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

Third Edition
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World Health Organization
Bangladesh

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Message

Although Bangladesh has achieved notable progress in improving a multitude of health indicators over the last decade including tuberculosis (TB) treatment, TB remains a major public health concern in the country, & substantial inequities & challenges in access to & continuity of TB care also persist particularly in vullnerable groups like multio-drug resistant TB (MDR-TB) patients.

In Bangladesh, available information from recently concluded national drug reesistance surveys suggest that the proportion of MDR/RR-TB among TB patients is relatively low. However, this translates into a large absolute number of patients that need to be treated with second line anti-TB drugs. Specific measures are being taken within the NTP to address the DR-TB challenge through appropriate strengthening of the health system for an effective management of the disease and prevention of transmission of DR-TB.

NTP has recently developed the National Strategic Plan (NSP) 2021-25 to work towards achieving the goals of eliminating TB by 2025. We have seen excellent commitment and the progress to scaling up services for drug resistant TB. The Government of Bangladesh, together with its many and diverse partners from the public and private sectors, is committed to further intensify the TB control activity in order to sustain the achieved success and to reach the TB control targets linked to the WHO End TB Strategy.

NTP Bangladesh has updated the National Guidelines and Operational manual for programmatic management of drug resistant TB. This now aligns with the WHO End TB Strategy, Sustainable Development Goals (SDG) and WHO recent PMDT Gudelines in order to advance the country to scaling-up universal access to drug susceptibility testing for all diagnosed and notified TB patients and decentralized patient centric care of the drug resistant TB.

I recommend this guideline for intensive use in implementation of core interventions in PMDT Bangladesh, I would encourage all programme managers, providers, stakeholders, civil society and community members to work together for comprehensive implementation of these guidelines to combat and win over the threat of DR-TB in Bangladesh. I am hopeful that this Guideline will strengthen the capacity of the NTP for implementation of PMDT services in the country.

Md. Abdul Mannan

Director General (Health)
Directorate General of Health Services

Message

Bangladesh manages TB control through effective partnership achieving remarkable success in terms of case notification and treatment 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. The Government of Bangladesh has given priority to TB control. The services of which are available throughout the country.

Bangladesh commitment to end TB by 2030, combating drug resistance TB will be essential to meet this ambitious target. It is now time to decentralize DR-TB services to improve access, minimize patient travel and maximize patient satisfaction. Early diagnosis of drug resistance among all diagnosed TB patients need to be ensured by providing GeneXpert at Upazila level with the help of strong specimen collection and transportation system from the first point of contact where the patients choose to seek care. Similarly, treatment of DR-TB services needs to be available at least up to the district level through a team of specialists at district hospitals, medical colleges or through available partnership options substantiated with patient support systems.

Bangladesh is a pioneer in the use of the shorter treatment regimen (STR) for MDR-TB. In 2016, WHO recommended use of shorter MOR-TB regimen for treatment of MDR/RR-TB patient as well as use of newer drugs i.e. Bedaquiline/Delaminid with a suitable background regimen for the management of MDR-TB patients with advanced diseases or additional resistance to second line drugs. The guideline is aligned to these recommendations.

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. I am very hopeful that this guideline will play a pivotal role in enhancement of services provided for DR-TB patients in the country, an essential intervention to ensure that we witness the end of TB from Bangladesh.

Prof. Dr. Abul Bashar Mohammad Khurshid Alam

Director
Mycobacterial Disease Control and
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Message

Drug resistant TB threatens global TB care and prevention, and it remains a major public health concern in a number of countries and an obstacle to end TB. In Bangladesh second national drug resistance survey finds that the proportion of MDR/RR-TB among the TB patients is relatively low. The proportion of MDR/RR-TB is 0.7% and 12.2% in new and previously treated TB patients respectively, with geographic variations. However, this translates into a large absolute number of patients that need to be treated with second line anti-TB drugs. Specific measures are being taken within the NTP to address the DR-TB challenge through appropriate strengthening the health system for an effective management and prevention of transmission of DR-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 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.

Development of the Guidelines for Programmatic Management of Drug –resistant Tuberculosis Bangladesh 2020 is a major step forward in addressing this epidemiological reality and provide evidence-based guidance for meeting this unmet need. We hope this manual will provide useful reference for all clinician involved in management of tuberculosis. This guideline is based on the WHO TB guideline along with international recommendations. We are grateful to The WHO for their support for printing this guideline.

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 this guideline that obviously helps for clinician for saving life of TB patient.

Prof. (Dr) Md. Shamiul Islam

World Health Organization
Bangladesh

WHO Representative to Bangladesh

Message

Globally, countries have made substantial progress in the fight against tuberculosis (TB) to reduce the prevalence, enhance specialized care and raise public awareness of this preventable and curable disease. Through a multisectoral strategic approach which includes the involvement of high-level representatives, the World Health Organization (WHO) has been closely working with countries, partners and civil society all around the world in scaling up the TB response and translate commitments into actions.

Much has been achieved in recent decades to end the tuberculosis epidemic. Global efforts to combat TB have saved an estimated 63 million lives since the year 2000. However, TB remains a public health threat, affecting vulnerable populations and killing almost 4 000 people every day.

Tuberculosis occurs in every part of the world, but over 95% of cases and deaths are registered in developing countries. In 2019, 87% of new TB cases occurred in the 30 high TB burden countries, with eight countries accounted for two thirds of the new TB cases, including Bangladesh.

There has been significant progress in testing, detection and treatment of Multidrug-resistant tuberculosis (MDR-TB). The global TB report in 2020 revealed that 61% of people with bacteriologically confirmed TB were tested for rifampicin resistance, compared to 51% in 2017 and 7% in 2012. Coverage of testing was 59% for new and 81% for previously treated TB patients. In 2019, Bangladesh witnessed a coverage of testing for rifampicin resistance of 26% for new TB patients, 98% for previously treated TB patients, and 43% overall among notified TB patients leaving a large unmet need.

The World Health Organization (WHO) is honored to be associated with the Government of Bangladesh through the Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare (MOHFW) to address unreached populations with early diagnosis and provide appropriate treatment to patients suffering from various forms of TB and DR-TB. The second National anti-TB Drug Resistance Survey (DRS) conducted by National Tuberculosis Programme (NTP) in 2018-19 with technical assistance from WHO indicated a low level of multi-drug resistance in Bangladesh: 0.7% MDR-TB among newly diagnosed TB cases and 12.2% among previously treated cases.

WHO has been working with the NTP and other implementing and collaborating partners to design key interventions linked to diagnosis and treatment of DR-TB. On these new initiatives, WHO emphasizes on quality service delivery that ensures all diagnosed cases are placed timely on treatment. 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.

The Guidelines for PMDT in Bangladesh adds to the wide range of important TB documents from Bangladesh that will be effective for the Global DR-TB control. These guidelines offer technical and operational instruction to treating doctors, health care providers and programme managers for early and quality diagnosis and management of DR-TB. Wider dissemination of these guidelines through various platforms and trainings of public and private doctors is vital.

WHO is committed to providing necessary technical guidance and assistance to the central and state governments in translating these guidelines into quality services for the patients and also continue evidence generation through surveillance and research for future refinement of the policies and strategies to align with the growing global evidences. We will also continue to work with all stakeholders and implementing partners in order to fight against TB.

I am hopeful that these Programmatic Management of Drug Resistant TB (PMDT) guidelines will strengthen the capacity of the NTP for implementation of PMDT services in the country, envisioning a world free of tuberculosis.

Dr Bardan Jung Rana

Abbreviation and Acronyms

ACPH	Air Change Per Hour
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
ADRAC	Adverse Drug Reaction Advisory Committee
ADRM	Adverse Drug Reaction Monitoring
AFB	Acid - Fast Bacilli
ARV	Antiretroviral
AZT	Zidovudine
BMDC	Bangladesh Medical and Dental Council
BMI	Body Mass Index
CDC	Chest Disease Clinic
CDH	Chest Disease Hospital
CHCP	Community Health Care Provider
CPC	Cetylpyridinium 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 Treatment
DOTS	Directly Observed Treatment Short Course
DRS	Drug Resistance 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
GGT	Gamma-Glutamyl Transferase
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

MODC	Medical Officer for Disease Control
MOTT	Mycobacteria Other Than Tuberculosis
MTB	Mycobacterium Tuberculosis
MTB/RIF	Mycobacterium Tuberculosis/Rifampicin
NGO	Nongovernmental Organization
NIDCH	National Institute of Diseases of the Chest and Hospital
NTP	National Tuberculosis Control Programme
NTRL	National Tuberculosis Reference Laboratory
PCP	Pneumocystis Carinii Pneumonia
PCR	Polymerase Chain Reaction
PMDT	Programmatic Management of Drug Resistant Tuberculosis
PO	Program Organizer
PV	Pharmacovigilance
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	Drug	Abbreviation
Group A	Levofloxacin	Lfx
	(*OR* Moxifloxacin)	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B	Clofazimine	Cfz
	Cycloserine	Cs
	(*OR*) Terizidone	Trd
Group C	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem–cilastatin *OR* meropenem	Ipm–Cln Mpm
	Amikacin	Am
	(*OR* streptomycin)	(S)
	Ethionamide *OR* Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

CHAPTER 1

Background of Drug-resistantTuberculosis

1.1 Global situation of Drug-resistant TB (DR-TB)

Resistance to tuberculosis (TB) drugs is a major public health problem and a formidable obstacle to effective TB care and prevention globally. Drug-resistant TB (DR-TB) is multifactorial and fueled by “improper” treatment of patients, poor management of supply and quality of drugs, and airborne transmission of resistant bacteria. The term "improper" may be in the form of a number of actions including administration of inappropriate treatment regimens and failure to ensure that patients complete the whole course of treatment. Case management becomes difficult and the challenge is compounded by catastrophic economic and social costs that patients incur while seeking help and on treatment. Essentially, drug resistance arises in areas with weak TB control programes. A patient who develops active disease with a drug-resistant TB strain can also transmit this form of TB to other individuals.

Drug-resistant TB continues to be a public health crisis. The burden of drug-resistant TB is of major interest and concern at global, regional and country levels. In 2019, there were approximately half a million new cases of rifampicin-resistant TB (of which 78% had multidrug-resistant TB). The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (8%).

Globally, 3.3% of new TB cases and 17.7% of previously treated cases had MDR/RRTB, with the highest proportions (>50% in previously treated cases) in countries of the former Soviet Union. Overall, there were an estimated 465 000 (range, 400 000–535 000) incident cases of MDR/RR-TB in 2019. The global proportion of RR-TB cases estimated to have MDR-TB was 78%. In 2019, there were about 182 000 (range, 113 000– 250 000) deaths from MDR/RR-TB. A global total of 206 030 cases of multidrug-resistant TB or rifampicin resistant TB (MDR/RR-TB) were notified in 2019, up from 186 883 in 2018. However, despite these improvements, the number of people enrolled in treatment in 2018 was equivalent to only 38% of the estimated incidence. Treatment success rates at 57% for MDR/RR-TB and 39% for extensively drug-resistant TB. By the end of 2019, at least one case of XDR-TB had been reported by 131 WHO Member States. Average proportion of MDR-TB cases with XDR TB was 6.2% (95% CI: 4.4–8.2%). This is lower than the 8.5% that was published in the 2019 WHO global TB report.

