National Guidelines and Operational Manual for Programmatic Management of Drug Resistant TB (PMDT)

Second Edition
(April, 2013)

National Tuberculosis Control Programme
Directorate General of Health Services
Dhaka, Bangladesh

World Health Organization
Country Office for Bangladesh

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Design & Printed by
Real Printing and Advertising
K.R Plaza, 31 Purana Paltan
Dhaka-1000, Bangladesh

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Contributions

Staff members at the National TB Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare, Dhaka, the National Institute of Diseases of Chest and Hospital, Dhaka, the World Health Organization, technical partners BRAC, Damien Foundation, USAID (TBCARE II) and other partners contributed to the development and regular updating of the NTP PMDT (erstwhile DOTS Plus) guidelines.

Faculty from Medical Colleges and teaching hospitals; experienced Chest Specialists from specialized Institutes contributed to the updating of the guidelines to its recent version.

List of contributors is in annex 7.

Preface

TB services are integrated under the new Health Population and Nutrition Sector Development Programme (HPNSDP), implemented through the primary health care of the country. Bangladesh is an outstanding example of implementing TB control in partnership with NGOs.

While Bangladesh has made remarkable progress in basic DOTS, challenges are many to detect and treat Multi Drug Resistant Tuberculosis (MDR TB). Among them capacity in diagnosis, managing patients through ambulatory care, treating adverse reactions to second line anti-TB drugs and infection control needs more strategic directions.

The revision of this guideline is a timely and appropriate step taken by the National TB Control Programme to address the issues in programmatic management of drug resistant TB (PMDT) for sustaining success in TB control programme.

This guideline will provide information and guidance to health care professional at different level of health care system, patients and general population and will act as an PMDT framework from which other programmes will also be benefitted.

I recommend this guideline for intensive use in implementation of core interventions in PMDT and wish every success.

M.M. Neazuddin
Secretary
Ministry of Health and Family Welfare
Bangladesh Secretariat, Dhaka

Message

Tuberculosis is a major public health problem in Bangladesh. The country ranks sixth on the list of the 22 high burden TB countries. The Government of Bangladesh has given priority to TB control. The services of which are available throughout the country.

Bangladesh manages TB control through effective partnership achieving remarkable success in terms of case notification and treament success. However, tuberculosis still remains as a major public health problem in Bangladesh. The most cost effective public health measure for control of tuberculosis is early and correct diagnosis, and cure of infectious TB patients through standardized treatment regimen..

Data from previous drug resistance surveys (DRS) indicate low levels of MDR TB. The last results available from the DRS indicates 1.4% MDR TB among newly diagnosed cases and 28.5% among previously treated cases.

There are needs for effective management of MDR TB cases within the framework of the National TB Control Programme. I sincerely thank and appreciate the initiative of revising this guideline and believe that the National TB Control Programme will be benefitted by using this guideline by all level of service providers.

I would also like to express my sincere thanks to all who were involved in providing technical support to develop this document.

Prof. Dr Khondhaker Md. Shefyetullah
Director General
Directorate General of Health Services
Ministry of Health and Family Welfare

Message

Tuberculosis remains as a major public health problem in Bangladesh. Though the country has achieved commendable success in Tuberculosis control, yet this success may deem out unless effective TB control measures are taken based on strong policy guidance for the disease.

Early case detection remains one of the most important interventions for reducing the risk of TB transmission and adherence to treatment reduces the risk of emergence of multi-drug resistant TB.

The term "Programmatic Management of Drug Resistant TB" (PMDT) refers to programme based MDR TB diagnosis, management and treatment. These guidelines promote full integration of basic TB control and PMDT activities under the National TB Control Programme (NTP), so that patients with TB are evaluated for drug-resistance and placed on appropriate treatment regimen and properly managed from the outset of treatment, or as early as possible.

On behalf of Mycobacterial Disease Control (MBDC) Directorate, I express my sincere thanks to the working team of NTP including technical partners and stakeholders who contributed much for developing these guidelines.

Dr Md Ashaque Husain
Director, MBDC and Line Director, TB-Leprosy
DGHS, Mohakhali, Dhaka

Acknowledgement

The emergence of resistance to anti TB drugs, and particularly multidrug-resistant tuberculosis (MDR-TB), has become a significant public health problem in a number of countries and an obstacle to effective global TB control. MDR-TB remains are essentially a man- made phenomenon. Prevention of acquired drug resistance through effective DOTS programme is one of the priorities in dealing with MDR-TB control.

NTP is facing with the challenge of growing pool of persons with MDR-TB. As management of patients with Drug Resistant Tuberculosis (DR TB) are demanding, complex and costly, specific measures now being taken within the National Tuberculosis Control Programme (NTP) to address the DR TB problem.

Drug Resistant TB issue has been addressed by the NTP through appropriate management of patients and strategies to prevent the propagation of DR TB under the leadership of MOH&FW. I express my sincere thanks and gratefulness to Government of Bangladesh for their commitment and support to National TB Control Progrramm.

I acknowledge The Global Funds to Fight AIDS, Tuberculosis and Malaria (GFATM), USAID and other partners of NTP for their contribution in implementing Programmatic Management of Drug Resistant Tuberculosis (PMDT) . I recognize technical support of WHO for the development of MDR-TB guideline and overall strategic direction for PMDT program. On be half of NTP I also express my thanks for the contributors, national as well as international experts and stakeholders who contributed their time and efforts for developing this guideline.

Dr. Md. Nuruzzaman Haque
Deputy Director MBDC and
Program Manager, TB
National Tuberculosis Control Program (NTP)
DGHS, Mohakhali, Dhaka

Foreword

The member states in the World Health Organization's (WHO) South-East Asia Region have achieved significant strides towards attaining the Millennium Development Goals (MDGs) over the last decade. The incidence, prevalence and mortality of all forms of tuberculosis have shown marked improvement, and are on track in terms of the likelihood of meeting the MDG targets, in most countries.

With regard to drug-resistant tuberculosis (MDR-TB), data from the first nation-wide drug resistance survey 2010-11 indicates low levels of multi-drug resistance in Bangladesh, which is 1.4% MDR-TB among newly -diagnosed TB cases and 28.5% among previously treated cases. The WHO is currently putting out concerted efforts, in tandem with other health partners, to further lower the transmission and prevalence of this illness.

WHO has been working with the National Tuberculosis Programme (NTP) and other partners to design key interventions linked to diagnosis and treatment of Drug Resistance TB (DR TB). On these new initiatives, WHO emphasizes on quality service delivery that ensures all diagnosed cases are placed timely on treatment. Efforts are underway to scale up the Programmatic Management of Drug Resistant TB (PMDT), especially in high-burden DR TB districts of Bangladesh.

WHO also supports the NTP to develop innovative approaches in DR TB care delivery through existing Public-Private Mix (PPM) models. WHO has been assisting the Government with training and normative manuals in order to enhance capacity of human resources in PMDT.

On the other hand, the role of the civil society and community involvement are very crucial for the success of PMDT. WHO attaches immense importance to initiating extra tempo to its work relating to the mobilization of community leaders and local health workers so that they meaningfully engage in this noble endeavour and join hands with the NTP to scale up community -based care for PMDT.

I am hopeful that this Guideline will strengthen the capacity of the NTP for implementation of PMDT services in the country.

Dr Thushara Eraj Indranath Fernando
WHO Representative to Bangladesh

Abbreviations and Acronyms

AFB	Acid - Fast Bacilli
ADR	Adverse Drug Reaction
ARV	Antiretroviral
AZT	Zidovudine
BMDC	Bangladesh Medical and Dental Counil
BMI	Body Mass Index
CDC	Chest Disease Clinic
CDH	Chest Disease Hospital
CHCP	Community Health Care Provider
CPC	Cetylpyridinum chloride
c-PMDT	Community-based Programmatic Management of Drug Resistant TB
CSF	Cerebrospinal Fluid
CT	Computerized Axial Tomography
DM	Diabetes Mellitus
DNA	Deoxyribonucleic acid
DOT	Directly Observed Therapy
DOTS	An Internationally recommended strategy for TB control
DRS	Drug Resistant Survey
DR TB	Drug Resistant Tuberculosis
DST	Drug Susceptibility Testing
ECG	Electrocardiogram
FWA	Family Welfare Assistant
GDF	Global Drug Facility
GFR	Glomerular Filtration Rate
gGLC	Global Green Light Committee
GLC	Green Light Committee
HA	Health Assistant
HIV	Human Immunodeficiency Virus
HPNSDP	Health, Population and Nutrition Sector Development Programme
IC	Infection Control
INGO	International Non-government Organization
IUATLD	International Union Against Tuberculosis and Lung Disease
LED	Light Emitting Diode
LJ	Lowenstein Jensen
LPA	Line Probe Assay
MDR TB	Multidrug Resistant Tuberculosis

MGIT	Mycobacteria Growth Indicator Tube
MO	Medical Officer
MODCS	Medical Officer for Disease Control and Surveillance
MOTT	Mycobateria Other Than Tuberculosis
MTB	Mycobaterium Tuberculosis
MTB/RIF	Mycobaterium Tuberculosis/Resistance to Rifampicin
NGO	Nongovernmental Organization
NIDCH	National Institute of Diseases of the Chest and Hospital
NTP	National Tuberculosis Control Program
NTRL	National Tuberculosis Reference Laboratory
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PMDT	Programmatic Management of Drug Resistant Tuberculosis
PO	Program Organizer
QA	Quality Assurance
QC	Quality Control
r-GLC	Regional Green Light Committee
RTRL	Regional Tuberculosis Reference Laboratory
SNRL	Supra National Reference Laboratory (for TB)
SOP	Standard Operating Procedure
SS	Shasthya Shebika
TAG	Technical Advisory Group
TB	Tuberculosis
TLCA	Tuberculosis & Leprosy Control Assistant
TSH	Thyroid Stimulating Hormone
UH&FPO	Upazila Health and Family Planning Officer
UHC	Upazila Health Complex
WHO	World Health Organization
WRD	WHO approved Rapid Diagnostic Tools
XDR TB	Extensively Drug Resistant TB

Anti-tuberculosis Drug Abbreviations

Group	Description	Drug	Abbreviation
1	First-line oral antituberculosis drugs	Isoniazid	H
		Rifampicin	R
		Ethambutol	E
		Pyrazinamide	Z
		Rifabutin	Rfb
2	Injectable antituberculosis drugs	Kanamycin	Km
		Amikacin	Amk
		Capreomycin	Cm
		Viomycin	Vm
		Streptomycin	S
3	Fluoroquinolones	Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Ofloxacin	Ofx
4	Oral bacteriostatic second-line antituberculosis drugs	Ethionamide	Eto
		Prothionamide	Pto
		Cycloserine	Cs
		Terizidone	Trd
		para-aminosalicylic acid	PAS
5	Antituberculosis drugs with unclear efficacy or unclear role in MDR TB treatment (not recommended by the WHO for routine use in MDR TB patients)	Clofazimine	Cfz
		Linezolid	Lzd
		Amoxicillin/clavulanate	Amx/Clv
		Thioacetazone	Thz
		Clarithromycin	Clr
		Imipenem	Ipm

Antiretroviral Drug Abbreviations

Drug Class	Name	Abbreviation
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Efavirenz	EFV
	Nevirapine	NVP
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Zidovudine	AZT
	Lamivudine	3TC
	Stavudine	D4T
	Didanosine	ddI
	Zalcitabine	ddC
	Abacavir	ABC
	Tenofovir	TDFa
Protease Inhibitors (PIs)	Indinavir	IDV
	Ritonavir	RTV
	Saquinavir	SQV
	Nelfinavir	NFV
	Lopinavir/Ritonavir	LPV/RTV

[a] TDF is a nucleotide reverse transcriptase inhibitor but is typically grouped with this class.

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 Bangladesh, the available information from the routine drug resistance surveillance and recently concluded DRS (2010-2011) suggests that the rate of MDR TB is relatively low. 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 National Tuberculosis Control Programme (NTP) to address the MDR TB problem through appropriate management of patients and strategies to prevent the propagation and dissemination of MDR TB.

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

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

CHAPTER 1 Background Information on Drug Resistant Tuberculosis

1.1 The Global Epidemiological Situation of Drug Resistant TB (DR TB)

Anti-tuberculosis (TB) drug resistance is a major public health problem that threatens progress made in TB care and control worldwide. Drug resistance results from improper use of antibiotics in chemotherapy of drug-susceptible TB patients. This "improper use" may be in the form of a number of actions including, administration of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with weak TB control programmes. A patient who develops active disease with a Drug Resistant TB strain can transmit this form of TB to other individuals.

The incidence of drug resistance has increased since the first TB drug treatment was introduced in 194Os. The emergence of multi-drug resistant TB (MDR TB), is defined as strains of TB resistant to at least isoniazid and rifampicin. MDR TB can be treated with the use of second-line anti-TB drugs, however, the improper use of these drugs has fuelled the generation and subsequent transmission of highly resistant strains of TB termed extensively Drug Resistant TB (XDR TB). XDR TB strains are resistant to at least one of the fluoroquinolone drugs, as well as, a second line injectable agent, in addition to isoniazid and rifampicin. According to the Global TB Report 2012 (WHO),there were an estimated incidence of 310 000 (range, 220 000-400 000) MDR TB cases among notified TB patients with pulmonary TB . Globally, almost 60 000 cases of MDR TB were notified to WHO in 2011 represented only 19% of the estimated 310 000 cases of MDR TB among reported TB patients with pulmonary TB.

Globally, 3.7% (2.1-5.2%) of new cases and 20% (13-26%) of previously treated cases are estimated to have MDR TB. Extensively Drug Resistant TB, or XDR TB, has been identified in 84 countries in 2011; the average proportion of MDR TB cases with XDR TB is 9.0% (6.7-11.2%).

The number of TB cases tested for MDR TB, diagnosed with MDR TB and successfully treated for MDR TB are far from reaching the targets set in the Global Plan , which aim to test new cases of TB considered at high risk of MDR TB for drug susceptibility (estimated at about 20% of all new cases) and 100% of retreatment cases by 2015.

The Bangladesh National TB Control Program hopes to meet the goals set forth in the Global Plan and The South-East Asia Regional Response Plan for Drug Resistant TB Care and Control 2011-15, drastically improving the coverage of diagnostic DST and subsequent treatment of Drug Resistant TB.

1.2 The Situation of Drug Resistant TB in Bangladesh

At present, MDR TB cases in Bangladesh are relatively low and a few XDR TB cases exist. The National Tuberculosis Control Program (NTP), through a well functioning TB program, is in the position to keep MDR TB low with few sporadic XDR TB cases.

The NTP has carried out its first nation-wide drug resistance survey (DRS) in tuberculosis patients in collaboration with WHO and SNRL, Antwerp, Belgium in 2010-2011. The result shows the overall number of MDR TB cases is low, 1.4% among new cases and 28.5% among re-treatment cases.

In new case, Rifampicin mono resistance is low (0.2%)., though relatively higher, primary mono resistance to isoniazid (1.5%) and streptomycin (6.6%).. Table 1.1 shows the prevalence of anti-tuberculosis drug resistance in Bangladesh.

Table 1.1 Prevalence of Anti-TB Drug Resistance in Bangladesh

Drug resistance pattern	DRS 2010-11		
	New % (n = 1049)	Previously treated % (n = 291)	Total% (n = 1343)
Susceptible to all drugs (%)	87.7	56.8	81.3
Mono resistance H (%)	1.4	2.5	1.6
Mono resistance R (%)	0.2	0.4	0.3
Mono resistance E (%)	0.2	0.0	0.2
Mono resistance S (%)	6.6	7.1	6.7
Resistance HE	0.1	0.0	0.0
Resistance HES	0.0	0.7	0.2
Multi Drug Resistant (MDR TB)	1.4	28.5	7.0
Resistance to all 4 drugs (HRES)	0.5	14.1	3.3

Source: DRS Data (2010-2011) , NTP, Bangladesh

In addition to the survey conducted by the NTP, the Damien Foundation also conducted two drug-resistance studies in 1995 and 2001, which comprised of 645 and 1041 patients respectively. The 1995 study showed that 0.7% and 6.8% MDR TB cases were identified among new and previously treated TB patients respectively. Similar findings were reported in the 2001 study, such that 0.4% and 3% were MDR TB among new and previously treated TB patients respectively.

Although the rates of MDR TB in Bangladesh do not appear to be high, the absolute number of MDR TB cases is higher considering the overall high TB burden. MDR TB prevalence of 1.4% in new cases and 28.5% in retreatment cases translates approximately an estimate of 3800 MDR TB cases among notified pulmonary TB cases in 2011 (source Global TB report of WHO 2012).

1.3 Causes of DR TB

Anti-TB drug resistance is said to be present if growth of M. tuberculosis isolates are observed in spite of presence of anti-TB drugs. Although its' causes could be microbial, clinical and/or programmatic, Drug Resistant TB is essentially a man-made phenomenon. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a Drug Resistant strain to become the dominant strain in a patient infected with TB. Table 1.2 summarizes the common causes of inadequate treatment.

Table 1.2 Causes of Inadequate Anti-TB Treatment*

Health-care providers: inadequate regimens	Drugs: inadequate supply or quality	Patients: inadequate drug intake
• Inappropriate guidelines or non-compliance with guidelines; • Absence of guidelines; • Poor training; • No monitoring of treatment and poor DOT; • Poorly organized or funded TB control programmes.	• Poor quality; • Unavailability of certain drugs (stock-outs or delivery disruptions); • Poor storage conditions; • Wrong dose or combination of drugs.	• Poor adherence; • Lack of information; • Adverse effects of treatment; • Social barriers (stigma, restrictions); • Mal-absorption due to other causes; • Substance dependency disorders; • Mental disorders; • Non-cooperative; • Education level; • Lack of transportation; • Lack of money.

*adapted from WHO programmatic management of Drug Resistant tuberculosis guidelines: Emergency Update 2008

It is important to note, the ongoing transmission of infection from MDR TB cases in a population contributes to new primary Drug Resistant cases. In fact, most people who have MDR TB got it from someone else, and it is not because they did not take TB drugs adequately.

Nevertheless, the treatment of MDR TB with Category 1 or Category 2 may potentially create even more resistance to the drugs in use. This has been termed the "amplifier effect" of short-course chemotherapy.

1.4 Addressing the Sources of DR TB

Any ongoing clinical or programmatic problems resulting in the creation of new cases of DR TB should be addressed urgently. Both prevention and treatment measures should be incorporated into NTP operational plans to have the greatest effect on DR TB control. Well-administered first-line treatment for susceptible cases is the best way to prevent acquisition of resistance. Timely identification of DR TB and adequate treatment regimens with second-line drugs administered early in the course of the disease are essential to stop primary transmission. Standardized infection control measures in all health facilities and contact tracing of Drug Resistant TB cases are also very critical for prevention, In short, the integration of the national DOTS program with treatment of DR TB works synergistically to eliminate all the potential sources of TB transmission.

1.5 Background and the use of this Operational Manual

Operational Manual for the Management of Multi Drug Resistant TB(MDR TB) was first published in 2009. This 2013 edition expands upon the most recent WHO guidance on the Programmatic Management of Drug Resistant TB (update 2011), which makes recommendations addressing critical issues concerning the programmatic management of Drug Resistant TB (PMDT): case-finding, treatment regimens, monitoring the response to treatment and selecting models of care. The WHO 2011 update also encourages the extensive use of rapid drug-susceptibility testing with molecular techniques to detect TB patients with Rifampicin and or Isoniazid resistance and provide adequate treatment.

In addition, this revised national guidelines and operational manual are complemented with the Standard Operating Procedures (SOP): Community-based Programmatic Management of Drug Resistant Tuberculosis, Bangladesh, 2013. This complementary SOP provides practical step-by-step guidance on how to organize, implement, and monitor community-based care for MDR TB. Both documents target program managers and medical practitioners working in TB treatment and control, as well as, partners and organizations providing technical and financial support for the care of Drug Resistant TB.

CHAPTER 2 Framework for Effective DR TB Control

2.1 DOTS Framework as Applied to the Management of DR TB

Management of Drug Resistant TB in Bangladesh is an integral part of the NTP, which ensures access to MDR/XDR TB treatment. The main objective of the NTP is to deliver effective treatment under proper case management conditions and prevent the emergence of resistance to second-line drugs as well as to prevent transmission of DR TB infection. The framework for ensuring effective management of Drug Resistant TB in the country is based on the five components of DOTS, as outlined in Box 2.1.

Box 2.1. Five components of DOTS strategy as applied to DR TB

1. Sustained political commitment in the form of financial and human resources, training, legal and regulatory documents, infrastructure and coordination of all stakeholders involved in all aspects of the framework for control of DR TB. Elements include:
   - A well functioning DOTS Program;
   - Addressing the factors leading to the emergence of DR TB;
   - Long-term investment in staff and resources;
   - Coordination of efforts between communities, local governments, and international agencies.

2. Appropriate case-finding strategy, including quality-assured culture and DST
   - Rational triage of patients into DST and the DR TB control programme;
   - Relationship with supra-national TB reference laboratory.

3. Appropriate treatment strategies that use second-line drugs under proper case management conditions, including
   - Evidence-based treatment design;
   - Directly Observed Treatment (DOT);
   - Monitoring and management of adverse effects;
   - Properly trained and regularly supervised human resources.

4. Uninterrupted supply of quality-assured second-line anti-tuberculosis drugs and logistics

5. Recording and reporting system designed for the DR TB control programme that enables monitoring of performance and evaluation of treatment outcomes

2.2 Coordination and structure of the National Tuberculosis Control Programme

The successful management of Drug Resistant TB requires adequate coordination of the efforts and contribution of all the key stakeholders, organizations and external partners (reference Annex 1: Partnerships with NGOs in the Operational Responsibilities for DR TB Control). The responsibility for overall coordination of the DR TB control lies with the NTP. Additionally, the NTP has dedicated staff members at each level of care with specific roles and responsibilities (reference Annex 2: Roles and Responsibilities).

The infrastructure and management of Drug Resistant TB care while keeping the patient in the community is described in the "Standard Operating Procedures (SOP): Community-Based Programmatic Management of Drug Resistant TB, 2013".

CHAPTER 3 Definitions: Case Registration, Bacteriology and Treatment Outcomes

3.1 Definitions of Drug Resistance

Drug Resistant Tuberculosis (DR TB) is confirmed through laboratory tests that demonstrate growth of infecting isolates of Mycobacterium tuberculosis in-vitro in the presence of one or more anti-tuberculosis drugs. By definition, there are four different categories of drug resistance, namely:

- Mono-resistance: resistance to one anti-TB drug.
- Poly-resistance: resistance to more than one anti-TB drug, other than isoniazid and rifampicin.
- Multidrug-resistance (MDR): resistance to at least isoniazid and rifampicin, the two most potent anti-TB agents.
- Extensive drug-resistance (XDR): MDR TB, plus resistance to at least one of the fluoroquinolones, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin).

DR TB patients: Any patient who falls into one of the above listed categories of drug resistance is considered as DR TB patient. The WHO has stopped using the terms "DOTS-Plus". In these guidelines, we will no longer use these terms but refer to these patients as "DR TB patients". The "DOTS-Plus Clinical Management and Social Support Committee" has been changed to the "PMDT Clinical Management and Social Support Committee" .

3.2 Site of DR TB Disease (pulmonary and extra-pulmonary)

The recommended treatment regimens for Drug Resistant forms of TB are similar, irrespective of site of disease. However, defining the site remains important for recording and reporting purposes.

- Pulmonary TB: Tuberculosis involving only the lung parenchyma.
- Extrapulmonary TB: Tuberculosis of organs other than the lung parenchyma , e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges is considered to be extrapulmonary TB. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion without radiographic abnormalities in the lungs is also considered extrapulmonary TB.

Patients having both pulmonary and extrapulmonary TB should be classified as having pulmonary TB.

3.3 Bacteriological Examinations and Sputum Conversion

Sputum smear microscopy, culture and DST are the standard examinations

performed on DR TB patients. How often to perform smears and cultures during monitoring of the treatment are described in Chapter 6 and 7.

- Culture and sputum smear-positive at the start of DR TB treatment means the patient must have at least one pre-treatment culture and smear that was positive; and the collection date of the sample was less than 30 days before, or 7 days after, initiation of DR TB treatment.
- Sputum conversion is defined as two consecutive negative cultures from samples collected at least 30 days apart. The date of the first negative cultures is used as the date of conversion.

3.4 DR TB Patient Registration Group based on History of Previous Anti-TB Treatment

DR TB patients should be assigned a registration group based on their treatment history, which is useful in assessing the risk for DR TB. The registration group describes previous treatment and does not purport to explain the reason(s) for resistance.[1]

At the start of DR TB treatment, each DR TB patient should be classified in two different ways:

I. Classification according to previous Anti-TB drug use, mainly assign the appropriate treatment regimen.

- **New: No previous use of anti-tuberculosis drugs:** A patient who has received no or less than one month of anti-tuberculosis treatment.
- **Previously treated with first-line drugs only:** A patient who has been treated for one month or more for TB with only first-line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol or streptomycin).
- **Previously treated with second-line drugs:** A patient who has been treated for one month or more for TB with a second-line drug regimen, with or without first-line drugs. Patients who have had less than a month of exposure to fluoroquinolones for a reason other than TB is not considered to have been treated with second-line anti-tuberculosis drugs.

II. Classification according to the history of their previous treatment (commonly referred to as the patient's "registration group"):

The registration groups are the established groups used in the DR TB programme recording and reporting system with additional sub-grouping of patients treated after failure. This grouping allows analysis of the target groups for DST, epidemiological monitoring and projection of future numbers of DR TB cases. Classification is determined at the time the patient starts DR TB treatment. The groups are as follows:

1 These guidelines do not use the terms "primary" and "acquired" resistance because these types of resistance cannot be distinguished in most TB programmes for control of DR TB, it can only be done through DNA finger printing, which is not done in country at present.

Table 3.1 Definitions of DR TB Patient Registration Categories

Type of Category	Definition
New	• A patient who has never received anti-TB drugs; or • A patient who received anti-TB drugs for less than one month
Relapse	• Relapse patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
Treatment after loss to Follow up	• Treatment after loss to follow-up patients have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)
Treatment after failure (Category I/ II)	• A TB patient whose sputum smear or culture is positive at month 5 or later during treatment. OR • A new or retreatment smear-positive patient who was diagnosed with DR- TB during the course of treatment OR • A patient who was initially smear-negative and was found smear-positive at the end of the second month of treatment
Transfer In	• A patient already registered for treatment in a DOTS centre and who is subsequently transferred to another registration unit
Other	These are types of patients who may not fit into any of the above categories. Examples include the followings: sputum smear-positive patients with unknown previous treatment outcome; sputum smear-positive patients who received treatment other than Category I or II (possibly in the private sector); patients who have received several unsuccessful treatments, were considered incurable by health staff and who have lived with active TB disease with no or inadequate treatment (eg: "chronic" patients); extrapulmonary and smear negative in special cases

In addition to determining the treatment registration category of the DR TB patients, all patients should have their HIV status recorded at the start of treatment. Rapid HIV testing should be performed according to national protocol if there is any doubt about the patient's HIV status, or if the patient has not been tested recently.

3.5 Treatment Outcome Definitions for DR TB Treatment

The treatment outcome definitions for DR TB patients are based on the use of laboratory smear and mycobacterial culture as monitoring tools. There are six mutually exclusive DR TB outcomes corresponding to the DR TB outcome categories for drug-susceptible TB. All patients should be assigned the first outcome they experience for the treatment being evaluated for recording and reporting purpose. The outcome definitions are as follows:

Treatment outcome	Definition
Cured	A DR TB patient who has completed treatment according to NTP protocol without evidence of failure and has at least three consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.
Treatment Completed	A DR TB patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than three cultures were performed in the final 12 months of treatment).
Died	A DR TB patient who dies for any reason during the course of DR TB treatment.
Failed	Treatment terminated or need for permanent regimen change of at least 2 anti- TB drugs because of • lack of [a]conversion in the continuation phase or, • bacteriological [b]reversion (two positive cultures taken at least 30 days apart) in the continuation phase after conversion (two negative cultures taken at least 30 days apart) to negative, or • evidence of additional acquired resistance to fluoroquinolones and 2nd line injectable drug, or • adverse drug reaction.
Lost to follow up	A DR TB patient whose treatment was interrupted for two or more consecutive months for any reason.
Transferred out	A DR TB patient who has been transferred to another reporting and recording unit (and for whom the treatment outcome is unknown).

