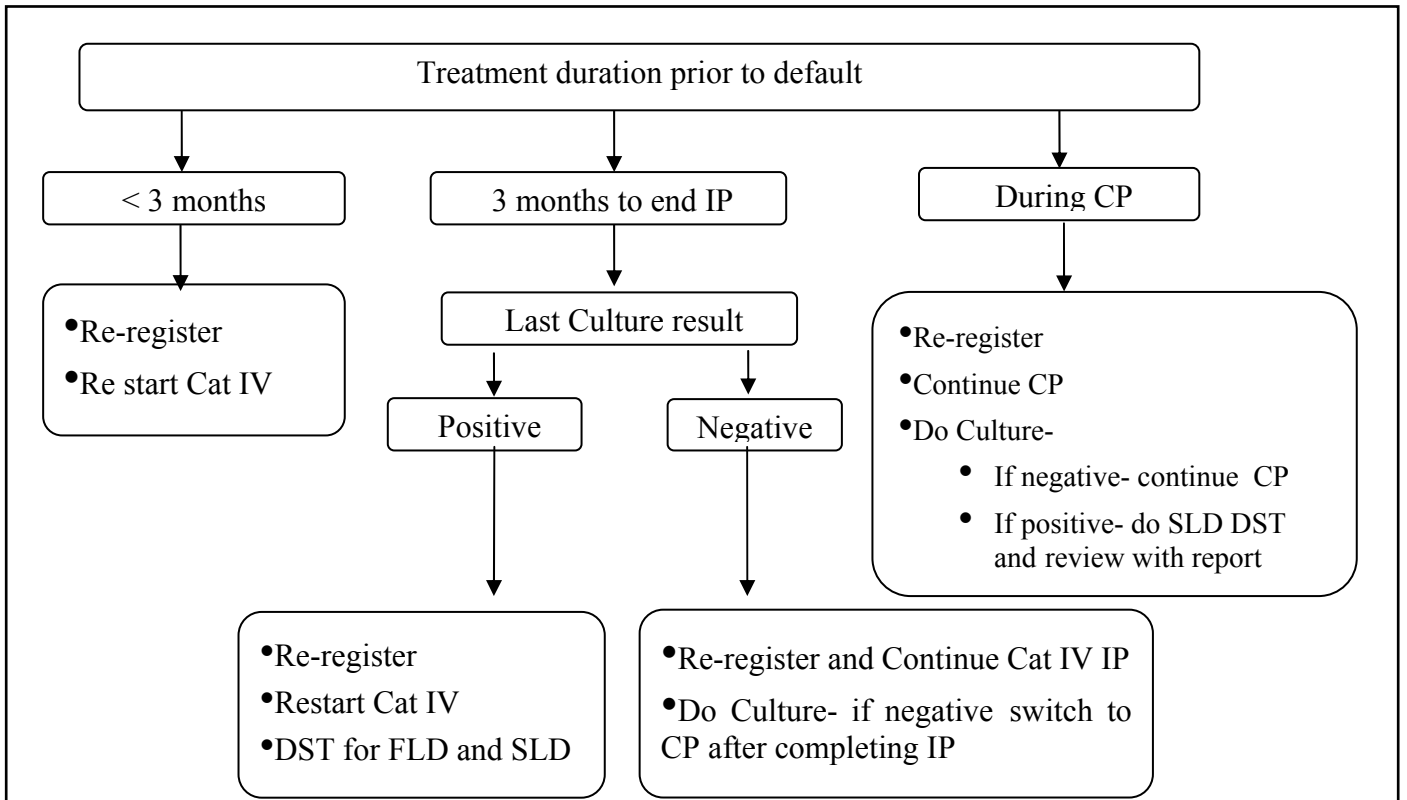
- **Cat IV patients who interrupt treatment for less than 2 months during CP:**

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.

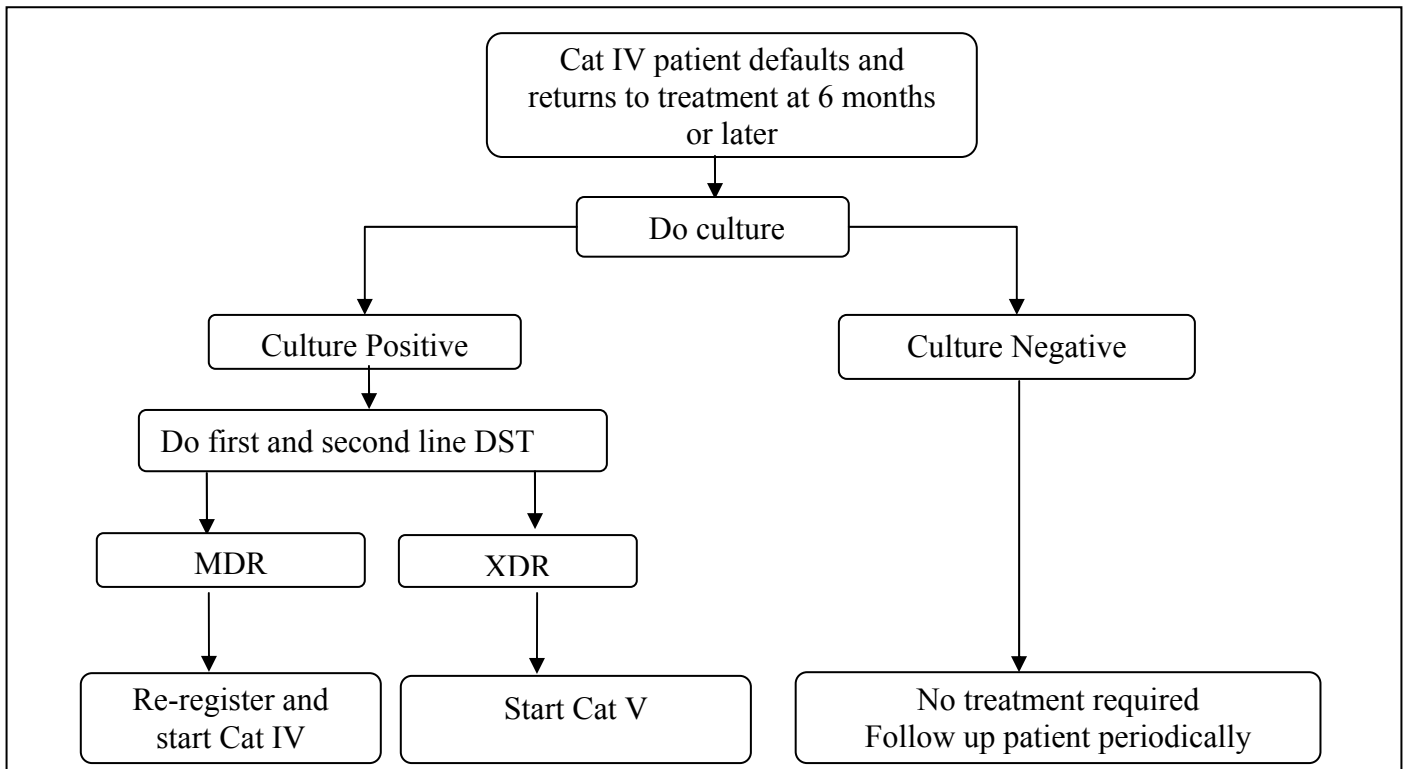
- **Cat IV patients who default (interrupt treatment for 2 or more months) and return back for treatment:**

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 Figures 3 and 4 on the next page. Re-registration of patients will be done by the DOTS Plus site.

**Figure 3: Management of Cat IV patients who default and return for treatment within 6 months of discontinuing Cat IV treatment**



**Figure 4: Management of Cat IV patients who default and return for treatment 6 months or later of discontinuing Cat IV treatment**



### 7.4.7 Treatment Outcomes

Standardised treatment outcome definitions are to be used following treatment of an MDR-TB case and are as follows:

- **Cure:** An MDR-TB 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:** An MDR-TB 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.
- **Death:** An MDR-TB patient who dies for any reason during the course of MDR-TB treatment
- **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.
- **Treatment default:** An MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reasons.
- **Transfer out:** An MDR-TB patient who has been transferred to another reporting unit (DOTS Plus site in this case) and for whom the treatment outcome is not known. Till the time the DOTS Plus services are available across the country, the Cat IV patients can be transferred out only to those districts, within or outside the state, where these services are available. If a Cat IV patient moves from one district to another, both of which are covered by the same DOTS Plus site, transfer out will not be required.
- **Treatment stopped due to adverse drug reactions:** A patient on MDR-TB treatment who develops severe adverse reactions and could not continue the MDR-TB treatment in spite of the management of the adverse reactions as per the defined protocols and decision has been taken by the DOTS-Plus site committee to stop treatment
- **Treatment stopped due to other reasons:** A patient on MDR-TB treatment who could not continue the MDR-TB treatment for any other medical reason (than adverse drug reactions), and a decision has been taken by the DOTS-Plus site committee to stop treatment.
- **Switched to Category V treatment:** A Category IV patient who during treatment is identified as an “XDR-TB suspect” and who is found to have XDR-TB on testing by an NRL, who subsequently has had their Category IV treatment stopped and RNTCP Category V treatment initiated.
- **Still on treatment:** An MDR-TB patient who, for any reason, is still receiving their RNTCP CAT IV treatment at the time of the submission of the RNTCP DOTS- Plus Treatment Outcome Report.

## **7.5 Providing Counseling to Patient and Family Members**

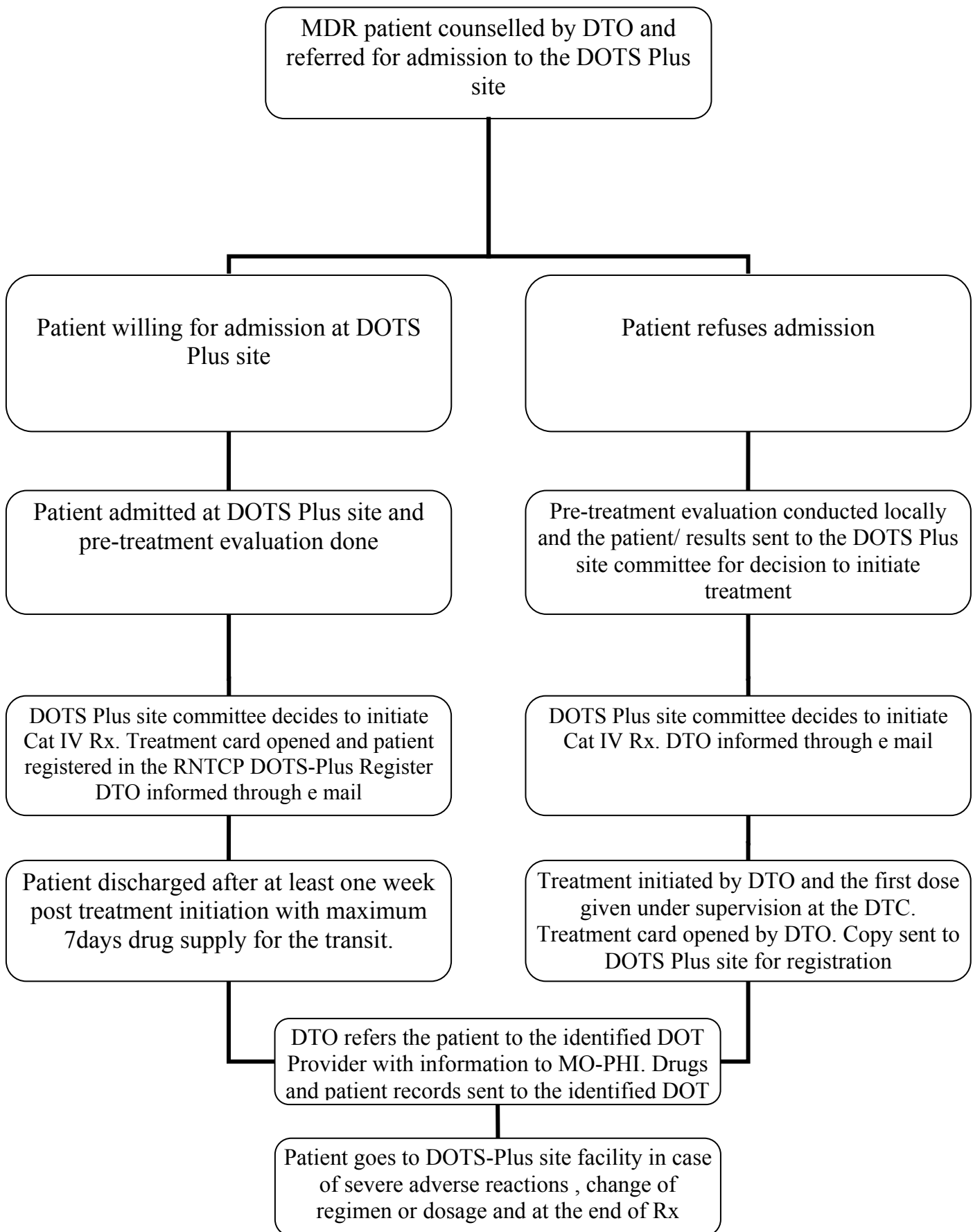
Providing counselling and health education to the MDR-TB patient and their family members about the disease and about the necessity of taking regular and adequate treatment is of utmost importance.