1.2 Bangladesh situation of Drug-resistant TB (DR-TB)

According to WHO Global TB Report 2020, Bangladesh is one of the high TB/MDR-TB burden countries and has an estimated MDR/RR-TB incidence of 2/100,000 populations. In 2019, there were an estimated 3,300 MDR/RR cases. An estimated 0.7% of new TB cases and 11% of previously treated cases had MDR/RR-TB.

However, in 2019, 1400 (42.4%) patients were diagnosed and 1,200 (85.7%) started on second line treatment. The case notification has been steady for the past several years and a large number of MDR-TB cases remain undetected and untreated.

The NTP has carried out its second nation-wide drug resistance survey (DRS) in tuberculosis patients in collaboration with WHO and SNRL, Antwerp, Belgium in 2018-2019. The result shows the overall number of RR TB cases is low, 0.7% among new cases and 12.2% among re-treatment cases.

The second national DRS focused on rifampicin resistance among enrolled cases (new and previously treated). The following table shows prevalence of resistance to other drugs among RR-TB cases

1.3 Prevalence of resistance to other drugs among RR-TB cases in Bangladesh

	Total Tested	Total Resistant	% (95% CI)
Isoniazid	28	23	82.1 (60.7 - 93.2)
Streptomycin	28	19	67.9 (51.0 - 81.1)
Ethambutol	28	10	35.7 (16.7 - 60.5)
Ethionamide	28	10	35.7 (18.9 - 56.9)
Levofloxacin	27	3	11.1 (3.9 - 27.9)
Ofloxacin	28	6	21.4 (11.2 - 37.1)
Any fluoroquinolone	28	6	21.4 (11.2 - 37.1)

1.4 Background and the use of this Operational Manual

Operational Manual for the Management of Multidrug-resistant TB (MDR TB) was first published in 2009. This 2020 edition expands upon the most recent WHO consolidate guidelines on drug resistant tuberculosis treatment (update 2020), 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 2019 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.

This complementary document provides practical step-by-step guidance on how to treat DR TB patients and to organize, implement, and monitor DR TB patients at community-based care for DR TB as well as implementation of aDSM on routine DR TB program. All 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

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 NSP and WHO END TB strategy.

The End TB Strategy, developed in the context of the UN SDGs, is a logical evolution and a paradigm shift from past global TB strategies. The overall goal is to "End the global TB epidemic", and there are three high-level, overarching indicators and related targets (for 2030 – linked to the SDGs – and for 2035) and milestones (for 2020 and 2025). The three indicators are:

- The number of TB deaths per year;
- The TB incidence rate (new cases per 100 000 population per year); and
- The percentage of TB-affected households that experience catastrophic costs as a result of TB disease.

2.1 END TB Strategy (2020 to 2035)

Vision: A world free of TB (Zero deaths, disease and suffering due to TB)

Goal: End of global TB epidemic

Principles

- Government stewardship and accountability, with monitoring and evaluation
- Strong coalition with civil society organizations and communities
- Protection and promotion of human rights, ethics and equity
- Adaptation of the strategy and targets at country level, with global collaboration

Pillars and Components

1. **Integrated patient-centered care and prevention**
   - Early diagnosis of TB, including universal drug-susceptibility testing and systematic screening of contacts and high-risk groups
   - Treatment of all people with TB, including drug-resistant TB, and patient support
   - Collaborative TB/HIV activities, and management of co-morbidities
   - Preventive treatment of persons at high risk, and vaccination against TB
2. **Bold policies and supportive systems**
   - Political commitment with adequate resources for TB care and prevention
   - Engagement of communities, civil society organizations, and public and private care providers
   - Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
   - Social protection, poverty alleviation and actions on other determinants of TB
3. **Intensified research and innovation**
   - Discovery, development and rapid uptake of new tools, interventions and strategies
   - Research to optimize implementation and impact, and promote innovations

2.2 Coordination and structure of the National Tuberculosis Control Program

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 also described in this operational manual

CHAPTER 3

DR TB Definitions

The confirmation of drug resistance depends on a quality assured laboratory diagnosis. The conventional method is to show that strains of Mycobacterium tuberculosis grow on culture media in the presence of one or more anti-TB drugs (phenotypic testing). Newer genotypic (molecular) techniques are now available to detect mutations, which are associated with resistance to certain drugs. Different patterns of drug resistance carry different implications for treatment and management.

3.1 Site of DR TB Disease

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	TB involving only the lung parenchyma
Extra pulmonary TB	TB of organs other than the lung parenchyma, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges etc. is considered to be extra pulmonary TB. Intrathoracic TB lymphadenopathy (mediastinal and/or hilar) or TB pleural effusion without radiographic abnormalities in the lungs is also considered extra pulmonary TB
Extensive TB Disease	Refers to the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.
Severe extra pulmonary TB	Refers to the presence of miliary TB or TB meningitis. In children aged under 15 years, extra pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe
Drug resistance	Drug-Resistant tuberculosis (DR-TB) refers to active tuberculosis disease caused by Mycobacterium tuberculosis bacilli that are resistant to one or more anti-TB medicines.
Mono-resistance	Resistance to one first line anti-TB drug.
Poly resistance	Refers to resistance to more than one first-line anti-TB drug, other than isoniazid and rifampicin together.
Rifampicin-resistant TB (RR-TB):	Strains are considered not to be susceptible to rifampicin on the basis of DST and as a result are eligible for treatment with DR-TB regimens. Rifampicin-resistant TB strains may be susceptible to isoniazid, or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line TB medicines (poly-resistant) or second-line TB medicines (e.g. XDR-TB)
Isoniazid-resistant TB (Hr-TB)	Refers to *Mycobacterium tuberculosis* strains in which resistance to isoniazid and susceptibility to rifampicin has been confirmed in vitro

Multidrug-resistant (MDR-TB)	TB caused by *Mycobacterium Tuberculosis (M. tuberculosis)* strains that are resistant to at least both rifampicin and isoniazid.
Pre-XDR-TB	TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone*
Extensively drug-resistant (XDR-TB)	TB caused by *Mycobacterium tuberculosis (M. tuberculosis*) strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A drug**

**The fluoroquinolones include levofloxacin and moxifloxacin, because these are the fluoroquinolones currently recommended by WHO for inclusion in shorter and longer regimens.*

***The Group A drugs are currently levofloxacin or moxifloxacin, bedaquiline and linezolid; therefore, XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline or linezolid (or both).*

3.2 Case definitions based on previous treatment history

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.
Treatment after Failure of new and retreatment cases.	• 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 TB treatment center 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 drug sensitive retreatment category (possibly in the private sector); patients who have received several unsuccessful treatments, were

Type of Category	Definition
	considered incurable by health staff and who have lived with active TB disease with no or inadequate treatment (eg: "chronic" patients); extra pulmonary and smear negative in special cases

Patients having both pulmonary and extra pulmonary TB should be classified as having pulmonary TB (6.3.4 Treatment of DR TB with CNS involvement)

3.3 Bacteriological Examinations and Sputum Conversion

Sputum smear microscopy, culture and DST are the standard examinations performed on DR TB patients.

- 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 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 of Short Term and Individualized regimen are as follows:

3.4.1 Definitions of treatment outcome

Outcome	Definition
Cure	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase*
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase*.
Failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: – lack of conversion** by the end of the intensive phase;* or – bacteriological reversion**in the continuation phase after conversion**to negative; or – evidence of additional acquired resistance to fluoroquinolones or second line injectable drugs; or – adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.

Not evaluated	patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.)
Treatment success	The sum of cured and treatment completed.

**For "treatment failed", lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested, to determine when the criteria for "cured", "treatment completed" and "treatment failed" start to apply*

***The terms "conversion" and "reversion" of culture are defined here as follows: conversion (to negative) – culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion; 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 positive. For defining "treatment failed", reversion is considered only when it occurs in the continuation phase*

3.5 Other definitions

Drug-susceptibility testing (DST)	Drug-susceptibility testing (DST) refers to in-vitro testing using either phenotypic methods to determine susceptibility or molecular techniques to detect resistance-conferring mutations to a medicine
Extent or severity of disease	In patients older than 14 years is usually defined by the presence of cavities *or* bilateral disease on chest radiography In children under 15 years, severe disease is usually defined by the presence of cavities *or* bilateral disease on chest radiography *or* extra pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) In children, the occurrence of advanced malnutrition (defined by syndrome or by metrics) *or* advanced immunosuppression
Intensive phase	As used in these guidelines and in the evidence reviews that informed the recommendations, is the initial part of a shorter or longer regimen for treating multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB). Regimens without an injectable agent are considered not to have an intensive phase (For longer regimen there will be no IP/CP. But the period when bdq will be used can be considered as IP)
Shorter MDR-TB regimen	Refers to a course of treatment for MDR/RR-TB lasting 9–11 months, which is largely standardized, and whose composition and duration follows closely the one for which there is documented evidence from different settings. The features and indications of this regimen are further elaborated in Section 3 under Recommendations and remarks in these guidelines.
Longer MDR-TB regimens	Are of at least 18 months in duration and are usually designed to include at least four anti-TB drugs considered to be effective based on patient history or drug-resistance patterns. These regimens avoid the use of injectable.

Second-line TB medicine (or drugs)	Is an agent reserved for the treatment of drug-resistant TB. First-line TB medicines used to treat drug-susceptible TB - ethambutol, isoniazid and pyrazinamide - may also be used in MDR-TB regimens
Serious adverse events (SAEs)	Serious adverse event (SAE) is an AE which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. SAEs that do not immediately result in one of these outcomes but that require an intervention to prevent it from happening are included. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event.
Close contact	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

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.

Cohort analyses should be carried out at 15 months for patients under STR regimen and 24 months and repeated at 36 months for the longer 20-month regimen after the last patient starts treatment. 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). (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, 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 20 months of 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 injectable second line drug 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 of further amplification of resistance;
- Reduces the progression to permanent lung damage;
- Results in higher cure rates.

4.1 Target Groups for DR TB and First-line DST

If rapid DST is available, preference for DST will be given for all presumptive before starting TB treatment. In case not available, then DST will be performed on following groups.

- All Retreatment cases at the beginning of diagnosis
  - ➢ Failure of Cat-1
  - ➢ Relapse
  - ➢ Treatment after loss to follow-up
- Non-Converter (remain positive at month 2 of treatment follow-up)
- Close contacts of DR TB patients with symptoms
- HIV Infected person, with /without TB S/S
- Pulmonary bacteriologically negative or extra pulmonary TB patient clinically not improved in spite of treatment as per NTP guidelines

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

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.

- All the patient diagnosed as **RR TB** by GeneXpert will be tested for second line drugs like the **SL-LPA**.
- Those with **resistant to Fluoroquinolones and**/ would be taken up for culture and DST (solid or liquid but liquid method preferred).
- Extended DST to Mfx 1µg/ml, Amk, Lzd, Cfz will be performed for guiding DST based treatment.