[a] **Conversion (to negative):** Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

b Reversion (to positive): Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase. Reversion during the intensive phase does not qualify as failure.

Patients who have 'transferred in' should have their outcome reported back to the treatment centre from which they were originally registered. The responsibility of reporting their final outcomes belongs to the original treatment centre. A patient for whom no treatment outcome is assigned, this includes cases "Transferred out" to another treatment unit as well as cases for whom the treantment outcome is unknown to the reporting unit.

3.6 Cohort Analysis

A DR TB patient cohort is defined as a group of patients diagnosed with DR TB and registered in the DR TB registration during a specified quarter.

The recommended time frame for Standardized Regimen cohort analysis reflects the long duration of DR TB regimens. Cohort analyses should be carried out at 24 months and repeated at 36 months after the last patient starts treatment.

Example:

Cohort of patients enrolled in the quarter of July 1, 2008 -Sept 30, 2008 will have cohort analyses on:

- 01 Oct, 2010 for the 24th month analysis (preliminary analysis)
- 01 Oct , 2011 for the 36th month analysis (final cohort analysis)

In order to perform adequate analysis on all patients that meet the criteria of MDR TB, three dates should be recorded:

1. Date of initial registration as a TB case (if applicable). (DOTS enrollment date in TB Register)
2. Date of specimen collection for DST
3. Date of registration in DR TB Register
4. Date of starting DR TB Regimen

Some patients will be registered as starting on the standard MDR TB (or XDR TB) but later will be found to have drug susceptible or mono or poly drug resistance except Rif resistant and HES resistant. These patients will stay in the register; however, they will not receive a final outcome. For these patients, a notation, "transferred back to Category I/II" or "Individualized regimen" should be incorporated into the comment section of the register. These patients will not be analyzed in the cohort of MDR TB patients if they are proven to not have MDR TB or DR TB by DST. Furthermore, patients who start the MDR TB treatment, but whose DST pattern is unknown (i.e. the culture did not grow) are also not to be included within the MDR TB cohort.

The analysis is conducted at 24 months because most patients will have finished treatment, thus, allowing for the preliminary assessment of treatment success rates. Since a few patients may require longer than 24 months for treatment, the cohort analysis is repeated at 36 months after the last patient started treatment. The 36-month evaluation is considered the final treatment cohort analysis result. Patients who remain on treatment at the end of a designated cohort treatment period must be identified as "still on treatment".

Note the following:

- Any case of XDR TB also gets put in to the MDR TB Register. The results of the DST should indicate that they are resistant to kanamycin or capreomycin and a fluoroquinolone. The XDR TB cases will be analyzed separately as an XDR TB cohort.

CHAPTER 4 Case Finding Strategies

The fundamental principle underlying the case-finding strategy for DR TB is the systematic and timely screening of patients at risk and prompt initiation of effective treatment. Early identification of DR TB and prompt treatment-

- Prevents the spread of the disease;
- Helps stop development presumptive DR TB (Priviously known as DR TB suspects) of further amplification of resistance;
- Reduces the progression to permanent lung damage;
- Results in higher cure rates.

4.1 Targeting Risk Groups for DST for First-line Drugs

The following groups will be targeted as presumptive DR TB (previously known as DR TB suspects) for drug susceptibility testing (DST):

High Risk:

- Failures of Category II
- Failures of Category I
- Close contact of a MDR TB patient with symptoms

Medium Risk:

- Non converters of Category II (remain positive at month 3)
- Non converters of Category I (remain positive at month 2)
- All relapses (Category I and II)
- All treatment after loss to follow up (Category I and II)
- Others: Any smear negative or extrapulmonary TB patient clinically not improved in spite of treatment as per NTP guidelines

Low Risk:

- All HIV infected persons

Note: Ensure proper history taking and quality lab performance including follow up sputum examination for identification of presumptive DR TB as per above groups

The following group could be considered for direct enrollment in DR TB regimens:

- Category II failures

All cases of DR TB will be reviewed by the Divisional PMDT Coordinator.

Conventional DST takes a few months (reference Chapter 6) to have the results of resistance. There are new rapid molecular tests, which look for the genetic

mutation responsible for resistance in the DNA of the bacteria. When possible, it is preferable to do a molecular rapid test because the choice of treatment can be made right away. The preferred screening method for DR TB is to use the molecular "DNA rapid DST," which goes by the name of Xpert MTB/RIF.

Xpert MTB/RIF is available in the National Tuberculosis Reference Laboratory (NTRL), all the Regional Tuberculosis Reference Laboratories (RTRL), in a number of CDCs, CDH, Medical colleges and in NGO facilities, while LPA and MGIT is available in NTRL only at present. NTP has plan to establish MGIT in other RTRLs. Presumptive DR TB cases should be sent for screening to the nearest facility with Xpert MTB/RIF testing centres.

4.2 Targeting Risk Groups for DST for Second-line Drugs

Drug susceptibility testing for second-line drugs enables case-finding for XDR TB and guides proper treatment.

The following groups will be targeted for DST to second-line drugs:

- Any patient who has had a past history with any previous second-line anti-TB drugs
- Any patient who remains culture positive on or after Month 4 of the Standard MDR TB Regimen or who revers to a positive culture after Month 4
- Contacts of an individual with documented XDR TB
- MDR TB/HIV patients

4.3 Case Finding in Peadiatric Patients

Children, especially younger ones, may not be able to produce sputum specimens on demand. Children should not be excluded from treatment solely on the basis of non-availability of sputum specimens. Children with active TB who are close contacts of patients with DR TB can be started on DR TB regimens if speaimen in not available.

Extra efforts can be used to get specimens for culture. Induced sputum, tissue biopsy (including fine needle lymph node biopsy), gastric aspirate, urine and/or stool can be sent to NTRL/RTRL for diagnosis.

4.4 Case Finding in HIV-infected Individuals

The diagnosis of TB in HIV-infected people is more difficult and may be confused with other pulmonary or systemic infections. As people living with HIV are more likely to have smear-negative TB or extra-pulmonary TB, the use of chest X-ray and culture is recommended to improve the ability to diagnose TB in smear-negative patients living with HIV. DST testing should be performed for all patients living with HIV and with active TB to prevent death due to unrecognized DR TB. The recommend screening test for MDR TB in HIV patients is the Xpert MTB/RIF.

People living with HIV who have MDR TB should also be screened for XDR TB with DST of second-line agents.

4.5 Case Finding in Contacts of DR TB

Close contacts of DR TB cases can be defined as individuals who are: 1) living in the same household, or 2) spending several hours per day together with the patient in the same indoor living or working space. Symptomatic contacts of DR TB patients should be screened by Xpert MTB/RIF.

4.6 Case Finding of Patients with mono and poly drug Resistance

Mono and poly-drug resistant strains are those that are resistant to anti-TB drugs, however, they are not resistant to both isoniazid and rifampicin. Patients with mono or poly drug resistance may require individualized regimens or may need to be moved to DR TB regimen (ex: HES, R).

4.7 Culture and DST Specimen Collection and Testing

Two sputum specimens (spot and early morning) should be submitted for culture.

Previously treated patients may have had DST in the past but it may no longer reflect the resistance pattern of the strain they have at the time of enrollment in the DR TB control programme. If no DST has been conducted in the previous 30 days, a DST should be done at the start of DR TB treatment. All anti-TB drugs should be stopped for at least 3 days prior to sputum collection for culture. Sputum samples for culture must be processed immediately. However, in case of delay, refrigeration at a temperature range of 2^0-8^0c is recommended, provided that a prompt transfer to Lab will be made within 7 days. Otherwise falcon tube with 1% cetylpyridinium chloride (CPC) in 2% NaCl (Sodium chloride) should be used.

CPC is not permitted for liquid media, therefore, specimens decontaminated with CPC cannot be used for MGIT (Mycobacteria Growth Indicator Tube) techniques. CPC is permitted for LJ solid media only.

Instructions for sputum sample delivery to NTRL/RTRLs/Xpert MTB/RIF testing centres from the referral facility and reporting processes: (The "Referring Facilities" include: UHCs, Urban DOTS Centers, District Hospitals, CDCs, CDHs , Medical College Hospitals etc)

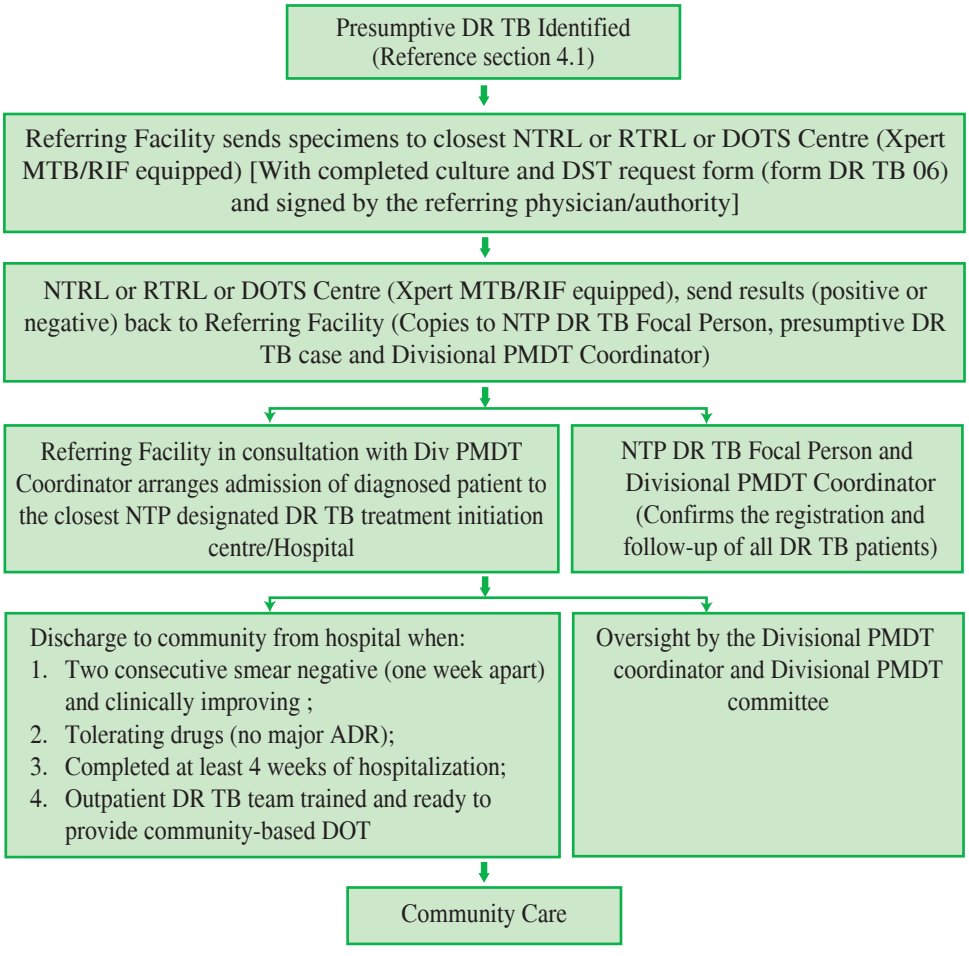
- Any health worker in the field can collect sputum from a presurptive DR TB (as per section 4.1).
- The specimen is sent from the field to a referring facility in a regular sputum cup the same day it is collected. (Note: It is encouraged to send the sputum specimen, not the patient. In complicated cases the patient may be sent to the referring centres for specimen collection and a full evaluation by the DR TB treatment team).
- The specimen is processed within a few hours at the referring facility by

transferring 3- 5 ml of sputum into the Falcon tubes containing 5ml of CPC for solid cluture and DST only.

- For Xpert, fresh specimen should be sent to Xpert facility without CPC (Cetylpyridinium chloride) solution.
- Sputum sample with CPC in the falcon tube will be sent to NTRL or the RTRL via a transport system set up by NTP within 7 days of collection.
- DST results will be sent back in paper system and electronically to the referring facility that sent the specimen with a copy to NTP focal person and respective divisional PMDT coordinator.

Figure 4.1 is a summary of the flow of how a patient gets referred for DR TB screening under NTP. Each UHC or Urban DOTS Centre should have regular scheduled weekly transportation of the specimens.

Figure 4.1. Referral Flow Chart



Test results should be returned to the referring facility from which the sample originated. An important part of case-finding is the reporting of the results and ensuring that all patients diagnosed with DR TB are promptly started on therapy. The referring facilities should ensure enrollment and hospitalization of a patient after getting results from the diagnostic facilities. For DR TB patients, an initial hospitalization will take place to an approved MDR TB ward. Hospitalization will be a minimum of four weeks with patients returning to community-PMDT program when two consecutive sputum smear microscopy become negative one week apart. Patient transition back into the community and how care will be organized within the community is described in the "Standard Operating Procedures (SOP): Community-Based Programmatic Management of Drug Resistant TB 2013" and the care and treatment are described in Chapters 7 through 10 of this manual.

CHAPTER 5 Laboratory Aspects

5.1 General Considerations and Tests offered at the NTRL and RTRLs

The mycobacteriology reference laboratories will provide the following services: (1) primary culture, (2) identification of M. tuberculosis complex and (3) testing for susceptibility to Isoniazid (H), Rifampicin (R), Ethambutol (E) and Streptomycin (S). NTRL currently incorporated liquid culture (BACTEC MGIT) and a multiplex polymerase chain reaction line-probe assay (Hain GenoType MTBDR plus Assay). The NTRL also performing DST to second-line anti-TB drugs in presumptive XDR. Furthermore, NTP has introduced molecular "automated real time PCR," i.e. Xpert MTB/RIF at reference laboratories, CDC, Chest Disease Hospital and selected TB care facilities.

All sputum examinations including smear, culture and DST are free of charge. The transport and flow of specimens is described in Chapter 4.

Clinical laboratory services including: basic haematology, biochemistry, serology and urine analysis are provided through central and district hospitals, as to ensure that the proper evaluation and monitoring of patients occur.

The NTRL and RTRLs also take part in monitoring levels of drug resistance to first and second-line drugs in the population. The NTRL is linked with super National referance laboratory (SNRL) in Antwerp, Belgium.

5.2 Microscopy, Culture, and M. Tuberculosis Identification in DR TB

This section describes basic information about the role of microscopy, culture and identification test for the DR TB.

- **Microscopy.** Acid-fast Bacilli (AFB) examined under the microscope cannot distinguish between drug-susceptible and Drug Resistant M. tuberculosis. AFB also cannot differentiate between species of bacteria. It can not differentiate between live and dead bacilli, Therefore, the main use of microscopy for Drug Resistant TB is limited to assessing the infectiousness of patients and confirming that microbes growing on (or in) artificial media are mycobacteria rather than contaminants. Microscopy gives early results that are not affected by transport delays or other reasons for false negative results of cultures. They will regularly be of value, and they should always be considered together with the clinical condition and culture results.
- **Culture**. Delays in specimen transport, excessively harsh or insufficient decontamination, poor-quality culture media or incorrect incubation temperature can adversely affect the culture yield. Laboratory errors, such as mislabeling or cross-contamination between specimens during aerosol-

producing procedures, may lead to false-negative or false-positive results. In this context, laboratory findings should always be correlated with the patient's clinical condition and any diagnostic test should be repeated, if necessary, will be retained a single culture with low colony counts should be repeated on two fresh samples as soon as possible. Persistent positive cultures or any positive culture combined with clinical deterioration should be regarded as significant. At this time, culture is only done on LJ Medium at the reference laboratories. NTRL may also perform 2nd line DST and species indintification by MGIT, LPA and other devices endorsed by WHO.

- **Identification of M. Tuberculosis.** Due to the high burden of TB in Bangladesh, most mycobacterial isolates will be M. tuberculosis complex. For confirmation, NTRL and RTRLs will conduct standard identification tests on all cultures.

5.3 Drug Susceptibility Testing (DST)

DST is done on LJ Medium using the proportion methods at the reference laboratories. The initial culture can take up to two months, and then DST is performed from a positive culture, which can take up to an additional 6 weeks. On average full turnaround time for a DST report is 60 to 90 days after the collection of the sputum. DST is done for the following drugs: H, R, E, PZA and S.

Under the indications described in Chapter 4, DST is performed on second line anti-TB drugs: kanamycin (Km), and ofloxacin (Ofx)/levofloxacin (Lfx) at NTRL.

5.4 Molecular Testing

Molecular tests can confirm whether a patient has TB and if there is evidence of resistance within a few hours. The two types of molecular tests are available described below:

- **Automated real time PCR (Xpert MTB/RIF).** The Xpert MTB/RIF system gives two types of information: (1) If M. Tuberculosis (MTB) is present in the specimen, and (2) if there is MTB, the genetic mutations for Rifampicin resistance.

  In contrast to other techniques (in vitro cultures, DST and conventional molecular techniques), the Xpert MTB/RIF can be used in peripheral laboratories and does not require sophisticated equipment and/or very skilled personnel. It can diagnose pulmonary TB and EP TB resistance to Rifampicin from sputum samples or other tissue or body fluids (not blood). It works on a real-time PCR basis and identifies genetic sequences of the bacteria. It is a highly automated (only 3 manual steps required) test run in a closed system with one cartridge per sample, thus it is less prone to contamination than other PCR based test within 2 hours. Published results from evaluation studies have showed that for TB detection the assay has sensitivities of 98% for smear-positive, culture positive samples, and 72% for smear-negative, culture-

positive samples (sensitivity can reach 90% if the test is repeated 3 times).

For Rifampicin resistance, the sensitivity compared with conventional DST on culture is 97.6%. The test has a high negative predictive value, so Rifampicin-negatives can be considered to be true negatives. The positive predictive value is lower. Thus, false positives for Rifampicin resistance can occur, especially if the pre-test probability of the patient having MDR TB is less than 10%. Therefore, confirmation tests with conventional DST will be done for all new patients testing Rifampicin resistant with Xpert MTB/RIF. Xpert MTB/RIF does not eliminate the need for conventional microscopy, culture and DST; all of which are required to monitor treatment progress and to detect resistance to drugs other than Rifampicin. Due to the fact that Xpert MTB/RIF can detect dead bacilli, it is not used as a substitute for monitoring cultures while patients are on DR TB treatment.

The following is a general description of what to do with the results for patients tested using Xpert MTB/RIF:
MTB-/RIF-: (suggest collecting a second specimen if clinically indicated).
MTB+/RIF-: No further culture or DST is needed.
MTB+/RIF+: Do confirmation by culture and DST for all new cases.

Line probe assays (Hain test) This is also a molecular method that provides results within 3 days. Unlike the Xpert, it has numerous steps and needs a highly equipped laboratory with high level of biosafety. HAIN also allows for the detection of both Rifampicin and Isoniazid resistance. The commercial HAIN tests are very good at detecting Rifampicin resistance among smear-positive patients (sensitivity and specificity > 99%), however, the HAIN test for Isoniazid has a lower sensitivity (about 70%).

Constraints of HAIN test remain the high cost, high infrastructure requirement, high level of technical training and the risk of cross-contamination.

NTRL may perform operational research on new diagnostic tools.

5.5 Limitations of DST

The clinician needs to understand the limitations of DST and interpret the results accordingly. DST provides an indication as to the likelihood of a drug being effective or not.

5.6 Time for Testing and Reporting: Turnaround Time

Growth detection and identification of M. Tuberculosis may take about 3-8 weeks on LJ solid media. DST of an M. Tuberculosis isolate takes an additional 6 weeks in LJ solid media. Using the Liquid MGIT System, the turn around time for culture is 10 to 14 days and an additional 12 days for DST. Molecular test turn around time is one day.

5.7 Quality Control and Quality Assurance

The procedures for internal quality control will be performed periodically to monitor the quality of primary culture. The quality control of DST will be done during each batch of tests using control strains. The external quality assessment will be done by exchange of strains with the Supra National Reference Laboratory.

A comprehensive, routine system of internal quality control and external quality assessment is implemented at the NTRL and all RTRLs. The NTRL is linked to SNRL in Antwerp, Belgium and participates in regular validation of DST.

5.8 Summary of Bacteriological Exams

Table 5.1 Summarizes the types of bacteriological tests and turn around times for culture and DST.

Table 5.1 Summary Table of Bacteriological Examinations

Test	Sensitivity AFB/ml	Average turn around time for detection of AFB.	Additional turn around time for the DST (average)	Location
Microscopy	> 5 000	2h	N/A	NTRL, RTRLs, DOTS Centres
LJ Culture solid	around 100 cfu/ml (colony forming unit)	majority by 4 weeks	6 weeks	NTRL, RTRLs
Culture liquid (MGIT)	around 10 cfu/ml (colony forming unit)	10-12 days	12 Days	NTRL
Hain Geno Type	only on smear positive	3 days	N/A	NTRL
Xpert MTB/RIF	around 10 cfu/ml (colony forming unit)	2 hrs	N/A	NTRL, RTRLs and DOTS Centres (Xpert equiped)

CHAPTER 6 Treatment Strategies for MDR TB and XDR TB

6.1 Background on the Treatment Strategy for MDR TB and XDR TB

The treatment strategies designed for all forms of DR TB are described in this chapter. The DR TB Programme in Bangladesh will use different types of regimens depending on resistance pattern.

The standard DR TB regimen for patients who are identified to have (or very likely to have) MDR TB, but unlikely to have XDR TB, will be referred to as the "Standard MDR TB Regimen". The standard regimen designed to treat XDR TB will be referred to as the "Standard XDR TB Regimen"; while both regimens are standardized, there are circumstances that will allow for some individual adjustment. This chapter also provides standard regimens for mono- and poly-drug resistance patterns.

The regimens outlined in this manual are designed based on currently available DRS data.

All MDR TB and XDR TB regimens will consist of two phases: the first phase is the period in which the injectable agent is used (referred to as the intensive phase), and the second phase is after it is stopped (referred to as the continuation phase) up to the end of treatment. Treatment regimen for XDR TB cases can be constructed individually based of DST profiles and availability of drugs.

Adverse drug reaction (ADR) should be immediately and adequately managed in order to minimize the risk of treatment interruptions and to prevent increased morbidity and mortality due to serious adverse drug reactions. Adverse drug reaction (ADR) are discussed in Chapter 9.

Each dose is given as directly observed therapy (DOT) throughout the treatment for all DR TB Regimens. Treatment card is marked for each observed dose.

One of the most important principles of the treatment of DR TB is to diagnose the patient early, before there is extensive lung damage, and promptly start treatment. All DR TB regimens perform better (i.e. higher cure rates) when there is less extensive lung damage at the start of treatment.

6.2 Groups of Anti-Tuberculosis Drugs

The classes of anti-tuberculosis drugs have traditionally been divided into first- and second-line drugs, with isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol being the primary first-line drugs. These guidelines will often refer to this classification system; yet, will also use a group system based on efficacy, experience of use and drugs classes. These groups are referred to in the

following sections and are very useful for the design of DR TB treatment regimens. The different groups are shown in Table 6.1. Not all drugs in the same group have the same efficacy or safety profiles

Table 6.1. Classification (Groups) of Anti-TB drugs

Grouping	Drugs	Remarks
Group 1 First-line oral agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z);	These are the most potent and best tolerated drugs. Pyrazinamide is used in the Standard MDR TB regimens because it is thought to retain some susceptibility in many cases of MDR TB. However, caution is warranted, because whenever a drug was used in a previous regimen that failed, it should not be heavily relied upon as a key drug.
Group 2 Injectable agents	Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Streptomycin (S)	All regimens to treat MDR TB or XDR TB includes; an injectable agent. Given the greater ototoxicity with streptomycin and high rates of streptomycin resistance in DR TB cases, it will not be used to treat DR TB in Bangladesh. Amikacin and kanamycin are considered to be very similar and have a high frequency of cross-resistance. There is low cross-resistance with kanamycin (or amikacin) and capreomycin.
Group 3 Fluoroquinolones	Moxifloxacin (Mfx); Levofloxacin (Lfx); Ofloxacin (Ofx)	All patients should receive one of the fluoroquinolones. The most potent available fluoroquinolones in descending order based on in vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin> ofloxacin. Levofloxacin is the fluoroquinolone on the Standard MDR TB Regimen while moxifloxacin will be used in the Standard XDR TB Regimen.
Group 4 Oral bacteriostatic second-line agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); *p*-aminosalicylic acid (PAS)	The Standard MDR TB Regimen in Bangladesh employs at least two agents from Group 4. In general, avoid the combination of PAS with ethionamide (or prothionamide) because of increased gastrointestinal side effects and hypothyroidism, however, sometimes this combination is needed. The drugs in Group 4 may be started at a low dose and escalated over seven days (this is called drug ramping).
Group 5 Agents with unclear role in DR TB treatment (not recommended by WHO for routine use in DR TB patients)	Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/Clavulanate (Amx/Clv); Clarithromycin (Clr); Thioacetazone (Thz); Imipenem/Cilastatin (Ipm/Cln); High-dose Isoniazid (High-dose H);[a]	These drugs are not recommended by the WHO for routine use in DR TB treatment because their contribution to the efficacy of multidrug regimens is unclear. However, they can be used in cases of XDR TB. Only clofazimine and amoxicillin/ clavulanate are used routinely in Bangladesh for the Standard XDR TB regimen. Other drugs may be added in consultation with an expert in the treatment of XDR TB. If strains resistant to low concentrations of INH, but are susceptible to higher concentrations, then high-dose INH[a] can be considered

[a] High-dose H is defined as 16–20 mg/kg/day.

6.3 The Standard MDR TB Regimen

The recommended Standard MDR TB Regimen is as follows:

8{Km-Z-Lfx (Ofx)-Eto-Cs}/12{Lfx (Ofx)-Eto- Cs-Z}

The numbers in front of the drug abbreviations represent the average number of months the drugs are to be given. For exact length of the intensive phase and total treatment lengths refer to Sections 6.7 and 6.8 within this chapter. Four are second-line anti-TB drugs, one of which is an injectable (Km). Pyrazinamide is added to this regimen, although it is first line drug because the probability of susceptibility is still high.

If kanamycin is not available, amikacin can be substituted. Additionally, prothionamide can be substituted for ethionamide.

6.4 The Standard XDR TB Regimen

The recommended Standard XDR TB Regimen is as follows:

12(Cm-Z-Mfx-PAS-Cs-Amx/Clv- Lzd -Cfz) / 12(Z-Mfx-PAS-Cs-Amx/Clv- Lzd -Cfz)

XDR TB and failures of the Standard MDR TB Regimen should be treated with the above regimen. If the injectable agent, capreomycin, is resistant and kanamycin has retained susceptibility, kanamycin can be used. If both kanamycin and capreomycin are resistant, it is still advisable to include one of them in the regimen, with a preference to the agent to which the patient has had less exposure. This is because DST for injectable agents is not perfect and options are limited. Ethionamide can be added if there is evidence to suggest it is still susceptible. Additional drugs from Group 4 or 5 can also be added under the review by a PMDT committee or an expert in the field of XDR TB treatment. Individualized treatment based on DST results (if possible) is best for management of XDR TB (if possible). The exact regimen (individualized) for all XDR TB patients will be determined by Clinical Management Committee considering DST reports.

6.5 Dosing of Second line Anti-TB drugs

Dosing of anti-tuberculosis drugs is based on the weight of the patient. Therefore, monthly monitoring of patient body weight is important, especially in paediatric cases where the adjustment of doses should be monitored closely since children gain weight rapidly. Similarly, when adults gain weight or move into a higher weight class, their medication dose should be adjusted as well (reference Table 6.2).

- **Adult dosing of anti-TB drugs.** The adult dosages of anti-TB drugs are shown in Table 6.2, which provides the drug abbreviations and the average daily dose and the dosing as per three different adult weight classes for adults. All drugs listed in Table 6.2 are not used in Bangladesh for DR TB, however, This table provides an overview of anti TB drugs.