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 DOTS-Plus site 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.

In addition to the emphasis on regular treatment, health education also attempts to cross check the manner and the number of drugs/injections being taken, the occurrence of side-effects like yellowish skin and/or eyes, pain and swelling of joints, imbalance etc. if any, and the frequency of sputa examinations being performed.



**Figure 3. Patient flow: treatment**



## **Chapter 8: Monitoring and management of adverse drug reactions**

### **8.1 Chapter objective:**

This chapter provides information on the identification and management of adverse reactions when patients are treated with Category IV regimen. It addresses the following:

- Monitoring for early detection of adverse reactions
- Commonly encountered adverse reactions with second line drugs
- Strategies for managing adverse reactions.

### **8.2 Monitoring for early detection of adverse reactions**

Close monitoring of patients is necessary to ensure that the adverse effects of Category IV anti-TB drugs are recognized early by the DOT provider. DOT makes it possible to closely monitor patients. Patients will not be asked any leading question to elicit any adverse reaction.<sup>1</sup> However, if the patient makes any spontaneous complaint, s/he will be interrogated in detail and the necessary action taken. Commonly, patients will volunteer if they experience any adverse effects. The DOT provider should be trained to recognize adverse reactions like nausea, vomiting, diarrhoea, skin rash, ototoxicity, peripheral neuropathy, psychiatric symptoms and jaundice.<sup>2-5</sup> Training should also be provided on the management of minor reactions and when the patients should be referred to the medical officer.

In addition to clinical monitoring, certain laboratory investigations may be required to detect certain occult adverse effects.

### **8.3 Common adverse reactions to the drugs used**

#### **8.3.1 Aminoglycosides – Kanamycin**

- Ototoxicity<sup>6,7</sup>
- Nephrotoxicity
- Vertigo
- Electrolyte imbalance

#### **8.3.2 Quinolones - Ofloxacin<sup>8,9</sup>**

- Gastro Intestinal symptoms: diarrhoea, vomiting, and abdominal pain
- Central nervous system (CNS): dizziness and convulsions
- Phototoxicity and photosensitivity



- Tendinopathy and tendinitis
- Nephrotoxicity
- Skin rash
- Cardiotoxicity
- Arthralgia

### 8.3.3 *Ethambutol*

- Visual disturbance

### 8.3.4 *Pyrazinamide*

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

### 8.3.5 *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

### 8.3.6 *Cycloserine*<sup>10</sup>

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

### 8.3.7 *PAS*

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

## **8.4 Adverse effects, suspected drugs, and management strategies**

### **8.4.1 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 or H2 receptor inhibitor (omeprazole, famotidine, ranitidine). 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.

### **8.4.2 Giddiness**

Giddiness could be due to aminoglycosides, ethionamide, quinolone 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.

### **8.4.3 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.

### **8.4.4 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 DOTS-Plus site 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 DOTS-Plus site committee.

#### **8.4.5 Arthralgia**

The offending drugs are likely to be pyrazinamide and/or quinolones. 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 200mg three times a day), and uric acid checked if indicated. If there is still no improvement, or if the arthralgia worsens, the dosage of pyrazinamide and/or ofloxacin should be reduced or the drug withheld temporarily.

#### **8.4.6 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, quinolones, kanamycin and lastly pyrazinamide. After identification, the offending drug will be terminated.

#### **8.4.7 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 (bilirubin, serum AST, serum ALT, GGT, LDH and serum alkaline phosphatase). 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 DOTS-Plus site committee.

#### **8.4.8 Neurological symptoms**

##### **8.4.8.1 Peripheral neuropathy**

The common offending drugs are cycloserine and ethionamide. To prevent the occurrence of such adverse reaction, all patients on an RNTCP Category IV regimen 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.

##### **8.4.8.2 Seizures**

The offending drug could be either quinolones 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.

#### **8.4.9 Psychiatric disturbances <sup>11</sup>**

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

##### **8.4.10 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.

##### **8.4.11. 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 DOTS-Plus site facility.

## **8.5. Role of DOTS Plus committee in the management of adverse reactions**

Whenever a patient has serious adverse reactions to any of the Cat IV drugs, he/she is ideally admitted at the DOTS-Plus site 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 to Category IV drugs are essential components of the DOTS-Plus programme. 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.

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## CHAPTER 9: MDR-TB in special situations

### 9.1 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.<sup>1,2</sup>

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. Management of contacts of MDR-TB

### 9.2 MDR-TB in pregnancy<sup>3-7</sup>

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 counseled 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

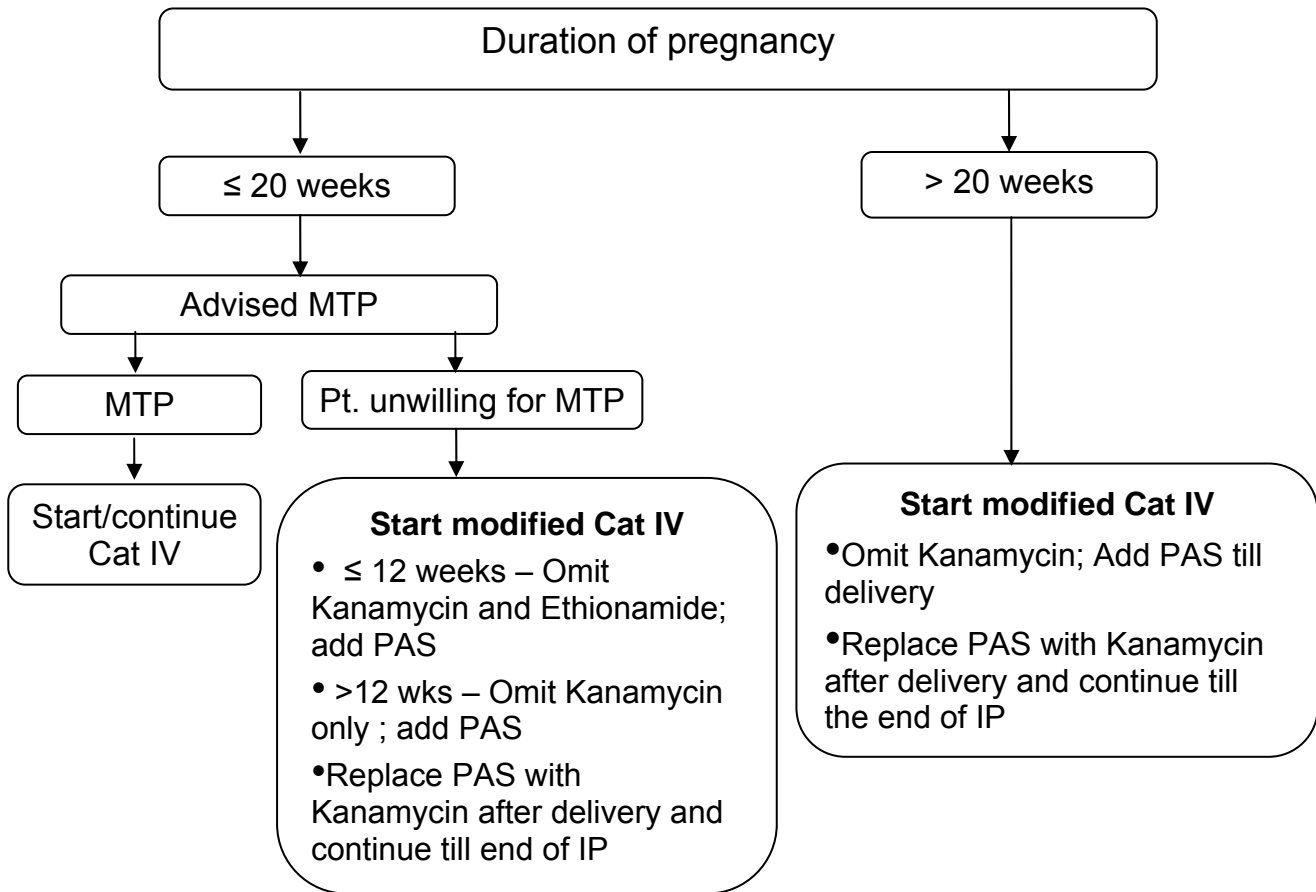
Further management of MDR-TB patients who are pregnant prior to initiation of Cat IV treatment or whilst on Cat IV treatment are based on the duration of pregnancy.

- 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 Cat IV treatment can be initiated (if the patient has not started Cat IV treatment) or continued (if the patient is already on Cat IV treatment) by the DOTS Plus site 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 Cat IV should be started as detailed below:
  - For patients in the first trimester ( $\leq 12$  weeks), kanamycin and ethionamide are omitted from the Cat IV 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 Cat IV 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:

## Pregnancy with MDR-TB



### 9.3 MDR-TB with HIV co-infection<sup>8-13</sup>

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 immunocompromised, the clinical presentation is proportionately more likely to be extrapulmonary 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.

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

### 9.3.1 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. The following table 9.1 is based on the WHO guidelines for initiating ART in relationship to treatment for MDR TB.

**Table 9.1**

<b>CD 4 Cell count</b>	<b>ART Recommendation</b>	<b>Timing of ART in relation to treatment for MDR TB</b>
$\leq 350 \text{ cells/mm}^3$	Recommend ART	After 2 weeks, as soon as the treatment for MDR TB is tolerated.
$> 350 \text{ cells/mm}^3$	Defer ART	Re-evaluate patient monthly for consideration of ART. CD4 testing is recommended every 3 months during treatment for MDR TB
Not available	Recommend ART	After 2 weeks, as soon as the treatment for MDR TB is tolerated.

For patients who are already on ART at the time of MDR-TB diagnosis be continued on ART when 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. 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.

## **9.4 Role of surgery in management of MDR-TB** <sup>14-17</sup>

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.

## **9.5 MDR-TB in patients with renal impairment** <sup>18</sup>

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 8.1).

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 9.2 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

## 9.6 MDR-TB in patients with pre-existing liver disease <sup>19</sup>

In the RNTCP Category IV regimen, 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.**

## 9.7 MDR-TB in patients with seizure disorders <sup>19, 20</sup>

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 quinolones. 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.

### **9.8 MDR-TB in patients with psychosis**<sup>21, 22</sup>

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 counseling, 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.

## **9.9 Management of contacts of MDR-TB** <sup>23-27</sup>

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 smear positive pulmonary TB disease, he/she will be identified as an "MDR-TB suspect". The patient will be initiated on Cat I/II based on their history of previous anti-TB treatment. Simultaneously two sputum samples will be transported for culture and DST to a RNTCP accredited C&DST laboratory. If the patient is confirmed to have MDR-TB, the patient will be admitted to the DOTS-Plus site ward for pre-treatment assessment and initiation of Category IV treatment.

## **9.10 Chemoprophylaxis of contacts of MDR-TB cases**

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.

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## **CHAPTER 10: TREATMENT DELIVERY AND ADHERENCE**

### **10.1 Chapter objectives**

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

### **10.2 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.

### **10.3 Treatment delivery settings**

In DOTS Plus projects in other countries, multiple strategies have been used for the delivery of MDR-TB treatment, including hospitalization, clinic-based, and community-based care.<sup>1,2</sup> 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 DOTS-Plus 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.<sup>1</sup> Whatever the setting, care should be delivered by a multidisciplinary team of providers including physicians, nurses, social workers, and community health workers or volunteers.