- ➢ Since Kanamycin and Capreomycin are no longer recommended the DST should be performed only for Amikacin and Sm (in case there is resistance to Amikacin)
- ➢ DST for **Z, BDQ and DLM (by MGIT)** will be started at NTRL and RTRLs in phased manner.

4.3 Case Finding in Pediatric 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 specimen in not available.
- Extra efforts can be used to get specimens for culture. Induced sputum, tissue biopsy (including fine needle aspiration), gastric aspirate, urine, and stool can be sent for testing by GeneXpert to NTRL/RTRL for diagnosis.

For diagnosis follow the algorithm. Extended DST for 2nd line drugs should be performed if specimen for culture is available.

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 in addition to rapid molecular tests 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 with active TB to prevent death due to unrecognized DR TB. The recommended screening test for diagnosing RR in HIV patients is chest X-ray followed by GeneXpert
- People living with HIV who have MDR TB should also be screened for XDR TB with DST of second-line drugs.

4.5 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 MDR (resistant to Rifampicin and isoniazid)
- All retreatment cases and non-converters should ideally go for FL-LPA and will be implemented as soon as facilities are available in RTRL

4.6 Specimen Collection for Culture and DST Testing

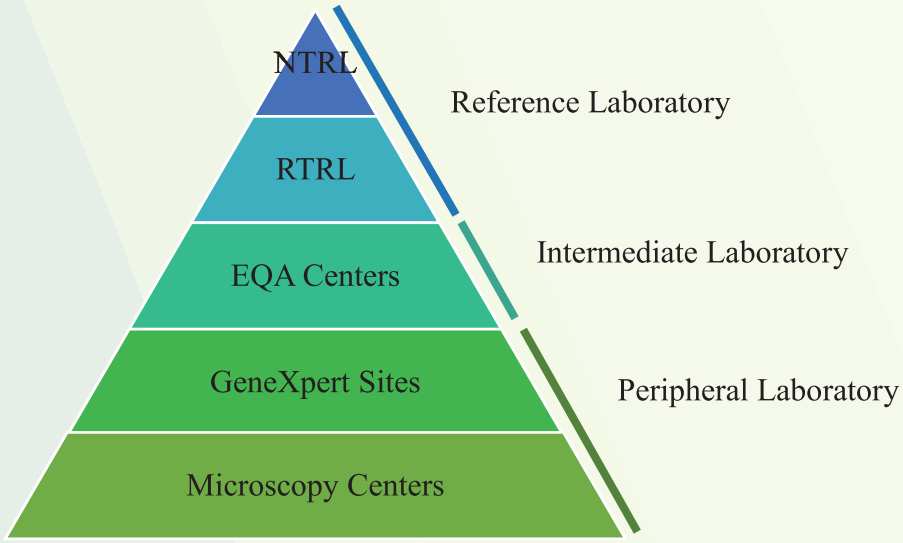
- Previously treated patients may have had DST in the past, but it may no longer reflect the resistance pattern of the strain they have at the time of enrollment in the DR TB control program. If no DST has been performed in the previous 30 days, a DST should be done at the start of diagnosis for all cases.
- 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◦-8◦c is recommended, provided that a prompt transfer to lab available with culture facility will be made within 3 days.
- Otherwise cold chain or falcon tube with CPC (mixture of 1% cetylpyridinium chloride and 2% Sodium chloride) should be used (only for solid culture). CPC should not be used as the sample cannot be tested by Xpert MTB/RIF, LPA and liquid culture and DST.
- Specimen from patients diagnosed as MTB Detected will be sent to NTRL/RTRLs/ for second line LPA and Culture/DST (solid and liquid) from the referral facility as decided by the program. (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 presumptive DR TB
- 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 centers for specimen collection and a full evaluation by the DR TB treatment team).
- For GeneXpert, fresh specimen should be sent to Xpert facility without CPC solution.
- For MDR follow-up culture (solid) and DST sample should be collected in CPC containing falcon tube.
- Sputum sample will be sent to NTRL or the RTRL via courier or convenient transport method within 3 days of collection for culture/DST and LPA. In case of delay of more than 3 days the samples should be transported in cold chain/CPC.
- Results of culture/DST and LPA will be sent back in paper system (through courier) and electronically to the referring facility that sent the specimen with a copy to NTP focal person and respective divisional PMDT coordinator.

CHAPTER 5
Laboratory Aspects

Early detection of drug resistance allows the use of appropriate treatment regimens for patients, which has an important impact on improved TB control. Advancement in TB diagnostic tools are now available which are evaluated and validated by WHO. Definitive diagnosis of drug-resistant TB requires that Mycobacterium tuberculosis bacteria be detected and resistance to anti-TB drugs determined. This can be done by isolating the bacteria by culture, identifying it as belonging to the M. tuberculosis complex (MTBc), and conducting drug susceptibility testing (DST) using solid or liquid media or by performing a WHO endorsed molecular test to detect TB DNA and mutations associated with resistance.

NTP Laboratory network



5.1 Responsibilities of the TB laboratory network at different levels

5.1.1 National TB reference laboratory

- Acts as supervising reference laboratory for the regional laboratories.
- Performs, culture for mycobacterium, both solid & liquid (MGIT), Molecular Line Probe Assay (LPA), drug susceptibility testing (1st & 2nd line) and species identification as well as microscopy and Xpert MTB/RIF assay (GeneXpert) in special situation.
- Takes the lead in reviewing and introducing new diagnostic tools in country
- Ensures proficiency of the NTP staff for carrying out good quality diagnosis by providing technical training and periodic supervision of the activities of the regional laboratories.
- Collaborates with the WHO-accredited supranational reference laboratory (SNRL) designated for Bangladesh.
- Implements quality assurance for regional and, if necessary, other Tertiary Labs like chest diseases clinics and hospitals, upazilla and other special services laboratories.
- Provides guidance to the National TB Control Program on strengthening the TB Laboratory Network

- Conducts operational research, studies, surveys etc.
- Ensures recording and reporting as per national policy.
- Capacity building for peripheral laboratory staff by providing trainings on different diagnostic tools and procedures.

5.1.2 Regional TB reference laboratory

- Performs, culture for mycobacterium, both solid & liquid (MGIT), Molecular Line Probe Assay (LPA), drug susceptibility testing (1st & 2nd line) and species identification as well as microscopy and Xpert MTB/RIF assay (GeneXpert) in special situation.
- Trains the staff and supervises the activities of the designated intermediate laboratories
- Carries out External Quality Assessment (EQA) of smear microscopy for microscopy centres as a second controller
- Implements quality control for district, chest diseases clinic/hospital, upazilla and other special services laboratories
- Participates in drug resistance survey/surveillance
- Ensures recording and reporting as per national policy

5.1.3 Intermediate laboratory at district level

- Performs microscopy/ Gene Xpert MTB/RIF
- Serves as the 1st controller in blinded re-checking program for microscopy centres
- Trains the staff and supervises the activities of the peripheral laboratories
- Prepares and distributes reagents for the peripheral laboratories
- Implements quality control for microscopy centres
- Ensures recording and reporting as per national policy

5.1.4 Peripheral laboratory

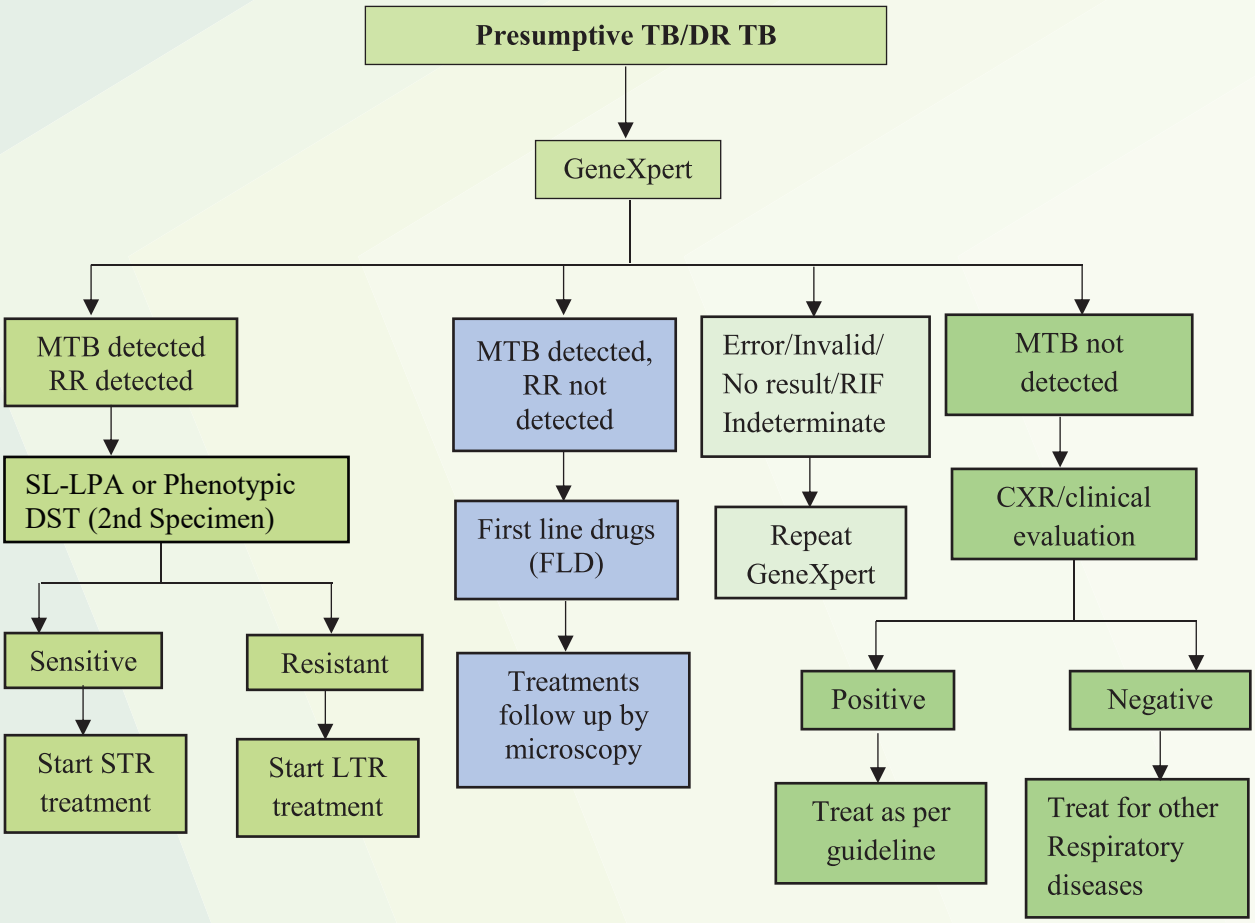
- Performs microscopy/GeneXpert MTB/Rif assay
- Participates in EQA
- Ensures recording and reporting as per national policy

NTRL incorporated liquid culture (BACTEC MGIT) and a multiplex polymerase chain reaction line-probe assay. The NTRL also performing DST to second-line anti-TB drugs in presumptive XDR. Furthermore, 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 hematology, 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 supra-National reference laboratory (SNRL) in Antwerp, Belgium.