Table 6.2. Adult Dosages of Second line Anti-tuberculosis Drugs

Drug*	<33 Kg mg/kg/day	33-50 kg mg/kg/day	51–70 kg mg/kg/day	>70 kg (max dose) mg/kg/day
Pyrazinamide (Z) (500mg)	**30–40 mg**	**1000-1750 mg**	**1750-2000 mg**	**2000-2500 mg**
Amikacin (Am) (1 g vial)	15–20 mg	500-750 mg	1000 mg	1000 mg
Kanamycin (Km) (1 g vial)	**15–20 mg**	**500-750 mg**	**1000 mg**	**1000 mg**
Capreomycin (Cm) (1 g vial)	15–20 mg	500-750 mg	1000 mg	1000 mg
Levofloxacin (Lfx) (250 mg, 500 mg)	7.5-10 mg	750mg	750 mg	750-1000 mg
Moxifloxacin (Mfx) (400 mg)	7.5-10 mg	**400mg**	**400 mg**	**400mg**
Ofloxacin (Ofx) (200 mg	15-20 mg	800 mg	800mg	800-1000 mg
Ethionamide (Eto) (250 mg)	**15–20 mg**	**500mg**	**750 mg**	**750–1000 mg**
Protionamide (Pto) (250 mg)	15–20 mg	500mg	750 mg	750–1000 mg
Cycloserine (Cs) (250 mg)	**15–20 mg**	**500mg**	**750 mg**	**750–1000 mg**
P-aminosalicylic acid (PAS) (4 g sachets)	150 mg	8 g	8 g	8 -12 g
Group 5 drugs				
Clofazimine (Cfz)	50mg	100mg	100mg	200mg
Amoxicillin/Clavulanate (Amx/Clv)	Normal dose 875/125mg twice daily (Preferably) or 500/125 three times daily			
Clarithromycin (Clr)	Usual adult dose is 500 mg twice daily.			
High-dose INH (H)	16-20mg/kg daily			
Linezolid (Lzd)	Usual adult dose is 600 mg twice daily. Most reduce the dose to 600 mg once a day after 4 to 6 weeks to decrease adverse effects.			
Thioacetazone (Thz)	Usual adult dose is 150 mg per day			
Imipenem/cilastatin (Ipm/Cln)	Usual adult dose is 500-1000 mg IV every 6 hours.			

*Drugs in the Standard MDR TB Regimen are Bolded.

Paediatric dosing of anti-TB drugs. The dosing for pediatric patients is described in Table 6.3. For children, all drugs in the standard MDR TB regimen, including the fluoroquinolones, should be dosed at the higher end of the recommended ranges.

Table 6.3 Paediatric Dosages of Second-line Anti-tuberculosis Drugs

Drug	Daily dose (mg/kg)	Frequency	Maximum daily dose
Isoniazid (H) (50 mg, 100 mg, 300 mg, 50mg/5ml solution)	10 (10 - 15)	Once daily	300 mg
Rifampicin ® (150 mg, 300 mg)	15 (10 - 20)	Once daily	600 mg
Pyrazinamide (Z) (400 mg, 500 mg)	35 (30 - 40)	Once daily	
Ethambutol (E) (100 mg, 400 mg)	15 (15 - 25)	Once daily	
Streptomycin (S) (1 g vial)	20 - 40	Once daily	1 g
Kanamycin (Km) (1 g vial)	15 - 30	Once daily	1 g
Amikacin (Am) (1 g vial)	15 - 22.5	Once daily	1 g
Capreomycin (Cm) (1 g vial)	15 - 30	Once daily	1 g
Ofloxacin (Ofx) (200 mg)	15 - 20	Once daily	1000 mg
Levofloxacin (Lfx) (250 mg, 500 mg)	15 - 20 < 5years 10 > 5 years	Once daily	1000 mg
Moxifloxacin (Mfx) (400 mg)	7.5 - 10	Once daily	400 mg
Clarithromycin (Clr)	20 mg	Twice daily	
Ethionamide (Eto) (250 mg)	15 - 20	Once daily	1 g
Prothionamide	15 - 20	Once daily	1 g
Cycloserine (Cs) (250 mg)	10 - 20	Once or twice daily	1 g
PAS (4 g sachets)	300	Twice or thrice daily	12 g
Clofazimine (Cfz) (50 and 100mg)	2-3	Twice daily	200 mg
Amoxycillin/Clavulanate (Amx/Clv) (500/125) – dosing is base on Amoxacillin component.	30 mg (< 3 months) 45 mg (> 3 months and less than 40 kg)	Twice daily.	2000 mg

Important notes :

All patients receiving cycloserine should also receive pyridoxine. The recommended daily dose is 50 mg of pyridoxine for every 250 mg of cycloserine.

Once daily dosing for all drugs is preferred. However, many patients cannot tolerate once-daily dosing of ethionamide, cycloserine or PAS. These drugs may be given in divided doses twice-daily, strictly under DOT. Injectable agents, fluoroquinolones and pyrazinamide, are always given in a single daily dose (do not split dosage over the day).

6.6 Length of the Intensive Phase of the MDR TB and XDR TB Regimen

The recommended administration duration of the injectable agent is guided by culture conversion (reference Table 6.4 and 6.5).

- **Patients on the Standard MDR TB Regimen:** the injectable agent should be given for four months past culture conversion and for a minimum of at least 8 months. It is given seven days a week. Injectable agent should be continued for at least 8 months. For patients who have completed 4 months of treatment having documented culture conversion and are clinically doing well, consideration to decrease the injectable to three times a week can be made by the xpert clinician. Do not decrease the injectable to three times a week for patients who have not culture converted (unless suffering from severe adverse reaction). In case of re-conversion, the duration should be determined by Clinical Management Committee.
- **Patients on the Standard XDR TB Regimen:** Proposed duration of treatment is minimum 24 months (Intensive phase minimum 12 months + Continuation phase minimum 12 months). However, the final decision will be taken by Clinical Management Committee.

6.7 Length of MDR TB and XDR TB Treatment

The Standard MDR TB Regimen should be given for a minimum of 20 months and at least 18 months past sustained cultrue conversion (reference Table 6.4). The Standard XDR TB Regimen should be given for at least 22 months past culture conversion.

Table 6.4 Length of Treatment for the Standard MDR TB Regimen

Date of first sustained conversion*	Length of injectable agent	Length of Total treatment for Standard MDR TB regimen
Between month 0 and 4	8 months	20 - 22 months
Between months 5 and 8	Add 4 months from conversion date	Add 18 months from conversion date

*Date of first negative smear and culture by two consecutive months

- **Patients still culture positive after month 4 of treatment:** Patients who have not converted by month 4 should be ruled out for XDR. IF XDR TB is found, stop the Standard MDR TB Regimen, the Standard XDR TB Regimen should be started and other additional management can be stated as per decision of Clinical Management Committee.

Table 6.5 Length of Treatment for Standard XDR TB Regimen

Date of first sustained conversion*	Length of injectable agent	Length of Total treatment for Standard MDR TB regimen
Between month 0 and 2	12 months	24 months
Between months 3 and 6	Add 10 months from conversion date	Add 22 months from conversion date

Patients still culture positive after month 6 of treatment: Patients who have not converted by month 6 consider surgical intervention or adding compassionate use drugs. **

Patients still culture positive after 12 months of treatment: Consider stopping*** the XDR TB Regimen and starting palliative care.

* Date of first negative smear and culture of two negative consecutive months

** Compassionate use drugs are new anti-TB drugs that have not yet gained approval from stringent drug authorities but are used for compassionate use. Detailed in Annex-3.

*** Stopping DR TB therapy should only be done in agreement with the patient. The process is described in Section 6.12 and 6.13.

Notes on MDR TB and XDR TB Standard Regimens:

A culture with a few colonies may be a lab contaminant or lab error. Treatment may not need to be extended if a single culture or smear is considered as false positive.

Most patients on the Standard MDR TB Regimen will convert to negative smear and culture between months 0 and 2 and will need only 20 months of treatment.

Box 6.1 Example of Stopping the Injectable Agent

Example: You are examining the bacteriology of a patient on Month 8. The available culture report is up to month 06 with month 07, and 08 pending . Month 06 bears the second negative smear and culture i.e sustained conversion. The patient is still on kanamycin.

What is the date of conversion?

The date of the conversion will be the date on which month 05 sputum was submitted.

What is the recommended length of the injectable agent?

For this patient the total duration of injectable should be 9 months (Date of 1st culture conversion i.e 05 months Plus 04 months)

What is the recommended total treatment length?

For this patient, the total treatment length should be given 18 months past month 1st culture conversion i.e 05 months. The total duration of treatment should be 23 months (05 Months Plus 18 Months).

6.8 Treatment of Extrapulmonary DR TB

Extrapulmonary DR TB is treated with the same strategy and duration as pulmonary DR TB. Please note, the fluoroquinolones have variable CSF penetration, with better penetration seen in the later generations. i.e.Moxifloxacin.

6.9 Treatment of Mono and Poly-Resistant Strains of TB

Non-MDR TB cases that started on the Standard MDR TB regimen will be put back on Category II or an individualized treatment regimen as per the decision of the PMDT Committee based on the strategy outlined in Table 6.6. Exceptions will need to be made for patients with mono-and poly-resistant drug patterns that include: rifampicin or poly-resistant to isoniazid, ethambutol plus streptomycin. These patients will continue with the Standard MDR TB regimen.

Table 6.6 provides a guide for suggested regimens depending on the resistance pattern of mono- and poly-resistant cases. When using this table, it is essential to consider whether resistance has been acquired to any of the drugs that will be used in the recommended regimen.

- If development of further resistance is suspected, do not use Table 6.6. For example, if a patient had a DST specimen collected at the start of Category I and the results show mono-isoniazid resistance three months after the start of treatment, then the patient will have had one month or more of mono-therapy with rifampicin (i.e. patient is taking isoniazid-rifampicin in the continuation phase, but the strain is isoniazid resistant). In such cases , it should be considered that rifampicin is compromised (the strain probably has developed resistance to rifampicin). Table 6.6 should not be used, and need to be screened for R resistant by Xpert, If patient is found as Resistant to R, the patient should be enrolled under Standard MDR TB Regimen.
- Before starting an individualized regimen, check rifampicin resistance with a rapid genetic test. Before starting a patient on a modified regimen, check a specimen for rifampicin resistance with Xpert MTB/RIF test.

Table 6. 6 Recommended Treatment Regimens for Mono and Poly Resistant Cases

Pattern of resistance	Suggested regimen	Minimum duration of treatment (months)	Comments
H (± S)	* R, Z, E	9	Perform Xpert MTB/RIF prior to starting regimen
H and E	*R, Z, Fq	12	Perform Xpert MTB/RIF prior to starting regimen
R	Give Standard MDR TB regimen and enter into the DR TB register.	Minimum 20	Even though this is not MDR TB, rifampicin resistance will warrant a number of second-line drugs to be used. This is best done with the Standard MDR TB regimen.
H, E, S	Give Standard MDR TB regimen and enter into the DR TB register.	Minimum 20	Even though this is not MDR TB, such high resistance will warrant a number of second line drugs best done with the Standard MDR TB regimen.

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin
*For easy administration, 4FDC can be given.

6.10 Adjunctive Therapy in DR TB Treatment

A number of adjunctive modalities are used to lessen morbidity and improve DR TB treatment results. These include nutritional support (considered the most important) and the use of corticosteroids, surgery.

- **Nutritional support:** DR TB not only causes malnutrition, but, it can also be exacerbated by poor nutritional status. Without nutritional support, patients can become enmeshed in a vicious cycle of malnutrition and disease especially those already suffering from baseline hunger. The second-line anti-tuberculosis medications can also further decrease appetite, making adequate nutrition a greater challenge. Nutritional needs should be addressed in DR TB patients, including having an adequate source of protein.

  Vitamin B6 (pyridoxine) should also be given to all patients receiving cycloserine to prevent adverse neurological effects. Vitamin B6 can be given to patient on cycloserine in a dose of 50 mg per 250 mg cycloserine. If needed, other vitamins and mineral supplements can be given to a patient as well. If minerals (zinc, iron, calcium, etc.) are given, they should be administered at a different time from the fluoroquinolones, as they can interfere with the absorption of these drugs.

- **Corticosteroids:** The adjuvant use of corticosteroids in DR TB patients has been shown to reduce morbidity and can be beneficial in conditions such as
  1. Severe respiratory insufficiency
  2. Central nervous system involvement
  3. Pericardial involvement
  4. Adrenal insufficiency
  5. Ocular involvement.

Prednisolone is commonly used, starting at approximately 1 mg/kg for 6 weeks and gradually decreasing the dose by 5-10 mg per week, when a long course is indicated. Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisolone may be given in a short course of 1-2 weeks at a dose of 1 mg/kg body weight. Injectable corticosteroids (Hydrocortisone/ Dexamethasone) are often used initially when a more immediate response is needed.

- **Surgery:** If there is significant localized lung damage, some DR TB patients may get benefit from surgical interventions. The most common operative procedure in patients with pulmonary DR TB is resection surgery (taking out part or all of the diseased lung). It is usually not indicated in patients with extensive bilateral disease. At present, specialized surgical facilities with

stringent infection control measures, and post-operative care facilities with mechanical ventilation, are available on a limited basis for such patients in Bangladesh. Therefore surgery is not offered routinely as adjunctive therapy in Bangladesh. However, for patients who remain sputum culture-positive after 8 months of treatment, have strains resistant to a high number of drugs, and have localized pulmonary disease surgical resection can be performed. Surgery is not indicated in patients with extensive bilateral disease.

At least two months of MDR/XDR therapy should be given before surgical resection to decrease the bacterial infection in the surrounding lung tissue. The MDR TB or XDR TB regimen should be continued without interruption except for the immediate one or two days during the postoperative period. Even with successful resection, an additional 12-24 months of anti-TB therapy should be given and the criteria of 18 months past conversion should be followed.

Resection of an entire lobe or an entire lung is the most common procedure, as it has been shown to be effective and safe under appropriate surgical conditions. Regardless of the specific procedure, surgery should be timed to offer the patient the best possibility of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower, for example, when the disease is still localized to one lung or one lung lobe.

6.11 Assessment of Patients at Risk for Failure

After four months of treatment, patients who do not show signs of improvement are at risk for treatment failure. Patients who show clinical, radiological, bacteriological evidence of progressive active disease or reappearance of disease, should be considered as being at high risk for treatment failure. The following steps are recommended in such patients:

- The treatment card should be reviewed to confirm that the patient has adhered to treatment.
- Non-confrontational discussions with the patient (with and without the presence of the DOT provider) on whether doses have been missed should be conducted.
- Non-confrontational discussions with the DOT provider (without the patient) on whether doses have been missed should be conducted. Questions should be asked to rule out the possibility of treatment manipulation by the DOT provider. If manipulation is suspected, the patient with suspected treatment failure should be assigned to a new DOT provider.
- If culture positive at month 4, DST to second-line drugs should be performed
- Consider added nutritional support
- Consider the possibility of non tubercular mycobacterial infection (NTM) . All isolates cultured from the 4th month onwards will be sent for DST for first- and second line drugs at NTRL.
- Repeat chest x-ray as radiographic deterioration may indicate that the present

regimen is not effective or may show other causes as to why the patient is clinically getting worse (i.e. pnuemothorax, bulla, pleural effusions, Carcinoma etc.).

- Other illnesses that may decrease absorption of medicines (e.g.chronic diarrhoea) or that may result in immune suppression (e.g. Diabetes Mellitus, Patients on immunosuppressive therapy, HIV infection etc.) should be excluded.
- If persistently positive at month 4 or beyond, evaluate if surgical resection is feasible.

6.12 Approach to Patients with Unequivocal Second-line Treatment Failure

The approach to suspending therapy should start with discussions among the clinical team, including all physicians, nurses and DOT workers involved in the patient's care. Once the clinical team decides that treatment should be suspended, a clear plan should be prepared for approaching the patient and the family. This process usually requires a number of visits and takes place over several weeks. Home visits during the process offer an excellent opportunity to talk with family members and the patient in a familiar environment. It is not recommended to suspend therapy before the patient understands and accepts the reasons to do so, and the patient agrees with the supportive care offered.

6.13 Supportive and Palliative Measures for DR TB

The patients where DR TB treatment is being stopped because of failure, it is very important that medical visits be continued and that the patient is not abandoned. The supportive measures are described in detail in the Integrated Management of Adolescent and Adult Illness guidelines produced by WHO in a booklet titled Palliative care: symptom management and end-of-life care (1). The supportive measures are summarized in Box 6.2.

Box 6.2 Supportive measures for end-of -life care and for very sick patients (but who may not necessarily be at the end-of life)

- Preventive General measures: Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important.
- Nutritional support. Small and frequent meals are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient's condition deteriorates and during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- Relief of respiratory insufficiency. Oxygen therapy if indicated, short acting bronchodilator through volumetric spacer may be used to alleviate respiratory.
- Pain control and symptom relief. Paracetamol, or codeine with paracetamol, gives relief from moderate pain. Codeine also helps to control cough. Other cough suppressants can be added. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable.

- Regular medical visits. When therapy stops, regular visits by the treating physician and support team should not be discontinued.
- Continuation of ancillary medicines. All necessary ancillary medications should be continued as needed. Depression and anxiety, if present, should be addressed.
- Infection control measures. The patient who is taken off antituberculosis treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued.
- Hospitalization, hospice care or nursing home care. Having a patient die at home can be difficult for the family. Hospice-like care should be offered to families who want to keep the patient at home. Inpatient end-of-life care should be available to those for whom home care is not available.

6.14 Management of Patients with Relapse of Second-line Treatment

Patients who are cured under the DR TB program should be instructed to report back to their Outpatient DR TB Team every 6 months post treatment for follow-up visits for 2 years. Besides clinical examination, these follow-up visits include testing of one morning sputum sample by AFB-microscopy and culture for MTB. Any patient with a positive result need to be referred to the PMDT committee for proper management.

CHAPTER 7 Treatment of DR TB in Special Situations

7.1 Pregnancy

All female patients of childbearing age (15-49 years) should be tested for pregnancy upon initial evaluation for DR TB. Pregnancy is not a contraindication for treatment of active Drug Resistant TB. So treatment of DR TB should be instituted to save the lives of both the mother and fetus. However, birth control is strongly recommended for all non-pregnant women receiving therapy for Drug Resistant TB because of the potential consequences from frequent and severe adverse drug reactions to mother and fetus.

Pregnant patients should be carefully evaluated, taking into consideration gestational age and severity of the drug-resistance. The risks and benefits of treatment of Drug Resistant TB should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. The followings are some general guidelines.

- Start treatment of drug resistance in second trimester or sooner if condition of patient is severe. Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester. This decision is primarily based on clinical judgment (usually reflected in extent of weight loss and lung involvement during the previous weeks). When therapy is started, three or four oral drugs with demonstrated efficacy against the infecting strain should be used, and then this treatment regimen should be reinforced with an injectable agent and possibly other oral drugs immediately postpartum.

  Avoid injectable agents. For the most part, aminoglycosides should not be used in the regimens of pregnant patients since they can be particularly toxic to the developing fetal ear. Capreomycin may carry the same risk of ototoxicity, but the injectable is the drug of choice if an injectable agent cannot be avoided. It is suggested to use capreomycin if there is extensive lung damage, shortness of breath, severe weight loss and/or fear that without the injectable agent the patient is unlikely to be cured.
- Avoid ethionamide. Ethionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies. If possible, ethionamide should be avoided in pregnant patients.
- A suggested regimen for MDR TB during pregnancy is the following:

  Lfx-Cs-PAS-Amx/Clv Z (plus or minus Capreomycin)

The above mentioned measures should be carried out until delivery, at which point standard DR TB treatment should be resumed.

7.2 Breast feeding

- Breast feeding woman with active MDR TB should receive the standard DR TB regimens as any other patient.
- In lactating mothers on treatment, most anti-TB drugs are found in the breast milk in concentrations that would equal only a small fraction of a therapeutic dose used in an infant.
- Close contact between the mother and her baby should be minimized and the patient should wear a cloth sursical mask in the presence of the infant until the patient is documented culture negative. Contact is preferably at outdoors or in a very well ventilated area. If the mother is sputum smear-positive, the care of the infant should be left to family members until she becomes sputum smear-negative, if this is feasible.

7.3 Contraception

- There is no contraindication to taking oral contraceptives while on the Standardized DR TB regimen.
- Patients who vomit directly after taking an oral contraceptive can be at risk for decreased absorption of the drug, and therefore, decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-TB treatment.
- Barrier method should be encouraged.

7.4 Patients with Alcohol Problems and Narcotic Drug Users

- Patients with substance dependency problems should be offered treatment for their addiction or psychotherapy. Complete abstinence from alcohol or other substances should be strongly encouraged. If the treatment is repeatedly interrupted because of the patient's addiction, therapy should be suspended until successful addiction treatment or measures to ensure adherence are established. Good DOT gives the patient contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependency.
- Baseline liver enzyme estimation should be performed to check if the standardized regimen is appropriate. During treatment, liver enzymes will be monitored every three months.

7.5 Liver disorders

Patients with a history of liver disease can receive the Standardized DR TB regimens provided there is no active liver disease. However, hepatotoxic reactions to anti-TB drugs may be more common in these patients and should be anticipated.

In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

7.6 Children

Children should have culture and DST on specimens (gastric lavage, sputum, pus etc) under the same indications as adults.They should be started on the Standardized DR TB regimens with adjusted doses as shown in the table below.

- Children who have failed Category I and II should follow the same algorithm as adults. Sputum samples or gastric lavage should have to be tested in Xpert/MTB Rif. They should be started on the Standardized DR TB regimens with adjusted doses as shown in the Table 6.3.
- Children who have never taken anti-TB drugs before and are contacts of DR TB patients are eligible for Xpert/MTB Rif and culture and DST.
- Paediatric dosing of second line anti-TB drugs is given in Table 6.3
- Anti-TB drugs should be dosed according to body weight. Monitoring monthly weights is therefore important in pediatrics cases as in adults, with adjustment of doses as the child gains weight.
- All drugs in the Standardized DR TB regimens should be dosed at the higher end of recommended ranges whenever possible.
- In children who are not culture-positive initially, treatment failure is difficult to assess. Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement. In children, weight loss, or more commonly, failure to gain weight adequately, is of particular concern. It is often one of the first (or only) signs of treatment failure. This is another key reason to monitor weight carefully in children.

7.7 Diabetes Mellitus

Diabetic patients with DR TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus (DM) may potentiate adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. DM must be managed closely throughout treatment of Drug Resistant TB. Insulin is preferred but oral hypoglycemic agents are not contraindicated during the treatment of Drug Resistant TB, however they may require the patient to increase the dosage. Use of ethionamide may make it more difficult to control insulin levels. Serum creatinine and serum electrolytes (esp. Potassium) levels should be monitored more frequently, often weekly for the first month, and then at least monthly thereafter.

7.8 Renal Insufficiency

Renal insufficiency caused by longstanding TB infection itself or previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Table 7.1.

As described in Chapter 9, all patients are monitored every month for creatinine and potassium level while on the injectable agent for new or worsening nephrotoxicity.

Table: 7.1 Dosage for renal Insufficiency

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receivinghaemodialysis
isoniazid	No change	300 mg once daily, or 900 mg three times per week
rifampicin	No change	600 mg once daily, or 600 mg three times per week
pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
ofloxacin	Yes	600–800 mg per dose three times per week (not daily)
levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
moxifloxacin	No change	400 mg once daily
cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per weekd
prothionamide	No change	250–500 mg per dose daily
ethionamide	No change	250–500 mg per dose daily
p-aminosalicylic acide	No change	4 g/dose, twice daily
streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)f
capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)f
kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)f
amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily)f

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

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

Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and further renal damage.

Patients receiving haemodialysis should get DR TB drugs after dialysis.

7.9 Seizure Disorders

Some patients requiring treatment for Drug Resistant TB may 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 is needed before the start of Drug Resistant TB therapy.
- In addition, if other underlying conditions or causes for seizures exist, they should be corrected.

Since the Standardized MDR TB and XDR TB regimens contain cycloserine, it should be avoided in patients with active seizure disorders that are NOT well controlled with medication.

7.10 Psychiatric Patients

- Treatment with psychiatric medication, individual counseling, and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication. Group therapy has been very successful in providing a supportive environment for DR TB patients, and it may be helpful for patients with or without psychiatric conditions (adequate measures to prevent infection should be in place for the group therapy).
- The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse drug reaction from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potential higher risk of adverse drug reaction. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.

7.11 HIV Infected Patients

The same Standardized Regimens will be given to DR TB/HIV patients. Anti-retrovirals (ARVs) in TB improves survival and slows progression to AIDS. ARVs should be:

- Started as soon as the patient tolerates the DR TB regimen, regardless of CD4 count.
- If patient is already on ARVs, continue regimen and evaluate for possible failure (decreasing CD4 or viral load greater than 200).
- Avoid tenofovir during the injectable phase (if patient must use tenofovir, monitor for renal toxicity every 1 to 2 weeks while on the injectable agent).

In general, HIV patients have a higher rates of adverse drug reactions to both TB and non-TB medications, and therefore, need special socioeconomic support. Known adverse drug reaction of increased magnitude in co-infected patients include:

peripheral neuropathy (cycloserine, pyrazinamide), gastrointestinal adverse effects, renal toxicity (injectable agents with tenofovir) and neuropsychiatric effects (cycloserine and efavirance). The regimens together are particularly difficult to take, the stigma of both diseases can result in serious discrimination and the risk of mortality is very high.

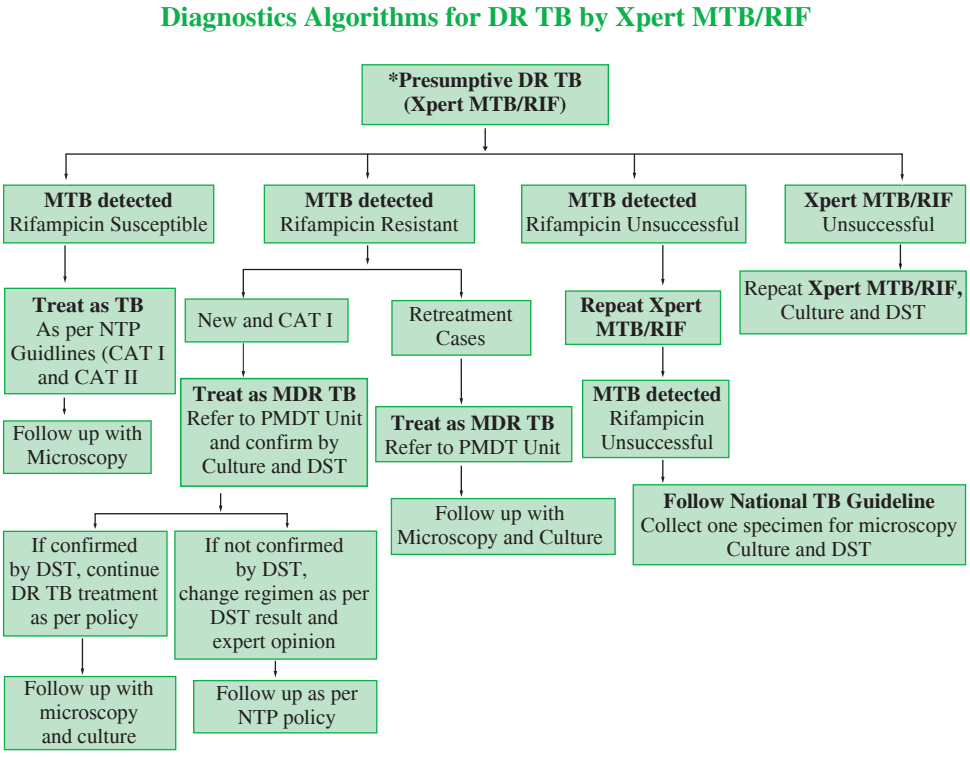
Monitoring of DR TB and HIV therapy is described in Chapter 9. ARVs are always given every day, seven days a week. While the treatment of DR TB is being administered, ARVs should be included with the DOT of DR TB medications. Monitoring of chest X-rays, smears and cultures in the DR TB/HIV patient is the same as for HIV-negative/DR TB patients. The interpretation of chest X-ray is more difficult in DR TB/HIV patients, and there are a number of pulmonary infections, such as Pneumocystic pneumonia (PCP) and systemic opportunistic infections, that can exist in HIV positive individuals making management difficult.