#### ***10.3.1 Initial in-patient care***

When an MDR-TB suspect is confirmed to have MDR-TB by the RNTCP accredited Culture and DST laboratory, the respective DTO who referred the patient for investigation, 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 State level DOTS Plus site in-door facility, with their DST result and the RNTCP "DOTS-Plus referral for treatment form" (*Annexure V*) and a copy of the drug-o-gram (*Annexure II*). Once the DOTS-Plus site committee decides upon RNTCP Category IV treatment for the patient, the patient is counselled, an RNTCP DOTS-Plus treatment card opened, a DOTS-Plus patient Identity Card issued to the patient, and Category IV treatment initiated.



The patient will be admitted in the designated State level DOTS-Plus site 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 Category IV regimen;
- Monitoring of patient tolerance of the Category IV regimen;
- Motivation, counseling 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 DOTS Plus site for at least seven days post treatment initiation, the patient can be discharged to the residence district with upto 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 DOTS-Plus referral for treatment form (*Annexure V*) which can be sent by email.

For patients who are unwilling for admission at the DOTS Plus site, the DTO will locally arrange for the pre-treatment evaluation. The results of the pre-treatment evaluation will be communicated to the DOTS Plus site committee for a decision to initiate the patient on Cat IV treatment. On receiving an affirmation from the DOTS Plus site 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 DOTS Plus site for their record and registration in the DOTS Plus register. On registration the DOTS Plus site will inform the DOTS Plus TB number to the DTO.

### ***10.3.2 Ambulatory care***

The DTO arranges for availability of the 3 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 DOTS Plus site, 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 accredited 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 accredited Culture and DST laboratory. Necessary arrangements for the supply of CPC bottles for follow up sputum culture examination should be ensured. The patient will need to return to the DOTS Plus site for the decision to end treatment, for managing severe adverse drug reactions, and for any change of regimen or dosage. All referrals from the DTC to the DOTS Plus site 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.

#### **10.4 Adherence**

Patients with MDR-TB may be more likely to have had problems with non-adherence in the past.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup>

MDR-TB treatment can be successful with high overall rates of adherence when adequate support measures are provided.<sup>1</sup> 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 DOTS-Plus site
- 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.

#### **10.5 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 Category IV treatment 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 Category IV treatment 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.

#### ***10.5.1 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.

### **10.6 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.

### **10.7 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 counseling 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.

### **10.8 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.

### **10.9 Early and effective management of adverse drug reactions**

Although rarely severe, the adverse effects of second-line TB drugs can be highly debilitating for patients. Patients experiencing higher rates of adverse drug reactions may be at increased risk of non-adherence. Therefore, early and effective management of adverse drug reactions should be part of adherence-promotion strategies in the management of MDR-TB. In most cases, management of the adverse effects can be accomplished using relatively simple and low cost interventions without compromising the integrity of the MDR-TB treatment regimen<sup>6</sup>.

### **10.10 Death Audit**

The DTOs should conduct an indepth 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.

#### **Box 10.1 Adherence promotion strategies for DOTS-Plus**

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

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## **CHAPTER 11: Human Resource Development for DOTS-Plus under RNTCP**

### **11.1 Chapter Objectives**

This chapter considers human resource development (HRD) for DOTS-Plus activities within the RNTCP, addressing a broad agenda which includes the overall management of training and issues related to staffing.

### **11.2 General considerations**

HRD for DOTS-Plus requires specific planning within the overall TB control plan. Besides organizing special training courses for DOTS-Plus, it is necessary to ensure the availability of enough staff of all categories of personnel involved in the DOTS-Plus activities at all levels, both clinical and managerial, to reach a specific long term goal for professional competence in DOTS-Plus implementation.

Ensuring competent and sufficient human resources for the implementation of the RNTCP DOTS-Plus activities of a high quality, requires ongoing management. As the programme implementation expands, the management of human resources will become more complex due to the continued and diversified demands on staff at all levels. HRD should be addressed as a key component of the DOTS-Plus strategy and HRD issues placed high on the agenda.

### **11.3 Challenges in HRD for DOTS-Plus**

Areas which need to be addressed in DOTS-Plus are broadly divided into

- (a) quality of the existing workforce and
- (b) quantity i.e. non-availability of enough trained manpower, which may be inappropriate staff placement or a shortage in staff position.

#### **11.3.1 Quality: Skills of existing staff**

DOTS-Plus being an new addition to the components of RNTCP, it is anticipated that many staff involved in existing TB control activities, will require training in DOTS-Plus activities. Inequalities in skills, or a mismatch between the type and level of training and the skills required for DOTS-Plus, are likely to arise. Specific measurable learning objectives have to be developed and incorporated in the training material, length of training is to be assessed, appropriate training methodologies are to be thought of and a system for evaluation of learning process is to be developed. This training should not be seen as 'a time limited activity and when the DOTS-Plus strategy has reached 100% coverage, training is no longer needed'. It is continuous

process, which involves adequate pre-service and continuous in-service training to maintain DOTS-Plus activities effectively.

### **11.3.2 Quantity: Positioning of staff**

Disparities in overall numbers is anticipated whenever a new component is introduced in the programme, which could lead to inequalities in distribution of staff in urban or rural areas, a high turnover of staff, or insufficient number of posts. A shortage of human resources for DOTS-Plus will lead to increased demands on the existing staff - not only by DOTS-Plus, but also because of other national and/or local programmes.

The issues related to staff placement and retention, work environment, remuneration etc., need to be addressed within the context of activities directed to the strengthening of the general health care services. RNTCP can assist by ensuring that appropriate training and supervision are provided to facilitate the availability of the skilled and motivated staff required for the provision of the required DOTS Plus services.

## **11.4 Framework for HRD**

HRD, properly focused, directed, and managed is an essential component of the DOTS-Plus activities for MDR-TB control. From a management point of view for HRD, countries will go through three different phases: (a) Initial implementation of the DOTS-Plus strategy; (b) expansion to entire country; and (c) sustainability and good quality assurance.

Districts where the DOTS-Plus activities have not been implemented yet, but where there are specific plans to introduce the same: From a human resource perspective, all staff that, based on their functions/job descriptions, are involved in TB control activities, need to be trained in the implementation of DOTS-Plus activities, and also to ensure there is enough staff in post.

Districts where the DOTS-Plus activities have been implemented and where the challenge is to sustain quality DOTS-Plus: From a human resource perspective, the issues are related to new staff due to staff turnover, performance problems in staff who have been trained, and/or not enough staff.

## **11.5 The long-term goal for HRD for DOTS-Plus**

To reach and sustain a situation where:

- Staff at different levels of the health system has the skills, knowledge, and attitudes (in other words are competent) necessary to successfully implement and sustain DOTS-Plus activities; and.

- There are sufficient numbers of all staff categories involved in DOTS-Plus (clinical and managerial) at all levels.

## **11.6 Challenges for RNTCP in reaching the goal**

Challenges are (a) ensuring that existing staff, managerial and clinical, is competent to implement all components of RNTCP including DOTS Plus activities and (b) ensuring that there is enough staff available at all times.

Key strategies to reach the goal are:

1. In-service training in DOTS-Plus districts for various categories of staff
2. In-service training for monitoring and supervision to:
  - Detect performance deficiencies
  - Identify new staff in need of training
  - Identify need for additional staff
  - Strengthen pre-service curricula
  - Co-ordinate with other in-service training programmes and HRD departments

## **11.7 System for HRD for DOTS-Plus**

1. Designate a focal point for all HRD activities related to DOTS-Plus at national and state levels (this should not be the National or state programme manager)
2. Develop short and medium term plans for human resource development for DOTS-Plus
3. Ensure regular review of the situation; and that a system for follow-up after training is in place;
4. Ensure that information for management of human resources for DOTS-Plus is made available and used (additional staff requirements, staff vacancies);
5. Plan for strengthening of basic training programmes;
6. Ensure that timely implementation of the plan and regular monitoring of the implementation is undertaken; and
7. Ensure that periodic evaluation of implementation of the plan is conducted and revision of the plan is undertaken as necessary.



To ensure sustainability after implementation:

a. Quality:

- i. Job descriptions should be available for all staff and should be based on task description.
- ii. Training courses/programmes should have skills based learning objectives, as per the task analysis and be linked to the job descriptions of the respective staff.
- iii. Training programmes/courses should use methodologies and time allocation that allows participants to meet the learning objectives
- iv. The ratio of participants to facilitators in each course, is to be at a level that allows participants to meet the learning objectives, and appropriate evaluation should ensure that the learning objectives have been met.
- v. Plans for implementation of training courses/programmes to be realistic to ensure quality.

b. Quantity – assessment of staffing needs and gaps:

- i. Assign tasks to specific categories of health workers and assess how many staff of the respective categories are needed to maintain the service delivery level.
- ii. Assess the time needed to implement those tasks, particularly at peripheral level, where changes in the number of cases diagnosed and treated have the biggest impact on the workload
- iii. Assess the number of staff of the relevant categories who are available at any point in time
- iv. Coordinate with other HR departments to fill gaps and develop a long-term strategy to increase the number of posts.

## CHAPTER 12: LOGISTICS OF SECOND-LINE ANTI-TB DRUGS

### 12.1 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.

### 12.2 RNTCP Category IV regimen: second-line anti-TB drugs

RNTCP Category IV is a standardized regimen for treatment of MDR-TB patients.

<b>RNTCP CATEGORY IV REGIMEN: 6 (9) Km Ofx (Lvx) Eto Cs Z E / 18 Ofx (Lvx) Eto Cs E</b>
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### 12.3 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.

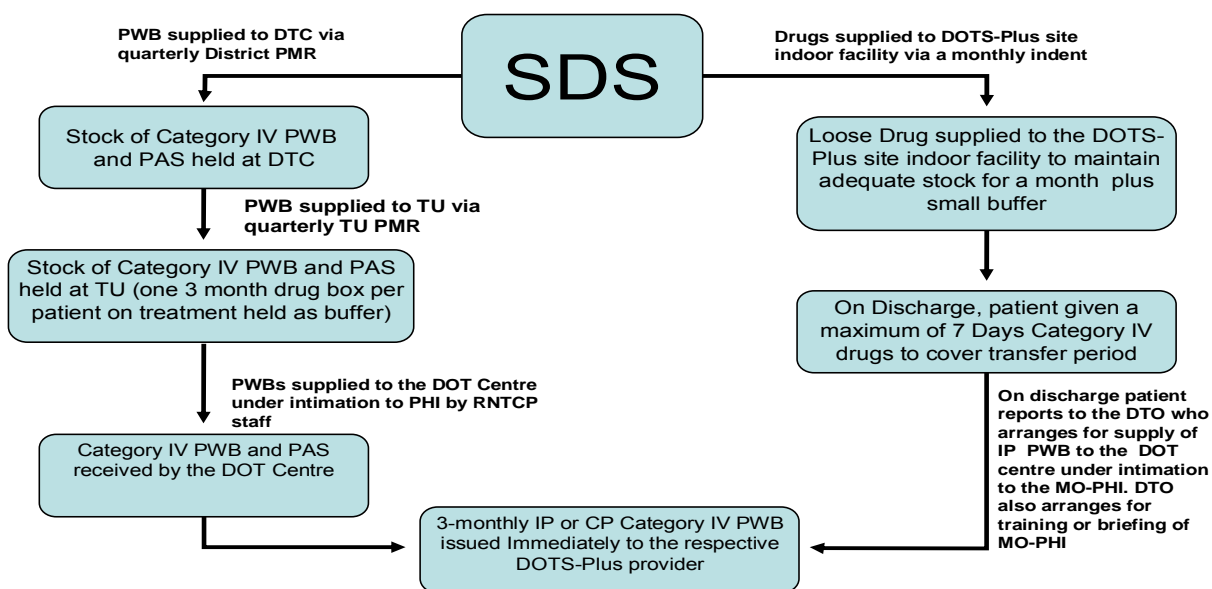
Accurate demand forecasting of second-line anti-TB drugs, i.e. correct quantification of the drug needs for a specific period of time, is one of the elements that guarantees an uninterrupted drug supply. There are two main approaches for demand forecasting:

- Usually, the most precise method for demand forecasting is the consumption-based approach, consisting of projection of future needs based on records of past consumption of individual drugs. This method assumes that the data are complete, accurate, and properly adjusted for stock-outs and anticipated changes in demand and use. This method is recommended once DOTS-Plus activities have been established for a period of time.
- The morbidity-based approach method is recommended for the initial phase of DOTS Plus activities. In this method, the standardized treatment regimen and the number of patients to be treated are taken into account. Several other key factors must also be considered, including the existing stock, lead time for delivery, safety stock needed and the shelf lives of the drugs. Unlike for first-line anti-TB drugs, expiry dates for second-line anti-TB drugs ranges from 24 to 36 months.