5.2 Diagnostic algorithm (TB/DR TB)



5.3 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., 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**. Mycobacterial culture and identification of M. tuberculosis provide a definitive diagnosis of TB significantly increases the number of cases found (often by 30-50%), and can detect cases earlier (often before they become infectious). Culture also provides the necessary isolates for conventional DST. However, Culture is much more complex and expensive than microscopy to perform, requiring facilities for media preparation,

specimen processing, and growth of organisms, specific laboratory equipment, skilled laboratory technicians, and appropriate biosafety conditions. Specimens have to be decontaminated prior to being cultured to prevent overgrowth by other micro-organisms. All decontamination methods are to some extent also harmful to mycobacteria, and culture is therefore not 100% sensitive.

Solid and liquid culture methods are suitable for national or regional reference laboratories. Solid culture methods are less expensive than liquid culture systems, but results are invariably delayed due to the slow growth of mycobacteria. Liquid culture increases the case yield by 10% over solid media, and automated systems reduce the diagnostic delay to days rather than weeks. Liquid systems are, however, more prone to contamination and the manipulation of large volumes of infectious material mandates appropriate and adequate biosafety measures.

Positive cultures have to be identified to differentiate M. tuberculosis from NTM. NTM are more common in HIV-infected patients and the prevalence varies from country to country. Treatment of NTM is entirely different from treatment of TB and drug-resistant TB. As a minimum, laboratories performing DST must differentiate M. tuberculosis from other NTM (further speciation is not recommended at programmatic level).

Delays in specimen transport, excessively harsh or insufficient decontamination, poor quality of 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.

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.

5.4 Drug Susceptibility Testing (DST)

Drug susceptibility testing is conducted to find out if a TB patient has drug resistant TB. This is essential to determine at the first contact to provide effective TB treatment. WHO now recommends universal DST for all TB patients with objective to reduce the spread of drug resistant TB. Liquid culture systems provide results significantly faster than solid culture techniques. Liquid DST for 2nd line anti TB drugs with MGIT is recommended by WHO.

Anti TB drugs for DST are as follows:

1st Line Drugs	H, R, E, S
2nd Line Drugs (Solid culture/DST)	Amk, Lfx, Mfx
2nd Line Drugs (Liquid culture/DST)	Lzd, Cfz, Z, Mfx, Lfx, BDQ and DLM.
Extended DST	MFX 1µg/ml, Amk, Lzd, Cfz will be performed for guidance the DST based treatment preferably by liquid DST

5.5 Molecular Testing

a. GeneXpert

An automated cartridge-based nucleic acid amplification test (CBNAAT) that simultaneously provides two types of information:

- Identify presence or absence of Mycobacterium tuberculosis (MTB) DNA in the specimen, and
- Identify the genetic mutations in Rifampicin susceptibility determining gene of MTB that is present in the specimen. Xpert Ultra Cartridges will be adopted in phased manner when they are available.

b. Line probe Assay (LPA):

Line probe assays are a family of DNA strip-based tests that determine the drug resistance profile of a MTBC strain through the pattern of binding of amplicons (DNA amplification products) to probes targeting the most common resistance associated mutations to first- and second-line agents and to probes targeting the corresponding wild-type (WT) DNA sequence. LPAs are WHO-approved tests for rapid detection of drug resistance to first- and second-line agents. They can be used for testing of culture isolates (indirect testing), as well as direct testing of acid-fast bacilli (AFB) smear microscopy positive specimens (FL-LPA), and both smear positive and smear negative sputum specimens (SL-LPA)

- 1st Line LPA (**Geno**Type **MTBDRplus**): The identification of rifampicin resistance is enabled by the detection of the most significant mutations of the rpoB gene (code for β-subunit of the RNA polymerase). For testing the high-level isoniazid resistance, the katG gene (code for catalase peroxidase) is examined and for testing the low-level isoniazid resistance, the promoter region of the inhA gene (code for NADH enoyl ACP reductase) is analyzed.
- 2nd Line LPA (**Geno**Type **MTBDRsl**): Enables the detection of mutations involved in resistance to second line injectable drugs as well as the resistance to fluoroquinolones.

5.6 Responsibilities of the TB laboratory network at different levels

The procedures for internal quality control (QC) will be performed periodically to monitor the quality of solid culture. The quality control of DST (phenotypic) 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 for culture as recommended. 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.

The internal QC of GeneXpert, LPA and liquid culture will be performed as per the SOP and manufacturer guideline. To ensure this networking within all laboratories under NTP should be developed.

5.7 List of diagnostic tool/technology available in the country and its turn-around time (TAT)

Sl. No.	Tools / Technology		Description	Lab TAT	Overall TAT	Advantages	Disadvantages
1	Smear Microscopy	Ziehl Neelsen	Time between receipt of specimens for smear at the laboratory and result reporting	48-72 hrs	3 days	Simple, low cost	Less sensitive
		Auramine				Sensitive compare to ZN Both could/should be used for treatment follow-up	Expensive
2	Xpert MTB/RIF		Time between testing and result reporting	24 hours	5 days for non-Xpert sites 48 hours for Xpert sites	97% Sensitive and 93% Sepcific , detects MTB and Resistance to Rif	Expensive and cannot be used for treatment follow up
3	Line Probe Assay for MDR/XDR-TB detection		Time between testing and result reporting.	Within 5 days from direct sample (From culture isolates, add this value to culture TAT)	Within 10 days	Sensitive , detects MTB and resistance to Rif and INH	Need trained-skill person, Bio-safety issue and cannot be used for treatment follow up
4	Culture	Solid	Time between receipt of specimens for culture at the laboratory and result reporting	2-8 weeks average for smear positive samples and 4–8 weeks average for smear-negative samples.	9 weeks	Sensitive, cost effective	Need trained-shill person, tedious and biosafety issue
		Liquid		8-10 days for smear-positive samples and 2–6 weeks for smear-negative samples	2 months	Short duration, ,More sensitive than solid, Could be used for treatment follow-up	Need trained-shill person, Tedious and biosafety issue
5	DST	Solid	Time between inoculation of DST and result reporting (mean, range and 90th percentile). For total DST TAT, add this value to culture TAT.	4-6 weeks	90 days/3 months	Cheaper and more widely available	Labor-intensive, less sensitive and slower than liquid culture.
		Liquid		After inoculation, 2 weeks	10 weeks	Reading of result automated. Facilitate processing of large numbers of specimens. Early TAT compared to solid DST.	Costly and more prone to contamination

5.8 General Definitions for laboratory

Phenotypic DST (conventional DST): Phenotypic testing determines if an isolate is resistant to an anti-TB drug by evaluating growth (or metabolic activity) in the presence of the drug

Genotypic DST (molecular DST): Genotypic testing detects mutations in the TB genome associated with specific drug resistance. (Note: genotypic testing is also used to identify M. tuberculosis by detecting the presence of TB-specific mycobacterial DNA).

Direct testing: Direct testing refers to testing directly from a clinical sample (most commonly a sputum specimen). In direct DST, processed clinical samples are directly inoculated onto media with and without drugs, or processed for molecular testing.

Indirect testing: Indirect testing refers to testing performed on cultured isolates of M. tuberculosis

Critical drug concentration: This is the lowest concentration of a drug that inhibits growth of 99% of M. tuberculosis strains isolated from patients who have never been treated with/exposed to that drug (i.e. presumably susceptible isolates), while at the same time not inhibiting growth of strains isolated from patients non-responsive to therapy with that drug (i.e., presumably resistant to that drug). For some drugs, such as ethambutol, there is no optimal drug concentration that meets this definition. For such drugs, the concentration that shows the greatest difference between presumably susceptible and presumably resistant isolates is used in phenotypic DST. Typically, isolates of M. tuberculosis are tested against only the critical concentration of a drug.

Reproducibility: The ability of a test to be accurately reproduced or replicated, under independent conditions. Intra-operator reproducibility relates to the agreement of test results when a sample is tested multiple times independently by the same operator. Inter-operator reproducibility relates to the agreement of test results across different operators or laboratories.

Reliability: The reliability of a test depends on both the accuracy and reproducibility of the test result. Accuracy is defined by comparing the test results with a gold standard and is usually expressed in terms of sensitivity and specificity, or in terms of positive and negative predictive values.

Validity: The validity of a test refers to whether a test is measuring what it is supposed to be measuring. Ideally, a drug susceptibility test result should predict clinical efficacy.

Cross resistance: Mutations that confer resistance to one anti-TB drug may also confer resistance to some or all of the members of the same drug family, and less commonly, to members of different drug families.

CHAPTER 6

Treatment Strategies for Drug-resistant TB

6.1 Background Treatment Strategy

All treatment delivered is align with WHO-recommended standards, including patient-centered care and support, informed consent where necessary, principles of good clinical practice, active TB drug safety monitoring and management (aDSM), and regular patient monitoring to assess regimen effectiveness.

- 100% of diagnosed DR-TB patients should be put on second-line treatment.
- The National TB program in Bangladesh used shorter and longer treatment regimens depending on eligibility criteria
- Those patients are identified as MDR/RR TB will be screened for eligibility to enroll for Shorter Treatment Regimen (STR). Those who are not eligible for STR will be enrolled on longer treatment regimen
- Adverse events (AEs) 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 events (AEs) are discussed in Chapter 13.
- Each dose is given as directly observed treatment (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, to stop transmission, 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 Options in drug-resistant TB treatment regimens

- Regimen for isoniazid-resistant TB: **6 (H) REZ-Lfx** (6-month treatment regimen composed of rifampicin, ethambutol, pyrazinamide, levofloxacin. Isoniazid can be added if 4-drug FDC (HREZ) will be used.
- Shorter regimen for MDR/RR-TB: All oral shorter treatment regimen:

  (4 -6) Bdq (6m or longer)-**Lfx-Pto/Eto-Cfz-Z-H** high dose **E/5 Lfx-Cfz-Z-E** (shorter all-oral Bedaquiline-containing regimen).
- Shorter regimen for MDR/RR-TB: Injectable shorter treatment regimen:

  (4 -6) Amk-Mfx-Pto-Cfz-Z-H high dose **E/5 Mfx-Cfz-Z-E**

For MDR/RR-TB patients without previous exposure to second-line medicines for more than 1 month, where there is no fluoroquinolone resistance and the patients do not have extensive TB disease or severe extra-pulmonary TB, the preferred treatment option is a shorter all-oral bedaquiline-containing regimen. In settings with a high probability of resistance to other medicines in the regimen (or in patients with confirmed resistance to other medicines), further modifications of the shorter all-oral bedaquiline-containing regimen using priority grouping of second-line TB medicines may be implemented under operational research.

- Shorter regimen for MDR/RR-TB with quinolone resistance: 6–9 Bdq-Pa-Lzd (6–9 month treatment regimen composed of bedaquiline, pretomanid and linezolid – BPaL regimen)

The 6–9 month treatment regimen composed of bedaquiline, pretomanid and linezolid (BPaL) may be used under operational research conditions in patients with MDR/RR-TB and additional fluoroquinolone resistance who have not had previous exposure to bedaquiline or linezolid (defined as <2 weeks). This regimen may not be considered for programmatic use until additional evidence on efficacy and safety has been generated.