CHAPTER 8 Initial Evaluation and Preparing the Patient for Treatment

8.1 Flow of Patients into Treatment

Patients considered for DR TB screening are described in Chapter 4. Once a patient has been screened, some patients can enter DR TB treatment based on the group from which they come from, before the results of the culture and DST return. The flow of patients into treatment has been diagramed in Figure 8.1.

Figure 8.1 Flow of patient into the DR TB programme



*Presumptive DR TB Case:

1) Failures of Category I (remain positive at month 5 or later and smear negative patients who become smear positive at month 2)
2) Failures of Category II (remain positive at month 5 or 8)
3) Non converters of Category I (remain positive at month 2)
4) Non converters of Category II (remain positive at month 3)
5) Relapses (Category I / Category II)
6) Treatment after loss to follow up (Category I / Category II)
7) Close contacts of MDR TB patient with symptoms.
8) HIV infected
9) Others (Specify……)

8.2 Pre-treatment Screening and Medical Evaluation

Pre-treatment assessment should be systematically conducted on all patients in order to identify those patients at greater risk of adverse drug reaction, poor outcomes and to establish a baseline. This must include a thorough medical history, physical examination and initial laboratory evaluations.

Certain pre-existing conditions, which may affect treatment progress, should be diagnosed early through more intensive baseline investigations and follow up. The management of DR TB when these conditions exist is described in **Chapter 7**. The conditions to be screened for are listed in below**.**

Conditions to be screened for at initial medical evaluation:

- Malnutrition
- Diabetes mellitus
- Hypertension
- Renal insufficiency
- Acute or chronic liver disease
- Thyroid disease
- Mental illness
- Drug or alcohol dependence
- Pregnancy
- Breast feeding
- Seizures
- Bowel disorder e.g. IBS
- HIV infection (option of HIV testing)

Pregnancy test should be done at baseline and whenever indicated. If increased nausea and vomiting occurs in a woman of child-bearing age, consider morning sickness and rule out pregnancy. Contraception should be strongly encouraged in all patients on DR TB treatment. Counseling for male partners should be provided as well.

Box 8.1 review the minimum criteria that need to be met to start the Standard MDR TB Regimen, but similar questions should be asked for any DR TB regimen.

Address the following questions before starting the Standard DR TB Regimen:	
1. Is the patient a household contact of a patient with M/XDR TB? 2. Is there jaundice or known liver disease? 3. Is there chronic illness, such as, diabetes mellitus, heart or kidney disease, etc.? 4. Has the patient ever taken second line anti-TB drugs? 5. Is the patient pregnant?	**If no to all** **Start Standard DR TB regimen**
YES to any question Do not start standardized DR TB regimen. Patient will need adjustments to the DR TB regimen.	

8.3 Pre-treatment Smears and Cultures

One sputum sample preferably of early morning specimen should be obtained for Xpert MTB/RIF. If Xpert MTB/RIF found "Rif resistant" in case of new or patient on Cat 1, a second early morning sample of sputum should be collected for culture and DST before start of treatment. If patient is on Cat 2 regimen, second sputum sample is not required.

At the start of DR TB treatment, the patient must have at least one pre-treatment culture and smear positive; and the collection date of the sample less than 30 days before, or seven days after, initiation of DR TB treatment.

8.4 Preparing the Patient for Treatment

Preparing the patient for treatment involves educating the patient on DR TB and how it differs from susceptible tuberculosis, including the drugs used, length of treatment, possible adverse drug reaction and support that will be available for the patient. It also includes information on how the patient can protect his/her family and household members from getting tuberculosis. Educating the patient should ultimately help the patient obtain better adherence.

CHAPTER 9 Monitoring Treatment Progress and Management of Adverse Drug Reaction

9.1 Monitoring Treatment Progress

Patients should be monitored closely for signs of both treatment efficacy (is the patient getting better?) and adverse drug reaction (ADR) of the medications. Initial evaluation is discussed in Chapter 8.

The best and most important way of monitoring response to treatment and ADR are through regular:

- History taking
- Physical examination
- Laboratory monitoring tests

The classic symptoms of TB are cough, fever and weight loss; generally improve within the one to two months of treatment and should be monitored regularly by health care providers. Laboratory tests often lag behind clinical response (especially culture) and are not sufficient on their own. On the other hand, the first sign that something is going wrong may be a laboratory test (the recurrence of a positive culture or a low potassium level etc).

The chest radiograph may be unchanged or show only slight improvement, especially in re-treatment patients with chronic pulmonary lesions. Chest radiographs should be done at the start and as needed during the treatment course (e.g. clinical deterioration or surgical intervention) and 6 monthly.

For children, height and weight should be measured regularly (at least monthly) to ensure that they are growing normally. A normal growth rate should resume after a few months of successful treatment.

For adults, weight should be recorded monthly.

All doses should be given under strict DOT.

9.2 Sputum Follow-up Examinations

The most important evidence that treatment is effective is conversion of the sputum smear and culture to negative. Sputum culture is more sensitive to monitor the efficacy of treatment. Sputum smear is still useful because of its shorter turnaround time. Sputum conversion is slower in DR TB than in drug susceptible TB.

Sputum smears should be monitored weekly until smear conversion then monthly upto the completion of treatment and Sputum culture monthly in the intensive phase and quarterly in the continuation phase.

9.3 Monitoring for Adverse Drug Reaction (ADR) during Treatment

Close monitoring of patients is necessary to ensure that adverse drug reaction of second line anti TB drugs are recognized quickly by healthcare personnel. The ability to monitor patients for adverse drug reaction daily is one of the major advantages of DOT over self-administration of DR TB treatment. The majority of adverse drug reaction are easy to recognize. The patients are to be encouraged to share any adverse drug reaction to health worker experienced by them. However, it is important to have a systematic method of patient interviewing since some patients may be reluctant to report adverse drug reaction.

While the patient is in hospital, clinic or community DOT providers/ health workers should be trained to screen patients regularly for symptoms and signs of common adverse drug reaction. These healthcare workers should know when to refer a patient to a healthcare facility for major adverse drug reaction versus when to manage simple adverse drug reaction within an outpatient setting. Common adverse drug reactions are listed in Box 9.1.

Box 9.1: Common adverse drug reactions of DR TB Therapy

• Nausea/vomiting	• Abdominal pain	• Visual disturbances
• Diarrhoea	• Anorexia	• Seizures
• Arthralgia	• Gastritis	• Hypothyroidism
• Dizziness/vertigo	• Peripheral neuropathy	• Psychosis
• Hearing disturbances	• Depression	• Suicidal tendency
• Headache	• Tinnitus	• Ideation
• Sleep disturbances	• Allergic reaction	• Hepatitis
• Electrolyte disturbances	• Rash	• Renal failure (nephrotoxicity)

Laboratory screening is very useful for detecting certain adverse drug reactions that are more occult (not obviously noted by taking the patient's history or through physical examination). The recommendations referenced in Table 9.1 represent the frequency of essential laboratory test and monitoring. More frequent screening is advisable, particularly for high-risk patients. The following is the rational of the regular monitoring tests:

- **Renal toxicity monitoring:** Nephrotoxicity is a known complication of the injectable drugs, both of the aminoglycosides (kanamycin and amikacin) and of capreomycin. This adverse drug reaction is occult in onset, but it can be fatal. The optimal timing for checking serum creatinine is unknown. These guidelines advise checking serum creatinine monthly while on the injectable agent. In addition, patients with a history of renal disease (including co-morbidities, such as HIV and diabetes), advanced age or any renal symptoms should be monitored more closely. These patients should be closely monitored at the start of treatment by having their creatinine levels assessed every two weeks. An estimate of the glomerular filtration rate may help to further stratify the risk of nephrotoxicity in these patients. When renal failure

exists, anti-TB drugs should be adjusted according to Table 7.1.

- **Electrolyte monitoring:** Electrolyte depletion is a known complication of the anti-tuberculosis injectable drugs, especially capreomycin. It can be fatal if the potassium or other electrolyte levels get too low. It is generally a late effect occurring after months of treatment, and it is reversible once the injectable drug is suspended. Since electrolyte depletion is often occult in the early stages and can be easily managed with electrolyte replacement, serum potassium should be checked monthly while on the injectable agent. It is especially important to regularly check in high-risk patients (HIV patients), and in all patients taking capreomycin. Annex 3 describes the management of electrolyte disturbances in more detail.
- **Monitoring for hypothyroidism:** Hypothyroidism is generally a late side-effect provoked by PAS and ethionamide/prothionamide. If the patient is only on one of these agents, it can be screened for by clinical assessment. It can be confirmed by testing the serum level of thyroid stimulating hormone (TSH). The use of these agents together (PAS plus ethionamide or protionamide) can produce hypothyroidism in up to 10% of patients. Since the symptoms can be subtle, it is recommended that patients who are taking both PAS and ethionamide/protionamide are screened for hypothyroidism with a serum TSH at baseline , every six months or sooner if symptoms arise.
- **Monitoring liver toxicity:** A chemical hepatitis can result from pyrazinamide, PAS and less commonly with the other second-line drugs. Liver enzymes should be checked for all patients who exhibit signs of hepatotoxicity. It is recommended for HIV positive patients on pyrazinamide to check serum liver enzymes monthly.
- **Ototoxicity:** Ototoxicity refers to damage of cranial nerve VIII, usually manifested by hearing loss and/or tinnitus. Other vestibular symptoms, such as, nystagmus, ataxia, and disequilibrium can also occur. Presentation is most commonly observed in patients receiving large cumulative doses of aminoglycosides and/or capreomycin. Concomitant use of furosemide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of these medications. Patients starting therapy with hearing loss at baseline from prior aminoglycoside use are at the highest risk. Hearing loss is generally not reversible upon discontinuation of therapy. Audiometry for baseline and/or follow-up test is required to pick up early hearing loss. It is recommended to do audiometry monthly while on the injectable agent. If hearing loss is detected, usually stopping the injectable agent is required although close monitoring (weekly audiometry) and decreasing the frequency of the injectable agent to three times be preferred in some cases where the injectable agent is thought critical to cure.
- **Psychosocial Assessment:** Psychosis and depression can result in thoughts of suicide and even successful suicide attempts. Assessment of the patient's psychosocial condition, including the specific question, "Are you having thoughts of suicide?," should be done routinely at the monthly visit. Similarly, signs of psychosis, anxiety, agitation and depression should be looked for monthly.

Table 9.1 Recommended Laboratory Monitoring Schedule for DR TB Treatment

Baseline	Follow-up
Sputum smear microscopy	Weekly until two consecutive smears are negative then monthly
Sputum culture	Monthly in intensive phase then quarterly in continuation phase.,
Drug susceptibility Testing (DST)	A Second-line anti TB drugs DST is indicated on any cultures that are positive at four months or beyond
Renal function tests (serum creatinine and electrolytes)	Every month while receiving injectable. Patients with baseline renal insufficiency should be monitored frequently.
Thyroid Stimulating Hormone (TSH)	Every six months if receiving PAS, ETO or PTO. TSH is sufficient for screening for hypothyroidism. It is not necessary to measure thyroid hormone levels, only TSH.
Liver Function Test (S. Billirubin, SGPT)	As clinically indicated for patients with symptoms of hepatitis. Every 1-3 monthly in patients who are at risk for hepatotoxicity (alcoholics, patients with a history of Hepatitis B or C virus infection), HIV infected and taking pyrazinamide.
HIV screening, CD4	Repeat HIV test as clinically indicated (CD4 every 6 months in HIV infected patients).
Pregnancy test (women of child-bearing age)	Repeat as clinically indicated. All women of child-bearing age should be provided with family planning counseling.
Complete blood count	As clinically required. For HIV-infected patients on zidovudine containing ART regimens, monitor monthly initially and then as needed based on symptoms.
Audiometry	Monthly while on the injectable agent.
Evalution by clinical	At baseline, and at least monthly until conversion, then every 2-3 month
Screening by DOT worker	At every DOT encounter
Weight	At baseline and then monthly
Chest radiograph	At baseline and then every 6 monthly
Serum potassium	Monthly while receiving an injectable agent. Every 1-3 weeks in HIV-infected patients, diabetics and other high-resk patients
Serum creatinine	At baseline, then monthly if possible while receiving an injectable drug. Every 1-3 weeks in HIV-infected parients, diabetics and other high-resk patients
Haemoglobin and white blood count	If on linezolid, monitor weekly at first, then mnthly or as needed based on symptoms; there is little clinical experience with prolonged use for HIV-positive patients on an ART regimen that includes AZT, monitor monthly initially and then as needed based on symptoms
Lipase	Indicated for work up of abdominal pain to rule out pancreatitis in patients on linezolid, D4T, ddl ddc.
Lactic acidosis	Indicated for work up of lactic acidosis in patients on linezolid or ART

9.4 Management of Adverse Drug Reactions (ADR)

This section focuses on the potential adverse drug reactions of drugs used to treat DR TB. Treating adverse drug reactions rapidly and aggressively is important in order to increase tolerance and improve outcomes.

- Second-line drugs have many more adverse drug reactions than the first-line anti-tuberculosis drugs.
- Proper management of adverse drug reactions begins with patient education. Before starting treatment, the patient should be instructed in detail about the potential adverse drug reactions that could be produced by the prescribed drug regimen. Additionally, they should be informed on if and when to notify a health care provider. All patients should be informed about some possible adverse drug reactions, especially at the start of therapy. It is generally within the first few weeks of treatment where the patient can feel quite un-well, such as nausea and vomiting, which are the most common adverse drug reactions. If patients do not anticipate this reaction and are not reassured that it will improve, they will frequently stop the therapy.
- Prompt evaluation, diagnosis and treatment of adverse drug reactions are extremely important, even if the adverse drug reactions is not particularly dangerous because adherence may be influenced. Patients may have significant fear and anxiety about an adverse drug reactions if they do not understand why it is happening. These emotions in turn may augment the severity of the adverse drug reactions, as in the case of nausea and vomiting. Long periods of time without medical evaluation can promote feelings of isolation and abandonment by the health-care system.
- If the adverse drug reactions is mild and not fatal, continuing the treatment regimen with the help of ancillary drugs, if needed, is often the best option. In patients with highly resistant TB, a satisfactory replacement drug may not be available, thus, suspending a drug will make the treatment regimen less potent. Some adverse drug reactions may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated.
- The adverse drug reactions of a number of second-line drugs are highly dose dependent. Reducing the dosage of the offending drug is another method of managing adverse drug reactions, but it should only be done in cases where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen. With cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose. Unfortunately, given the narrow therapeutic margins of these drugs, lowering the dose may also affect efficacy, so every effort should be made to maintain an adequate dose of the drug according to body weight. Lowering the dose by more than one weight class should be avoided.
- Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurological adverse effects. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.

- Psychosocial support is an important component of the management of adverse drug reactions. This is one of the most important roles played by DOT providers, who educate patients about their adverse drug reactions and encourage them to continue treatment.

Table 9.2. Common adverse drug reactions of Second line Anti-TB drugs and Recommended Management Strategies

Adverse Durg Reaction(s)	Suspected Agent(s)	Suggested Management Strategies	Comments
Rash, allergic reaction and anaphylaxis	**Any drug**	1. Stop all therapy until resolution of any severe allergic reaction. In the case of anaphylaxis, manage with standard emergency protocols. 2. Eliminate other potential causes of allergic skin reaction (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include • Antihistamines • Hydrocortisone cream • Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful. 4. Consider suspending most likely agent permanently. Reintroduce remaining drugs, one by one, with most likely offending drug(s) last. Do not reintroduce the offending drug(s).	1. History of previous drug allergies should be carefully reviewed. 2. Any drug that resulted in anaphylaxis or Steven-Johnson syndrome should never be re-introduced to the patient.
Gastritis and abdominal pain	**PAS, Eto, Pto, Cfz, H, E, and Z**	1. H2-blockers, proton-pump inhibitors, (Do not use antacids as they decrease absorption of fluoroquinolones) 2. For severe abdominal pain, stop suspected agent(s) for short period of time (e.g, one to seven days). 3. Lower dose of suspected agent, if this can be done without compromising regimen. 4. Discontinue suspected agent, if this can be done without compromising regimen.	1. Severe gastritis, as manifested by haematemesis, or melaena is rare. 2. If antacids must be used (not recommended), they should be carefully timed so as to not interfere with the absorption of anti-TB drugs (take 2 hours before or 3 hours after anti-TB drugs). 3. Reversible upon discontinuation of suspected agent(s). 4. Severe abdominal distress and acute abdomen have been reported with the use

Adverse Durg Reaction(s)	Suspected Agent(s)	Suggested Management Strategies	Comments
			of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended.
Nausea and vomiting	**Eto, Pto, PAS, H, E, Z, Amx/Clv, Cfz**	1. Assess for danger signs including: dehydration, electrolyte disturbances and hepatitis; initiate rehydration therapy if indicated and correct any electrolyte disturbances. 2. Initiate stepwise approach to nausea and vomiting. • Phase 1: Adjust medications without lowering over all doses (give at night, give Eto or PAS twice or thrice daily). • Phase 2: Start antiemetic(s). • Phase 3: Decrease dose or discontinue suspected agent, if this can be done without compromising regimen - rarely necessary to suspend agent completely.	1. Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. 2. Electrolytes should be monitored and imbalance should be corrected (if any). 3. Reversible upon discontinuation of suspected agent.
Diarrhoea and/or flatulence	**PAS, Eto/Pto**	1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhea (no blood in stool and no fever) with loperamide; 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours.	1. Consider other causes of diarrhoea • Pseudo-membranous colitis related to antibiotics such as the flouroquinolones • Parasites • Lactose intolerance, especially if patient has been exposed to new foods in a hospital not normally part of their diet.
Diarrhoea and/or flatulence	**PAS, Eto/Pto**	1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhea (no blood in stool and no fever) with loperamide; 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours.	1. Consider other causes of diarrhoea • Pseudo-membranous colitis related to antibiotics such as the flouroquinolones • Parasites • Lactose intolerance, especially if patient has been exposed to new foods in a hospital not normally part of their diet.

Adverse Durg Reaction(s)	Suspected Agent(s)	Suggested Management Strategies	Comments
Hepatitis	**Z, H, R, Pto / Eto and PAS**	1. Stop all therapy until resolution of hepatitis. 2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis being the two most common). 3. Consider suspending most likely agent permanently. Reintroduce remaining drugs, one at a time, with the least hepatotoxic agents first while monitoring liver function. If the most likely culprit is not essential, consider not re-introducing it.	1. History of previous drug hepatitis should be carefully analysed to determine most likely causative agent(s); these agents should be avoided in future regimens. 2. Viral serology should be done to rule out other etiologies of the hepatitis if available, especially to A, B, and C. 3. Alcohol use should be investigated and alcoholism addressed if found. 4. Generally reversible upon discontinuation of suspected agent.
Hypo-thyroidism	**Eto/Pto, PAS**	1. Most adults will require 100 to 150 mcg of thyroxine daily. Start levo-thyroxine in the following manner: • Young healthy adults can be started on 75 to 100 mcg daily; • Older patients should begin treatment with 50 mcg daily; • Patients with significant cardiovascular disease should start at 25 mcg daily; 2. Monitor TSH every 1 to 2 month and increase dose by 12.5-25 mcg until TSH normalizes. Adjust dose more slowly in the elderly and patients with cardiac conditions.	1. Do not start treatment unless TSH is above 1.5 or 2.0 times upper normal limit 2. Completely reversible upon discontinuation of PAS and/or ethionamide/ protionamide. 3. The combination of ethionamide/ protionamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug.
Arthralgias	**Z, fluoro-quinolones**	1. Initiate therapy with non-steroidal anti-inflammatory drugs (Indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day). 2. Lower dose of suspected agent (most commonly pyrazinamide), if this can be done without compromising regimen. 3. Discontinue suspected agent, if this can be done without compromising regimen.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. Allopurinol is often use in such cases, although there is little evidence that it is helpful.

Adverse Durg Reaction(s)	Suspected Agent(s)	Suggested Management Strategies	Comments
Electrolyte disturbances (hypoka-laemia and hypomagne-saemia)	**Cm, Km, Am, S**	1. Check potassium. 2. If potassium is low also check magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalemia). 3. Replace electrolytes as needed.	1. If severe hypokalaemia is present, consider hospitalization. 2. Spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.
Renal toxicity	**S, Km, Am, Cm**	1. Discontinue suspected agent. 2. Consider using capreomycin, if an aminoglycoside had been the prior injectable in regimen. 3. Consider other contributing etiologies (NSAIDS, diabetes, other medications, dehydration, urinary obstruction…etc) and address as indicated. 4. Monitor creatinine and electrolytes closely, every 1 to 2 weeks. 5. Consider dosing at 3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). 6. Adjust all TB medications according to the creatinine clearance.	1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although, patients with these co-morbidities may be at increased risk for developing renal failure. 2. Renal impairment may be permanent.
Vestibular Toxicity (tinnitus and dizziness)	**S, Km, Am, Cm, Cs, FQs, H Eto, Lzd**	1. If early symptoms of vestibular toxicity appear, change the dosing to 2 or 3 times a week and continue the injectable agent for another month or more. 2. Prior to stopping the injectable agent (the most likely agent), evaluate whether these and/or other medications (Cs, FQs, H Eto, Lzd), are causing the symptoms. 3. If tinnitus and unsteadiness develop and these are attributed to vestibular toxicity, stop the injectable agent.	1. This is one of the few adverse reactions that cause permanent intolerable toxicity and necessitate discontinuation of a class of agents. 2. If an aminoglyco side is being used, capreomycin can be tried. Often the drug induced vestibular toxicity can continue. All injectable agents should to stop to avoid ongoing severe disability and ataxia.

Adverse Durg Reaction(s)	Suspected Agent(s)	Suggested Management Strategies	Comments
Hearing loss	**S, Km, Am, Cm, Clr**	1. Document hearing loss and compare with baseline audiometry, if available. 2. Change parenteral treatment to capreomycin, if patient has documented susceptibility to capreomycin. 3. Decrease frequency and/or lower dose of suspected agent, if this can be done without compromising the regimen (consider administration 2 to 3 times per week). 4. Discontinue suspected agent, if this can be done without compromising the regimen.	1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR TB therapy. 2. Hearing loss is generally not reversible. 3. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen. 4. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.
Peripheral neuropathy	**Cs, Lzd, H, S, Km, Cm, H, FQs, rarely Pto/Eto, E**	1. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Change injectable to capreomycin, if patient has documented susceptibility to capreomycin. 3. Initiate therapy with tricyclic antidepressants, such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. 4. Lower dose of suspected agent, if this can be done without compromising regimen. 5. Discontinue suspected agent, if this can be done without compromising regimen.	1. Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be irreversible, however, some patients may experience improvement when offending agents are suspended.
Depression	**Socio-economic circum-stances, chronic disease, Cs, fluoro-quinolones H**	1. Improve socioeconomic conditions. 2. Group or individual counselling. 3. Initiate antidepressant therapy (amitryptiline, fluoxetine or similar). 4. Lower dose of suspected agent, if this can be done without compromising the regimen.	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may

Adverse Durg Reaction(s)	Suspected Agent(s)	Suggested Management Strategies	Comments
		5. Discontinue suspected agent, if this can be done without compromising regimen.	improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of the agents listed, but it may increase the likelihood of depression developing during treatment.
Suicidal Ideation	**CS, H, Eto/Pto**	1. Hospitalize the patient and put under 24-hoursurveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation 4. Initiate antidepressant therapy 5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable	1. Keep the patient in the hospital until risk of suicide has passed. 2. If no improvement occurs after holding cycloserine, hold H and Eto/Pto
Psychotic symptoms	**Cs, H, fluoro-quinolones,**	1. Stop suspected agent for a short period of time (1-4 weeks) while psychotic symptoms are brought under control. 2. Initiate antipsychotic therapy. 3. Lower dose of suspected agent, if this can be done without compromising regimen. 4. Discontinue suspected agent, if this can be done without compromising regimen.	1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. 2. Previous history of psychiatric disease is not a contraindication to the use of agents listed here, but it may increase the likelihood of psychotic symptoms developing during treatment. 3. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.
Seizures	**Cs, H, fluoro-quinolones**	1. Suspend suspected agent pending resolution of seizures. 2. Check serum electrolytes, calcium, and magnesium. 3. Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid). 4. Increase pyridoxine to maximum daily dose (200 mg per day). 5. Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen. 6. Discontinue suspected agent, if this can be done without compromising regimen.	1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving

Adverse Durg Reaction(s)	Suspected Agent(s)	Suggested Management Strategies	Comments
			anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available). 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy
Optic neuritis	**E, Eto/Pto**	1. Stop Ethumbutol. 2. Refer patient to an ophthalmologist.	1. Usually reverses with cessation of Ethumbutol. 2. Rare case reports of optic neuritis have been attributed to streptomycin.
Metallic Taste	**Eto/Pto, Clr, FQs**	1. Encourage the patient to tolerate this side effect. 2. Sucking hard candy or chewing gum can be helpful.	1. Normal taste returns when treatment is stopped.
Gynecomastia	**Eto/Pto**	1. Breast enlargement can be a troublesome side effect of Eto/Pto therapy, especially for male patients. Galactorrhea has also been reported. 2. Encourage patients to tolerate this side effect.	1. Resolution occurs after treatment is stopped.
Alopecia	**H, Eto/Pto**	1. Hair loss or significant thinning of the hair can occur, but this is temporary and not progressive during treatment. 2. Significant cosmetic change has not been reported.	
Superficial fungal infection and thrush	**FQs and other anttibiotics**	1. Topical antifungal agents or short-course oral antifungal drugs are helpful. 2. Exclude other diseases if response to treatment is not prompt (such as HIV).	1. Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.
Tendonitis and tendon rupture	**FQs**	1. Fluoroquinolones should generally be stopped. 2. Administer nonsteroidal anti-inflammatory agents. 3. Rest the joint.	

Adverse Durg Reaction(s)	Suspected Agent(s)	Suggested Management Strategies	Comments
Lactic Acidosis		1. Stop Linezolid if lactic acidosis occurs.	
Dysglycemia and Hyperglycemia	**Gfx, Eto/Pto**	1. These guidelines do not recommend the routine use of Gatifloxacin in DR TB treatment.	
QT Prolongation	**FQs**	1. Keep electrolytes within normal range 2. Avoid other drugs that increase the QT intervals. 3. The patient's renal and hepatic function should be monitored and adjust dose of fluorquinolones if impairment is present. 4. If significant risk to the patient with other risk factors to cause Torsades de Pointes consider suspension of the fluroquinolone.	1. Currently, electrocardiogram monitoring prior to the initiation and during DR-TB therapy is not recommended, as the benefits of the fluorquinolones in DR-TB therapy is considered to outweigh the risk of QT prolongation. 2. Some member of the fluorquinolones cause more QT prolongation than others: moxifloxacin causes the greatest QT prolongation of the ones used to treat DR-TB. Levofloxacin and ofloxacin have a low risk of QT prolongation.
Hematological abnormalities	**Linezolid**	1. Stop Linezolid if myelosuppresson (suppression white blood cells, red blood cells or platelets) occurs.	1. Hematological abnormalities (leukopenia, thrombocytopenia, anemia, red cell aplastia, coagulation abnormalities, and eosinophilia) can also occur with a number of other anti-TB drugs. See individual drug sheets.