An inventory management system needs to be set up in order to assure a safety stock and optimal stock movement and to provide an accurate source of information for drug demand forecasting.

The drugs for the treatment of MDR TB patients will be supplied directly to the state drug stores (SDS) by the supplier. The movement of drugs will be as shown in the figure below:

## Flow of drugs



Oral drugs will be supplied in single drug blister strips as loose drugs State Drug Store (SDS) where they are re-packed into 3 monthly drug boxes for IP and CP. Na PAS is also procured and supplied to deal with patients who need individual drugs substitution due to adverse drug reactions.

SDS supplies loose drugs to the indoor facility at the DOTS Plus site against a monthly indent for the treatment of the admitted patients. The DOTS Plus site is required to maintain adequate stock for a month with a small buffer. On discharge, the patient will be issued drugs for a maximum of 7 days for the transit period and sent to their respective district for continued treatment under DOTS-Plus. Patient will report to the respective DTO who will arrange for the supply of the 3 monthly drug boxes from the respective TU to the DOT Centre under intimation to the PHI. The DTO will also be responsible for:

- identification of the DOT provider in consultation with the MO-PHI and the patient
- training or briefing of the respective MO-PHI.

The SDS will supply drugs to the DTC in the form of 3 monthly drug box (excluding PAS which will be supplied separately) for both IP and CP. These drug boxes will be prepared at the SDS from the loose drugs supplied and will be of six different types:

- **IP Drug box for patients 16-25 Kgs**
- **IP Drug box for patients 26-45 Kgs**
- **IP Drug box for patients > 45 Kgs**
- **CP Drug box for patients 16-25 Kgs**
- **CP Drug box for patients 26- 45Kgs**
- **CP Drug box for patients > 45Kgs**

The 3 monthly drug boxes will be supplied to the DTC on a quarterly basis as per the PMR report (*Annexure XVI on page 105*). Adequate stock of these drug boxes (IP and CP) will be maintained at the DTC and supplied to the respective TUs against the quarterly PMR. Adequate stock will also be maintained at the TU including one 3 month drug box per patient on treatment as buffer. The drug boxes will be supplied from the TU to the DOT centre under intimation to the respective MO-PHI. The drug box will be transferred from the TU to the respective DOT Centre

- on instruction of the DTO for a new patient who has been discharged from the DOTS Plus site after initiation of treatment
- on instruction of the DTO for a new patient initiated on treatment at the DTC
- on demand from the DOT centre prior to the completion of the previous 3 monthly drug box so as to prevent any interruption of treatment

If the IP of the patient is required to be extended, the respective DOTS-Plus site committee shall inform the DTO who will intimate the same to the MO-PHI and the respective TU. The TU will release a 3 month IP drug box 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 TU will release a 3 month CP drug box 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 TU 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. When the patient is initiated on the CP, any left over drugs from the IP of the extension period will be returned to the DTC from where they will be transported at the earliest to the State Drug Store for

reconstitution. Similarly drug boxes of patients who die or default should be sent to the DTC onto the SDS for reconstitution.

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.

**Table 12.2 Main elements to consider when planning procurement of second-line ant-TB drugs**

- *Drug forecast based on treatment regimen, cohort size and expected cases to be treated in 1 year.*
- *Drug labeling*
- *Shelf-life of the products*
- *Lead-time for delivery of full drug request*
- *Delivery period*
- *No of Tranches*
- *Estimated size of buffer stock .*

## **CHAPTER 13: RNTCP DOTS-PLUS RECORDING AND REPORTING SYSTEM**

### **13.1 Chapter objectives**

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

### **13.2 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 MDR-TB notification;
  - the treatment outcome of MDR-TB patients treated with RNTCP Category IV treatment.
2. To aid the staff in the treatment units in providing adequate management of the individual patient.

### **13.3 Scope of the information system**

The information system for RNCTP DOTS-Plus 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 implement and monitor RNTCP Category IV regimens satisfactorily. 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.

### **13.4 Records, reports and flow of information**

The following describes the forms, registers and reports that will be used for RNTCP DOTS-Plus 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 Chapter 7.

#### ***13.4.1 DOTS-Plus treatment card (Annexure VIII on page 93)***

This card is a key instrument for the DOT Provider administering the drugs daily to the patient. The card will be initiated at the DOTS Plus site when the patient is admitted for starting Cat IV 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 Category IV register. The original treatment card will be maintained at the DOTS-Plus site and three duplicates will be kept at the DTC, at the PHI/STS, and with the DOT provider. An accountable system has to be developed locally for updating cards at all levels.

When or if the patient moves from the DOTS Plus site 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:

Page 1 of the treatment card:

- **Basic demographic information.** Name, sex, age, address.
- **DOTS Plus TB number.** This is a new unique patient identification number given to the patient at the DOTS Plus site on initiation of Cat IV treatment. The DOTS Plus TB number should include the following – S.No./Name of the DOTS Plus site/year of initiation of treatment. E.g. DOTS Plus TB number of the first patient started on Cat IV treatment at Nagpur DOTS Plus site in 2009 will be 1/Nagpur/2009. Every year the DOTS Plus TB number will be started at 1.
- **Previous Tuberculosis Treatment.** This section lists and describes the details of the Cat II treatment taken by the patient previously. This includes the TB No.; type of case; date of registration and outcome and details of the respective district and TU.
- **DOTS Plus site Committee meetings.** There should be periodic meetings of the DOTS-Plus site committee, with the caregivers involved with the Category IV 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 etc.

Page 2 of the treatment card:

- **Monitoring of smear and culture.** Record the date, sample number and result of the monitoring smears and culture examinations. The smear and culture date is the date on which the sputum was collected from the patient for these tests.
- **DST.** Record the date 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 accredited laboratory.
- **CXR:** Details of the report of the Chest X rays performed should be entered in the relevant section.

Page 3 and 4 of the treatment card:

- **Regimen.** The RNTCP Category IV regimen, the initial weight, appropriate weight band along with the height is 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.
- **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 5.
- **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 4.

### ***13.4.2 RNTCP DOTS-Plus Register (Annexure IX on page 97)***

The DOTS Plus TB register will be used for registering and recording the details of all patients who receive RNTCP Category IV treatment. The Category IV 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 DOTS-Plus, facilitating quarterly reporting and analysis of case finding and treatment outcome

The RNTCP DOTS-Plus register will be held at the DOTS Plus site. A person should be identified for maintaining this register by the DOTS Plus site Committee. The register should be updated as soon as it is decided that a “new” MDR-TB patient is to be started on Category IV treatment. The DOTS-Plus register is filled in based on the information contained in the individual patient’s Category IV treatment card.

The person responsible for maintaining the RNTCP DOTS-Plus register at the DOTS-Plus site should enter a “new” patient into this register as soon as the patient is initiated on an RNTCP Category IV treatment regimen. This entry in the register will define the date of MDR-TB registration. The patients should be entered consecutively by their date of registration. There should be a clear separation (extra line) when a new quarter is started. Information from the treatment card, including smear and culture results, as well as final outcome can be completed once a month during the patient review at the monthly DOTS-Plus site committee meeting.



For patients who are unwilling for admission at the DOTS Plus site and are initiated on Cat IV treatment at the DTC, the DTO will send the requisite information to the DOTS Plus site coordinator along with a copy of the treatment card. The coordinator will register the patient and communicate the DOTS Plus TB number to the DTO electronically.

Usually only the first thirteen columns, except column number 8, of the DOTS-Plus 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 DOTS-Plus register:

- **DOTS Plus TB No.** This is a unique patient identification number for patients that are initiated on RNTCP Category IV. The DOTS Plus TB number should include the following – S.No./Name of the DOTS Plus site/year of initiation of treatment. E.g. DOTS Plus TB number of the first patient started on Cat IV treatment at Nagpur DOTS Plus site in 2009 will be 1/Nagpur/2009. Every year the DOTS Plus TB number will be started at 1.
- **Date registered.**
- **Name, sex, age, address, RNTCP district of residence and name of PHI providing DOT.**
- **Previous RNTCP TB number.** This is the TB number given to the patient during their RNTCP Category I/II/III treatment.
- **Date of DST and result.** Date and results of DST need to be recorded here. Patients may have had more than one DST. Enter the DST that resulted in the patient being registered as a Category IV patient.
- **Category IV regimen.** The date of treatment start and regimen used, are recorded here.
- **Smear and culture monitoring results.** Date and results of all smear and culture examinations should be recorded in this section. For smear results enter ‘Neg’ for Negative and grading if Positive (Sc, 1+, 2+, 3+). For culture enter ‘Neg’ for Negative and ‘Pos’ for Positive.
- **Final treatment outcomes.** See Chapter 7 for outcome definitions.
- **Comments.** This section is reserved for any additional information that may need to be given in the register.

#### ***13.4.3 Patient Identity Card (Annexure X on page 98)***

When a patient is diagnosed as having MDR-TB and is placed on a Category IV regimen, a new RNTCP Cat IV 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, TB identification number, essential information about the treatment (start date, regimen, and severe adverse

reactions to drugs), and the health centre where the patient will receive treatment. It also has a place to write the date of the next appointment for follow up at DTC and the DOT Plus site.

#### ***13.4.4 RNTCP Request for Culture and DST form (Annexure I on page 86)***

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 top of form is for smear result performed at the DMC, the middle portion is for reporting the culture results and the bottom portion for reporting the DST results by the culture and DST laboratory. The same form is sent back to the treating unit with the results. MO-PHI/DMC will initiate three copies of this form, two copies to be sent to DTO. DTO sends one copy to the laboratory. DOTS Plus site will initiate 2 copies for follow up and send 1 copy to the Culture & DST laboratory which will send the results electronically to the DOTS- Plus site and DTO.

#### ***13.4.5 Culture and DST Register (Annexure IV on page 89)***

The RNTCP accredited laboratory register for Culture and DST is used to record culture and DST examination results. This register should be compared regularly with the RNTCP DOTS Plus register to ensure that all MDR-TB cases to be started on RNTCP Category IV treatment are entered in the DOTS Plus register and in the quarterly reports on case finding.

#### ***13.4.6 Quarterly report of Category IV case finding (Annexure XI on page 100)***

The RNTCP quarterly report of Category IV case finding is filled in from the laboratory culture and DST Register and the DOTS Plus register held at the DOTS Plus site, and is designed to report

- The number of MDR suspects whose sputa were collected and received by the laboratory for culture and DST in the particular quarter. Suspects whose samples were collected but were not received by the RNTCP accredited Culture and DST laboratory due to various reasons (e.g. delay in transportation etc.) should not be included.
- Number of MDR cases diagnosed in the particular quarter (on the basis of the culture and DST results reported in the culture and DST register).
- Number of MDR cases registered and put on RNTCP Category IV treatment in the particular quarter.

The case finding report will be filled and submitted in the month following the end of the quarter (e.g. report of the 1 Q 2008 will be filled and submitted in April 2008) by the DOTS-Plus site co-ordinator.

#### ***13.4.7 Six Month Interim Report (Annexure XII on page 101)***

Each quarterly cohort defined by the date of the start of Category IV registration should have an interim or preliminary outcome report after 6 months of treatment. This report should be developed by the DOTS Plus site co-ordinator based on the Category IV treatment register. Since reporting at the end of treatment is very late (after two or even three years), preliminary results are desirable for all cohorts.