- Longer regimen for MDR/RR-TB: **20 Bdq(6m)-Lfx-Lzd-Cfz-Z** (20-month treatment regimen composed of bedaquiline for the first 6 months and levofloxacin, linezolid, clofazimine, Cycloserine and Pyrazinamide for 18 months).
- Longer regimen for MDR/RR-TB patients with extensive TB disease, additional resistance to fluoroquinolones (**Pre-XDR-TB)** or exposure to treatment with second-line medicines for more than 1 month: **6 Bdq-Dlm-Lzd-Cs-Cfz-Z/14 Lzd-Cfz-Cs-Z** (20-month treatment regimen composed of bedaquiline, delamanid for the first 6 months and linezolid, clofazimine, Cycloserine and Pyrazinamide for 20 months).
- Longer regimen **(XDR-TB)** patients with resistance to fluoroquinolones and at least one additional Group A drugs; designed from **an individualized longer regimen** using the WHO priority grouping of medicines
- MDR/RR-TB patients with severe forms of extra-pulmonary TB, additional resistance to fluoroquinolones or exposure to treatment with second-line medicines for more than 1 month will benefit from **an individualized longer regimen** designed using the WHO priority grouping of medicines

6.3 Groups of Anti-Tuberculosis Drugs

The anti-TB drugs recommended for treatment of MDR/RR TB patients are grouped based on efficacy, experience of use and drug class and aligned with revised classification as per WHO consolidated guidelines 2019. A new revised grouping of TB medicines was recommended for use in longer MDR TB regimens. Medicines have been regrouped into three categories (Table 1) and ranked based on the latest evidence about the balance of effectiveness to safety.

Table 1 Grouping of medicines recommended for use in longer MDR-TB regimens

Groups & steps	Medicine	
Group A:	Levofloxacin OR	Lfx
Include all three medicines	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B:	Clofazimine	Cfz
Add one or both medicines	Cycloserine *OR*	Cs
	Terizidone	Trd
Group C:	Ethambutol	E
Add to complete the regimen and when medicines from Groups A and B cannot be used	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem–cilastatin *OR*	Ipm–Cln
	meropenem	Mpm
	Amikacin	Am
	(*OR* streptomycin)	(S)
	Ethionamide *OR*	Eto
	Prothionamide	Pto
	p-aminosalicylic acid	PAS

6.4 Current regimen and care for DR TB

6.4.1 Regimen for rifampicin-susceptible and isoniazid-resistant TB

In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin and duration is 6 months

Regimen: 6 (H) R- E- Z- Lfx

- It is not recommended to add streptomycin or other injectable agents to the treatment regimen.
- In cases where a diagnosis of Hr-TB is strongly presumed (e.g. close contacts of Hr-TB cases with active TB but without laboratory confirmation of Hr-TB), **(H) REZ**–levofloxacin may be introduced and then modification of treatment based on DST result.
- DST results eventually indicate susceptibility to isoniazid
  - For new TB cases levofloxacin is stopped and the patient completes a **2HREZ/4HR** regimen.
  - For retreatment cases levofloxacin is continued with 2HREZ/4HR regimen.
- For other patients, in whom **Hr-TB** is detected after the start of treatment with the **2HREZ/4HR** regimen, the **(H) REZ** component drugs are continued (or pyrazinamide and ethambutol are reintroduced) and levofloxacin added once rifampicin resistance has been excluded.

Levofloxacin is recommended to (H) REZ in all patients with Hr-TB, exception of the following:

- In cases where resistance to rifampicin cannot be excluded;
- Known or suspected resistance to levofloxacin;
- Known intolerance to fluoroquinolones;
- Known or suspected risk for prolonged QTc interval; and
- Pregnancy or during breastfeeding (not an absolute contraindication).

*In Hr-TB cases in whom a fluoroquinolone cannot be used, the patient may still be treated with **6(H) REZ**. When additional resistance (especially to pyrazinamide) is suspected or confirmed, appropriate treatment regimens will have to be designed individually.*

Duration of treatment:

- The duration of an (H) REZ–levofloxacin regimen is usually determined by the need to complete 6 months of a levofloxacin-containing regimen.
- In cases where the diagnosis of Hr-TB is made after first-line TB treatment has already been initiated, the patient may receive more than 6 months of (H)REZ by the end of treatment.

- ❖ When the patient was diagnosed isoniazid resistance after the starting of treatment with a **2HRZE/4HR** regimen (e.g. 5 months after start during the continuation phase), the clinician would need to decide, based on an assessment of the patient's condition, whether a 6-month course of **(H)REZ–levofloxacin** needs to be started at that point or not.
- ❖ Patients with extensive disease (cavitary disease, persistence bacteriologically positive sputum at or after month 3) treatment duration more than 6 months could be considered
- ❖ **Extra pulmonary disease**, the regimen composition proposed is likely to be effective. However, the treatment of patients with extra pulmonary TB should be designed in close consultation with appropriate specialists and variations in treatment duration and supportive care as needed.

Treatment monitoring

The clinical monitoring of patients on Hr-TB treatment follows similar principles to first-line TB regimens. Bacteriological monitoring of sputum- direct microscopy at months 2, 5 and 6.

It is desirable to perform a culture together with smear microscopy (or at least in the last month of treatment) to check for any emergent resistance, especially to rifampicin. Non-response to treatment should be investigated with DST. Liver and kidney function and other blood tests may be necessary, based on clinical manifestations and medications in use.

Electrocardiography (ECG) for patients on 6(H) REZ-Lfx is not usually required unless there are other risks for QT interval prolongation.

6.4.2 Shorter MDR-TB Regimen (STR)

6.4.2.1 Shorter all-oral bedaquiline-containing regimen (STR)

Shorter all-oral bedaquiline-containing regimen of 9–11 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month and in whom resistance to fluoroquinolones has been excluded

Eligibility:

MDR/RR-TB (with at least confirmed resistance to rifampicin), for whom resistance to fluoroquinolones has been ruled out, in the following situations:

- no resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance)
- no exposure to previous treatment with second-line medicines in the regimen for more than 1 month (unless susceptibility to these medicines is confirmed)
- no extensive TB disease and no severe extra-pulmonary TB
- not pregnant
- children 6 years old and above.

Testing for susceptibility to at least fluoroquinolones is recommended before the start of a shorter all-oral bedaquiline-containing MDR-TB regimen, to ensure exclusion of resistance to fluoroquinolones.

Assessment of extent of TB disease:

Extent of TB disease is important to determine the regimen options, in addition to the DST and other considerations. Extensive TB disease is defined in this document as the presence of

- bilateral cavitary disease, or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.
- severe extra pulmonary TB is defined as the presence of miliary TB or TB meningitis. In children aged under 15 years, extra pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe

Regimen and duration of treatment:

The shorter all-oral bedaquiline-containing MDR/RR-TB regimen contains bedaquiline,

levofloxacin, clofazimine, ethionamide, ethambutol, isoniazid (high dose) and pyrazinamide for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive or culture positive at the end of the fourth month), followed by 5 months of treatment with levofloxacin, clofazimine, ethambutol and pyrazinamide. Bedaquiline use in this regimen is for 6 months. However, BDQ is safe to use beyond 6 months if needed.

All medicines were taken once a day during the course of treatment, except for bedaquiline, which was taken every day for the first 2 weeks, followed by three times a week in the remaining 22 weeks.

Regimen: ***(4 -6) $Bdq_{(6m)}$-Lfx-Eto-Cfz-Z- $H_{high\ dose}$-E / 5 Lfx-Cfz-Z-E***

Intensive phase: ***(4 -6) $Bdq_{(6m)}$-Lfx-Eto-Cfz-Z- $H_{high\ dose}$-E***

Continuation phase: ***5 Lfx-Cfz-Z-E***

Considerations for the all oral STR

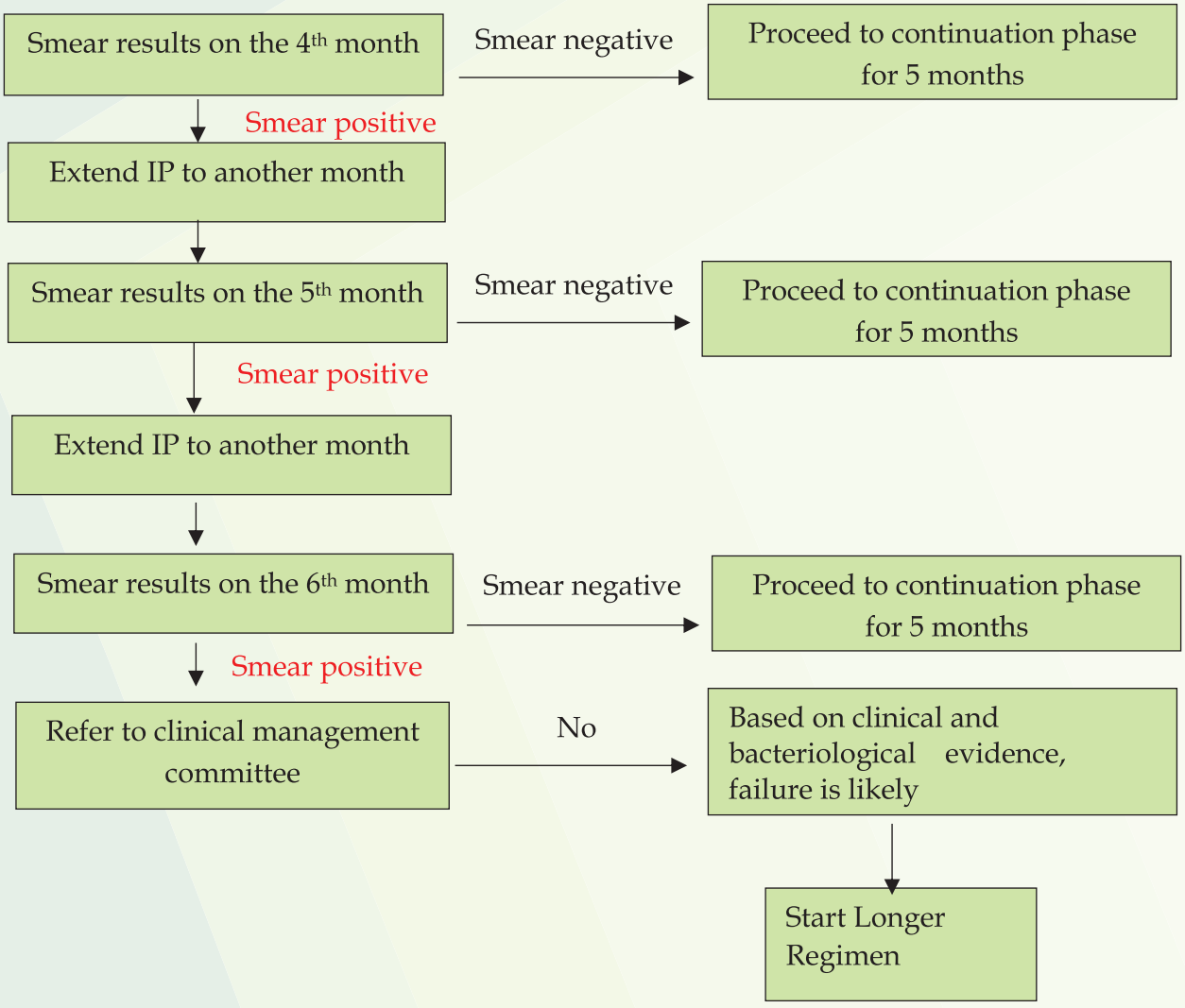
Any change the composition or the duration of the initial or continuation phase, or to prolong those phases in case of lack of response it is not advisable to using shorter all-oral bedaquiline-containing MDR/RR-TB regimen under programmatic condition; other than making the following modifications:

- If the sputum smear or culture does not become negative by the fourth month, the initial phase is prolonged until the sputum smear or culture converts; however, the initial phase is not prolonged for more than 6 months in total. The duration of the later phase remains fixed at 5 months regardless.
- Bedaquiline is used for 6 months or longer.
- Prothionamide may be used instead of ethionamide.
- Moxifloxacin may be used instead of levofloxacin.
- Other changes to the regimen (e.g. removing ethionamide or replacing ethionamide or clofazimine by linezolid) or other changes are not recommended in programmatic use.