Table 9.3. Commonly Used Ancillary Medications in Managing Adverse Drug Reactions of Second-line Anti-TB Drugs

Indication	Drug
Nausea, vomiting, abdominal upset	Metoclopramide, Meclizine Hcl, Domperidon, Dimenhydrinate, Prochlorperazine, Promethazine, Bismuth Subsalicylate or Ondansetron - Start with Metoclopramide, 10 mg by mouth given 30 minute,s before morning and/or afternoon dose of anti-TB drugs, to a maximum of 10 mg 3 times daily. *Note:* Avoid metoclopramide if neurological problems develop. - Ondansetron, 8mg BD (30 minutes before taking anti TB drugs), Metoclopramide can be continued. If Ondansetron (or a 5 HT3 receptor antagonist) is not available, Promethazine 25 mg or Domperidone 20 mg by mouth 30 minutes prior to anti-TB drugs or prior to meals, up to 3 times daily. If necessary, the dose may be increased to Promethazine 50 mg 3 times daily to control symptoms.
Heartburn, epigastric pain, sour stomach, ulcer	H2-blockers (Ranitidine, Cimetidine, etc.), Proton pump inhibitors (Omeprazole, etc.) Avoid antacids because they can decrease absorption of Flouroquinolones. - Start Omeprazole 20 mg once a day by mouth. The dose can be increased to 20 mg twice a day. - An alternative is H-2 blockers such as ranitidine.
Oral candidiasis (non-AIDS patient)	Fluconazole, Clotrimazole gel.
Diarrhea	ORS, Loperamide where necessary. - Treat with Loperamide, 4 mg by mouth initially, followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours.
Depression	Selective Serotonin reuptake inhibitors (Fluoxetine,), Tricyclic antidepressants (amitriptyline)
Severe anxiety	Diazepam
Insomnia	Benzodiazepines (Clonazepam/Nitrazepam)
Psychosis	Haloperidol, Risperidone (consider Benzotropine to prevent extrapyramidal effects)
Seizures	Phenytoin, Carbamazepine, Valproic acid, Phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B6)
Peripheral neuropathy	Pyridoxine (vitamin B6), Amitriptyline
Vestibular symptoms	Cinarizine, Meclizine, Prochlorperazine, Promethazine, Cinarizine plus dimene hydrinate

Indication	Drug
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, Paracetamol, Paracodeine
Cutaneous reactions, itching	Hydrocortisone cream, Calamine, Caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (Diphenhydramine, Chlorpheniramine, Dimenhydrinate), Corticosteroids (Prednisone, Dexamethasone)
Bronchospasm	Salbutamol, Inhaled beta 2 agonists (Salbutamol, Albuterol, etc.), inhaled corticosteroids (Beclomethasone, etc.), oral steroids (Prednisolone), injectable steroids (Hydroscortisone, Dexamethasone, Methylprednisolone)
Hypothyroidism	Levothyroxine: Most adults will require 100 to 150 mcg of thyroxine daily. Start Levothyroxine and adjust in the following manner: • Young healthy adults can be started on 75 to 100 mcg daily; • Older patients should begin treatment with 50 mcg daily; • Patients with significant cardiovascular disease should start at 25 mcg daily; • Monitor TSH every 1 to 2 month and increase dose by 12.5–25 mcg until TSH normalizes; • Adjust dose more slowly in the elderly and patients with cardiac conditions.

Box 9.2 Field Tips for Monitoring Treatment and Management of Adverse Drug Reactions

Educate the patient to seek care urgently if they have:

- Skin rash
- Severe abdominal pain
- Yellow eyes
- Strange visions or thoughts
- Fatigue
- shortness of breath
- Ringing in the ears or decreased hearing ability
- Severe pain in the legs
- Coughing up blood

Monitor DR-TB treatment outcome:

- Look for signs of treatment failure:
  - Weight loss
  - Persistence or reappearance of TB symptoms (fever, cough, sputum)
  - Persistently positive sputum smears or cultures
  - Smear or culture positive after being negative for some time
- Other opportunistic infections, like HIV, can be easily confused with treatment failure. Seek advice from a doctor when needed
- Collect sputum samples every month.
- Check the treatment card each month and discuss with the DR DOT Provider how treatment is going.

- Encourage the patient to continue receiving treatment.
- Find out what caused any treatment interruptions.
- Follow all the algorithms for monitoring and treating adverse effects.

For all monthly visits at the treatment centre, perform a clinical review of symptoms , signs, medication , adverse effects and complications as shown below:

Ask	Look

• How have you been?
• Have you needed urgent medical care? If yes, ask for record/diagnosis.
• Have your TB symptoms improved?
  ◦ Cough? Sputum?
  ◦ Difficult breathing?
  ◦ Fever/night sweats?
  ◦ Weight loss?
 	
• Have you had any adverse effects?
  ◦ Nausea/vomiting?
  ◦ Fatigue?
  ◦ Skin rash?
  ◦ Tingling in hands or feet?
  ◦ Deafness? Ringing of ears?
  ◦ Headache?
  ◦ Seizures? Loss of consciousness?
  ◦ Feeling anxious? Feeling sad or unhappy?
 	
• What problems have you had taking the medicines? Have you missed any dose? Ask questions in a respectful and non-judgmental way. Pose the questions in a manner that makes it easier for patients to be truthful:
  ◦ ÒMany patients have trouble taking their medications. What trouble do you have?Ó
  ◦ ÒWhen is it most difficult for you to take the pills? Have you missed any dose?Ó
 	
• If the patient has missed doses determine what was the reason
• Have you had any problem with your treatment supporter?
• What else do you want to talk about?
	In all patients:
	• Weigh patient. Calculate weight gain or loss. Record. If weight loss, ask about food intake.
	• Measure temperature.
	• Count respiratory rate.
	• Look for pallor. If pallor, check haemoglobin.
	• Look at whites of the eye-yellow?
	• Look for thrush.
	
	If any new symptoms:
	  ◦ Do further assessment of symptoms.

9.5 Summary

The timely and intensive monitoring for, and management of, adverse drug reactions caused by second-line drugs are essential components of DR-TB control programs. Poor management of ADR increases the risk of default or irregular adherence to treatment, and may result in death or permanent morbidity. The healthcare worker of the control programme should be familiar with the common adverse drug reactions of DR-TB therapy. Patients experiencing adverse drug reactions should be referred to medical doctors.

CHAPTER 10 Treatment Delivery and Adherence

The delivery of DR TB treatment will start with a short hospitalization (minimum 4 weeks). During hospitalization smear microscopy should be done weekly and then move to home-based care when two consecutive sputum smear result become negative and the patient will receive daily DOT from a well trained Drug Resistant DOT Provider (DR TB DOT Provider). In addition, the patient will regularly visit a highly trained Outpatient DR TB team located at the Upazila/Urban DOTS Centre.

Medication supplies, including ancillary drugs for adverse drug reaction management, will be ensured to all patients free of charge. All treatment should be taken under DOT support. The patient should be followed, such a way that monthly clinical visits throughout treatment and smear microscopy, sputum culture and other follow up tests should be performed as per NTP policy during the intensive phase and continuation phase. All laboratory monitoring tests should be provided free of cost. All treatment settings should have infection control strategies to prevent further transmission of the disease.

10.1 Hospitalization

All patients will be hospitalized at the start of treatment in a facility designed for the management of DR TB patients. While in the hospital, patient living conditions should be acceptable. Patients should also be provided with nutritional and other social support throughout the duration of their hospital stay. All doses of Anti-TB drugs should be under strict observation by trained hospital health staff. The reasons for the initial hospitalization are multifold:

- To have an intensive time period for patient education while on treatment.
- To document that the patient is tolerating the medicines well.
- To make the patient smear negative and less infectious.
- To allow time for outpatient home-based care to be set up.

Occasionally, patients may need to be re-admitted to the hospital. The criteria for re-admission to the hospital are as follows:

- Patient is very sick, clinically and physically unfit to receive care at home or on an ambulatory basis.
- Treatment adherence problems.
- Severe adverse drug reactions.
- Immobility.

If patients become smear and/ or culture + or for the assessment of possible XDR, the UHC/DOTS centre out patient DR TB team will follow the patient

while he receives home-based DOT within the community. During the intensive phase the patient accompanied by the DR TB DOT provider should initially visit the team once in a month during intensive phase and subsequently once in every two months during continuation phase. Whenever there is a problem, complication or emergency, the patient and the DR TB DOT provider should seek support from the team anytime.

Following criteria should be met before discharge of patients from hospital

- The patient is smear negative (at least two consecutive smear nagetive one week apart) and clinically improving
- The patient is tolerating drugs well (no major adverse drug reactions observed)
- The patient has completed at least 4 weeks of hospitalization
- The outpatient team is trained and ready to provide community/home-based DOT and patient's household is ready to receive the patient (infection control assessment conducted)

Upon discharge, a discharge note should be written in the discharge certificate by the hospital responsible authority/ divisional PMDT coordinator to the outpatient DR TB team of the referred Upazila/Urban DOTS centre in triplicate (main copy remains at DR TB inpatient facility in the patient's file, second copy is sent with the patient or accompanying health care provider to submit to the out patient DR TB team, and third one is sent to the NTP).

Upon discharge, the patient and accompanied health care provider will receive following items:

1. Discharge certificate from the facility;
2. DR TB Identity Card;
3. Second Line Anti TB drugs (SLD), required ancillary drugs (if available) with "Chalan";
4. Copy of the Treatment Card;
5. Patient Education Material on DR TB;
6. Information on follow up visits.

The accompanied health care provider should submit all of the above mentioned items to the team leader of the outpatient DR TB Team.

Vulnerable patients (e.g. disadvantaged orphans or the mentally, socially or physically handicapped) often need special attention. Extra support need to be in place to deliver comprehensive home-based care to the patient.

If any patient deny or unable to admit hospital for initiation of treatment in that case treatment can be started at home in consultation with local/central DR TB team.

10.2 Community-based Care

The model of community-based care is described in detail in "Standard Operating Procedures (SOP): Community-Based Programmatic Management of Drug Resistant TB". Only the highlights of the document are included here.

The "Outpatient DR TB Team" should supervise the community-based management of the patient.

Upazilla Health Complex (UHC) based outpatient DR TB team should be consist of:

- Upazila Health and Family Planning Officer (UH&FPO)-Team Leader;
- Medical Officer of Disease Control (MODC)-Member Secretary;
- Residential Medical Officer (RMO)/Medical Officer (MO) [for back up, if MODC is not available or gets transferred out];
- TB and Leprosy Control Assistant (TLCA). He/she will act as the DR TB DOT Supervisor (and can also be a DR TB DOT Provider if patient lives near-by);
- Statistician for medical record keeping;
- Medical technologist-Lab (GO/NGO);
- Representative from Partner NGO.

If TLCA acts as DR TB DOT provider, he/she should be supervised by the MO or MODC.

In urban settings, DR TB team should be formed according to respective organogram of the organization. The team leader of the team in the urban areas should be a registered medical doctor under the Bangladesh Medical and Dental Council (BMDC).

DR TB DOT providers should be selected by the team from an existing pool of community workers. This pool should already have received some training in health and TB.

The selection of DR TB DOT Providers in order of preference is:

1. TB and Leprosy Control Assistant (TLCA);
2. Health Assistants (HAs);
3. Family Welfare Assistants (FWAs);
4. Community Health Care Provider (CHCP).

In circumstances where no DR TB DOT Provider is available from the above four categories, then the DR TB DOT Provider can be selected from:

5. Local Pharmacy holder / Village doctor.
6. Paramedic/Medical assistant (in urban settings);
7. Shasthya Shebika (SS)- an NGO Community Health Volunteer (who can read and write English and Bangla well).

The SOP for Community-Based Programmatic Management of Drug Resistant TB describes in detail:

- How to set up an Outpatient DR TB team and community-based program;
- How to promote early case finding;
- The supervision and supporting the DR TB-DOT Provider;
- Tips on how to be an efficient DR TB-DOT Provider;
- How to ensure quality DOT
- Responsibilities of the DR TB-DOT Supervisor (usually the TLCA);
- Follow up visit;
- Drug distribution mechanism;
- Contact tracing;
- Patient Education;
- Infection control (IC) at home;
- Socioeconomic interventions and emotional support
- Defaulter tracing system;
- Advocacy ,Communications and social mobilization to decrease stigma;
- Procedure to deliver medicines, including injectable agents;
- Ways to improve treatment adherence;
- Recording and reporting.

CHAPTER 11 Drug Resistance and Infection Control

DR TB is transmitted in the same manner as drug-susceptible TB. DR TB is transmissible, especially among highly vulnerable populations and within institutional settings. Moreover, because DR TB patients may respond to treatment slower and remain sputum smear-positive longer than drug susceptible TB patients, they may infect more contacts.

DR TB infection control strategies mirror the three key components of drug-susceptible TB. By order of importance, they are as follows: administrative controls, environmental controls and personal protective equipment.

11.1 Administrative Controls

Administrative controls should be implemented as a first priority because those have been shown to reduce transmission of TB more potently in health-care facilities. Administrative controls are comprised of policies and procedures that are intended to promptly identify, separate and treat infectious cases so that additional precautionary measures can be taken to minimize DR TB transmission. Thus, the main point of these controls is to diagnose and effectively treat DR TB as early as possible.

An important aspect of administrative control measures is the physical separation of known or presumptive TB/DR TB patients (especially smear-positive cases) from other patients.

Other administration controls include:

- Patient education on basic infection control measures e.g: covering the nose or mouth during coughing or sneezing (cough etiquette) discarding used tissue into covered bins etc
- Contact tracing to detect DR TB case early

11.2 Environmental Controls

Environmental control measures maximize dilution and air exchange and decontaminate air when adequate ventilation cannot be reached in high risk areas. In choosing a ventilation system (i.e. natural, mechanical, artificial or mixed-mode), it is important to consider local conditions, such as building structure, climate, regulations, culture, cost and outdoor air quality. Any ventilation system must be monitored and maintained on a regular schedule. Maintenance facilities should be kept in hand. Adequate resources (budget and staffing) for maintenance are critical.

In warm climates, infection control is most effective by strong natural

ventilation. A few examples include: open windows on opposite walls, interior hallways designed so that air is not trapped and waiting areas are open at least on three sides.

Use of UVGI (Ultraviolet germicidal irradiation) lights or fixture is another environmental control and a very efficient way to destroy M. tuberculosis in indoor facility therefore the use of these fixtures is particularly important in DR TB in patient wards. However UVGI lights need regular monitoring and the health care workers should be aware of radiation hazards.

11.3 Personal protective equipment

In addition to implementation of administrative and environmental controls, use of particulate respirators (special mask e.g: N 95, FFP2) is recommended for health care workers when caring for patients. Health care workers should use particulate respirators during high-risk aerosol-generating procedures associated with high risk of TB transmission (e.g. bronchoscopy, intubation, sputum induction procedures, aspiration of respiratory secretions, and autopsy or TB lung surgery). Visitors should also wear particulate respirators when in enclosed space with infectious DR TB cases.

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

11.4 Chapter Summary

For a comprehensive summary of all policies on infection control, reference the, National guidelines for Tuberculosis Infection Control (1st edition, September 2011. Box 11.1 is a summary of specific items that can be done in and around infection control of DR TB:

Box 11.1 Specific Infection Control (IC) Measures

Administrative Controls
Implement NTP's National guidelines for Tuberculosis Infection Control
Educate all healthcare providers for DR TB on infection control. Restrict attendants presence as minimum as possible
Educate all healthcare providers for DR TB on infection control. Restrict attendants presence as minimum as possible
Separate smear positive TB patients from other patients in the wards/outdoor
Separate HIV patients from patients with DR TB (they are more susceptible to highly resistant strains)
Isolate MDR TB treatment failure cases, presumtive and documented cases of XDR TB
Implement home-based infection control protocols (see SOP on management of Community PMDT)

Provide surgical or cloth masks to the smear positive patients. The patient should wear the mask when visitors are in the ward, when outside the ward and while in contact with others. The patient need not to use the mask while sleeping, sitting outside in the open air and staying away from others.

Early tracing of contacts should be done for every DR TB patient by the DOT Supervisor (TLCA) or by the assigned representative from GO/NGO

Advocacy, Communication and Social mobilization to educate patients, families and to increase community awareness

Environmental Controls

Ensure well ventilated waiting areas for DR TB patients

DR TB indoor facilities will have good natural ventilation and back up exhaust fans

Medical consultation rooms should have good cross –ventilation (open windows on opposite walls) or an exhaust fan. Sitting arrangement should be in a way that air flows between the provider and the patient.

Personal Protective Equipments

Wearing of respirator (e.g: N 95, FFP2 etc) by the helth care provider while seeing DR TB patients who are smear positive and presumtive DR TB cases and UVGI fixtures

1

Cup the nosepiece in your hand with the nosepiece at fingertips allowing the headbands to hang freely below hands

2

Position the respirator under you chin. The nosepiece should be over the bridge of your nose.

3

Pull the top strap over head so it rests high on the back of head.

4

Pull the bottom strap over your head and position it around neck bolow ears.

5

Using both heads, mold the metal nosepiece (if present) to the shape of your nose by pushing inward while moving fingertips down both sides of the nosepiece.

6

SEAL CHECK: The respirator seal MUST be checked before each use. To check fit, place both hands over the respirator and exhale. If air leaks around your nose, adjust the nosepieces as described in step 5. If air leaks at respirator edges, adjust the straps back along the sides of your head. Check again.

CHAPTER 12 Management of DR TB drugs and Consumables

DR TB Control requires the availability of adequate quantities of second line anti-TB drugs (SLD), related consumables and ancillary drugs to treat adverse drug reaction. Second-line TB drugs must be precisely ordered because over ordering is costly and under ordering can lead to stock-outs, and consequently, the development of XDR TB. Furthermore, forecasting and ordering is further complicated by: 1.) Short shelf life of some of the second-line anti-TB drugs, e.g: Cap Cycloserine and 2.) Long lead time required between placing the order and the arrival of the order.

12.1 Selection and Forecasting of Second-line Anti-TB drugs

The management cycle of second-line anti-TB drugs and consumables is comprised of six elements: drug selection; assessment of drug requirements; management of procurement and distribution including storage and inventory control; assurance of drug quality and ensuring rational drug use. Accurate forecasting and placement of order of second-line anti-TB drugs at right time is one of the elements that guarantees an uninterrupted drug supply. Because some challenges could be faced during procuring SLDs:

- Lead time (LT) can be longer because no SLDs are kept in stock by suppliers
- Manufacturers produce SLDs only on demand

There are two main approaches for forecasting:

- **The consumption-based approach.** This approach consists of making projections of future individual drug needs based on past consumption records. This method assumes that the data are complete, accurate, properly adjusted for stock-outs and anticipated changes in demand and use. This method is recommended once PMDT activities have been established for a period of time.
- **The morbidity-based approach.** This approach is recommended for the initial phase of the PMDT or when rapid scale-up from a pilot project is underway. In this method, the standardized treatment regimen and the number of patients to be treated are predicted based on the best projection considering all local factors.

The selection on second-line anti-TB drugs is based on the drugs used in the Standard Regimens for MDR TB and XDR TB. Ordering second-line TB drugs is a very important activity conducted at the central level. Table 12.1 provides guidance that can be used to calculate second-line drug orders.

Table 12.1 - Ordering Anti-TB Drugs to Treat DR TB

Drug (Unit)	Quantity Needed	Assumptions	Standard Regimen
Pyrazinamide (500 mg tab)	Q*D*P		MDR- and XDR TB
Kanamycin (1 gr vial)	1*D*P	Discard unused portion of vial	MDR TB
Capreomycin (1 gr vial)	1*D*P	Discard unused portion of vial	XDR TB
Ethionamide (250 mg tab)	Q*D*P		MDR TB
Cycloserine (250 mg tab)	Q*D*P		MDR- and XDR TB
p-aminosalicylic acid (4 gr sachet)	Q*D*P		XDR TB
Levofloxacin (250 mg tab)	Q*D*P		MDR TB
Ofloxacin (400mg tab)	Q*D*P		MDR TB
Moxifloxacin (400 mg tab)	Q*D*P		XDR TB
Clofazimine (Cfz) (50 mg Tab)	Q*D*P		XDR TB
Amoxicillin/Clavulanate (Amx/Clv) (625 mg)	Q*D*P		XDR TB
Linezolid (Lzd)	Q*D*P		XDR TB

P = Number of patients taking the drug
Q = Number of drugs needed as per body weight per day (Reference: Chapter 06, Treatment strategies for MDR TB and XDR TB)
D = Number of days that patients receive treatment in the time period

12.2: Distribution and Storage of DR TB Drugs and Consumables

Drugs will be ordered centrally by the NTP, and will be stored according to the requirements of good storage at the central warehouse (at Shyamoli). Quarterly drug deliveries from the central warehouse will be made to each DR TB inpatient facility according to their indent (needs) where there will be a designated storage room under temperature and humidity control. Transportation should be effective and timely. The inventory control should be accurate.

Patients while admitted in designated hospital/inpatient facility for M/XDR TB, the hospital/inpatient facility authority will get a quarterly supply of drugs from NTP central store at Shyamoli with buffer for one month. When patients will be discharged from hospital/inpatient facility for community-based / ambulatory treatment for M/XDR TB will get supply of drugs from the respective designated hospitals with "Chalan" and will be delivered to respective DOTS centers following the available transportation mechanism (GO/NGO support). The supply quantity will be, for a month during intensive phase (IP) and for a quarter during continuation phase (CP) with buffer for 15 days. The respective DOTS centre will store the received drugs in their drug store and should maintain proper record as first line drugs. For storage, GOB facility will be preferred but NGO facility can also be an option where GOB facility is not available. The storage site should be cool, dry, away from direct sunlight, well ventilated and secured.

Requisition form for M/XDR TB drugs/Ancillary drugs/other logistics and consumables is an annex Form DR TB 07

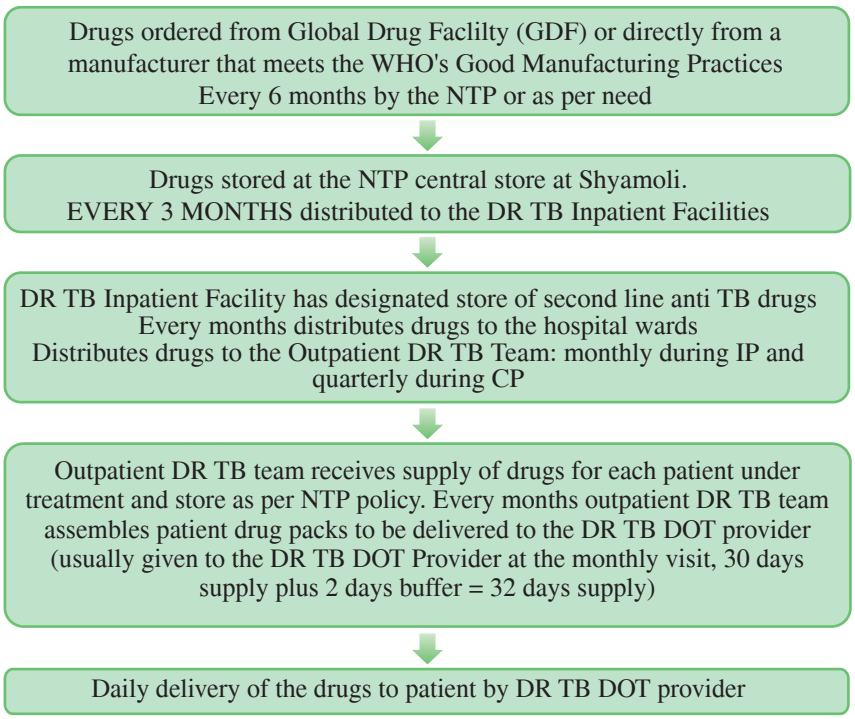
Signing of the requisition will be similar to that of first line.
Requisition may also include N-95 respirator, surgical mask, syringe, needles, water for injections, recording and reporting formats etc.

Selected M/XDR TB store of the district / upazila / urban DOTS centre will deliver drugs monthly for 32 days (including buffer for 2 days) to the DR TB-DOT provider preferably in a package with proper requisition form. Ancillary drugs to treat side effects should also be included based on availability. Extra drugs will be adjusted during the supply of the next month.

Drugs saved from patients who have died/lost to follow up/transfer out during the month will be brought back to the out patient DR TB team for use to other patients.

For laboratory logistics like sputum cup, falcon tube etc. will be supplied along with basic lab requirements following the present NTP guidelines.

Figure 12.1 Flow of Second-line Anti-TB Drugs



The Outpatient DR TB team, usually assisted by the pharmacist/store keeper at the facility, will be responsible for delivery of the drugs each month to DR TB DOT Providers after receiving indent/ requisition form. The Supervisor of the DR TB DOT Providers should verify each patient pack and sign the logbook before delivering the packs to the DR TB DOT Provider.

12.3 Rational Use of Medications

NTP discourages the use of any anti-TB drugs outside the program. Anti-TB medicines can often be bought over the counter in some private pharmacies; however, the quality of these medications is not always assured. Second line anti-TB drugs are quite expensive and more toxic, and there are few patients that can afford a proper course when being treated outside the program. Furthermore, providers who do not follow national guidelines and who do not apply appropriate measures to ensure treatment adherence can end up doing more harm to the patient than good. Providers should be trained on rational use of medications and provide appropriate information to the patients on use of drugs and ensure a proper use of drugs by patient. Drugs adverse reaction should be recorded. Providers should be cautiously monitor to ensure proper use of guidelines.

All patients with DR TB will be treated free of costs with quality assured medications through the NTP.

12.4 The Global GLC, Regional GLC and the Global Drug Facility

The Green Light Committee (GLC) was set up in 2000 by the WHO and its partners within the Stop TB Working Group on DOTS-Plus. GLC-approved projects purchase directly from agent(s) contracted by the WHO to procure drugs. As of July 2011, there is a new global framework to help countries scale up DR TB diagnosis with a Global GLC, Regional GLCs (and one being set up for WHO South-East Asia, r-GLC Secretariat) and the Global Drug Facility. The Global DR TB Initiative (GDI) has been recently constituted as a working group for DR TB related issues replacing the previous MDR TB working group and the Global Green Light committee (GLC). The GDF in continuously trying to expand the number of quality assured drug suppliers.

The Terms of Reference of SEAR r-GLC MDR TB Advisory Committee are:

- Review and provide inputs to the regional strategies and/or action plans for scale up of programmatic management of Drug Resistant TB (PMDT);
- Review and analyze GLC monitoring mission reports and surveillance data;
- Provide an opinion to donors/funding agencies on their request on country PMDT scale-up plans and the subsequent technical assistance needs addressing identified gaps, via the global GLC secretariat (g-GLC) Secretariat;
- Oversee the provision of supportive monitoring missions and technical assistance missions to countries;
- Liaise with the g-GLC and exchange information on plans of the GLC South-East Asia 's activities, seek inputs and advice as and when required, and inform the g-GLC of technical and political issues relevant to TB and MDR TB prevention and control;
- In collaboration with WHO Regional Office and Partners, to convene advocacy efforts for PMDT scale up, access to and rational use of quality medicines, and coordinate and report on progress related to data collection in respective regions.

CHAPTER 13 Supervisory Support to DR TB Treatment Units

This section describes the supervisory and monitoring activities that occur at facilities involved in DR TB treatment. In theory, supervision, monitoring and evaluation are distinct management steps. In practice, these three activities are closely linked with considerable overlap and a common approach.

Regular supervisory visits will take place by the central NTP and the Divisional PMDT team/ District team at each Facility with an Outpatient DR TB Team. In addition, the DR TB DOT Supervisor will regularly monitor and evaluate the DR TB DOT Provider (described in the Standard Operating Procedures: Community-based Programmatic Management of DR TB, 1st edition).

13.1 Activities of the Supervisory Visit

Supervisory visits involve five main units: (1) the laboratory facility (2) the drug store (3) inpatient wards (4) the DR TB outpatient treatment facility (5) the office where records and reports are stored (Data and Records corner) and (6) patient residence. Supervisory visit will be conducted using checklist (Annex:5A and 5B).

Supervision is the observation of health workers in their workplace, performed on a regular basis ,with the aim of developing their knowledge, perfecting their skills, solving problems, correcting errors, improving attitudes towards their work and increasing staff motivation. It is also termed "on-the-spot training". Supervision should be educative and supportive, not punitive. The supervisory relationship should be positive and encouraging for the supervised staff. Quarterly supervision from central and Divisional/District level and monthly by out patients DR TB team is expected.

13.2 Aims of Supervisory and Monitoring Visits

The aim of supervision and monitoring is for a rapid managerial assessment of the overall performance of each facility, institution, district, and division with the ultimate goal of improving performance.