The interim results will be reported 9 months past the closing day of the notified cohort reported on. Reporting at 9 months past the closing date, allows culture information for the first 6 months of treatment to be included for all patients reported in the respective cohort. For example, TB patients registered during the 1 Q 2008 should have the Preliminary Six Month Interim Outcome Report filled out in January 2009 (1Q 2009). 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 the number of patients who are likely to go on to be cured.

#### ***13.4.8 Culture conversion Report of Category IV Cases (Annexure XIII on page 102)***

Each quarterly cohort defined by the date of the start of Category IV registration should have a culture conversion report submitted after 12 months of treatment. This report should be developed by the DOTS-Plus treatment site co-ordinator based on the Category IV treatment register. Since reporting at the end of treatment is very late (after two or even three years), preliminary results are desirable for all cohorts.

The conversion results will be reported 15 months past the closing day of the notified cohort reported on. Reporting at 15 months past the closing date, allows culture information for the first 12 months of treatment to be included for all patients reported in the cohort. For example, MDR-TB patients registered during 1 Q 2008 should have the Culture Conversion Report filled out in July 2009 (3Q 2009).

#### ***13.4.9 Treatment Outcome Report of Category IV Cases (Annexure XIV on page 103)***

This report shows the final result of treatment by quarterly cohort since the start of treatment of all Category IV cases notified in the respective cohort. Since treatment is of long duration, the results reflect retrospectively the management of treatment over a prolonged period. The report is submitted 31-33 months after patients in the respective cohort started treatment. For example, MDR-TB patients registered during the 1Q 2008 would have their treatment outcomes reported in October 2010 (4Q 2010).

### **13.5 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, development of an electronic format of the DOTS Plus register will be undertaken by RNTCP.

### **13.6 Training**

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

## RNTCP Request for Culture and Drug Sensitivity Testing

**Annex I**

(MO-PHI/DMC will initiate three copies, two copies to be sent to DTO. DTO sends one copy to Culture and DST laboratory. The laboratory will send electronic copies with Culture & DST results to the DTO and DOTS- Plus site)

Date \_\_\_\_\_ Name and address of referring health facility (PHI/DMC/DOTS-Plus site): \_\_\_\_\_

Name and address of DTC: \_\_\_\_\_

Patient Name: \_\_\_\_\_ Cat I/ Cat II / Cat III/ DOTS-PLUS TB No. : \_\_\_\_\_

Age: \_\_\_\_\_ Sex: M  F

Address (with landmarks) \_\_\_\_\_

Sputum: Date of Collection: Sample 1 \_\_\_\_\_ Sample 2 \_\_\_\_\_

Diagnosis

Follow up 

3	4	5	6	7	8	9	10	11	12	15	18	21	24	27
---	---	---	---	---	---	---	----	----	----	----	----	----	----	----

Any other  specify month/s  Second line DST  Specify month/s

Signature of MO of PHI/ DMC/DOTS-Plus site: \_\_\_\_\_

### Smear results:

Lab. Serial No.: DMC \_\_\_\_\_

Date of Examination	Specimen	Visual appearance (M, B, S)*	Results (Neg or Pos)	Positive (grading)			
				3+	2+	1+	Scanty **

\* M = Mucopurulent, B = Blood stained, S = Saliva    \*\* Write actual count of AFB seen in 100 oil immersion fields

Date: \_\_\_\_\_ Signature of MO-DMC/PHI \_\_\_\_\_ Signature of DTO \_\_\_\_\_

### Culture results:

Date Received	Specimen	Laboratory Specimen No.	Smear result	Culture Result (check one)					
				Neg	1 – 19 colonies	+	++	+++	Contaminated/ Other result
	A								
	B								

Date \_\_\_\_\_

Reported by (Name & Signature) \_\_\_\_\_

No growth reported	0
Less than 20 colonies	Report number of colonies
20 -100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

### DST Results: (Note: Enter 'S' if susceptible and 'R' if resistant)

Date DST Initiated	Laboratory Specimen No.	S	H	R	E	Z	Km	Ofx	Eto	Others		

Reported by (Name and Signature) \_\_\_\_\_ Date \_\_\_\_\_

**Electronic copies of completed form with results should be sent promptly from Culture & DST Laboratory to DOTS Plus Site and DTO)**

**Drug-o-gram**

**Annexure II**

*(MO-PHI to initiate 3 copies. One copy sent to the DTO with the MDR TB suspect. One copy sent to the DOTS Plus site\* when referring the confirmed MDR-TB case for treatment initiation and the third copy for record)*

**Name of the Patient:** \_\_\_\_\_

**History of All Prior Anti-Tubercular Drug Treatment** *(To be filled in chronological order)*

S. No	Dates	Source (Govt./ Pvt)	Regimen / Drugs & Doses	Duration	Regular/ Irregular	If irregular, reasons	Sputum report Pre & Post Rx	Outcome/Remarks **
1.								
2								
3								
4								

*\*If the DOTS Plus site elicits and records additional information in the drug-o- gram, a copy of the revised drug-o-gram should be sent to the DTO for information*

*\*\* If the patient was on DOTS mention treatment outcome (cured/treatment completed/default) and if on any other treatment mention improved/deteriorated. For the present treatment mention “patient on treatment” in the remarks column.*

**MDR-TB suspect & Referral for Culture-DST Register for diagnosis and Follow-up cultures**

**Annexure III**

S. No.	Name of patient	Age/Sex	Postal address	Name of TU, PHI and DOTS centre	Reason for referral				Date of referral to Laboratory	Culture result (Pos / Neg / other) With Date and Lab no.	Date of receipt of DST result	Results of DST for positive cultures † For diagnostic specimens					Date of referral to DOTS-Plus Site	Remarks#
					For diagnosis (¥)		For follow-up					S	H	R	E	Z		
					Type	Last TB No.	DOTS Plus TB No.	Month of follow up										

\* Also mention the month of follow up Culture examination with in brackets

† Write 'R' for resistant and 'S' for Sensitive

# In Remarks column please specify the date of initiation of DOTS Plus treatment and DOTS Plus TB no. OR the reason for not initiating DOTS Plus treatment amongst diagnosed MDR TB patients

¥ Specify 1=Cat-I failure/ 2=Cat-III failure/3=MDR-Contacts and 4=Cat-2 sputum positive at 4 months or later

**RNTCP Laboratory Culture and DST Register**

**Annexure IV**

Lab No.	Name of patient	Age & Sex	Address	Name of DMC & District	For diagnosis * (specify Cat II TB No)	For Follow up **		Dates of receipt		With CPC (Y/N)		Smear Result		Culture results		DST results for culture positive specimens (enter the number of colonies in drug containing and drug free medium)					Date of reporting culture & DST results	Date of sending Culture & DST report to		Signature of Laboratory Microbiologist			
						DOTS Plus TB No.	Month of FU	A	B	A	B	A	B	A	B	A	B	S	H	R		E	Z		DTO	DOTS-plus Site	

*\*For diagnosis mention Cat II TB No. only. \*\*For follow up specify DOTS Plus TB No. and month of Culture examination s*



**Revised National Tuberculosis Control Programme (Annexure V)**  
**DOTS-Plus Referral for Treatment Form**

*(Fill in duplicate. Send one copy to the respective facility receiving the patient, and keep the duplicate copy on file)*

Name and address of Referring unit (District TB Centre/DOTS Plus site) \_\_\_\_\_  
\_\_\_\_\_

Email address of referring unit \_\_\_\_\_

Name of DOTS Plus site / District TB Centre to which the patient is referred \_\_\_\_\_

Name of patient \_\_\_\_\_ Age \_\_\_\_\_ Sex M  F

Complete Address \_\_\_\_\_

**Details of treatment taken by the patient at the time of diagnosis of MDR**

Category _____	Disease Classification	Type of Patient
TB No. _____	<input type="checkbox"/> Pulmonary <input type="checkbox"/> Extra Pulmonary  (Site _____)	<input type="checkbox"/> New <input type="checkbox"/> TAD <input type="checkbox"/> Failure <input type="checkbox"/> Others  <input type="checkbox"/> Relapse

**Sputum culture and DST details**

Date of sputum collection: \_\_\_\_/\_\_\_\_/\_\_\_\_

Date of culture result: \_\_\_\_/\_\_\_\_/\_\_\_\_

Date of DST result: \_\_\_\_/\_\_\_\_/\_\_\_\_

DST result\*: R  H  S  Z  E

**Details of Category IV treatment**

DOTS-Plus TB number: \_\_\_\_\_

Name of DOTS-Plus site: \_\_\_\_\_

Date Category IV regimen started: \_\_\_\_\_

Number of doses taken: \_\_\_\_\_

Date of referral to DOTS-Plus Site / DTC : Day \_\_\_\_\_ Month \_\_\_\_\_ Year 20\_\_\_\_

Referred for:  Initiation of treatment       Routine follow up  
 Adverse drug reaction (give details) \_\_\_\_\_  
 Any other (give details) \_\_\_\_\_  
 Ambulatory treatment(if the patient is referred to DTC)

Name and designation of the referring Doctor \_\_\_\_\_

**Reminder for the health facility where the patient has been referred**

***Please send an email to the referring unit, informing the referring doctor of the date that the above named patient reported at the receiving health facility.***

**Schedule for sputum smear microscopy, culture and sensitivity follow up examinations**

		IP monthly follow up examinations				Extension of IP (1-3 months)			CP Quarterly follow up examination in months						
		1 <sup>st</sup> FU	2 <sup>nd</sup> FU	3 <sup>rd</sup> FU	4 <sup>th</sup> FU				1 qtr	II qtr	III qtr	IV qtr	V qtr	VI qtr	
ension	→	3	4	5	6	-	-	-	7	9	12	15	18	21	24
on 1 month	→	3	4	5	6	7	-	-	8	10	13	16	19	22	25
on 2 months	→	3	4	5	6	7	8	-	9	11	14	17	20	23	26
on 3 months	→	3	4	5	6	7	8	9	10	12	15	18	21	24	27

\* The number in each cell indicates the month of follow up examination

\*\* CP will have follow up sputum examination on 7 occasions irrespective of the duration of treatment.

The first quarter in the CP will have two examinations and the rest 5 will be in the subsequent quarters till the end of treatment

- Two specimens for AFB at the end of 3, 4, 5, 6, 7, 9, 12, 15, 18, 21, 24 months
- Two specimens for culture at the end of 3, 4, 5, 6, 7, 9, 12, 15, 18, 21, 24 months
- Monthly weight
- Chest radiograph during pre-treatment evaluation, end of IP, end of treatment and whenever clinically indicated
- Physician evaluation including adverse drug reaction monitoring every month for six months, then every three months for two years
- S. Creatinine monthly for first 3 months, then every 3 months during the injectable phase
- Thyroid Function Test during pre-treatment evaluation and when indicated

## Checklist for Initial Evaluation and Treatment Surveillance

Initial Evaluation		
	Done	Not done
Initial physician evaluation		
Smear for AFB		
Culture		
Drug Susceptibility testing (DST)		
Chest radiograph		
Laboratory analysis (includes liver function tests, Creatinine, blood urea , complete blood count, Thyroid Function Test, Urine-R & M)		
Pregnancy test		
Home visit		
Family planning		
Contact screening (as per RNTCP guidelines)		

## Routine Surveillance

*During treatment*

AFB smear and culture at the end of months 3, 4, 5, 6 and 7, and at months 9, 12, 15, 18, 21 and 24

Monthly weight for first 6 months and 3-monthly thereafter

Chest radiograph during pre-treatment evaluation, end of treatment and as and when clinically indicated

Physician evaluation every month for six months, then every three months

Creatinine monthly for 3 months, then every 3 months during injectable phase

# RNTCP DOTS-Plus Treatment Card

Annexure VIII

Patient's Name: \_\_\_\_\_ Domiciliary DOT-provider: \_\_\_\_\_

Sex: M  F  Age \_\_\_\_\_ Name of PHI: \_\_\_\_\_

DOTS-Plus TB Number: \_\_\_\_\_

Date of DOTS-Plus registration: \_\_\_/\_\_\_/\_\_\_

Address: \_\_\_\_\_

Contact Telephone No. \_\_\_\_\_

State / District: \_\_\_\_\_

DOTS Plus site: \_\_\_\_\_

TB No. of previous CAT II/Cat I RNTCP Rx: \_\_\_\_\_ Type: \_\_\_\_\_

Date of registration: \_\_\_/\_\_\_/\_\_\_ District: \_\_\_\_\_

Date of outcome: \_\_\_/\_\_\_/\_\_\_ TU: \_\_\_\_\_

**DOTS-Plus site Committee meetings – dates and decisions\***

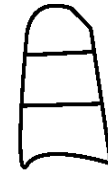
Date	Decision	Next Date

\* Enter details of decisions regarding change of IP to CP, completion of Rx, severe adverse reactions, change of treatment etc.