If a patient is started on the shorter all-oral bedaquiline-containing MDR/RR-TB regimen and later found to be ineligible because of undetected resistance at the start of the treatment or emergence of additional resistance, it is assumed that further acquisition of resistance may have developed. Repeated DST at that point is necessary to guide the composition of the longer regimen.

Patients who started on a longer regimen and later found to be eligible for the shorter regimen can be switched, if that treatment has not lasted for more than 1 month. If patients are switched in this way, the shorter all-oral bedaquiline-containing MDR-TB regimen is given for the full duration, without any changes to its composition or duration.

Shifting from intensive phase to continuation phase in shorter regimen



If the interruption is for less than 2 months, the clinician needs to decide whether the shorter MDR-TB regimen can be continued based on clinical condition and repeat laboratory test results, and whether the missed doses will be added to the rest of the treatment or a longer regimen should be started.

Shifting from Shorter all-oral bedaquiline-containing regimen to longer regimen:

At times, the shorter all-oral bedaquiline-containing MDR-TB regimen may need to be switched to a longer MDR-TB regimen; this is most likely to happen when:

- reliable DST results show resistance to key medicines in the shorter all-oral bedaquiline-containing MDR-TB regimen: this may reflect the actual situation at the start of treatment (that was unknown at that time) or the acquisition of additional resistance during treatment;
- there is a lack of response to treatment (e.g. no sputum smear conversion from positive to negative by 6 months, or deterioration of clinical condition despite treatment);
- treatment of a patient is interrupted for 2 months or more after being treated for more than 1 month; or

- another disqualifying criterion emerges (e.g. pregnancy, intolerance or toxicity to a medicine in the regimen, or clinical deterioration).

6.4.3 Key subgroups for all oral Shorter regimen:

PLHIV: The shorter all-oral bedaquiline-containing MDR-TB regimen can be used in PLHIV, including those who are receiving ART. For PLHIV with pulmonary disease, there may be a potential for overlapping, additive toxicities or for drug–drug interactions between some antiretroviral medicines and TB drugs such as moxifloxacin and clofazimine and bedaquiline. In addition, ritonavir may also increase bedaquiline exposure, which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, the combination of bedaquiline with ritonavir should be avoided and to change dolutegravir based regimen in patients with high cardiovascular risk.

Children: The shorter all-oral bedaquiline-containing regimen may also be used in children aged 6 years and above. Child-friendly (i.e. dispersible and palatable) formulations of the medications should be used whenever possible. Bedaquiline tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole, and can therefore be used to treat drug-resistant TB in children until a child-friendly formulation becomes available.

In children below 6 years of age, bedaquiline is not yet recommended by WHO, mainly because of the lack of safety data and the absence of data on its use as part of the shorter all-oral regimens.

Pregnant and lactating women: The regimen contains ethionamide, which is usually contraindicated in pregnancy because of adverse effect on the fetus, and there are no adequate and well-controlled studies in humans. During pregnancy and lactation is needed, individualized longer regimens to avoid known toxicities until better safety profiles are established.

Rifampicin-resistant TB without MDR-TB: All patients – children over 6 years of age or adults – with rifampicin-resistant TB in whom isoniazid resistance is not confirmed may be treated with the shorter all-oral bedaquiline-containing MDR-TB treatment regimen.

Patients with extensive disease: In patients with extensive disease, preference should be given to the all-oral longer regimen.

Severe extrapulmonary TB disease: Some of the components of the shorter all-oral bedaquiline-containing regimen (e.g. ethambutol) do not penetrate the cerebrospinal fluid (CSF) well. In addition, CSF penetration of clofazimine and bedaquiline are lacking. Therefore, no recommendation to use the shorter all-oral bedaquiline-containing MDR-TB regimen in patients with complicated extra pulmonary TB disease.

Patients with diabetes mellitus: There are no data on the use of the shorter all-oral bedaquiline-containing regimen among people with diabetes mellitus. Thus, shorter all-oral bedaquiline-containing regimen may be considered as an option, it may be careful to monitor closely for hepatotoxicity among this patient group.

6.4.4 Using modified all-oral shorter MDR-TB regimens under operational research

At present, there is little evidence to support modified all-oral shorter MDR-TB regimens. Any change/modification the composition is only done under operational research condition to assess the effectiveness, safety, feasibility, acceptability, cost and impact (including on quality of life) of the use of modified all-oral shorter drug regimens for patients with drug-resistant TB.

All-oral shorter MDR-TB regimens are usually designed as a four-drug or five-drug standardized regimen and patients must be able to follow for one year post-treatment for recurrent TB; also, there must be documentation that the all-oral shorter MDR-TB regimen is not resulting in a high relapse rate.

The main elements to these conditions are:

- a study protocol, which must include a 12-month follow-up after the end of treatment;
- a clinical treatment guide that includes a patient consent process;
- an approval by the national ethics review board or ministry of health; and
- at a minimum, an "aDSM core package"

6.4.5 Longer MDR TB Regimens (LTR)

All MDR/RR-TB patients may be treated with longer regimens; however, the longer regimen is preferably given to those MDR/RR-TB patients who are not eligible for shorter all-oral regimens, including those with quinolone resistance.

Principles of Longer MDR-TB regimen formulation:

- In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment after bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it (Conditional recommendation)
- Kanamycin and Capreomycin are no longer recommended for use in longer regimens. (Conditional recommendation)
- Levofloxacin or Moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. (Strong recommendation)
- Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years (Conditional recommendation)
- Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens (Strong recommendation)
- Clofazimine and Cycloserine may be included in the treatment of MDR/RR-TB patients on longer regimens (Conditional recommendation)
- Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens (Conditional recommendation)
- Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens (Conditional recommendation)
- Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation). Pyrazinamide is counted as an effective agent only when DST results confirm susceptibility.
- Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens (Conditional recommendation). Every dose of imipenem–cilastatin and meropenem is administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

- Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. (Conditional recommendation).
- Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible (Conditional recommendation).
- P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.
- The optimal use of bedaquiline and delamanid is not known and use of them beyond six months are considered to be "off label" and should follow the best practice in "off label" use.

Regimen:

20 Bdq (6m)-Lfx -Lzd-Cfz-Z

In this example, the first 6 months of treatment comprises four second-line agents. The remaining 14 months includes the same agents except for bedaquiline, bringing the total duration to 20 months. All medicines apart from bedaquiline are given 7 days a week. Bedaquiline, when prescribed on-label, is given daily for the first 2 weeks and three times weekly thereafter (see Annex I for more details on dosing). Regimens without an injectable agent (i.e. all-oral regimens) are considered not to have an initial phase.

6 Bdq-Dlm-Lzd-Cs-Cfz-Z/14 Lzd-Cfz-Cs-Z

Longer regimen for MDR/RR-TB patients with extensive TB disease, additional resistance to fluoroquinolones (**Pre-XDR-TB**) or exposure to treatment with second-line medicines for more than 1 month: **20 Bdq-Dlm (6m)-Lzd-Cfz-Cs-Z** (20-month treatment regimen composed of bedaquiline, delamanid for the first 6 months and linezolid, clofazimine, Cycloserine and Pyrazinamide for 20 months)

Eligibility

- Any patient – child or adult – with MDR/RR-TB is eligible for longer MDR-TB regimen
- If the shorter all-oral bedaquiline-containing MDR-TB regimen cannot be used, the patient needs to be reassessed, with a view to starting a longer MDR-TB regimen.
- A patient started on the shorter all-oral bedaquiline-containing MDR-TB regimen can later be transferred to a longer MDR-TB regimen, if condition arise.

Once a patient is placed on a longer MDR-TB regimen for at least 4 weeks, normally that patient can no longer be switched to the shorter all-oral bedaquiline-containing MDR-TB regimen because this 4-weeks treatment would represent an exposure to second-line medicines.

Both shorter and longer regimens are more likely to be effective if the composition is guided by reliable DST. If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid and fluoroquinolones should be performed promptly, to inform the decision about which medicines to use for the treatment of MDR/RR-TB. Ideally, all MDR/ RR-TB patients are tested for resistance to fluoroquinolones as a minimum before starting MDR-TB treatment.

Any patient with rifampicin-resistant TB – whether a child or an adult – in whom isoniazid resistance is absent or unknown, needs to be treated with a recommended MDR-TB regimen. The regimen could be a shorter all-oral bedaquiline-containing regimen or a longer MDR-TB regimen if the former cannot be used. High-dose isoniazid has also been shown to be an important component in paediatric regimens. Although high-dose isoniazid is not included in Groups A–C, it may still be used in patients with confirmed susceptibility, or in the presence of mutations that do not usually confer complete resistance to isoniazid.

6.4.6 BPaL Regimen

Treatment regimen lasting 6-9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), for treatment of multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, XDR-TB, intolerant and non-responsive MDR-TB, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks.

BPaL regimen may be used under operational research conditions which include research subject to ethical approval, patient-centered care and support, pre-defined eligibility criteria, patient informed consent, implementation according to the principles of good clinical practice, active drug safety monitoring and management, treatment monitoring, outcome evaluation, and comprehensive, standardized data collection.

BPaL regimen: 6–9 Bdq- Pa-Lzd

Eligibility criteria:

A patient is eligible for treatment with the BPaL regimen if he or she:

- is diagnosed bacteriologically confirmed pulmonary TB and has laboratory-confirmed resistance to rifampicin and fluoroquinolones with or without resistance to injectable agents; and
- is aged at least 14 years at the time of enrolment; and
- weighs 35 kg or more; and
- is willing and able to provide informed consent to be enrolled in the operational research project and to adhere to the follow-up schedule (signed or witnessed consent if the patient is illiterate, signed or witnessed consent from a child's parent or legal guardian); and
- if the patient is a premenopausal woman, is not pregnant or breastfeeding and is willing to use effective contraception; and
- has no known allergy to any of the BPaL component drugs; and
- has no evidence in DST results of resistance to any of the component drugs, or has not been previously exposed to any of the component drugs for 2 weeks or longer; and
- has no extra pulmonary TB (including meningitis, other CNS TB, or TB osteomyelitis).