Recording and Reporting is described in Chapter 14 and is a key part of monitoring and evaluation. The cohort analysis, which is produced from the recording and reporting system, is the key management tool used to evaluate the effectiveness of DR TB control activities in any given area. It can provide middle- or higher-level managers with timely, concrete indicators of achievement and performance.

The recording and reporting system also allows for targeted, individualized

follow-up of patients and to help patients who may not be making satisfactory progress. In summary, this strong system of accountability and crosschecks allows for accurate reporting of data, tracking of individual patients and provides timely information on the PMDT.

A key aim of the visit is to further develop the knowledge, skills, and problem solving abilities and to improve the attitudes and motivation of the staff. The most important part of the supervisory and monitoring visit is to identify gaps and problems and provide support to improve the program and management of patients and correct any errors. Often this consists of:

- Ensuring that training, supervision, logistics and communication activities are being carried out effectively;
- Reviewing the data collection in depth to assure accurate notification rates and treatment outcomes are being reported;
- Identifying technical and operational problems, specifying the reasons for the problems and taking the necessary corrective actions;
- Assisting staff to improve standards of practice;
- Identifying any problems in the quality of patient care and support then taking the necessary corrective actions.

CHAPTER 14 DR TB Recording and Reporting System

14.1 Aims of the Information System and Performance Indicators

The aims of the recording and reporting system are:

- To allow the NTP to monitor overall program performance at both the national and sub national level (e.g. number of patients tested for drug resistance, patients started on treatment and treatment results);
- To follow trends in the number of cases notified, to order and maintain adequate drugs and consumables and provide the basis for program and policy developments;
- To aid healthcare providers in the management of individual patients.

The performance indicators include:

- Number of DR TB suspects tested in the laboratory;
- Number of DR TB cases detected in the laboratory;
- Number of DR TB patients started on treatment;
- Quarterly case finding and interim treatment outcome of DR TB cases;
- Final evaluation of cases after completion of DR TB treatment.

14.2 Scope of the Information System

The information system for treatment of Drug Resistant TB is based upon, and is an extension of the basic DOTS information system. The forms have therefore been designed to be as similar as possible to the standard forms used in the National TB Control programme.

14.3 Main Forms/Registers and Flow of Information

Form DR TB 01 - DR TB Treatment Card

This card is a key instrument for health staff who administers drugs to patients on a daily basis. A patient registered for DR TB treatment should have a DR TB Treatment Card, which should be completed by a healthcare worker and should be initiated by NTP designated DR TB treatment initiation centre (mainly at Hospital). The card should be updated daily by ticking off the supervised administration of drugs. The card represents the primary source of information used to complete and periodically update the DR TB Register.

When a patient moves from the hospital facility to an Upazila/Urban DOTS center, the original copy of the card stays in the DR TB record room of hospital. Additional copy of treatment card should be provided to the Outpatient DR TB Team at Upazilla/Urban DOTS center. The copy at Upazilla/Urban DOTS center need to be updated fortnightly or monthly. Additional one copy should be kept by

the DR TB DOT Provider and is used for recording daily DOT.

The DR TB Treatment Card contains the following sections:

Page 1:

- Basic demographic and clinical information. Name, address (including mobile phone number of the patient and family members), sex, age, weight.
- DR TB registration number. This is a new unique patient identification number for patients who entered in DR TB treatment register. The main register book will stay with NTP designated DR TB Treatment initiation centre e.g, NIDCH, CDH Chittagong, Pabna, Khulna, Rajshahi etc and a copy should remain and be maintained at Upazilla/Urban DOTS centers after patient discharge from hospital;
- Date of DR TB registration; Date of entry in the DR TB register.
- DR TB treatment start date; Date of initiation of treatment
- Previous TB registration number and date of registration
- Registration group according to history of previous anti-TB treatment (e;g Failure of cat I or II, Relapse of cat I or II, Treatment after loss to follow up- cat I or II, Non converter of cat I or cat II etc.)
- Previous treatment episodes including DR TB. This section lists and describes any previous anti-TB treatment and outcomes. Start with the first episode of TB treatment and label it as number 1. The specific drugs can be placed in the block according to the standard code for anti-TB regimens. The outcome of any previous treatment is also noted here (cured, completed, failed or defaulted etc.).
- History of contact with TB/DR TB patients;
  - If yes, Relation and duration;
- Date of Discharge and referral; Date of discharge from Hospital and referral to the Upazilla/Urban DOTS center.
- Local Treatment/ DOTS center; Name and address of the Upazilla/Urban DOTS center
- Standardized Regimen for M/X-DR TB including dose; The initial DR TB regimen with doses are recorded on the table, and any changes with drugs and doses should be recorded also in the same table. One line is used for each date where a drug (or drugs) is changed.
- Treatment outcomes. At the end of treatment, the outcome should be recorded on the treatment card. Treatment outcome should be declared by the PMDT coordinator of the DR TB treatment initiation centre.
- Signature of the PMDT coordinator of the DR TB treatment initiation centre

Page 2:

- Monitoring of smear and culture. Record the date of sample collection, sample ID number and result of smear and culture. The date of the

sample collection for the smear and culture that determined the registration of the patient should be recorded in Month "0" row. The follow-up results of microscopy and culture should be recorded in the rest of the rows according to month of treatment.

- Durg Susceptibility (DST) Result: Record the method (Xpert MTB/RIF, LPA, LJ, Liquid culture), date of sample collection and results of all DST performed.
- List the adverse drug reactions (ADR) with date of ADR identified, suspected drugs and measures taken
- HIV status; If tested for HIV include date of testing and results
- Clinical management/PMDT Committee meetings. This section, if applicable, provides a space to record any major changes by the panel.

Pages 3:

- Record of daily observed administration of drugs. One line per month makes it easy to assess adherence. One box is marked with tick (✓) for each day dose is administered.
- Weight; Is to be recorded in the last column every month

Pages 4:

- Laboratory and Radiological investigation; Result of baseline laboratory and radiological investigations and monitoring investigations are to be recorded with date
- Detail identification of DOT provider
- Signature of assigned authority of DOTS centre: Signature of assigned authority of DOTS centre where patient referred after discharged from the DR TB treatment initiation centre

Form DR TB 02 - DR TB Register

The following information is recorded in the DR TB Register:

- DR TB registration number: This is a unique patient identification number for patients who qualify to enter DR TB treatment category. (Serial Number/ Year/Treatment Initiation Centre/District/Division

Example: 01/ 2013/NIDCH/Dhk/Dhk). The serial number will start from 01 in every new year.

- Date of registration: Date of registration in DR TB Register.
- Date of Starting treatment: Date of treatment initiation. Ideally date of registration and start of treatment should be the same. But in some instances, there might be little deference (Example:15-12-2013/15-12-13 or 22-05-2013/19-05-2013 or 05-06-2013/10-06-2013)
- Name, sex, age, address, mobile no.
- Recent and Previous (If any) TB registration number with Date/Year: if date is not available then write year
- Site of disease. Pulmonary or Extrapulmonary.
- Registration group: Code needs to be mentioned as per written as foot

note in the DR TB register

- Drug susceptibility test (DST)-Date of sample taken, method and results. If multiple methods of DST performed then mention all the *methods with results and date of collection of specimen.(*Method: 1) Xpert MTB/RIF 2) Line Probe Assay (LPA) 3) Liquid Culture 4) Solid culture(L-J))
- HIV Status: If tested for HIV include date of testing and results: Y= Yes, HIV infection; N=No HIV infection; Unk: HIV status unknown.
  Write Anti Retroviral Therapy (ART) status by Y/N and Date of start of ART Write Cotrimoxazole Preventive Therapy (CPT) status by Y/N and Date of start of CPT
- Reason for DR TB registration. Include reason for entering in DR TB register and Method of Diagnosis
  - Presumptive DR TB: If the status of DST is unknown but treatment started with second line drugs (SLDs)/ DR TB regimen, specify the reason for starting the regimen
  - Rifampicin Resistant TB (RR TB): Confirmed Rifampicin Resistant TB with or without resistant to other anti TB drugs except Isoniazid (e.g: R, REZ, RES etc),
  - MDR TB= Resistant to Rifampicin (R)and Isoniazid (H),
  - XDR TB= MDR TB + Resistant to Inj Amikacin/Kanamycin/ Capriomycin (Amk/Km/Cm) and Any one of the Fluoroquinolones (Ofx/Lfx /Mfxetc)
  - Drug Resistant TB- Others (DR TB Others): Confirmed DR TB, Other then confirmed M/X DR TB and RR TB, Specify the DST pattern (e.g: HES etc)
- Sputum smear and culture results: during diagnosis (0 Month) and during treatment period (Follow up to monitor treatment progress)
- Final Treatment outcome with date and Comments (if any)
- Laboratory and Radiological Investigation result with Date

Form DR TB 03 - Patient Identity Card

A patient who has enterd in DR TB register should have a patient identity card completed by the designated health staff. This card should be along with patient.

Form DR TB 04 - Laboratory Register for Culture, Xpert MTB/RIF and DST (for NTRL/RTRLs)

The register is specific for Reference Laboratories. The Laboratory register should be compared regularly with the DR TB register to ensure that all cases diagnosed with DR TB have entered for treatment.

Form DR TB 05 - Laboratory Register for Xpert MTB/RIF

The register is specific for Xpert MTB/RIF sites. This register should be filled up completely to keep records of all suspects examined for diagnosis of TB and DR TB.

Form DR TB 06 - Request and Reporting form for Diagnosis/Follow up of Drug Resistant TB

This form should be kept in all DOTS Centers, NTRL/RTRLs and Xpert MTB/ RIF sites. This form will be used for diagnosis in presumptive DR TB cases and for follow up of treatment in either the intensive phase or continuation phase. It is mandatory to fill the form completely (all four parts, A-D) and will be sent to NTRL/RTRLs or Xpert MTB/ RIF sites along with presumptive DR TB cases or samples for diagnosis or follow up from DOTS centers.

After examining samples for diagnosis in case of presumptive DR TB cases or follow up in DR TB cases during treatment the lower part (E) of the form should be filled up completely by NTRL/RTRLs or Xpert MTB/RIF sites and send back to requested sites (DOTS Centers) immediately.

Form DR TB 07- Requisition form for DR TB Drugs/Ancillary Drugs/Other logistics and consumables

This format is designed to request for second line drugs (SLDs), ancillary drugs and necessary logistics. This form should be filled every quarterly by the responsible person of the treatment initiation centre (eg; Hospital) duly signed by respective authority with a copy to the district authority and to be collected from central store of NTP (shyamoly). Outpatient DR TB centre should use this form to collect SLDs, ancillary drugs and necessary logistics from respective treatment initiation centre and DR TB DOT provider should also use this form. Outpatient DR TB centre and DR TB DOT provider need to fill the column 'd' with some modification in calculation as per buffer quantity fixed by NTP.

Form DR TB 08 - Quarterly Report on DR TB Case Registration

The quarterly report is completed from the DR TB Register and is designed to report the number of patients registered and treated for all forms of DR TB, especially MDR TB and XDR TB and RIF mono resistant. This form should be filled up completely and make three copies. One copy should be send to the district authority, one to the NTP Head Quarter in Dhaka and one should be kept in the respective reporting center (DOTS center) within 7 days after completion of a quarter. Example: Report of first quarter (January-March) should be send with 7 April. Total number of DR TB cases in Bock 1 should be equal to the that of Block 2 and Block 3.

Form DR TB 09 - Treatment Outcome report of DR TB patients

This report shows the final result of treatment by year since the start of treatment, in total and stratified by smear and culture results and by patient registration category. Since treatment is of long duration, the results reflect retrospectively the management of treatment over a prolonged period. Form 08 is completed at both 24 and 36 months after the last patient starts treatment in the cohort.

Example: The outcome report of the patients registered during 1st quarter 2013 (January- March, 2013) should be completed in 7 April 2015 and 7 April, 2016.

Most of the patients will have finished treatment by 24 months and this allows preliminary assessment of cure rates. Since a few patients may be on treatment for longer than 24 months, the form is completed again at 36 months after the last patient in the cohort starts treatment. The 36-month evaluation is considered the final Treatment Cohort Analysis result.

As noted above, patients who are entered into the DR TB Register, but later found to have drug-susceptible forms of TB, are placed back in the normal TB Register and their outcome is recorded there.

Form DR TB 10 A: Monthly report on Xpert MTB/RIF results

and

Form DR TB 10 B: Monthly Report of Enrolment status of Detected Drug Resistant Cases by Xpert MTB/RIF

These forms should be kept in all Xpert MTB/RIF sites .These reports should be completed and send to NTP Head quarter Dhaka monthly.

Form DR TB 10 A provide information about number of presumptive DR TB cases tested by Xpert MTB/RIF and results of tests. If any RR TB cases reported in the form DR TB 10 A then it is mandatory to fill form DR TB 10 B. Form DR TB 10 B provide detailed information about each detected RR TB cases.

Form DR TB 11: Quarterly Report of Culture and DST Results from NTRL/RTRLs

This form should be completed by NTRL/ RTRL and sent to NTP quarterly. This form provide culture and DST information done by L-J media, LPA and Liquid culture method

Annex

Annex 1: Partnerships

Area of collaboration	Government Commitment			NIDCH, CDHs, CDCs and other DR TB inpatient facilities.	NGO responsibility
	NTP	Divisional/ District	Upazila/DOTS Centres		
Case finding and holding	Equipment of supplies, service facilities, NTRL and RTRL	Identification of DR TB suspect and referral of suspect or to specimens NTRL/RTRL/ DOTS Centre (Xpert MTB/Rif equipped)	Identification of DR TB suspect and referral of specimens NTRL/RTRL/ DOTS Centre (Xpert MTB/Rif equipped)	Identification of DR TB suspect and referral of specimens NTRL/RTRL/ DOTS Centre (Xpert MTB/Rif equipped)	Referral of DR TB suspects from the community.
Implement-ation	National Guidelines, Overall coordination	Divisional/ DistrictDR TB teams	Out patient DR TB team	Initial hospitalization. Medical support to the Outpatient DR TB team	Home verification prior to enrolment, Assist in implementation as needed.
Training	Preparation of curriculum, materials, resource person, training of trainers, finance	Identification of trainers among DR TB team to supervise and train DR-DOT providers and new Outpatient DR TB teams.	UH&FPO and MODC to train staff in referral of DR TB suspects and train DR TB DOT providers	Training of DR TB team	Identify DR-DOT providers and ensure training.
Drug supply	Procurement, central storage and distribution	Receipt, storage of drugs. Distribution of drugs to the DR TB DOT Providers	Receipt, storage of drugs. Distribution of drugs to the DR TB DOT Providers	District level drug supply will most commonly be stored here	Collection of second-line anti-TB drugs from designated inpatient facility and Outpatient DR TB Team
Monitoring and supervision	Policy guidelines for supervision, overall monitoring, and quality control	Outpatient DR TB team	Outpatient DR TB team and DR TB DOT provider	Outpatient DR TB team and DR TB DOT provider	Supervision, monitoring and quality control
ACSM	National campaigns	Participate in National/Local campaigns	Participate in National/Local campaigns	Participate in National/Local campaigns	Local campaigns in line with NTP policy and participate in National campaigns

Annex 2 Roles and Responsibilities

Organization/ Institute	Designation	Responsibilities
National Tuberculosis Control Programme (NTP)	Director / PM	• Develop and enforce policies, guidelines and plans for the DR TB programme with guidance from the Technical Advisory Group (TAG) in line with the global policy • Ensure adequate funding through timely resource mobilization • Support supervision and monitoring of PMDT programme at all leves • Coordinate with in country governmental and non-governmental organization partners • Coordinate with National and International tecnical and development partners • Ensure timely procurement and supply of quality ensured second-line drugs, drugs for adverse effects management and other supplies for the DR TB programme (equipment, recording and reporting and other documentation and health educational materials) • Support to strengthen MIS • Plan and undertake human resource development responsibility • Provide support for proper functioning of NTRL/RTRLs and other DR TB diagnostic facilities • Plan and implement drug susceptibility testing survey and operational research • Ensure community involvement with DR TB programme • Review policy and guideline as needed
National Tuberculosis Control Programme (NTP)	Focal Person for PMDT	• Ensure implementation of NTP policy as per PMDT guidelines • Support for DR TB Programme expansion • Ensure supply of regular and uninterrupted supply of second line drugs and logistics • Monitor enrollment of all diagnosed DR TB patients • Provide support in capacity building at all levels • Ensure proper maintainace of MIS • Support in establishment of quality suppervition and monitoring system at all level • Ensure establishment of TB IC in all treatment centres
National Institute of Diseases of the Chest and Hospital (NIDCH)	Director NIDCH	• Supervises the activities of the personnel involved in DR TB management at NIDCH as per NTP policy • Designate necessary doctors, nurses and support staff for optimum management of DR TB patients • Ensure uninterrupted supply of necessary drugs and logistics for DR TB patient and proper storage • Provides administrative approval for DR TB activities • Facilitates the overall cooperation between the NIDCH, NTP, NGOs and relevant organizations • Ensure implementation of TB IC policy
National Tuberculosis Reference Laboratory (NTRL)	**NTRL Coordinator**	• Ensure proper implemention and functioning of the NTRL/RTRLs/other TB laboratories as per NTP policy • Monitoring of maintenance of proper recording and reporting of laboratory results • Maintain liason with PMDT Coordinators for ensuring registration of all DR TB patients diagnosed at NTRL • Coordinate and Conducts all related training to appropriate staff • Maintains the stocks of reagents • Ensure submission of report to NTP timely • Responsible for quality control and expansion of the laboratory network of NTP • Supervise laboratory activities at all levels • Ensure sending of all feedback (reports) to reffering units • Responsible for internal quality control and also taking part in EQA • Ensure implementation of TB IC policy

Organization/ Institute	Designation	Responsibilities
PMDT Coordinator (Divisional)	**PMDT Coordinator (Divisional)**	• Ensure registration of all DR TB patients diagnosed at NTRL/RTRLs/Geuexpert centres • Ensure that all registered patients getting NTP recommended regimen • Ensure ADRs (Adverse drug reactions) managed promptly, urgently and effectively • Ensure all DR TB patients on treatment getting DOT of every dose • Ensure all lost to follow up DR TB patients return back and put on treatment accordingly • Ensure proper and effective coordination between NTP and DR TB treatment facilities • Ensure strong and effective coordination with GO-NGO pertners • Act as facilitator in different orientation and training at different levels • Act as suppervisory personnel as authority needs • Responsible for maitenance of DR TB patients recording, reporting and sending reports to NTP • Ensure proper management and storage of SLDs and other logistics • Suport expansion of PMDT • Ensure implementation of TB IC policy
Regional Tuberculosis Reference Laboratories (RTRL)	**RTRL Coordinator**	• Ensure proper implemention and functioning of the RTRL as per NTP policy • Monitoring of maintenance of proper recording and reporting of laboratory results • Maintain liason with PMDT Coordinators for ensuring registration of all DR TB patients diagnosed at RTRL • Coordinate and Conducts all related training to appropriate staff • Maintains the stocks of reagents and other logistics • Ensure submission of report to NTP timely • Responsible for internal quality control and also taking part in EQA • Supervise laboratory activities • Ensure sending of all feedback (reports) to reffering units • Ensure implementation of TB IC policy
DR TB treatment initiation centres/CDH/ Hospitals	**Head of the DR TB treatment initiation centres/CDH/ Hospitals**	• Supervises the activities of the personnel involved in DR TB management at respective institutes as per NTP policy • Designate necessary doctors, nurses and support staff for optimum management of DR TB patients • Ensure uninterrupted supply of necessary drugs and logistics for DR TB patient and proper storage • Provides administrative approval for DR TB activities • Facilitates the overall cooperation between the NIDCH, NTP, NGOs and relevant organizations • Ensure implementation of TB IC policy
District based supervisory DR TB team	• Civil Surgeon Team Leader • 1 Junior/ Senior Consultant • 1 Medical Officer • 1 Public Health Nurse • 1 Program organizer • 1 Statistical Officer • 1 MO/DM from NGO Partner	• Provide training to UHC based team • Monitor the patient on regularly scheduled visit • Supervise the activities, and provide guidance to UHC based team • Ensure proper management of the complicated referred cases or if there is any emergency. • Provide medical consultation during monthly scheduled visit or when required. • Collect the report from UHC and submits to central PMDT team. • Links the DOTS program to refer suspect for DR TB diagnosis and ensure registration of the patient under PMDT programme. • Ensure implementation of TB IC policy

Organization/ Institute	Designation	Responsibilities
Out patient DR TB team	**At upzila** • UH & FPO Team Leader • MODC • 1 Medical Officer • 1 TLCA • 1 Statistician • 1 Medical Technologist lab • 1 NGO representative **At urban** • As per organizational structure of the respective NTP partner	• Ensure proper management of DR TB patient as per NTP policy • Select DR TB DOT provider • Responsible for ensuring enrollment of DR TB patients after receiving DST report from NTRL/RTRLs/Xpert MTB Rif centres. • Responsible for storing and recording of second line drugs, logistics, ensure regular supply of the drugs and logistics to the DR TB DOT provider • Calculate appropriate drug doses and modify as per requirement • Orient the DOT provider • Provide medical consultation during monthly visit and in case of any emergency; • Address and manage any adverse drug reactions; Refer complicated cases if required; • Ensure transportation of the sputum sample by the DOT provider to respective reference Lab; • Supervise DOT provider regularly • Ensure proper recording and reporting system as per NTP policy • Maintain regular liason with DR TB treatment initiation centre/NTRL/RTRL • Links the DOTS program to refer suspect for DR TB diagnosis • Ensure implementation of TB IC policy
NGO Responsibilities (at local level)		
Respective partner NGOs of NTP		• Support proper implementation of PMDT programme as per NTP policy • Ensure referral of DR TB suspects from the DOTS program. • Home verification prior to enrolment, Assist in implementation as needed. • Identify DR TB DOT provider to be trained. • Collection of second-line anti-TB drugs from the central warehouse to the Outpatient MDR TB Team • Local ACSM campaigns in line with NTP policy • Support Out patient DR TB team as required • Provide support for enrollment of DR TB patients after receiving DST report from NTRL/RTRLs/Xpert MTB Rif centres. • Support to trace lost to follow up DR TB patient and ensure treatment • Ensure implementation of TB IC policy
Ward/Union/Village Level		
DR TB DOT Supervisor	DR TB DOT Supervisor	• Regular monitoring DR TB DOT Provider for each patient • Ensure training of DR TB DOT Provider (initial and refresher training) • Communicate with the DR TB DOT Provider in case of emergencies • Visit patients' home to asses the quality of care • Ensure implementation of TB IC policy
DR TB DOT Provider	DR TB DOT Provider	• Supervise intake of all doses of drugs and keep records on DR TB treatment card • Reports any ADR • Accompany the patient to all medical consultations • Attend trainging/refresher training • Collect and transport follow-up sputum specimens (monthly in the initial injectable phase and every three months in the continuation phase) to the respective reference laboratory • Provides health education to the family members about PMDT and TB IC

Annex 3 : Potential New Drugs for Drug Resistant Tuberculosis Treatment

In recent years, considerable research has been conducted in the hunt for new medicines/derivatives of existing compounds and new forms of therapy that will improve TB treatment and accelerate disease control. Four principal avenues are under study: 1) new anti-TB drugs, 2) new uses of exiting anti-microbials, 3) immunomodulators, and 4) new routes of drug administration. For DR TB management, first two avenues of study are important.

Unfortunately, as with most pharmacotherapeutic development, the discovery process of a new anti TB drug take 10 to 15 years. Some 10000 substances must customarily be analysed, at a cost of many millions of dollars, to find a single promising compound for clinical use. To be accepted as a new medication, it must go through complex stages of validation in experiments on animals and humans, shich usually entails 10-15 years of research. Despite these obstacles, several dozen new chemical compounds are currently in varying stages of development. Of all the drugs under study for DR TB treatment, only TMC207 (Bedaquiline) and OPC67683 (Delamanid) are in phase III trial. We may therefore be able to turn to these two compounds in the near future. For many of the compounds be low, it is too early to discern the potential role they might play in the initial treatment of drug-sensitive TB.

Diarylquinolines (TMC207 [Bedaquiline])

There are currently high expectations here to publications showing that a derivative of the diarylquinolines, R-207910 (TMC207), acting on both sensitive and resistant bacilli and in active growth and latent phases, could cut TB treatment time in half. It is more bactericidal than H (its initial early bactericidal activity is less than H and R but equals it at 14 days), and when combined with R or Z, it enhances the sterilizing power of these drugs. In rats, the combination of TMC207, rifapentine and Z administered once a week was much more effective than the standard regimen of H+R+Z five times a week. It appears to be synergistic with Z. The appeal of TMC207 is that it is the first anti-TB drug in the last 40 years with a totally new mechanism of action: it acts by inhibiting the M. tuberculosis ATP synthase. This drug is currently in phase III trials for the treatment of MDR TB patients and has generated high expectations. There are already publications on its use in MDR/XDR TB patients showing very promising results. In a Phase IIb study in MDR TB, the addition of TMC207 to a treatment regimen with SLDs versus placebo plus SLDs administered over 8 weeks showed sterilized sputum in 48% of the patients versus 9% for the placebo group. After 2 years of treatment, 81% of patients who received TMC207 + the standard regimen were cured vs. 57% of those who received only the standard regimen. We must be cautious, however, because it appears that it may have unfavorable interactions with R, although it appears to lose no bactericidal activity.

Nitroimidazopyrans (PA-824 and OPC-67683 [Delamanid]

A series of nitroimidazopyrans originally investigated as rediosensitisers for use in cancer chemotherapy were shown to have in vitro and in vivo activity against M. tuberculosis. Newer derivatives showed substantial activity against M. tuberculosis and lacked mutagenicity shown previously with bicyclic nitroimidazoles. There is considerable in vivo activity (in mouse studies) against M. tuberculosis, comparable to that of H. Their

action involves inhibition of fatty acid and mycolic acid synthesis. Similar to the nitroimidazoles (to which metronidazole belongs), these drugs show substantial in vitro bactericidal activity against bacilli held in a hypoxic stationary phase.

A series of nitroimidazoles, related to metronidazole, have shown to be bactericidal against M. buberculosis both in vitro and in vivo Experimental studies with a nitroimidazopyran called PA-824, which proved to be the most active metronidazole, showed action similar to H, with a spectrum of action very specific to TB. Like H, PA-824 acts on the biosynthesis of cell wall lipids but in different metabolic states, and also inhibits protein synthesis, Also like H, PA-824 acts on the bacilli in the exponential multiplication phase, although in an anaerbobic culture model it also appears to act on latent bacilli. It has shown effectiveness against strains of M. tuberculosis that are resistant to the usual drugs. More study is needed, but it may become a good alternative first-line drug. Otsuka Pharmaceutical is testing a new compound from the nitroimidazoles series, a dihydroimidaze-oxazol (OPC-67683 (Delamanid)), on patients that appear to have great anti-mycobacterial activity. It is already in Phase III testing and showing very promising results.

Source: Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis 2013, International Union Against Tuberculosis and Lung Disease

Annex 4: Management of Electrolyte Disturbances

Although often asymptomatic, low serum potassium and magnesium may present as fatigue, myalgias, cramps, paresthesias, lower extremity weakness, behaviour or mood changes, somnolence, and confusion. More severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias. The magnitude of total body depletion of potassium (K+) and magnesium (Mg++) may be far lower than that which is reflected in serum levels.

Hypokalemia (defined as a serum potassium less than 3.5 mEq/L) is and hypomagnesemia (defined as a serum magnesium less than 1.8 mEq/L) are not uncommon in patients receiving MDR TB therapy and are caused by the following:

- Direct renal tubular effect of aminoglycosides and capreomycin
- Vomiting and diarrhea.

Once hypomagnesemia or hypokalemia is diagnosed:

- Underlying causes such as vomiting and diarrhea should be treated.
- Arrhythmogenic medications (such as digoxin, tricyclic anti-depressants) should be discontinued if possible.
- An electrocardiogram should be performed in patients with significant electrolyte disturbances; if the QT segment is prolonged, any drugs contributing to QT prolongation- including certain fluoroquinolones, haloperidol, fluconazole, and cisapride- should be held.