Month of treatment	Sputum Microscopy at DMC		
	Date *	Lab no.	Result
Diagnosis			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			

Month	Culture and Smear Results			
	Date *	Sample No.	Smear	Culture
Diagnosis				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12/13/14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				

Patient's name: \_\_\_\_\_



Date of X-ray



Date of X-ray



Date of X-ray

*\*All dates in both tables are the dates the sputum was collected from the patient*

**DRUG SUSCEPTIBILITY TESTING RESULTS:** Enter 'R' for Resistant 'S' for Susceptible

Date	S	H	R	E	Z	Second line drugs <sup>\$</sup> (if required)					

*\$ write the name of second line drugs*

**Patient's name:** \_\_\_\_\_

**Initial Weight (kgs):** \_\_\_\_\_ **Kgs**    16-25kg        26- 45kg        >45kg        **Height (cm):** \_\_\_\_\_

<b>Intensive Phase (tick as appropriate)</b>						
<b>Drug</b>	<b>Km</b>	<b>Eto</b>	<b>Cs</b>	<b>Ofx/Lvx</b>	<b>E</b>	<b>Z</b>
<b>Date intensive phase started:</b>						

<b>Continuation Phase (tick as appropriate)</b>				
<b>Drug</b>	<b>Eto</b>	<b>Cs</b>	<b>Ofx/Lvx</b>	<b>E</b>
<b>Date continuation phase started:</b>				

Date of regimen change and details of change: \_\_\_\_\_  
 \_\_\_\_\_

**ADMINISTRATION OF DRUGS (one line per month):**

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

Mark in the boxes: ✓ = directly observed; (✓) = Unsupervised; O = drugs not taken

Patient's name: \_\_\_\_\_

**Administration of drugs (continued)**

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

Mark in the boxes: ✓ = directly observed; (✓) = Unsupervised; O = drugs not taken

Date and Details of adverse drug reaction and action taken	Details of default retrieval action	Treatment outcome	Tick one	Date
		Cured		
		Treatment completed		
		Died		
		Failed		
		Defaulted		
		Transferred out		
		Treatment stopped due to adverse drug reaction		
		Treatment stopped due to other reason		
		Switched to Category V		

Note: Use extra sheets for recording detailed clinical notes, management of adverse drug reactions and default retrieval action

# RNTCP DOTS-Plus Treatment Register (Page 1)

DOT-plus TB no.	Date Registered	Name (in full)	Sex M / F	Age	Address	RNTCP District of residence	PHI providing DOT	Previous CAT II TB Register Number and Type	Site of disease (P/EP)	Date sample taken for DST	Result of Drug Resistance Test pre-treatment (A) (enter the DST result that resulted in the patient being registered as a Category IV patient  R=resistant S=susceptible C=contaminated					Category IV treatment	Month 3		Month 4		Month 5		Month 6			
											R	H	E	S	Other		Regimen (in drug initials and whether 16-25 Kg, 26-45 Kgor >45Kg) Date started		S	C	S	C	S	C	S	C
											dd/mm/yy		dd/mm/yy		dd/mm/yy		dd/mm/yy									
1															Date:	//	//	//								
2				/											Date :	//	//	//								
3				/											Date :	//	//	//								
4				/											Date:	//	//	//								
5				/											Date :	//	//	//								



# RNTCP DOTS-Plus Treatment Register (Page 2)

Mont h 7	Mont h 8	Mont h 9	Mont h 10	Mont h 11	Mont h 12	Mont h 13	Mont h 14	Mont h 15	Mont h 16	Mont h 17	Mont h 18	Mont h 19	Mont h 20	Mont h 21	Mont h 22	Mont h 23	Mont h 24	Mont h 25	Mont h 26	Mont h 27	Treatment outcome	Comments					
S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S			C	S	C	S	C
dd/m	m/yy	dd/m	m/yy	dd/m	m/yy	dd/m	m/yy	dd/m	m/yy	dd/m	m/yy	dd/m	m/yy	dd/m	m/yy	dd/m	m/yy	dd/m	m/yy	dd/m			m/yy	dd/m	m/yy	dd/m	m/yy
//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//						
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# RNTCP Cat IV TB Identity Card

Annexure X

## RNTCP CAT IV TB IDENTITY CARD

Name: \_\_\_\_\_  
 Address (in full) \_\_\_\_\_  
 Sex M F Age: \_\_\_\_\_

**Treatment regimen**

RNTCP TB Number: \_\_\_\_\_  
 Category IV registration number: \_\_\_\_\_

**Date Treatment Started**  
 .....  
 Day Month Year

DOTS Plus Site : \_\_\_\_\_  
 District TB Unit: \_\_\_\_\_  
 Local DOTS Centre: \_\_\_\_\_  
 Name of DOT Provider : \_\_\_\_\_

**Date of culture conversion**  
 .....  
 Day Month Year

<b>Intensive Phase</b>	<b>Continuation Phase</b>
_____	_____
_____	_____
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### Appointment Dates (DTC and DOTS Plus site)

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### REMEMBER

1. Take care of your card
2. You can be cured if you follow your treatment regimen by taking your prescribed drugs regularly.
3. Tuberculosis can spread to other people if you do not take your medication.
4. Report any side effects to your DOT Provider at once
5. Remember to report to the health facility on appointment date given to you

# RNTCP Quarterly report on Category IV case finding

Annexure XI

Name of DOTS-Plus site and state: \_\_\_\_\_

Patients registered in the Category IV register during \_\_\_\_ quarter of year \_\_\_\_\_

Name of DOTS-Plus site coordinator: \_\_\_\_\_

Date of completing this form: \_\_\_\_\_

Signature:

**“Suspect MDR-TB” patients tested at RNTCP accredited Culture and DST laboratory and confirmed MDR-TB cases registered and started on Category IV treatment during the quarter**

	Number
<b>“Suspect MDR-TB” patients whose sputum were collected and received at the RNTCP accredited Culture and DST laboratory for testing</b>	
<b>MDR-TB cases diagnosed</b>	
<b>MDR-TB cases registered and started on Category IV treatment</b>	

# RNTCP DOTS-Plus Six Month Interim Report

Annexure XII

Name of DOTS-Plus site: \_\_\_\_\_

Patients registered in the Category IV register during Quarter \_\_\_\_\_ of Year \_\_\_\_\_

Date of completion of the report: \_\_\_\_\_

DOTS-Plus site coordinator: \_\_\_\_\_

Signature:

Number of MDR-TB cases registered on CAT IV regimen	Smear and culture results after 6 months of treatment (of patients still on treatment)									Outcomes of other patients in the cohort			
	Smear Negative			Smear Positive			Smear Unknown			Died	Default	Transfer red Out	Treatment stopped due to adverse reactions
	Cul Neg	Cul Pos	Cul NK	Cul Neg	Cul Pos	Cul NK	Cul Neg	Cul Pos	Cul NK				

# RNTCP DOTS-Plus 12 month Culture Conversion Report Annexure XIII

Name of DOTS-Plus treatment site and state: \_\_\_\_\_

Patients registered in the Category IV register during Quarter \_\_\_\_\_ of Year \_\_\_\_\_

Date of completion of the report: \_\_\_\_\_

DOTS-Plus site coordinator: \_\_\_\_\_

Signature: \_\_\_\_\_

<b>Number of MDR-TB cases registered on CAT IV regimen in the quarter</b>	<b>Culture results after 12 months of treatment</b>								
	<b>Culture Negative</b>	<b>Culture positive</b>	<b>Culture Unknown</b>	<b>Died</b>	<b>Default</b>	<b>Transferred Out</b>	<b>Treatment stopped due to adverse reactions</b>	<b>Treatment stopped due to other reasons</b>	<b>Switched to Category V</b>



### Evaluation at Completion of Category IV Treatment

(To be maintained at state level DOTS-Plus site)

Patient name .....

Patient ID.....

Follow-up bacteriological results

Bacteriological examination	Result		
Smear results of last three quarters			
Smear results of last three months (if positive in any of the last three quarters)			
Culture results of last three quarters			
Culture results of last three months (if positive in any of the last three quarters)			

Was patient evaluated by clinician after completion of treatment?	Yes	No
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If Yes:

Date \_\_\_\_\_ complaint \_\_\_\_\_ action \_\_\_\_\_  
 Date \_\_\_\_\_ complaint \_\_\_\_\_ action \_\_\_\_\_  
 Date \_\_\_\_\_ complaint \_\_\_\_\_ action \_\_\_\_\_

Name and Signature of DOTS-Plus Physician

RNTCP Quarterly report on Cat IV drug logistics

Annexure XVI

SNo	Item	UOM	Stock on the first day of the Qtr	Stock received during the Qtr	Consumption during the Qtr	Stock on last day of the Qtr	Quantity Requested for DTC/TU (e x 2) – f
						(c+d) – e	
	(a)	(b)	(c)	(d)	(e)	(f)	(g)
1	IP (16-25 Kgs Body Weight Patient)	PWB					
2	IP (26- 45Kg Body weight Patient)	PWB					
3	IP (>45Kg Body weight Patient)	PWB					
4	CP (16-25 Kgs Body Weight Patient)	PWB					
3	CP (26- 45Kg Body weight Patient)	PWB					
4	CP (>45Kg Body weight Patient)	PWB					
5	PAS	Carton of 3 Boxes					



**National DOTS-Plus Committee**

1. Formulate policies and develop guidelines for all categories of staff, including monitoring and evaluation mechanisms.
2. Routinely review implementation status of DOTS-Plus activities, and provide recommendations to CTD for improvement and/or change.

**National Reference Laboratories**

1. Ensure availability of staff at NRL trained in DST for first and second line drug sensitivity testing.
2. Assist in finalization of training modules for NRLs, IRLs, STLSs, and LTs at DTC and DMC.
3. Assist in accreditation of IRLs for performing culture and DST.
4. Undertake periodically on site evaluation for EQA in smear microscopy and culture/DST
5. Perform proficiency testing in TB bacteriology of IRLs
6. Obtain accreditation from the designated SNRL for first and second line drugs and participate in periodic proficiency testing by the SNRL
7. Perform DST for first and second line drugs

**Intermediate Reference Laboratories**

1. Develop infrastructure as per RNTCP guidelines, including availability of adequately trained staff, equipments, consumables, and civil structure.
2. Get accreditation for culture and DST from the designated NRL.
3. Train the DTOs, MOTCs, STS in identifications of MDR suspects, definitions of patients for DOTS Plus, follow up schedules. Train STLS, LTs of DTC and DMCs in transportation of specimens for DOTS-Plus.
4. Perform DST for first line drug, and communicate the result to the DTO and the DOTS-Plus site committee.
5. Develop a plan of action for receiving the follow up specimens for culture and DST for all patients started on DOTS-Plus.
6. Send specimens from patients who remain culture positive after an extended intensive phase (i.e. 9 months) of DOTS-Plus treatment to the respective NRL for second line drug DST.
7. IRL microbiologist to be member of the state level DOTS-Plus and the DOTS-Plus site committees.
8. Logistics and distribution of material to DTOs for collection of sputa sample

**State DOTS Plus Committee**

1. Develop plan of action for implementation, expansion, and maintenance of DOTS-Plus in the respective state.
2. Periodically review the implementation status of DOTS-Plus in the respective state to ensure that RNTCP DOTS-Plus policies and guidelines are being followed.
3. In co-ordination with the respective STO, ensure that drug ordering and distribution is managed in a timely and appropriate manner.