Patients who are not eligible for the BPaL regimen can benefit from the individualized longer treatment regimen that is composed of medicines using the priority grouping of medicines

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 (reference Table 2).

The adult dosages of anti-TB drugs are shown in Table 2, which provides the drug abbreviations and the average daily dose and the dosing as per different weight classes for adults. All drugs listed in Table 2 are not used in Bangladesh for DR TB, however, this table provides an overview of anti TB drugs.

Table: 2 dosing of Medicine used in Second line DR TB regimen (older than 14 years)

Group	Medicine	30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg	Usual upper daily dose
A	Levofloxacin	750 mg	750 mg	1000 mg	1000 mg	1000 mg	1.5 g
	Moxifloxacin high dose	400 mg	600 mg	600 mg	800 mg	800 mg	800 mg
	Bedaquiline	• 400 mg once daily for first 2 weeks • then 200 mg 3 times per week for 22 weeks					400 mg
	Linezolid	600 mg	600 mg	600 mg	600 mg	600 mg	1.2 g
B	Clofazimine	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
	Cycloserine	500 mg	500 mg	750 mg	750 mg	750 mg	1 gm
C	Ethambutol	800 mg	800 mg	1200 mg	1200 mg	1200 mg	
	Delamanid/ Pretomanid	100 mg twice daily (200 mg total daily dose) for 24 weeks					200 mg
	Pyrazinamide	1000 mg	1500 mg	1500 mg	1500 mg	2000 mg	
	Amikacin	500 mg	750 mg	750 mg	1000 mg	1000 mg	1 gm
	Ethionamide or Prothionamide	500 mg	500 mg	750 mg	750 mg	1000 mg	1 gm
	P-aminosalicylic acid (PAS)	4 g	8 gm	8 gm	8 gm	8 gm	12 gm
	Isoniazid	450 mg	450 mg	600 mg	600 mg	600 mg	

CHAPTER 7

Management of Drug-Resistant Tuberculosis in Children

A diagnosis of TB in children can be made on clinical and radiological grounds in the majority of cases, even though bacteriological confirmation may not be possible. The diagnosis of TB in children relies on thorough assessment of all the evidence derived from a careful history of exposure, clinical examination and relevant investigations. Most children with TB have pulmonary TB. Although bacteriological confirmation of TB is not always feasible, it should be sought whenever possible by microscopy, culture or WHO-endorsed genotypic (molecular) testing (i.e. Xpert MTB/RIF) of respiratory or no respiratory samples as indicated by clinical presentation.

Criteria for presumptive child DR-TB

- History of previous treatment within the past 6-12 months
- Close contact with a person known to have DR-TB, including household and school contacts
- Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment
- Failure to improve clinically after 2-3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvement is frequently delayed)

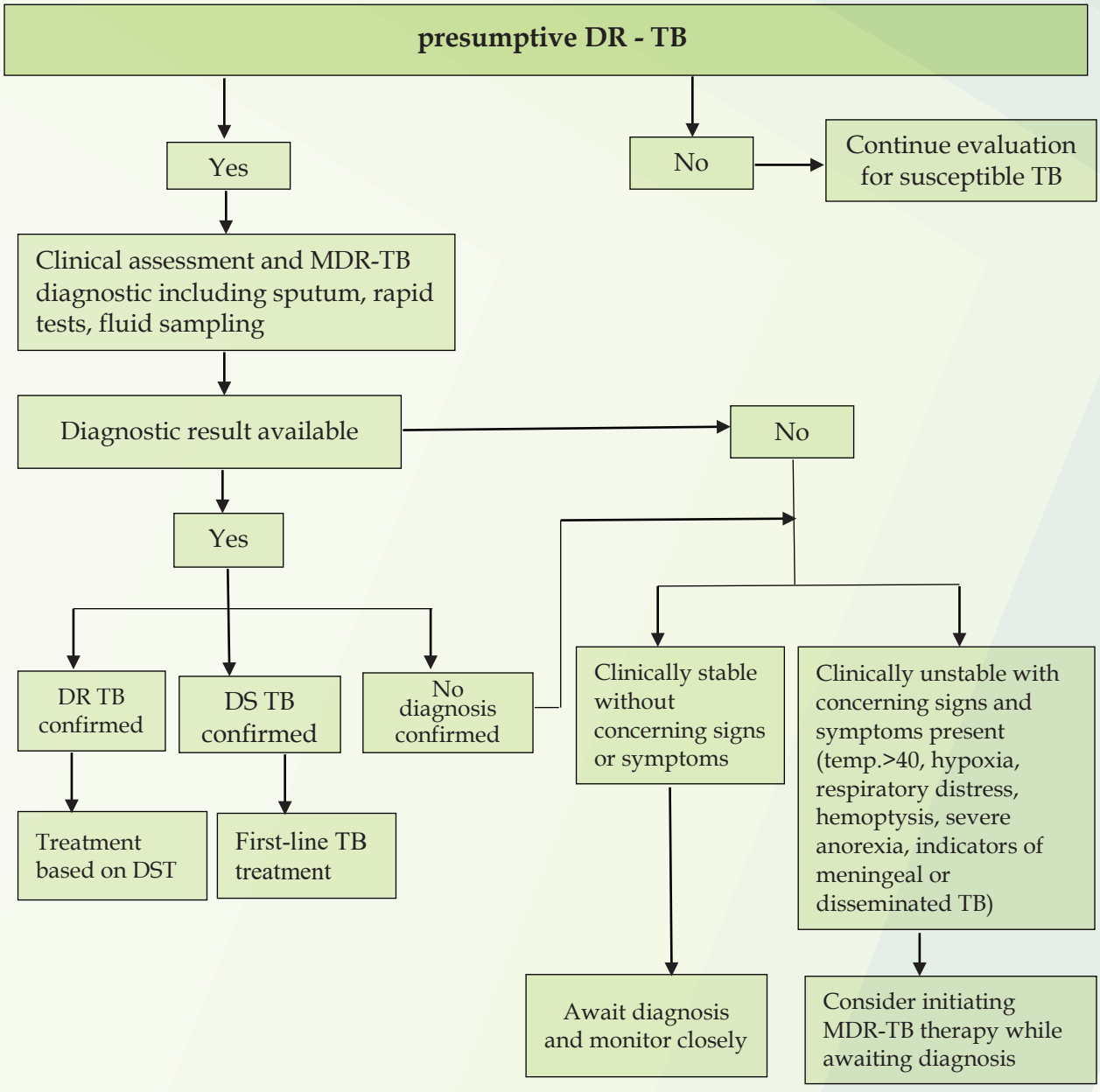
7.1 Diagnosis of Child DR TB

The diagnosis of DR-TB in children is mostly made on clinical and radiological grounds with consideration of risk factors for DR-TB (e.g. recent DR-TB exposure). There are multiple specimen types that can be taken from children to diagnose DR TB, and these can be sent for a variety of tests, including smear, liquid medium culture (i.e. MGIT), solid medium culture, pathology, or rapid diagnostic testing with the GeneXpert or GenoType MTBDRplus line probe assay.

- When DR-TB is suspected confirm the diagnosis by obtaining specimens for culture and drug susceptibility testing (DST).
- Clinical samples include sputum (expectorated or induced), gastric aspirates and other specimens depending on the site of TB disease (e.g. lymph node biopsy)
- Bacteriological confirmation should be attempted, but is often not possible due to paucibacillary disease or extra pulmonary (EP) disease
- Rapid DST of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis.
- The use of molecular tests (line probe assay and Xpert MTB/RIF) may provide evidence of resistance within hours to 2-3 days of specimen testing

Note: In all cases of confirmed DR-TB, second-line DST should be performed to exclude XDR-TB and to help establish an effective treatment regimen.

7.1.1 Algorithm for presumptive DR-TB in a Child



7.2 Treatment of Child DR TB

7.2.1 Principle of regimen design

In general, children with DR-TB should be managed according to the same principles that guide adult therapy. For children the following principles are recommended during designing the regimen

- Treatment should be based on the DST pattern of the most likely source case if the child does not have a DST of his or her own
- Always attempt to treat children with injectable-free regimens, especially very young children and those with mild disease. Absence of malnutrition, serious forms of extra pulmonary disease, cavitation on chest radiography or HIV infection.
- The use of Amikacin in children is to be accompanied with regular audiometry.

  With severe forms of extra-pulmonary DR-TB. Treatment of DR-TB meningitis should be guided by the medicines' ability to cross the blood-brain barrier. (See 8.1.0 Treatment of DR TB with CNS involvement for more details)

- Regimens should consist of at least 3 effective drugs to which the organism is likely to be susceptible for the duration of therapy, with possible addition of a 4 drug for the first few months of therapy in cases with severe or multi-bacillary.
- Regimen construction should prioritize the WHO Group A and B drugs, as well as delamanid in children aged more than 3 years of age
- Bedaquiline is recommends for the treatment of children aged 6 years and above and the use of delamanid for the treatment of children aged 3 years and above with careful monitoring.
- Although linezolid is a Group A drug with proven effectiveness, its use has been associated with frequent toxicity.
- Pyrazinamide should only be used if there is demonstrated susceptibility
- The composition of MDR-TB treatment regimens is largely the same in children living with HIV. Efavirenz should be avoided in children who need bedaquiline for the duration of their bedaquiline treatment, as efavirenz lowers the concentrations of bedaquiline.
- Amoxicillin-Clavulanic acid should be administered with every dose of imipenem-cilastatin or meropenem to aid its efficacy. It should not be counted as an additional medicine or used as a separate agent
- Child-friendly formulations of the medications should be used whenever possible.
- Monitoring and management of adverse events is essential

7.2.2 Duration of treatment

- The duration of treatment in children depends upon the site and severity of disease: children with non-severe disease can be treated for 9 to 11 months
- Children with severe disease will require 12-18 months of therapy depending on their clinical progress

Of note, WHO recommendations define severe disease as follows:

In children <15 years, severe disease is usually defined by the presence of

- Cavities
- Bilateral disease on chest radiography
- Extra pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)
- Advanced malnutrition (defined by syndrome or by metrics)
- Advanced immunosuppression or positive TB bacteriology (smear, Xpert MTB/RIF, culture)

7.2.3 Treatment

- **Mono resistant TB:** Where mono resistance to isoniazid is known or suspected the regimen is

  6 (Levofloxacin+ Ethambutol + rifampicin+ pyrazinamide)

  For patients with more extensive disease, consideration should be given to prolonging treatment to a minimum of 9 months.

  Mono resistance to rifampicin should be treated with MDR-TB regimen in a similar way to adults

- **Treatment of multidrug-resistant TB:** Children with MDR-TB are treated in a similar way to adults with MDR-TB. One practical difference is that confirmation and DST may not possible, so that empirical treatment is often required for children with suspected MDR-TB.