Treatment of hypokalemia and hypomagnesemia:

- May be administered orally if electrolyte disturbance is not severe (it is safer to give electrolytes, especially potassium, orally than IV). Intravenous treatment is required for patients with gastrointestinal disorders or when the potassium deficiency is severe and life threatening.
- If severe, hold the injectable agent until potassium is in a safe range.
- Replacement may be needed during the whole course of the use of the aminoglycoside or capreomycin.
- The electrolyte abnormalities will correct after suspension of the injectable in the intensive phase. If electrolyte abnormalities do not correct once the injectable is suspended, suspect another etiology
- Preliminary antidotal observations indicate that capreomycin may cause electrolyte abnormalities more frequently than other injectables. Consider changing CM to AMK or KM if the strain is susceptible.
- Hypokalemia will be refractory to treatment unless hypomagnesemia is also treated (it is acceptable to screen electrolyte disturbances with a serum potassium. If low obtain a serum magnesium and calcium. (If unable to screen for magnesium empiric magnesium replacement with the potassium replacement is often essential, since potassium wasting will continue in hypomagnesemic states).
- Normal renal function should be confirmed prior to instituting repletion, although even patients with renal failure should receive repletion in smaller doses.

- In cases of refractory electrolyte abnormalities, amiloride or spironolactone may be used to decrease potassium and magnesium wasting in the renal tubules (amiloride 5-10 mg once daily or sprionolactone 25 mg once daily). Frequent potassium monitoring must be used when potassium-sparing diuretics are given in conjunction with potassium supplements, as hyperkalemia may result. Continue with potassium and magnesium supplements, but often can use lesser quantity

The following are general recommendations for electrolyte replacement. Optimal replacement schedules have not been determined and individual programs may vary:

Potassium

Oral Supplementation

- Occasional gastric intolerance.
- May dilute KCl tablets in water or take as pills.
- May split dose and give two or three times per day.
- Supplement diet with banana, orange/tomato/grapefruit juice.

IV Supplementation

- May produce burning at infusion site.
- Should NOT exceed more than 20 meq/h of KCl.
- Normal preparation is 40 meq in 1 liter of NaCl 0.9%, maximum preparation is 60 meq/L.

Table : Frequency and replacement table for potassium

Potassium Level	**Quantity of KCl**	**When to do next control** (sooner if pt has vomiting or diarrhea)
4.0 or more	None	Monthly
3.7 – 4.0	None	Monthly
3.4 – 3.6	20 - 40 meq	Monthly
3.0 – 3.3	60 meq	Two weeks
2.7 – 2.9	80 meq	One week
2.4 – 2.6	80-120 meq	1 – 3 days
2.0 – 2.3	60 meq IV and 80 meq PO	
<2.0	60 meq IV and 100 meq PO	Every 6 to 24 hrs Every 6 hrs with aggressive IV replacement. Consider holding injectable until >2.4

Notes on Dosing Potassium: The Dosage of potassium supplements is usually expressed as mEq of potassium. Forty mEq of potassium is provided by approximately the following quantities:

3.9 g of potassium acetate
4.0 g of potassium bicarbonate
3.0 g of potassium chloride
4.3 g of potassium citrate
9.4 g of potassium gluconate

The acetate, bicarbonate, chloride, citrate, and gluconate salts of potassium can all be administered orally. Potassium chloride and potassium acetate may be administered by IV infusion. Intravenous vials often come the percentage of potassium. For example, a 10 ml vial of 10% potassium chloride is 1 gram of potassium chloride and would be 13.3 mEq of potassium.

Magnesium

Oral Supplementation

- Presentations:
- Magnesium citrate
- Magnesium glycinate
- Magnesium lactate
- Magnesium chloride
- Magnesium oxide
- Different preparations have different amounts of elemental magnesium.
- While magnesium oxide is probably the most common form given for replacement (because of it's low cost, magnesium oxide does not have high bioavailability (i.e. the body does not absorb mg oxide that well). For example, magnesium chloride, lactate, citrate and glycinate each have around the bioavailability 4 times greater than the oxide form. Magnesium citrate is probably the best in terms of absorption. (Patients with hypomagnesaemia will benefit from Mg Oxide so if the price of the other formulas not affordable magnesium oxide can be used. Other forms (chloride, lactate, citrate or glycinate) in tablet form are preferable.
- Quantities greater than 2000 mg are often more easily given IV or IM.

IV Supplementation

- Maximum concentration: 5 g or 40 meq $MgSO_4$ in 1 liter of NaCl 0.9% or Dextrose 5%
- Do NOT exceed 150 mg per minute.
- If not emergency:
- 2 g in 100 ml administered over 1-2 hours
- 4 g in 250 ml administered over 2-4 hours

Intramuscular Supplementation

- 1 g (or up to 250 mg/kg) of $MgSO_4$ without dilution IM every 6 hours.
- No advantage over IV magnesium.
- Indicated if supplementation cannot be received PO or IV.
- Potassium sparing diuretics may also help with magnesium wasting.

Table :Frequency and replacement table for magnesium

Magnesium level	Quantity of Mg (Total daily dose)	When to do next control
2.0 or more	None	Monthly
1.5 – 1.9	1000 mg – 1200 mg	Monthly
1.0 – 1.4	2000 mg (consider IM)	1–2 weeks
<1.0	3000 mg – 6000 mg (give IV or IM)	1–6 days

Calcium

- Symptomatic hypocalcemia should be treated on an emergency basis with 2 grams of calcium gluconate (180 mg elemental calcium or 20 ml 10% calcium gluconate) IV over 10 minutes, followed by infusion of 6 grams calcium gluconate in 500 ml D5W over 4-6 hrs. The IV infusion should be tapered. The initial oral dose during the transition from IV to oral therapy is 1-2 g elemental calcium three times a day.
- For long-term therapy the typical dose is 0.5-1.0 g PO TID.
- Hypomagnesemia must be treated if present.
- Total serum calcium levels need to be adjusted for low albumin (if the laboratory tests for serum ionized levels of calcium, theses do not need to be adjusted). The total serum calcium can be corrected by adding 0.8 mg/dl for every 1 g/dl decrease of serum albumin below 4 g/dl. By doing this calculation one can determine if true hypocalcemia is present:

Corrected calcium = 0.8(4.0 - measured albumin) + reported calcium

Calcium level (total calcium adjusted for low albumin)	Dose of Calcium	When to do next control
>8.5 mg/dl (>4.2 meq/L)	None	Monthly
7.5 – 8.4	500 mg TID	1–2 weeks
7.0 – 7.4	1000 mg TID	1–4 days
<7.0	Consider IV and taper to 1000 mg TID	

Final note: Always give any electrolyte replacement a few hours a part from the flouroquinolones and the cations of K+, Mg++, and Ca+ can combine with the anions of the flourquinolones and decrease absorption.

Annex 5 : Checklist for supervisory visit of PMDT.

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
PMDT Supervision Checklist

Name and address of Centre: _____

_____

Upzila _____ District _____ Division _____

Name of the Divisional PMDT Coordinator/ DR TB team leader _____

Name and Designation of Supervisor: _____

Organization _____ Date of Visit _____

Follow up of previous visit

Date of last visit: …….. / …….. / 20

Issues identified and recommendations of last visit:

_____
_____
_____
_____
_____

Status of implementation according to recommendations:

_____
_____
_____
_____
_____

Training status of health worker (s), related to PMDT at the time of the visit:

Name and Designation	Name of Training	Duration and Date

Availability of NTP DR TB manual Yes ☐ No ☐

Catchment Population: _____

Estimated Number of TB patients: _____

Information of Notified TB cases:

Period: .....

New cases Notified: Bacteriologically Pos ..... Bacteriologically Neg .....

EP ..... Total .....

Previously treated cases Notified: Bacteriologically Pos ……. Bacteriologically Neg …….

EP..... Total .....

Information about presumptive and detected DR TB cases:

Expected no of DR TB cases			Presumptive DR TB cases indentified	Presumptive DR TB cases tested	DR TB cases detected	DR TB cases Enrolled	Remark
New	Pre. Treated	Total					

DR TB patient under treatment of the facility:

MDR/RR TB cases			XDR TB cases			Other DR TB cases		
Intensive phase	Continuation phase	Total	Intensive phase	Continuation phase	Total	Intensive phase	Continuation phase	Total

Facility	Enter number Or indicate 1=Poor 2=Good 3= Excellent	Comments Not applicable (N/A)
A. Laboratory Facility		
List type of TB tests done at laboratory: 1. 2. 3. 4. 5.		
Are sputum requests forms (DR TB 06) for DR TB diagnosis and monitoring filled out correctly?	1 2 3	
Do the laboratory receive all feedback reports regularly?	1 2 3	
Do the laboratory send all feedback reports to the relevant authority/s regularly?	1 2 3	
Are laboratory registers correctly filled out and up to date?	1 2 3	
Are information of all presumptive and identified M/XDR/RR-TB patients in Laboratory register?	1 2 3	
Does the laboratory staff know the indications of when do perform a diagnostic test in a presumptive cases?	1 2 3	
Is case finding strategies being followed?	1 2 3	
Are Quality Assurance/Quality control (QA/QC) activities conducting routinely?	1 2 3	
What was the performance in the last QA/QC?	1 2 3	
Number of laboratory staff		
Are ancillary tests for monitoring adverse effects done on time?		

B. Drug Store		
Is there a safe, locked, dry and temperature controlled place for second line anti TB durgs?	1 2 3	
Are there temperature chart, bin card maintained properly?	1 2 3	
Are medicines being packed correctly and sent to the outpatient DR TB team/DR TB DOT Provider as per policy?	1 2 3	
Have there been any stock outs of second line anti-TB drugs (SLD)?	Yes/No, if yes specify name and duration	
Have there been any stock outs of ancillary drugs for management of adverse drug reaction?	Yes/No, if yes specify name and duration	
Are there any expired SLD and Ancillary drugs?	Yes/No, if yes specify name and duration	
Is the ordering and delivery of drugs going smoothly?	Yes/No, if yes specify	
Are all documents (stock register, challan etc) maintained correctly?	1 2 3	
C. Inpatient Facility (where applicable)		
Number of Hospital beds for DR TB treatment		
Number of isolation rooms for XDR TB patients		
Hospital hygiene	1 2 3	
Visitor protocols	1 2 3	
Is Patient counselling perfomed regularly?	1 2 3	
Is clinical checkup perfomed regularlywith documentation?	1 2 3	
Number of the staff in inpatient ward		
Are medicines given under strict DOT?	1 2 3	
Are sputum monitoring tests done on time?	1 2 3	
Are ancillary tests for baseline/monitoring adverse effects done on time?	1 2 3	
Are all documents (Discharge certificate etc) maintained correctly?	1 2 3	
Integrated TB/HIV care	1 2 3	
D. DR TB Outpatient Treatment Facility (where applicable)		
Are outpatient DR TB Team formulated and functioning as per NTP policy	Yes/No	
Who is the DR TB DOT Supervisor?		Name: Telephone number:
Are patients coming on time for their regular visit?	1 2 3	
Do the DR TB DOT providers come regularly with patients for visits?	1 2 3	
Is clinical checkup perfomed regularlywith documentation?	1 2 3	
Integrated TB/HIV care	1 2 3	

Is Patient counselling perfomed regularly?	1 2 3	
Medicines given under strict DOT	1 2 3	
Identification of non-adherent/defaulter patients	1 2 3	
Measure taken for non-adherent /defaulter patients	1 2 3	
Monthly monitoring of sputum smear microscopy	1 2 3	
Are ancillary tests for baseline/monitoring adverse effects done on time?	1 2 3	
Monitoring cultures done on time	1 2 3	
E. Infection Control		
Infection Control – administrative protocols	1 2 3	
Infection Control – natural ventilation	1 2 3	
Infection Control – mechanical ventilation	1 2 3	
Infection Control – UV lights	1 2 3	
Infection Control – N-95 Mask use by staff	1 2 3	
Infection Control – Surgical Mask use by patient	1 2 3	
F. Recording and Reporting		
Registers are maintained correctly?	1 2 3	
Individual Patient records are maintained correctly?	1 2 3	
Treatment cards are maintained correctly?	1 2 3	
Quarterly Reports are submitting correctly?	1 2 3	
Criteria for treatment outcomes are being used correctly?	1 2 3	
G. Other Comments and overall assessment:		
H. Recommendation(s)		
Signature:	**Date:**	

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)

DR TB Patient Supervision Checklist

Patient Name : ……..
Age: …….
Address with cell no. : …….
Name and address of designated DOTS centre
.....
Name and designation of supervisor
.....
Name, designation and organization of DR TB DOT provider
.....

Date of visit _____/_____/_____
DR-TB Registration No. : .....
Registration group : ……
Date of Treatment Started : ……/……/……...…
Date of Discharge from Hospital : ……/……/……
Medical diagnosis other than TB : ……...…….
Type of drug resistance MDR/XDR/RR/Other (specify)
Month of treatment (at present) .....

A. Medical presentation

Fever	Yes ☐ Duration	No ☐	Haemoptysis	Yes ☐ Duration	No ☐
Weight Loss	Yes ☐ Duration	No ☐	Dispnoea	Yes ☐ Duration	No ☐
Cough	Yes ☐ Duration	No ☐			
Other symptoms (specify):					

Measure taken (if any)

B. Adverse drug reaction :

Adverse drug reaction	Question to Ask Patient	Patient Response	MeasureTaken (if any)
Hearing loss	Are you having trouble hearing?	Yes ☐ Duration ..... No ☐	
Tinnitus and dizziness	Do you have any ringing in your ears or dizziness?	Yes ☐ Duration ..... No ☐	
Nausea	Have you had nausea?	Yes ☐ Duration ..... No ☐	
Vomiting	Have you had vomit?	Yes ☐ Duration ..... No ☐	
Diarrhoea	Have you had diarrhea?	Yes ☐ Duration ..... No ☐	
Abdominal Pain	Have you had abdominal pain?	Yes ☐ Duration ..... No ☐	
Anorexia	Do you have a poor appetite?	Yes ☐ Duration ..... No ☐	
Neuropathy	Have you had pain or burning in your legs?	Yes ☐ Duration ..... No ☐	
Low Potassium	Have you had leg cramping?	Yes ☐ Duration ..... No ☐	
	Do you feel weak?	Yes ☐ Duration ..... No ☐	
Psychosis	Do you feel sad?	Yes ☐ Duration ..... No ☐	
	Do you have thoughts of committing suicide?	Yes ☐ Duration ..... No ☐	
Depression	Do you feel anxious or agitated?	Yes ☐ Duration ..... No ☐	
Anxiousness	Do you hear voices or see things that may not be there?	Yes ☐ Duration ..... No ☐	
Hepatitis	Have you noticed yellowing of your eyes and/ or skin?	Yes ☐ Duration ..... No ☐	
Allergy	Do you have any rashes?	Yes ☐ Duration ..... No ☐	
Joint Pain	Do you have any joint pain?	Yes ☐ Duration ..... No ☐	

C. Laboratory Result

Follow up Sputum Done Routinely Yes ☐ No ☐
Most recent sputum smear: Date of Test ……./……../…….. Result : ……
Most recent sputum Culture: Date of Test ……./……../…….. Result : ……

Name of Test	Date Due	Date of Test	Result
Sputum Microscopy			
Sputum Culture			
Liver Function Test (SGPT)			
Renal Function Test (S. Creatinine)			
Thyroid Function Test (TSH)			
Chest X-Ray			
Others :			

D. Infection Control:

1. What is the number of people sharing the household with the patient? ……..
2. Patient living in a Single room / Sharing Room
3. Room is Well Ventilated/ Poorly ventilated
4. How many are under 5 or over 50 years of age? Under 5 years …… Over 50 years ……
6. How many suffer from another chronic disease (including HIV) among family members? ……
7. Do patients use surgical or cloth mask regularly Yes ☐ No ☐
8. Patient follows the cough etiquette Yes ☐ No ☐
9. Waste products (e;g syringe and needles, vials etc) are properly disposed Yes ☐ No ☐
10. Patient and household member's knowledg

Interview patient and household members to assess knowledge and satisfaction of services available

- Name of the disease he/she is suffering from Yes ☐ No ☐
- Sign/symptom of presumptive DR TB Yes ☐ No ☐
- Duration of treatment Yes ☐ No ☐
- Understanding of consequences of irregular treatment Yes ☐ No ☐
- Is he/she getting social support regularly as per NTP policy Yes ☐ No ☐
- Availability of free treatment (who and where) Yes ☐ No ☐
- Does he/she satisfied with the available treatment services Yes ☐ No ☐

11. Interview with DR TB DOT provider:

- Knowledge of the disease Satisfactory ☐ Unsatisfactory ☐
- Sign/symptom of presumptive DR TB Satisfactory ☐ Unsatisfactory ☐
- Duration of treatment Yes ☐ No ☐
- Knowledge of treatment regimen Yes ☐ No ☐
- Understanding of consequences of irregular treatment Yes ☐ No ☐
- Understanding of adverse drug reaction Yes ☐ No ☐
- Understanding of follow up/monitoring of the treatment Yes ☐ No ☐
- Does DR TB DOT provider use N95 regularly Yes ☐ No ☐
- Is he/she getting incentive regularly as per NTP policy Yes ☐ No ☐
- Does he/she accompany patient during clinical check up at facility Yes ☐ No ☐

Over All Comments and recommendations: .....

.....

.....

.....

.....

.....

Signature: ..... Date: .....

Annex 6

Recording and Reporting Format for PMDT

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
DR TB Treatment Card (Page 01 of 04)

Form DR TB 01

Name of Initial Treatment Center:……
Address of Initial Treatment Center:……
Name of Patients: .....
Father's/Husband's name:……
Address:.....
.....
Mobile no: ……
Sex: ❑ M ❑ F Age: ……. Initial weight (kg):……
DR TB registration Number:.....
Date of DR TB registration: ...../...../.....
Date of DR TB treatment started: : ...../...../.....
Site: ❑ Pulmonary ❑ Extra pulmonary (Specify :…….)
Medical diagnosis other than TB.....
History of contact with TB/DR TB patients: Yes / No
Relation and duration (If yes):

Registration group	Put tick
CAT I Non converter (Remain positive at month of 2)	
CAT I Failure (Remain pos. at 5 m or later/ Negative patient positive at month 2)	
Treatment after loss to follow up- CAT I	
CAT I Relapse	
CAT II Non converter (Remain positive at month of 3)	
CAT II Failure (Remain pos at 5 or 8 month)	
Treatment after loss to follow up- CAT II	
CAT II Relapse	
Close Contact of DR TB with S/S	
Transfer in (from another DR TB treatment initiation center)	
HIV infected patients	
Otthers (Specify) : a) Pulmonary- clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB treatment history. d) New (Pulmonary), bacteriologically confirmed	a ❑ b ❑ c ❑ d ❑

Previous tuberculosis treatment episodes including DR TB

No.	Start date (if unknown, year)	TB registration number with Date	Regimen (write regimen in drug abbreviations)	Outcome

Drug abbreviations

First line drugs	Second line drugs	
H = Isoniazid	Km = Kanamycin	Clf=Clofazimine
R = Rifampicin	Ofx = Ofloxacin	Lzd= Linezolid
E = Ethambutol	Lfx= Levofloxacin	Trd= Terizidone
Z = Pyrazinamide	Eto = Ethionamide	Amx/Clv= Amoxicillin+
S = Streptomycin	Cs = Cycloserine	Clavulanate acid
	PAS= Para-aminosalicylic Acid	Mfx= Moxifloxacin
	Cm=Capreomycin	Other……

Date of Discharge from Hospital and Referral to the Local treatment/DOTS centre: ……..
Name & address of the Local Treatment/ DOTS center: .....

Standardized MDR TB Regimen: **Intensive phase** ZKmEtoCsOfx/ Lvx **Continuous phase** ZEtoCsOfx/Lvx
Standardized XDR TB Regimen: I**ntensive phase** Cm-Z-Mfx-PAS-Cs-Amx/Clv- Lzd -Cfz/
Continuous phase Z-Mfx-PAS-Cs-Amx/Clv- Lzd-Cfz
Others regimen (if any): I**ntensive phase**…… **Continuous phase**: ..……

Outcome	Mark one	Date
Cured		
Completed		
Died		
Failed		
Lost to follow up		
Transferred out		

Regimen and Drug Doses

*Date	Z (mg)	Km (gm)	Ofx/Lfx (mg)	Eto (mg)	Cs (mg)	Cm (gm)	PAS (gm)	Clf mg)	Amx/Clv (mg)	Trd (mg)	Lzd (mg)	Mfx (mg)	Other	Comments

* Date treatment started and doses, Change of doses (if any)

Type of resistance:

MDR TB/XDR TB/ Poly Resistance……
Mono resistance……

Signature of the Divisional PMDT Coordinator/Authoriry of the DR TB Treatment Initiation Centre

Name and Designation: .....
Contact Number: .....

DR TB Treatment Card (Page 02 of 04)

Form DR TB 01

Microscopy Results:

Month #	Week	Sputum smear microscopy		
		Date of sample collection	Lab ID.	Result
0				
1	1			
	2			
	3			
	4			
2	1			
	2			
	3			
	4			
3	1			
	2			
	3			
	4			
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

Month #	Sputum smear microscopy		
	Date of sample collection	Lab ID	Result
22			
23			
24			

Culture Results

Month #	Date of sample collection	Lab ID	Result
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
15			
18			
21			
24			

Adverse Drug Reaction

Date	Adverse Drug Reaction	Suspected Drugs	Measure Taken

Drug susceptibility (DST) results

*Method	Date	S	H	R	E	Km	Ofx/Lfx	Eto	Other	Other	Other

Notation symbol for DST:

R = resistant
S = susceptible
C = contaminated

*Method: 1) Xpert MTB/RIF 2) Line Probe Assay (LPA) 3) Liquid Culture 4) Solid culture(L-J)

Meeting Dates and Decisions of Clinical Management/PMDT Committee:

Date	Decision	Next date

HIV Status:
Date:
Pos ☐ Neg ☐ Unknown ☐

DR TB Treatment Card (Page 03 of 04)

Form DR TB 01

Administration of Drugs (one row per month):

Patient name: .....

Month	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	Weight (kg).

Mark in the boxes : ☑ = directly observed
⊟ = not supervised
⊡ = drugs not taken

Form DR TB 01

DR TB Treatment Card (Page 04 of 04)

Laboratory and Radiological Investigation

Patients Name.....

Month	Date	Chest X-ray	Hb/g/dl	ESR	Blood glucose	Serum Bilirubin	SGPT	Alkaline Phosphate	Serum Creatinine	Serum Potasium	TSH	Pregnancy Test	Others (Specify)	Others (Specify)

Name of DOT Provider : .....

Designation : .....

Organization : .....

Address : .....

Mobile : .....

Comments : .....

Remarks:

.....

Name and Signature of assigned authority of DOTS center

Date:

Form DR TB 02

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
DR TB Register (Page 1 of 4)

Unique DR TB Registration No. SI/Yr/Center/ Dist./ Div	DR TB registration and treatment starting date (if different)	Name (in full)	Sex M or F	Age	Address and mobile no.	TB Registration number and Date or at least Year (Recent and previous if any)	Site of disease (P/EP)	Regis tration group* (see code below)	Result of drug susceptibility test (DST) (Enter the DST result. If the DST is pending it should be filled in when the results are known. See treatment card for full history of DST data) R = resistant S = susceptible C = contaminated								Date of sample taken for DST and **Method of DST	HIV status with date (Yes/ No/Unknown)
									R	H	E	S	Km/ Cm	Ofx/Lfx	Eto	Other(Specify)		If Yes on ART (Y/N) and Date
																		On CPT (Y/N) and Date
																		Status
																		ART
																		CPT
																		Status
																		ART
																		CPT

* Registation group (Code): 1= Failures of CAT I ; 2 = Failures of CAT II; 3 = Non Converters of CAT I; 4 = Non Converters of CAT II ; 5 = Relapse CAT I, 6 = Relapse CAT II ; 7 = Treatment after loss to follow up CAT I; 8 Treatment after loss to follow up CAT II; 9= Close Contact of MDR TB with S/S; 10= HIV infected patients ; 11 = Others (Specify) : a) Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB treatment history; d) New (Pulmonary), bacteriologically confirmed

**Method: 1) Xpert MTB/RIF 2) Line Probe Assay (LPA) 3) Liquid Culture 4) Solid culture(L-J)

Form DR TB 02

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
DR TB Register (Page 2 of 4)

Reason for entering in DR TB Register				Week	Smear (s) and culture results during treatment (if more than one smear or culture done in a month, enter the most recent positive result)																											
					Start of treatment month 0		Month 1		Month 2		Month 3		Month 4		Month 5		Month 6		Month 7		Month 8		Month 9		Month 10		Month 11		Month 12		Month 13		Month 14	
MDR TB Confirmed	XDR TB Confirmed	RR TB *** Method	DR TB (Others)		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	S	C
					d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y	
				1st																												
					/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	
				2nd																												
					/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	
				3rd																												
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				4th																												
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				5th																												
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				1st																												
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				2nd																												
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				3rd																												
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				4th																												
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DR TB= Drug Resistant TB, MDR TB= Resistant to Rifampicin (R)and Isoniazid (H), XDR TB= MDR TB + Resistant to Inj Amikacin/Kanamycin/Capriomycin (Amk/Km/Cm)and Any one of the Fluoroquinolones (Ofx/Lfx /Mfxetc), RR TB= Rifampicin Resistant with or without resistant to other anti TB drugs except Isoniazid (e.g: R, REZ, RES etc), DR TB (Others): Other then M/X DR and RR (e.g: HES etc)

Form DR TB 02

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
DR TB Register (Page 3 of 4)

	Smear (s) and culture results during treatment (if more than one smear or culture done in a month, enter the most recent positive result)																															
Unique DR TB Registration No. Sl/Yr/Center/ Dist./ Div	Month 15		Month 16		Month 17		Month 18		Month 19		Month 20		Month 21		Month 22		Month 23		Month 24		Month 25		Month 26		Month 27		Month 28		Month 29		Month 30	
	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	S	C	S	C	S	C
	d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y	
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Form DR TB 02

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
DR TB Register (Page 4 of 4)

Final Outcome:

Laboratory and Radiological Investigation:

Unique DR TB Registration No. Sl/Yr/Center/ Dist./ Div	Outcome: Cured/Treatment Completed/Treatment Failed/Died/Lost to follow up/Transferred Out	Comments	Chest X-ray	Hb/ g/dl	ESR	Blood glucose	Serum Bilirubin	SGPT	Alkaline Phosphate	Serum Creatinine	Serum Potasium	TSH	Pregnancy Test	Others (Specify)
	Date and Outcome		Date And Result											

MYcRvZšx evsjv‡`k miKvi
RvZxq h²v wbqšY Kgm¨P, evsjv‡`k
†cvMv‡gwUK g¨v‡bR‡g›U Ae ¨vM †iwR‡÷›U wUDevi K‡j¨vmm
wWAvi wUwe †ivMxi cwiPq cÎ

bvg : .....

wW Avi wUwe †iwRt bs : .....

cY wVKvbv : .....

.....

†gvevBj bs : .....

wj½ : ☐ ci“l ☐ gwnjv eqm : .....

wPwKrmv ïi“i ¯vb : .....

¯vbxq wPwKrmv †K›`ª ¯vb : .....

†iv‡Mi †kYx web¨vm	wPwKrmv ïi“i ZwiL
☐ dmdm ☐ dmdm ewnfZ ¯vb :	w`b gvm eQi

Type of Patient

Specify .....

Type of Resistance

☐ MDR TB ☐ XDR TB ☐ RR ☐ Poly resistance ..... ☐ Other resistance .....

Treatment regimen:

Initial regimen	Intensive phase:
	Continuation phase:
Altered regimen (if any):	

Adverse drug reactions (if any): .....

.....