**DOTS-Plus site committee**

1. Periodically review the implementation status of DOTS-Plus in the respective DOTS-Plus site to ensure that RNTCP DOTS-Plus policies and guidelines are being followed.
2. Receive the DST results from the IRL and enter the details in the DOTS Plus register of the DOTS Plus site.
3. Arrange for examination of MDR-TB patients referred for DOTS-Plus for their treatment eligibility, open treatment book and start DOTS-Plus regimen for all eligible patients.
4. Admit all DOTS-Plus patients in the indoor facilities of the DOTS-Plus site for an initial period of upto seven days.
5. Ensure respective DTOs are informed of patients discharge in a timely manner
6. Submit regularly reports to the State TB Cell and State DOTS-Plus committee.
7. In co-ordination with the respective STO and DTOs, ensure that drug ordering and distribution is managed in a timely and appropriate manner.

**Job responsibilities for various categories of staff under DOTS-Plus**

**Director STDC**

1. Develop a plan of action for implementation, expansion, and maintenance of DOTS-Plus in state in consultation with the State DOTS-Plus Committee, State TB Officer, and staff of STC, STDC, RNTCP ACCREDITED CULTURE AND DST LABORATORY and DTOs.
2. Review periodically the status of DOTS-Plus in the state in consultation with hospital DOTS Plus committee.
3. Plan and obtain sufficient human resource for implementation, expansion and maintenance of DOTS-Plus throughout the state
4. Periodically review the laboratory activities along with the Microbiologist and STDC/IRL staff, and forward the RNTCP accredited culture and DST Laboratory reports to the DOTS-Plus site Committee, STO, NRLs and CTD as per DOTS Plus guidelines.

**DTOs**

1. Confirm that the referrals from the respective MO-PHI are actual “MDR-TB suspects”
2. Receive the documents of confirmed MDR-TB suspects, and arrange for collection and transportation of specimen along with the documents to RNTCP accredited culture and DST Laboratory for DST of first line drugs.
3. Receive the DST results from RNTCP accredited culture and DST Laboratory for all the patients investigated by DST and take necessary actions for treatment of these patients as per guidelines.
4. To trace those patients identified as MDR-TB, based on RNTCP accredited culture and DST Laboratory results, and counsel the patients prior to referral to the DOTS-Plus site committee for assessment and inclusion in DOTS-Plus.
5. Assess the HR requirement in the district needed for the implementation, expansion, and maintenance of DOTS-Plus, and arrange to resolve any deficiency identified in manpower, training, etc.
6. Monitor the identification of proper DOT provider (health care worker or community worker/volunteer) for each patient and arrange for the training and supervision.
7. In co-ordination with the respective STO and DOTS-Plus site committee, ensure that drug ordering and distribution is managed in a timely and appropriate manner.

**MO-PHIs**

1. For all Category II patients who are smear positive after fourth months of treatment, complete the RNTCP DOTS-Plus Culture & DST request form and send the patient to the DTC, along with xerox copies of the patient’s Category II treatment card.
2. Receive the DST results from DTC for all the patients belonging to TU and referred for the DST, and take necessary actions for their referral of treatment as per guidelines.
3. Those patients identified as MDR-TB based on RNTCP accredited culture and DST Laboratory results belonging to the PHI area, should be traced and sent to

the DTO for referral to the DOTS-Plus site for assessment of inclusion in DOTS-Plus.

4. Assess the HR requirement in the TU required for DOTS-Plus for implementation, expansion, and maintenance of DOTS-Plus and arrange to ratified the deficiency in manpower, training, periodic evaluation etc.
5. Patients discharged from the in-door facilities at the DOTS-Plus site should be provided DOT for the DOTS-Plus regimen by an appropriate DOT provider (health care worker or community worker/volunteer), who should be sent for training at DTC.
6. Ensure availability of injection services for DOTS-Plus patients.
7. Supervise and monitor provision of the DOTS Plus treatment by the DPs belonging to the PHI area.
8. Ensure patient(s) are provided with adequate and prompt treatment for any side effects of the DOTS-Plus regimen.
9. Ensure that the patient is sent to the DTC for arrangement of the follow up examinations as per guidelines.
10. Complete the DOTS-Plus treatment card as per guidelines.
11. In co-ordination with the respective MO-TC, ensure that drug ordering and distribution is managed in a timely and appropriate manner.

#### **LTs of DMC**

1. Send the completed laboratory form to the MO of the DMC for all Category II patients found to be smear positive after fourth months of treatment.
2. Collect sputum and perform follow-up smear examinations as per RNTCP DOTS Plus schedule.

#### **STS**

1. Undergo training in RNTCP DOTS Plus.
2. Ensure that all DOTS Plus patients are given their treatment under daily supervision by a HCW or community DOT Plus provider who have received training in RNTCP DOTS Plus.
3. Supervise the DOT provider and provide feedback to the MOTC and DTO.
4. In co-ordination with the respective MO-TC and MO-PHI, ensure that drug ordering and distribution is managed in a timely and appropriate manner.

#### **STLS**

1. Undergo training in DOTS Plus laboratory methods, including transportation and specimens for DST at RNTCP accredited laboratory, follow up examinations and definitions of diagnosis and follow up for DOTS Plus
2. Take part in the training of LTs in DOTS-Plus lab methods.
3. Ensure the DOTS Plus patients are either referred to the DTC for follow up examinations as per the RNTCP DOTS Plus schedule.

## Second-line anti-TB drug information sheets

CYCLOSERINE (Cs)	
<b>Drug Class:</b>	Analog of D-alanine
<b>Activity Against TB, Mechanism of action, and metabolism:</b>	<b>Bacteriostatic</b> , competitively blocks the enzyme that incorporates alanine into an alanyl-alanine dipeptide, an essential component of the mycobacterial cell wall. No cross resistance with other TB drugs. 60-70% excreted unchanged in the urine via glomerular filtration; small amount excreted in faeces; small amount metabolized.
<b>Preparation and Dose:</b>	250mg tablets. 10-15mg/kg daily (max 1000mg), usually 500-750 mg per day given in one or two divided doses.
<b>Storage:</b>	Room temperature in airtight containers.
<b>Oral Absorption:</b>	Modestly decreased by food (best to take on an empty stomach); 70-90% absorbed.
<b>Distribution, CSF Penetration:</b>	Widely distributed into body tissue and fluids such as lung, bile, ascitic fluid, pleural fluid, synovial fluid, lymph, sputum. Very good CSF penetration ( 80-100% of serum concentration attained in the CSF, higher level with inflamed meninges)
<b>Special circumstances:</b>	<b>Pregnancy/breastfeeding:</b> Safety class - C. Breastfeeding with complement B6 to the infant. <b>Renal disease:</b> Doses of cycloserine should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 250 mg/day, or 500 mg/dose 3x/week. The appropriateness of 250 mg/day doses has not been established. There should be careful monitoring for evidence of neurotoxicity; if possible, measure serum concentrations and adjust regimen accordingly.
<b>Adverse Reactions:</b>	<b>Frequent:</b> Neurological and psychiatric disturbances, including headaches, irritability, sleep disturbances, aggression, and tremors, gum inflammation, pale skin, depression, confusion, dizziness, restlessness, anxiety, nightmares, severe headache, drowsiness. <b>Occasional:</b> Visual changes; skin rash; numbness, tingling or burning in hands and feet; jaundice; eye pain. <b>Rare:</b> Seizures, suicidal thoughts
<b>Drug interactions:</b>	Ethionamide - additive nervous system side effects; Isoniazid - additive nervous system side effect; Phenytoin - may increase phenytoin levels. Toxic effect if combined with alcohol, increases risk of seizures. Vitamin B6 decreases CNS effect
<b>Contraindications:</b>	Hypersensitivity to cycloserine Epilepsy Depression, severe anxiety, or psychosis Severe renal insufficiency Excessive concurrent use of alcohol
<b>Alerting symptoms:</b>	<ul style="list-style-type: none"> <li>▪ Seizures</li> <li>▪ Shakiness or trouble talking</li> <li>▪ Depression or thoughts of hurting yourself</li> <li>▪ Anxiety, confusion, or loss of memory</li> <li>▪ Personality changes, such as aggressive behavior</li> <li>▪ Rash or hives</li> <li>▪ Headache</li> </ul>

<b>KANAMYCIN (Km)</b>	
<b>Drug Class:</b>	Aminoglycoside
<b>Activity Against TB, Mechanism of action, and metabolism:</b>	<b>Bactericidal;</b> Aminoglycosides inhibit protein synthesis by irreversibly binding to 30S ribosomal subunit; Aminoglycosides are not metabolized in the liver, they are excreted unchanged in the urine.
<b>Distribution</b>	0.2-0.4 L/kg; distributed in extracellular fluid, abscesses, ascitic fluid, pericardial fluid, pleural fluid, synovial fluid, lymphatic fluid and peritoneal fluid. Not well distributed into bile, aqueous humor, bronchial secretions, sputum and CSF.
<b>Preparation and Dose:</b>	Kanamycin sulfate, sterile powder for intramuscular injection in sealed vials. The powder needs to be dissolved in water for injections prior to use. The optimal dose is 15 mg/kg bodyweight, usually 750 mg to 1 g given daily, by deep intramuscular injection. Rotation of injection sites avoids local discomfort.
<b>Storage:</b>	Powder stable at room temperature, diluted solution should be used the same day.
<b>Oral Absorption:</b>	There is no significant oral absorption.
<b>CSF Penetration:</b>	Penetrates inflamed meninges only.
<b>Special circumstances:</b>	<b>Pregnancy/breastfeeding:</b> Safety class D. Eighth cranial nerve damage has been reported following in utero exposure to kanamycin. Excreted in breast milk. The American Academy of Pediatrics considers kanamycin compatible with breast feeding. <b>Renal disease:</b> Use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment is recommended for creatinine clearance < 30 ml/minute or hemodialysis (12-15 mg/kg two times or three times a week). <b>Hepatic disease:</b> Drug levels not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution - some patients with severe liver disease may progress rapidly to hepato-renal syndrome.
<b>Adverse Reactions:</b>	<b>Frequent:</b> Pain at injection site, renal failure (usually reversible) <b>Occasional:</b> vestibular and auditory damage-usually irreversible; genetic predisposition possible (check family for aminoglycoside ototoxicity), nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, often irreversible), peripheral neuropathy, rash, Ototoxicity potentiated by certain diuretics (especially loop diuretics), advanced age, and prolonged use. Nondepolarizing muscle relaxants effect may be increased. Penicillins: in vitro antagonism.
<b>Drug interactions</b>	Loop diuretics (Bumetanide, Furosemide, Ethacrynic acid, Torsemide) Co-administration of aminoglycosides w/ loop diuretics may have an additive or synergistic auditory ototoxicity. Ototoxicity appears to be dose dependent and may be increased with renal dysfunction. Irreversible ototoxicity has been reported. Avoid concomitant administration; if used together careful dose adjustments needed in patients with renal failure and close monitoring for ototoxicity required. Nondepolarizing Muscle Relaxants (Atracurium, Pancuronium, Tubocurarine, Gallamine Triethiodide) - Possible enhanced action of nondepolarizing muscle relaxant resulting in possible respiratory depression. Avoid co-administration, if concurrent administration is needed titrate the non-depolarizing muscle relaxant slowly and monitor neuromuscular function closely. Nephrotoxic agents (Amphotericin B, Foscarnet, Cidofovir) - Additive nephrotoxicity Avoid co-administration, if used together monitor renal function closely and discontinue if warranted Penicillins - In vitro inactivation (possible) Do not mix together before administration.
<b>Contraindications:</b>	Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular, or auditory impairment.
<b>Alerting symptoms:</b>	<ul style="list-style-type: none"> <li>- Problems with hearing; dizziness</li> <li>- Rash</li> <li>- Trouble breathing</li> <li>- Decreased urination</li> <li>- Swelling, pain or redness at injection site</li> <li>- Muscle twitching or weakness</li> </ul>