.....
KZc‡¶i bvg, c`ex Ges ¯v¶i

Form DR TB 03

MYcRvZšx evsjv‡`k miKvi
RvZxq h²v wbqšY Kgmv‡P, evsjv‡`k
†cvMv‡gvUK g¨v‡bR‡g›U Ae¨vwM †iwR‡÷›U wUDevi K‡jvwmm
wWAvi wUwe †ivMxi cwiPq cÎ

cieZx Dcv¯wZi Zvwi L :

DOT c`vbKvixi Z_¨vejx :

bvg : .....

c`ex : .....

ms¯v : .....

Kg¯j wVKvbv : .....

.....

†gvevBj :

Awdm .....

e¨vw³MZ .....

1| Avcbvi Kv‡Wi hZ wbb|
2| wbqwgZ, cwiwgZ I µ gvMZ Jla †meb Ki"b|
3| Am¤úY wPwKrmv gvivZ¥K h²v †iv‡Mi mwó K‡i hv mn‡R Av‡ivM¨ nq bv|
4| †hLv‡b †mLv‡b Kd I __ †dj‡eb bv|
5| nwP I Kwki mgq bvK-gL †X‡K ivLb|
6| Awbqwgz Jla MnY Ki‡j †iv‡Mi RxevY mgv‡Ri Ab¨vb¨ m¯¨ e¨vw³i †`‡n Qwo‡q co‡Z cv‡i|

Form DR TB 04

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Laboratory Register for Culture, Xpert MTB/RIF and Drug Susceptibility Testing (Page 1 of 3)
(for NTRL/RTRLs)

Laboratory serial number	Date of specimen received	Local Lab ID	Type of specimen received	Name of the Referring health facility with address and cell no	Patient name	Patient address and Cell phone number	Sex M/F	Age	HIV Status (Yes/No/ Unknown)	*Type of Patient	Current and previous TB Registration Number (if any)	Date of specimen collected	Date of specimen inoculated

* Type of Patient (Code): 1= Failures of CAT I ; 2 = Failures of CAT II ; 3 = Non Converters of CAT I; 4 = Non Converters of CAT II ; 5 = Relapse CAT I, 6 = Relapse CAT II ; 7 = Treatment after loss to follow up CAT I; 8 Treatment after loss to follow up CAT II; 9= Close Contact of MDR TB with S/S; 10= HIV infected patients ; 11 = Others (Specify) : a) Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB treatment history d) New (Pulmonary), bacteriologically confirmed

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Laboratory Register for Culture, Xpert MTB/RIF and Drug Susceptibility Testing
(for NTRL/RTRLs) (Page 2 of 3)

Form DR TB 04

Reason for examination			Examination Results		Result of confirmatory test for M. tuberculosis (positive or negative)	Culture sent for DST (Yes or No)	Date of results reported	Name of person reporting results	Signature	Date of result sent to Referring health facility	Comments
Diagnosis	Follow-up*		Culture (specify method) [a]	Xpert MTB/RIF [b]							
	Month	DR TB Reg No.									

* Patient on TB treatment indicates months of treatment at which follow-up examination is performed.

[a]Culture result reported as follows:

0 = No growth
(1-19) = < 20 colonies (report number of colonies)
1+ = 20 – 100 colonies
2 + = > 100 -200 colonies
3 + => 200, innumerable or confluent growth

[b]Xpert MTB/Rif test result reported as follows:

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

Form DR TB 04

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Laboratory Register for Culture, Xpert MTB/RIF and Drug Susceptibility Testing
(for NTRL/RTRLs) (Page 3 of 3)

Results of Drug Susceptibility Testing (DST)[c]											Method** of DST	Date of results reported	Name and Signature of person reporting results	Comments
H	R	E	S	Amk	Km	Cm	FQ	Others	Others	Others				

[c]Report results as S= Susceptible, R= Resistant, C= Contaminated –= Testing not done

**Method: 1) Xpert MTB/RIF 2) Line Probe Assay (LPA) 3) Liquid Culture 4) Solid culture(L-J)

Form DR TB 05

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Laboratory Register for Xpert MTB/RIF

Lab ID	TB Registration Number (Current)	Date of sample Collected and Received	Date of Sample Processed	Name and address of Referring Health authority with Cell phone number	Patients Name and Address and Cell Phone Number	Age	Sex (M/F)	HIV Status (Yes/No/ Unknown)	[a]Suspect Criteria/Reason for Test	Microscopy Result and Method (ZN/LED)	[b]Xpert Result	Date of Report	Date of Report send back to the referring health facility	DRTB treatment status and name of treatment centre with DR TB registration number	Name, Designation and Signature of designated person for Xpert MTB/RIF Test	Remarks

[a]Suspect Criteria/ Reason for Xpert MTB/RIF test (Code): 1= Failures of CAT I; 2 = Failures of CAT II; 3 = Non Converters of CAT I; 4 = Non Converters of CAT II; 5 = Relapse CAT I, 6 = Relapse CAT II ; 7 = Treatment after loss to follow up CAT I; 8 Treatment after loss to follow up CAT II; 9= Close Contact of MDR TB with S/S; 10= HIV infected patients; 11 = Others (Specify) : a) Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB treatment history d) New (Pulmonary), bacteriologically confirmed

[b]Xpert MTB/RIF test result reported as follows:

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

Form DR TB 06

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Request and Reporting form for Diagnosis/Follow up of Drug Resistant TB

A. Patient identification (ID):

TB registration No (Current): _____ Previous TB registration No (If any):_____ DR TB registration No: _____

Name of patient: _____ Age (yrs):_____ Sex:____ *HIV-status: Pos / Neg / Unknown

Address: _____

_____

Cell Phone #:_____

B. TB Disease type and treatment history

Site: Pulmonary Extra pulmonary (specify):_____

History:

1) Failures of Category I (remain positive at month 5 or later and smear negative patients who become smear positive at month 2)
2) Failures of Category II (remain positive at month 5 or 8)
3) Non converters of Category I (remain positive at month 2)
4) Non converters of Category II (remain positive at month 3)
5) Relapses (Category I / Category II)
6) Treatment after loss to follow up (Category I / Category II)
7) Close contacts of DR TB patient with symptoms.
8) HIV infected
9) Others (Specify) eg; Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB treatment history d) New (Pulmonary), bacteriologically confirmed

C. Origin of request:

Division name & ID:_____ District name & ID:_____ Local laboratory name & ID:_____

Local laboratory registration/serial number: _____ Date of test: ……/……/……. Smear result: 1st ___ 2nd _____specimen

Microscopy technique used: Ziehl-Neelsen (ZN) ☐ LED Fluorescence microscopy (FM) ☐

D. Request for testing at the reference laboratory:

1) Diagnosis 2) Follow Up: Month of ……

Date specimen(s) collected: ____/____/20____ Specimen Identification number (s): _____

Specimen: Sputum ☐ Sputum in preservative, type ☐ Other specify):_____

Requested tests: ☐ microscopy (type: ZN/LED ☐ culture (L-J / MGIT) ☐ Xpert MTB/RIF ☐ DST Conventional ☐ Line Probe Assay (LPA) :

Others (Specify)_____

Person requesting examination: Name:_____ Position:_____ Cell Number:_____

Organization: Government/Non Government (specify: _____ Signature (with official seal) and Date:_____

* Information that can be disclosed optionally

E. Reference laboratory results:

Date of specimen received/Collection in the Reference Laboratory _____ Reference Laboratory specimen ID:_____

1. Microscopic examination: Date reported _____ Previous Report and Date (If any) _____

ID #	Neg	Scanty	1+	2+	3+

hot Ziehl-Neelsen LED fluorescence Others (specify)_____
direct smear concentrated smear

2.Gene Xpert (MTB/RIF) result: Date reported _____ Previous report and Date (If any) _____

ID #	T= MTB detected, Rif resistance not detected	RR=MTB detected, Rif resistance detected	N=MTB not detected	I=invalid/no result/ error

3. Culture result: Method used: Solid (LJ) ☐ Liquid (MGIT) ☐ LPA ☐ Date reported _____ previous report and Date (If any) _____

ID #	Contaminated	Neg	Positive	Atypical Mycobacteria (species)	Mycobacterium tuberculosis complex			
					<20 =1-19 colonies Actual count	1+=20 – 100 colonies	2+=>100 - 200 colonies	3+=>200 colonies

4. Results of M. tuberculosis drug susceptibility testing: Date reported:_____

Method used: ☐Proportion method (L-J) ☐Liquid (MGIT 960 system) ☐Line Probe Assay (LPA)

ID #	Legend: S = susceptible; R = resistant; C = contaminated; ND = not done						
	INH (H)	Rifampicin (R)	Ethambutol (E)	Streptomycin (S)	Pyrazinamide (Z)	FQ : Ofloxacin/ Levofloxacin	Kanamycin (Km)
Result							

Date: _____/_____/20_____ Signature with official Seal _____

Form DR TB 07

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Requisition form for DR TB drugs/Ancillary drugs/
other logistics and consumables (page 1 of 2)

Quarter ..... Year .....

Name of the Treatment Center ..... Upazilla .....

District ..... Division .....

Name and Designation of the person filling the form .....

Cell number .....

DR TB Drugs

Name of drugs	Number of DR TB Cases on treatment = a			Quantity required per pt per month = *b (D=30 Days)	Stock in hand = c	Quantity required = **d= (a x 4 x b)-c	Actual quantity supplied	Remark
	MDR	XDR	Other DR					
Pyrazinamide (500 mg tab)				4xD				
Kanamycin-1 gm vial (only for IP)				1xD				
Ethionamide (250 mg tab)				3xD				
Cycloserine (250 mg tab)				3xD				
Ofloxacin (400 mg)				2xD				
Levofloxacin (250 mg tab)				3xD				
Moxifloxacin (400 mg tab)				1xD				
Clofazimine (Cfz) (50 mg Tab)				3xD				
Amox/Clav (500/125 mg (Tab)				3xD				
Linezolid (Lzd)				4xD				
Capreomycin-1gm vial (only for IP)				1xD				
PAS (4 gm sachet)				2xD				

Form DR TB 07

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Requisition form for DR TB drugs/Ancillary drugs/
other logistics and consumables (page 2 of 2)

Ancillary Drugs and other logistics and consumables

Name of drugs	Number of DR TB Cases on treatment = a			Quantity required per pt per month = *b (D=30 Days)	Stock in hand = c	Quantity required = **d= (a x 4 x b)-c	Actual quantity supplied	Remark
	MDR	XDR	Other DR					
Omeprazole (20 mg)				2xD				
Domperidone (10 mg)				3xD				
Pyridoxine (25 mg)				6xD				
Multivitamin				1xD				
Alprazolam (0.5mg)				1xD				
Others***								

* b = Average number of drugs needed per day per patient (assumption)

** d = This column is not required to fill up when supplying drugs and logistics to DOT Provider

*** Others = Example: N-95 respirator, surgical mask, syringe, needles, water for injections, recording and reporting formats etc

Signature : .....

Name and Designation of the treatment centre authority

.....

Date : .....

Recording and Reporting Format for PMDT

Form DR TB 08

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Quarterly report on DR TB case registration (page 1 of 2)

Name of PMDT Coordinator .....

Division .....

District .....

Treatment Centre .....

Signature .....

Number of Patients registered in the DR TB register .....

During ……..……. quarter of year …….

Date of completion of the form ……..……..

Block 1: Patient registered in DR TB register and started on DR TB regimen

Sex	Confirmed DR TB					Presumptive DR TB	Grand Total
	MDR	XDR	RR	Other DR	Total		
Male							
Female							
Total							

Block 2: Age and sex distribution

Type of DR TB	0-4		5-14		15-24		25-34		35-44		45-54		55-64		>65		Total	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
MDR																		
XDR																		
RR																		
Other DR																		
Presumptive DR TB																		
Total																		

Form DR TB 08

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Quarterly report on DR TB case registration (page 2 of 2)

Block 3: DR TB cases registered during the quarter

Bacteriologically confirmed (Pulmonary)											Other						Total	Grand total
New	Failure after cat II	Failure after cat I	Relapse after cat II	Relapse after cat I	Treatment after loss to follow up CAT II	Treatment after loss to follow up CAT I	Delayed converters cat II	Delayed converters cat I	Close Contact of DR TB with S/S	Total	Pulmonary (clinically diagnosed)			Extra pulmonary (Bacteriologically confirmed or clinically diagnosed)				
											New	Previously treated	Unknown TB treatement history	New	Previously treated	Unknown TB treatement history		

Block 4: Number of DR TB/HIV patient registered during the quarter

Age group	Male	Female	Total	Type of patient				Number of patient on ART	Number of patient on CPT
				Pulmonary		Extra pulmonary			
				Bacteriologically confirmed	Clinically diagnosed	Bacteriologically confirmed	Clinically diagnosed		
< 15 years									
15 years and above									
Total									

Name of the Person filled the form: ..... Designation: ..... Cell no. .....

Organization: Government/ Non Government (Specify): ..... Signature: ..... Date: .....

Recording and Reporting Format for PMDT

Form DR TB 09

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Treatment Outcome Report of DR TB patients
To be filled in 24 and 36 months past the closing date of year of treatment (page 1 of 2)

Name of PMDT Coordinator .....
Division .....
District .....
Treatment Centre .....
Signature & Date .....
Cell number .....

Reporting month: ☐ 24 month ☐ 36 month
Patients registered: During ..... quarter of year .....
Date of completion of this form .....

Block 1: Treatment outcome according to the types of DR TB patients

Patient group	Total number of DR TB patients registered during the quarter	No of Confirmed DR TB patients registered during the quarter	Cured	Treatment completed	Failure	Died	Lost to follow up	Transferred out	Still on treatment	Not Evaluated	Total
MDR											
XDR											
RR											
Other											
Presumptive DR TB											
Total											

Form DR TB 09

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Treatment Outcome report of DR TB patients
To be filled in 24 and 36 months past the closing date of year of treatment (page 2 of 2)

Block 2: Treatment outcome according to the registration group

Patient group	Total number of DR TB patients registered during the quarter	No of Confirmed DR TB patients registered during the quarter	Cured	Treatment completed	Failure	Died	Lost to follow up	Transferred out	Still on treatment	Not Evaluated	Total
1. New (Pulmonary- bacteriologically confirmed)											
2. Failures of CAT II											
3. Failures of CAT I											
4. Relapse CAT II											
5. Relapse CAT I											
6. Treatment after loss to follow up CAT II											
7. Treatment after loss to follow up CAT I											
8. Non Converters of CAT II											
9. Non Converters of CAT I											
10. Close contact of DR TB with S/S											
11. HIV infected patients											
12. Other											
a) Pulmonary, clinically diagnosed											
New											
Previously treated											
Unknown TB treatement history											
b) Extra pulmonary											
New											
Previously treated											
Unknown TB treatement history											

Name of person filled the form .....

Designation .....

Organization : Government/Non Government (Specify):

Contact No .....

Signeture: .....

Date: .....

Recording and Reporting Format for PMDT

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)

Form DR TB 10 A

Monthly Report on Xpert MTB/RIF Results

Name of the reporting unit .....
Division .....
District .....
Name and designation to the person completing the report .....
.....
Date of completion of the form .....
Signature ..... Cell Number .....

Reporting period : ……..... Month ..... Quarter of year ……

Date of Xpert MTB/RIF centre Establishment : .....

Date of Xpert MTB/RIF centre Functioning : .....

Block 1:
Number of Total Presumptive DR TB Cases Tested : _____
Result :
A) Number of MTB detected, Rif Resistance not detected (T): _____
B) Number of MTB detected, Rif Resistance detected (RR): _____
C) Number of MTB detected, Rif Resistance indeterminate (TI):_____
D) Number of MTB not detected (N): _____
E) Number of Invalid/ no result/ error (I) : _____

Block 2:

Number of :	Type of Patient													Total
	Failures of CAT I (remain positive at month 5 or later) Column (1)	Failures of CAT I (Smear negative patients become smear positive at month 2 Column (2)	Failures of CAT II (remain positive at month 5) Column (3)	Failures of CAT II (remain positive at month 8) Column (4)	Non converters of CAT I (remain positive at month 2) Column (5)	Non converters of CAT II (remain positive at month 3) Column (6))	Relapses (CAT I) Column (7)	Relapses (CAT II) Column (8)	Treatment after loss to follow up (CAT I) Column (9)	Treatment after loss to follow up (CAT II) Column (10)	Close contacts of MDR TB patient with symptoms Column (11)	HIV infected patients Column (12)	Others (Specify) a) Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB history d) New (Pulmonary), bacteriologically confirmed Column (13)	
Presumptive DR TB cases tested by Xpert MTB/RIF														
Sputum Smear Microscopy Result*														
MTB detected														
RR TB detected														

Total RR TB cases detected in the reporting month	Total RR TB patient Enrolled from reporting month	Remarks
		Fill Form DR TB 10 B as per total RR TB detected cases during this reporting month

Name and Designation of Coordinator/Authority of the centre: …….....……

Signature : ..... Date : .....
Cell Number : .....

* Write number of sputum smear Positive result only

Form DR TB 10 B

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Monthly Report of Enrolment status of Detected Drug Resistant Cases by Xpert MTB/RIF
Fill this format as per total RR TB detected cases during the reporting month reported in Form DR TB 10 A

Name and address of the reporting unit : ..... Reporting period : …….... Month ..... Quarter of year …….

Number of total RR TB detected in the reporting month : .....

Sl. No	Name of the RR TB patients	Age	Sex	Address and cell number	Name and address of the Referring Unit and cell number	Type of patient*	Current and Previous (if any) TB Registration Number	Result of Xpert MTB/RIF**	Name and address of the Hospital/ Treatment Initiation Centre for Enrollment of DR TB Treatment	Enrollment Status Y/N	Current status of the patient***	Remarks

*Type of patient (Code): 1= Failures of CAT I ; 2 = Failures of CAT II; 3 = Non Converters of CAT I; 4 = Non Converters of CAT II ; 5 = Relapse CAT I, 6 = Relapse CAT II ; 7 = Treatment after loss to follow up CAT I; 8 Treatment after loss to follow up CAT II; 9= Close Contact of MDR TB with S/S; 10= HIV infected patients ; 11 = Others (Specify) : a) Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB treatment history d) New (Pulmonary), bacteriologically confirmed

**Result of Xpert MTB/RIF: T = MTB detected, Rif resistance not detected, RR = MTB detected, Rif resistance detected, TI = MTB detected, Rif resistance indeterminate, N = MTB not detected, I = invalid/ no result/ error

***Example: died, absconded/Lost to follow up, under treatment etc

Recording and Reporting Format for PMDT

Government of the People's Republic of Bangladesh
National TB Control Programme
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Quarterly Report of Culture and DST Results from NTRL/RTRLs (page 1 of 4)

Form DR TB 11

Name of the reporting unit .....
Division .....
District .....
Name and designation to the person completing the report .....
.....
Date of completion of the form .....
Signature ..... Cell Number .....

Reporting period : ……..... Month ..... Quarter of year …….
Date of centre Establishment : .....
Date of Xpert MTB/RIF centre Functioning : .....
……. Quarter ……. Year

LPA	Type of Patient												
	Failures of CAT I (remain positive at month 5 or later)	Failures of CAT I (Smear negative patients become smear positive at month 2	Failures of CAT II (remain positive at month 5)	Failures of CAT II (remain positive at month 8)	Non converters of CAT I (remain positive at month 2)	Non converters of CAT II (remain positive at month 3)	Relapses (CAT I)	Relapses (CAT II)	Treatment after loss to follow up (CAT I)	Treatment after loss to follow up (CAT II)	Close contacts of MDR TB patient with symptoms	HIV infected patients	Others (Specify…….) a) Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB history d) New (Pulmonary), bacteriologically confirmed
	Column (1)	Column (2)	Column (3)	Column (4)	Column (5)	Column (6))	Column (7)	Column (8)	Column (9)	Column (10)	Column (11)	Column (12)	Column (13)
Suspect tested													
MTB detected													
MDR TB (HR)													
RR TB													
H Mono resistance													

Liquid culture	Type of Patient												
	Failures of CAT I (remain positive at month 5 or later)	Failures of CAT I (Smear negative patients become smear positive at month 2	Failures of CAT II (remain positive at month 5)	Failures of CAT II (remain positive at month 8)	Non converters of CAT I (remain positive at month 2)	Non converters of CAT II (remain positive at month 3)	Relapses (CAT I)	Relapses (CAT II)	Treatment after loss to follow up (CAT I)	Treatment after loss to follow up (CAT II)	Close contacts of MDR TB patient with symptoms	HIV infected patients	Others (Specify……..) a) Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB history d) New (Pulmonary), bacteriologically confirmed
	Column (1)	Column (2)	Column (3)	Column (4)	Column (5)	Column (6))	Column (7)	Column (8)	Column (9)	Column (10)	Column (11)	Column (12)	Column (13)
Suspect tested													
Total MTB complex													
Susceptible to all first line drugs													
MDR (HR)													
HRES													
HRS													
HRE													
HR													
HR, E and/or S undefined													
MDR + Km (or Cm or Ak)													
MDR + Fluoroquinolone (FQ)													
MDR + other second line													
MDR + FQ + injectable (XDR)													
Resistant against 3 drugs non-MDR													
HES													
RES													
Resistant against 2 drugs non-MDR													
HE													
HS													
ES													
RS													
RE													
Resistant to 1 drug													
H													
R													
E													
S													

Recording and Reporting Format for PMDT

Form DR TB 11

Lowenstein–Jensen media	Type of Patient												
	Failures of CAT I (remain positive at month 5 or later)	Failures of CAT I (Smear negative patients become smear positive at month 2	Failures of CAT II (remain positive at month 5)	Failures of CAT II (remain positive at month 8)	Non converters of CAT I (remain positive at month 2)	Non converters of CAT II (remain positive at month 3)	Relapses (CAT I)	Relapses (CAT II)	Treatment after loss to follow up (CAT I)	Treatment after loss to follow up (CAT II)	Close contacts of MDR TB patient with symptoms	HIV infected patients	Others (Specify……..) a) Pulmonary, clinically diagnosed, new/previously treated b) Extra Pulmonary, new/previously treated c) Unknown TB history d) New (Pulmonary), bacteriologically confirmed
	Column (1)	Column (2)	Column (3)	Column (4)	Column (5)	Column (6))	Column (7)	Column (8)	Column (9)	Column (10)	Column (11)	Column (12)	Column (13)
Suspect tested													
Total MTB complex													
Susceptible to all first line drugs													
MDR (HR)													
HRES													
HRS													
HRE													
HR													
HR, E and/or S undefined													
MDR + Km (or Cm or Ak)													
MDR + Fluoroquinolone (FQ)													
MDR + other second line													
MDR + FQ + injectable (XDR)													
Resistant against 3 drugs non-MDR													
HES													
RES													
Resistant against 2 drugs non-MDR													
HE													
HS													
ES													
RS													
RE													
Resistant to 1 drug													
H													
R													
E													
S													

Form DR TB 11

MDR TB detection and admission status	Number
Total RR TB patient detected	
Total RR TB patient enrolled	
Total MDR TB patient detected	
Total MDR TB patient enrolled	
Total XDR TB patient detected	
Total XDR TB patient enrolled	
Total OtherDR TB patient detected	
Total OtherDR TB patient enrolled	

Treatment monitoring (Follow up)	
No. of Patient tested	
No. of Sample tested	
Follow up prositive at month 4	

Date of Completion of this Form:

Name & Signature of Coordinator:
Date : .....

Annex 7: List of Contributors

Dr. Md. Ashaque Husain
Director MBDC and Line Director TB Control and Leprosy Elimination Program,
DGHS, Mohakhali, Dhaka.

Professor Dr. Md. Rashidul Hassan
Director, National Inustitute of Diseases of the Chest and Hospital, Mohakhali, Dhaka

Dr. Md. Nuruzzaman Haque
Deputy Director (MBDC) and Program Manager-TB, NTP, DGHS
Mohakhali, Dhaka.

Dr. S. M. Mostofa Kamal
Associate Professor, NIDCH and Coordinator, NTRL, Dhaka.

Dr. Asif Mujtaba Mahmud
Associate Professor (Respiratory Medicine), IEDCR, Dhaka and member of Regional Green Light Committee, SEARO, WHO

Dr. Md. Wahiduzzaman Akhanda
Assistant Professor (Respiratory Medicine), NIDCH and PMDT Coordinator, Dhaka.

Dr. Bashir Ahmed
Medical Superintendent, NIDCH, Mohakhali, Dhaka

Dr. Md. Mosaddek
Superintendent, TB Control And Training Institute, Chankherpool, Dhaka.

Dr. Md. Abul Quashem
Officer in Charge, National TB Control Project, Shyamoli, Dhaka.

Dr. Mirza Nizam Uddin
Deputy Program Manager (Admin and Finance), NTP, DGHS
Mohakhali, Dhaka.

Dr. M.A. Hamid
Deputy Program Manager (Procurement and Logistics), NTP, DGHS
Mohakhali, Dhaka.

Dr. Shamim Sultana
Deputy Program Manager (Coordination), NTP, DGHS, Mohakhali, Dhaka.

Dr. K. M. Alamgir
Deputy Program Manager (Training), NTP, DGHS, Mohakhali, Dhaka.

Dr. Md. Mokim Ali Biswas
Medical Officer, MBDC, DGHS, Mohakhali, Dhaka.

Dr. Md. Monjur Rahman
Medical Officer, MBDC, DGHS, Mohakhali, Dhaka.

Dr. Kausari Jahan
Medical Officer, MBDC, DGHS, Mohakhali, Dhaka.

Dr. Chowdhury Shamima Sultana
Medical Officer, MBDC, DGHS, Mohakhali, Dhaka.

Md. Mafizul Hoque
Statistical Officer, MBDC, DGHS, Mohakhali, Dhaka.

Dr. Md. Mojibur Rahman
National Program Consultant, NTP, Mohakhali, Dhaka.

Dr. Narendranath Dewri
Consultant, HR, NTP, Mohakhali, Dhaka.

Dr. Emdadul Hoque
M & E Specialist, NTP, Mohakhali, Dhaka.

Dr. Shakil Ahmed
Consultant PPM, NTP, Mohakhali, Dhaka.

Dr. M. H. M. Mahmudul Hassan
Consultant TBIC, NTP, Mohakhali, Dhaka.

Dr. Bishakha Ghose
Consultant Training, NTP, Mohakhali, Dhaka.

Dr. Fahmida Khanam
Consultant TB-Lab, NTP, Mohakhali, Dhaka.

Dr. Abu Sayem
Divisional Consultant, Rajshahi NTP

Dr. M. Lutfor Rahman
Program Consultant, UPHCSDP.

Dr. Shayla Islam
Sr.Programme Specialist, BRAC.

Dr. Zakia Sultana Siddique
Sr.Sector Specialist ,BRAC.

Dr. Bivakar Roy
Sr.Program Manager, BRAC.

Dr. Sharmin Ferdous
Sr.Sector Specialist, BRAC.

Dr. Aung Kya Jai Mang
Country Director, Damien Foundation.

Dr. Paul Daru
Technical Director, TB Care II, URC.

Dr. Md. Manjur-ul-Alam
Programme Specialist-MDR TB, TB Care II, URC.

Dr. Md. Sayeedur Rahman
Programme Specialist-M&E, TB Care II, URC.

Dr. Mohammad Hossain
Senior Technical Advisor, Clinical TB, TB Care II, URC.

Mr. Jewel Ahmed
Sr. Lab Specialist, TB Care II, URC.

Dr. A.T.M. Sanaul Bashar
Senior Technical Advisor-TB, MSH/SIAPS.

Dr. Md. Kamal Hossain
Technical Advisor-TB, MSH/SIAPS.

Mr. Mostafizur Rahman
Lab Coordinator, NTRL, NIDCH, TB Care II, URC.

Dr. Vikarunnessa Begum
NPO, TB CAP, WHO.

Dr. Md. Kamar Rezwan
NPO, TB Control, WHO.

Dr. Sabera Sultana
NPO, DR TB, WHO.

International Technical Assistance
Dr. Md Khurshid Alam Hyder
Regional Adviser TB, SEARO, WHO

Dr. Michael Rich
PIH, USA

National Guidelines and Operational Manual for Programmatic Management of Drug Resistant TB (PMDT)

National Tuberculosis Control Programme
Directorate General of Health Services
Dhaka, Bangladesh