## OFLOXACIN (Ofi)

<b>Drug Class:</b>	Fluoroquinolones
<b>Activity Against TB, Mechanism of action, and metabolism:</b>	<p><b>Bactericidal.</b> Acts by inhibiting the A subunit of DNA gyrase (topoisomerase) which is essential in the reproduction of bacterial DNA.</p> <p>There is no cross-resistance with other antituberculosis agents, but complete cross-resistance between ofloxacin and ciprofloxacin.</p> <p>There is limited metabolism to desmethyl and N-oxide metabolites; desmethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 65 to 80% of a dose is excreted unchanged in the urine over 24 to 48 hours, resulting in high urinary concentrations.</p>
<b>Preparation and Dose:</b>	200 or 400 mg tablets. Usual dose: 600 to 800 mg daily in one or two divided doses.
<b>Storage:</b>	Room temperature, airtight containers protected from light.
<b>Oral Absorption:</b>	90-98% oral absorption.
<b>Distribution, CSF Penetration:</b>	About 25% is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF, and tissue penetration is good. It crosses the placenta and is distributed into breast milk. It also appears in the bile.
<b>Special circumstances:</b>	<p><b>Pregnancy/breastfeeding:</b> Usually compatible with the breastfeeding.</p> <p><b>Renal disease:</b> Doses of ofloxacin should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 600 – 800 mg 3x/week.</p>
<b>Adverse Reactions:</b>	<p>Generally well tolerated.</p> <p><b>Occasional:</b> GI intolerance; CNS-headache, malaise, insomnia, restlessness, and dizziness.</p> <p><b>Rare:</b> allergic reactions; diarrhea; photosensitivity; increased LFTs; tendon rupture; peripheral neuropathy.</p>
<b>Drug interactions:</b>	<p>Fluoroquinolones are known to inhibit hepatic drug metabolism and may interfere with the clearance of drugs, such as theophylline and caffeine that are metabolised by the liver. Cations such as aluminium, magnesium, or iron reduce the absorption of ofloxacin and related drugs when given concomitantly. Changes in the pharmacokinetics of fluoroquinolones have been reported when given with histamine H2 antagonists, possibly due to changes in gastric pH, but do not seem to be of much clinical significance.</p> <p>The urinary excretion of ofloxacin and some other fluoroquinolones is reduced by probenecid; plasma concentrations are not necessarily increased.</p>
<b>Contraindications:</b>	Pregnancy, intolerance of fluoroquinolones
<b>Alerting symptoms:</b>	<ul style="list-style-type: none"> <li>– Pain, swelling or tearing of a tendon or muscle or joint pain</li> <li>– Rashes, hives, bruising or blistering, trouble breathing</li> <li>– Diarrhea</li> <li>– Yellow skin or eyes</li> <li>– Anxiety, confusion, or dizziness</li> </ul>

## LEVOFLOXACIN (Lfx)

<b>Drug Class:</b>	Fluoroquinolones
<b>Activity Against TB, Mechanism of action, and metabolism:</b>	<p><b>Bactericidal.</b> Acts by inhibiting the A subunit of DNA gyrase (topoisomerase) which is essential in the reproduction of bacterial DNA.</p> <p>Levofloxacin is generally considered to be about twice as active as its isomer, ofloxacin.</p> <p>Minimal hepatic metabolism; 87% of dose is excreted unchanged in the urine within 48 hours via glomerular filtration and tubular secretion.</p>
<b>Preparation and Dose:</b>	Tablets (250, 500, 750 mg). Usual dose: 750 mg daily in one or two divided doses.
<b>Storage:</b>	Room temperature (15-25 degrees C), airtight containers protected from light.
<b>Oral Absorption:</b>	Levofloxacin is rapidly and essentially completely absorbed after oral administration. Orally should not be administered within 4hrs of other medications containing divalent cations (iron, magnesium, zinc, vitamins, didanosine, sucralfate). No interaction with milk or calcium.
<b>Distribution, CSF Penetration:</b>	Distributes well in lister fluid and lung tissues, also widely distributed (kidneys, gall bladder, gynaecological tissues, liver, lung, prostatic tissues, phagocytic cells, urine, sputum and bile). 30-50% of serum concentration is attained in the CSF with inflamed meninges.
<b>Special circumstances:</b>	<p><b>Pregnancy/breastfeeding:</b> safety class C. There are no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Animal data demonstrated arthropathy in immature animals, with erosions in joint cartilage. Because of the potential for serious adverse effects from levofloxacin in nursing infants, as decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.</p> <p><b>Renal disease:</b> Doses of levofloxacin should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 750 – 1000 mg 3x/week.</p> <p><b>Hepatic disease:</b> given the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.</p>
<b>Adverse Reactions:</b>	<p>Generally well tolerated.</p> <p><b>Occasional:</b> GI intolerance; CNS-headache, malaise, insomnia, restlessness, dizziness, allergic reactions, diarrhoea, photosensitivity.</p> <p><b>Rare:</b> tendon rupture; QT prolongation; peripheral neuropathy.</p>
<b>Drug interactions:</b>	<p>Should not be given to patients receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or class III anti-arrhythmics (such as amiodarone and sotalol).</p> <p><b>Sucralfate:</b> decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate.</p> <p><b>Antacids:</b> (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): antacid binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy.</p> <p><b>Probenecid:</b> probenecid interferes with renal tubular secretion of fluoroquinolones, which may result in 50% increase in serum level of levofloxacin.</p> <p><b>Vitamins and minerals:</b> containing divalent and trivalent cations such as zinc and iron. Formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones.</p> <p><b>Mexiletine:</b> fluoroquinolones may inhibit cytochrome P450 1A2 resulting in increased mexiletine concentration.</p>
<b>Contraindications:</b>	Pregnancy, hypersensitivity to fluoroquinolones; prolonged QT
<b>Alerting symptoms:</b>	<ul style="list-style-type: none"> <li>– Pain, swelling or tearing of a tendon or muscle or joint pain</li> <li>– Rashes, hives, bruising or blistering, trouble breathing</li> <li>– Diarrhea</li> <li>– Yellow skin or eyes</li> <li>– Anxiety, confusion, or dizziness</li> </ul>



<b>ETHIONAMIDE (Eto)</b>	
<b>Drug Class:</b>	Carbothionamides group, derivatives of isonicotinic acid
<b>Activity against TB, Mechanism of action, and metabolism:</b>	<p><b>Bactericidal</b></p> <p>The mechanism of action of thionamides has not been fully elucidated, but it appears to inhibit mycolic acid synthesis.</p> <p>Resistance develops rapidly if used alone and there is complete cross-resistance between ethionamide and prothionamide (partial cross-resistance with thioacetazone).</p> <p>Ethionamide is extensively metabolised, probably in the liver, to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.</p>
<b>Preparation and Dose:</b>	Ethionamide is normally administered in the form of tablets containing 250 mg of active drug. The maximum optimum daily dose is 15-20mg/kg/day (max 1g/day), usually 500-750mg daily in one or two divided doses.
<b>Storage:</b>	Store at room temperature in airtight containers.
<b>Oral Absorption:</b>	100% absorbed but sometimes erratic absorption due to GI disturbances associated with the medication.
<b>Distribution, CSF Penetration:</b>	Rapidly and widely distributed into body tissues and fluids, with concentrations in plasma and various organs being approximately equal. Significant concentrations also are present in cerebrospinal fluid.
<b>Special circumstances:</b>	<p><b>Pregnancy/breastfeeding:</b> Safety class – C. Animal studies have shown ethionamide to be teratogenic. Newborns who are breast-fed by mothers taking ethionamide, should be monitored for adverse effects.</p> <p><b>Renal disease:</b> Doses of the thioamides are only slightly modified for patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 250 – 500 mg daily.</p> <p><b>Hepatic disease:</b> Thionamides should not be used in severe hepatic impairment.</p> <p><b>Porphyria.</b> Ethionamide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals or in-vitro systems.</p>
<b>Adverse Reactions:</b>	<p><b>Frequent:</b> Severe GI intolerance (nausea, vomiting, diarrhea, abdominal pain, excessive salivation, metallic taste, stomatitis, anorexia and weight loss). Adverse gastrointestinal effects appear to be dose related, with approximately 50% of patients unable to tolerate 1 gm as a single dose. Gastrointestinal effects may be minimized by decreasing dosage, by changing the time of drug administration, or by the concurrent administration of an anti-emetic agent.</p> <p><b>Occasional:</b> Allergic reactions; Psychotic disturbances (including mental depression), drowsiness, dizziness, restlessness, headache, and postural hypotension. Neurotoxicity (administration of pyridoxine has been recommended to prevent or relieve neurotoxic effects); transient increases in serum bilirubin; reversible hepatitis (2%) with jaundice (1-3%); gynecomastia; menstrual irregularity, arthralgias, leucopenia, hypothyroidism especially when combined with PAS.</p> <p><b>Rare:</b> reports of peripheral neuritis, optic neuritis, diplopia, blurred vision, and a pellagra-like syndrome, reactions including rash, photosensitivity, thrombocytopenia and purpura.</p>
<b>Drug interactions:</b>	<p>Cycloserine - Potential increase incidence of neurotoxicity.</p> <p>Ethionamide has been found to temporarily raise serum concentrations of isoniazid. Thioamides may potentiate the adverse effects of other antituberculous drugs administered concomitantly. In particular, convulsions have been reported when ethionamide is administered with. Excessive ethanol ingestion should be avoided because of possible psychotic reaction.</p>
<b>Contraindications:</b>	Thionamides are contraindicated in patients with severe hepatic impairment and in patients who are hypersensitive to these drugs.
<b>Alerting symptoms:</b>	<ul style="list-style-type: none"> <li>▪ Any problems with eyes: eye pain, blurred vision, color blindness, or trouble seeing</li> <li>▪ Numbness, tingling, or pain in hands and feet</li> <li>▪ Unusual bruising or bleeding</li> <li>▪ Personality changes such as depression, confusion, or aggression</li> <li>▪ Yellowing of skin</li> <li>▪ Dark-colored urine</li> <li>▪ Nausea and vomiting</li> <li>▪ Dizziness</li> </ul>

<b>Para-Aminosalicylate (PAS)</b>	
<b>Drug Class:</b>	Salicylic-acid. anti – folate
<b>Activity Against TB, Mechanism of action, and metabolism:</b>	<b>Bacteriostatic.</b> Disrupts folic acid metabolism. Acetylated in the liver to N-acetyl-p-aminosalicylic acid and p-aminosalicylic acid which are excreted via glomerular filtration and tubular secretion.
<b>Preparation and Dose:</b>	Granules of PAS in 100 gm boxes. 150 mg/kg or 10-12 g daily in one or two divided doses.
<b>Storage:</b>	PASER packets should be kept in the refrigerator or freezer. Other formulations may not require refrigeration (consult manufacturer's recommendations)
<b>Oral Absorption:</b>	Incomplete absorption (usually 60–65%)—sometimes requires increased doses to achieve therapeutic levels.
<b>Distribution, CSF penetration:</b>	Distributed in peritoneal fluid, pleural fluid, synovial fluid. Not well distributed in CSF (10-15%) and bile.
<b>Special circumstances:</b>	<b>Pregnancy/breastfeeding:</b> Safety class – C. Congenital defects in babies have been reported with exposure to PAS in the first trimester. Para-aminosalicylic acid is excreted into human breast milk (1/70th of maternal plasma concentration) <b>Renal disease:</b> No dose adjustment is recommended. PAS can exacerbates acidosis associated with renal insufficiency and if possible should be avoided in patients with severe renal impairment due to crystalluria. Formulations of sodium PAS should also be avoided in patients with severe renal impairment.
<b>Adverse Reactions:</b>	<b>Frequent:</b> GI intolerance (anorexia and diarrhea); hypothyroidism (increased risk with concomitant use of ethionamide). <b>Occasional:</b> hepatitis (0.3-0.5%); allergic reactions; thyroid enlargement; malabsorption syndrome; increased prothrombin time; fever. Careful use in patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency.
<b>Drug interactions:</b>	Digoxin - Possible decrease in digoxin absorption Monitor digoxin level, level may need to be increased; Ethionamide - Possible increase in liver toxicity, monitor liver enzymes, hypothyroidism in case of combined administration; Isoniazid - Decreased acetylation of isoniazid resulting in increased isoniazid level Dose may need to be decreased.
<b>Contraindications:</b>	Allergy to aspirin; severe renal disease; hypersensitivity to the drug
<b>Alerting symptoms:</b>	<ul style="list-style-type: none"> <li>▪ Skin rash, severe itching, or hives</li> <li>▪ Severe abdominal pain, nausea, or vomiting</li> <li>▪ Unusual tiredness or loss of appetite</li> <li>▪ Black stools or bleeding</li> </ul>