Treatment Regimen

<3 years (FLQ-R): Lzd-Cfz-Cs; Add one of Dlm, PAS or Eto Additional drugs if needed

(FLQ-S): **Lfx-Lzd-Cfz-Cs** Additional drugs if needed Dlm, PAS and Eto

<6 years (FLQ-R): **Lzd-Cfz-Cs-Dlm;** Additional drugs if needed PAS and Eto

(FLQ-S): **Lfx-Lzd-Cfz-Cs** Additional drugs if needed Dlm and PAS

>6 years (FQ-R): **Bdq-Lzd-Cfz-Cs** Additional drugs if needed Dlm and PAS

(FQ-S): B**dq-Lfx-Lzd-Cfz** Additional drugs if needed Cs and Dlm

7.3 Monitoring

- Diagnosing children with MDR-TB and designing an appropriate treatment regimen can be major obstacles in the management of pediatric MDR-TB.
- Another challenge is maintaining the patient on therapy and making sure that he or she is closely followed by physicians, nurses, health care workers, and caregivers.
- Children have been successfully treated for MDR-TB, but only with appropriate monitoring and follow-up. Monitoring is needed to evaluate therapeutic efficacy and to mitigate the development of adverse events.

7.4 Prevention of TB disease in child contacts of drug-resistant TB

- Current WHO guidelines do not recommend preventive therapy for contacts of DR-TB patients. Close contacts of DR-TB patients who develop TB disease usually have drug-resistant disease.

- All children with an infectious TB contact should be screened for TB disease, especially children living with HIV and child household contacts of DR-TB
- Careful clinical Guidance for in children follow-up of asymptomatic children (every 2-3 months for the first 6 months, then 6-monthly for at least 2 years) is recommended.
- If TB disease develops, treatment with an appropriate DR-TB regimen based on the DST pattern of the presumed source case should be initiated.

7.5 Dosing

Table: 1 Dosing of Medicine used in Second line DR TB regimen (under 14 years)

Group	Medicine	Formulation	5-6 kg	7-9 kg	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg	Usual upper daily dose
A	Levofloxacin 15-20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	>14 years	>14 years	>14 years	1.5 gm
		250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	>14 years	1.5 gm
	Moxifloxacin 10-15 mg/kg	100 mg dt	0.8	1.5	2	3	4	>14 years	>14 years	400 mg
		400 mg tab	2 ml	3 ml	5 ml	0.5 or 0.75	1	>14 years	>14 years	400 mg*
	Bedaquiline	100 mg tab	0	0	0	200 mg daily for 2 weeks then 100 mg 3 times per week for 22 weeks		400 mg once daily for first 2 weeks; then 200 mg 3 times per week for 22 weeks		**
	Linezolid 15 mg/kg od in <16 kg 10-12 mg/kg od in >15 kg	20 mg/ml susp	4 ml	6 ml	8 ml	11 ml	14 ml	15 ml	20 ml	600 mg
		600 mg tab	0.25	0.25	0.25	0.5	0.5	0.5	0.75	
B	Clofazimine 2-5 mg/kg	50 mg tab/cap	1 alt days	1 alt days	1 alt days	1	2	2	>14 years	100 mg ***
		100 mg tab/cap	M/W/F	M/W/F	1 alt days	2 alt days	1	>14 years	>14 years	
	Cycloserine 15-20 mg/kg	125 mg minicap	1	1	2	3	4	>14 years	>14 years	1 g
		250 mg cap	2-5 ml	5-6 ml	7-10 ml	2	2	2	>14 years	

Group	Medicine	Formulation	5-6 kg	7-9 kg	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg	Usual upper daily dose
	Ethambutol 15-25 mg/kg	100 mg dt	1	2	3	4	0	0	> 14 years	
		400 mg tab	3 ml	4 ml	6 ml	1	1 or 1.5	2	> 14 years	
	Delamanid	50 mg	0	0	0	0	100 mg	100 mg	200 mg	200 mg ****
	Pyrazinamide 30-40 mg/kg	150 mg dt	1	2	3	4 or 5	-	-	>14 years	
		400 mg tab	0.5	0.75	1	1.5 or 2	2.5	3	>14 years	
		500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	>14 years	
C	Amikacin 15-20 mg/kg	500 mg/2 ml vial	0.4 ml	0.6 ml	0.8 ml	1.2-1.5 ml	2 ml	>14 years	>14 years	1 gm
	Ethionamide or Prothionamide 15-20 mg/kg	125 mg dt	1	1	2	3	4	4	>14 years	1 gm
		250 mg tab	0.5	0.5	1	2	2	2	>14 years	
	PAS 200-300 mg/kg in 2 divided doses	PAS acid (4 g) sachet	0.5-0.75 g bd	0.75-1 g bd	1-2 g bd	2-3 g bd	3-3.5 g bd	>14 years	>14 years	*****
		PAS Sodium salt (4 g) sachet	0.5-0.75 g bd	0.75-1 g bd	1-2 g bd	2-3 g bd	3-3.5 g bd	>14 years	>14 years	
		PAS sodium salt 60% (9.2 g) sachet	1.5 g bd	2-3 g bd	3-4 g bd	4 or 6 g bd	6 or 8 g bd	8-12 g bd	8-12 g bd	
	Isoniazid 15-20 mg/kg (high dose)	50 mg/5 ml soln	8-10 ml	15 ml	20 ml	-	-	-	>14 years	******
		100 mg tab	1	1.5	2	3	4	4	>14 years	

Note:

- **Moxifloxacin: Use 10 mg/kg in < 6 months*
- *** Only in patients aged 6 years or more (lower dose from 15-29 kg, higher dose from >29 kg)*
- **** Give on alternate days if dose in mg/kg/day is too high*
- ***** Only in ptients aged 3 years or more (25mg bd in 3-5 years; 50 mg bd in 6-11 years; 100 mg bd in 12-17 years)*
- ****** Full dose can be given once daily if tolerated*
- ******* 300 mg isoniazid tablet can be used in patients >20 kg*

  Pyridoxine is always given with high dose isoniazid in children (12.5 mg od in <5 years old and 25 mg od in >4 years olds)

CHAPTER 8

Management of drug-resistant TB in special situations

Immune compromised conditions and situations such as chronic renal failure, liver disease, diabetes and pregnancy may increase risk of poor DR-TB treatment outcomes. These conditions frequently require laboratory investigations to monitor cardiac, liver and kidney functions etc., and may need modification of drugs, their dose and duration of therapy. This chapter outlines the management of drug-resistant TB in selected special situations. The special conditions would generally entail careful administration of drugs as well as monitoring of response.

8.1 Pregnancy

- Pregnancy is not a contraindication to treatment.
- The decision whether or not to treat should be based on an assessment of the risks and benefits for the mother and the fetus.
- If treatment is deferred: high risk of serious worsening of the mother's general condition during pregnancy, increased risk of abortion, low birth weight and risk of disseminated TB for the baby.
- 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
- 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

Regimen: Treat with three or four oral second-line anti-TB drugs which are likely to be highly effective and designing from an individualized longer regimen using the WHO priority grouping of medicines

- Amikacin, streptomycin, prothionamide, ethionamide, Clofazimine are usually contraindicated during pregnancy.
- Bedaquiline, delamanid, Linezolid, Cycloserine is not contraindicate during pregnancy. However, knowledge about the safety of bedaquiline and delamanid in pregnancy and while breastfeeding is sparse.
- It is recommended a longer regimen be individualized to include components with a safety profile that is better established.
- The outcomes of treatment and pregnancy, and postpartum surveillance for congenital anomalies should be documented.

8.2 Breast feeding

- Woman who is breastfeeding and has active drug-resistant TB should receive a full course of anti-TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby.
- In lactating mothers on treatment, most anti-TB drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant.

- Therefore, it is preferable to provide infant formula options as an alternative to breastfeeding. Clinicians and parents may agree to breastfeeding when the formula is not a feasible option.
- The mother and her baby should not be completely separated. However, 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
- When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask until she becomes sputum smear negative.

8.3 Contraception

- Birth control is strongly recommended for all women of reproductive age receiving therapy for drug-resistant TB because of the potential consequences for both the mother and fetus resulting from drug-resistant TB treatment during pregnancy
- 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.

For patients with mono- and poly-resistant TB but who are susceptible to Rifampicin, note that the use of Rifampicin interacts with the contraceptive drugs, resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving Rifampicin treatment may choose between two options following consultation with a physician, namely:

- use of an oral contraceptive pill containing a higher dose of estrogen (50 µg); and
- use of another form of contraception (barrier method)

8.4 HIV Infected Patients

- The composition of the treatment regimen for MDR-TB does not usually differ substantially for people living with HIV. Started as soon as the patient tolerates the DR TB regimen, regardless of CD4 count.
- A few drug–drug interactions may be avoided with careful attention (e.g. bedaquiline and efavirenz
- 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).

The shorter regimen may be used in PLHIV alongside timely initiation of ART in accordance with WHO guidelines, and careful monitoring of the effectiveness of ART and adverse reactions to it. PLHIV receiving the shorter regimen may also need prophylactic medication for opportunistic infections, as well as support for medication adherence, and close monitoring and follow up as part of routine HIV care.

8.5 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.

- All first-line drugs – isoniazid, rifampicin and pyrazinamide – are associated with hepatotoxicity. Of the three, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs.
- Among the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with fluoroquinolones.

8.6 Diabetes Mellitus

- Diabetic patients with drug-resistant TB may have worse treatment outcomes. Furthermore, the presence of diabetes may enhance adverse reactions to anti-tuberculosis drugs, particularly renal impairment and peripheral neuropathies.
- Diabetes should be closely monitored and treated throughout the duration of anti-tuberculosis treatment.
- Nevertheless, none of the anti-tuberculosis drugs is contraindicated. Creatinine and potassium levels should be regularly monitored more frequently.
- Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but may require the patient to increase the dosage as the use of ethionamide or prothionamide may make it more difficult to control insulin levels.
- The health care provider should be in close communication with the physician who manages the patient's diabetes.

8.7 Renal Insufficiency

- Caution should be used in the administration of SLIs to patients with renal impairment.
- 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
- The dosing is based on the patient's creatinine clearance, which is an estimate of the glomerular filtration rate or renal function.
- In case of creatinine clearance <60 ml/min despite dose reduction to 2-3 times/week, stop the injectable drug and replace it with Bdq or Dlm.
- All patients are monitored every month for creatinine and potassium level while on the injectable agent for new or worsening nephrotoxicity.

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

8.8 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.
- Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication.

- The prophylactic use of oral pyridoxine (vitamin B6) can be used in patients with seizure disorders to protect against the neurological adverse effects of isoniazid or cycloserine. The suggested prophylactic dose for at-risk patients on isoniazid is 10 to 25 mg/day and for patients on cycloserine is 25 mg of pyridoxine for every 250 mg of cycloserine daily.
- The optimal prophylactic dose of pyridoxine for children has not been established, nonetheless 1–2 mg/kg/day has been recommended in some reports with a usual range of 10–50 mg/day for paediatric patients at risk for neurological sequella.

8.9 Psychiatric Patients

- The use of cycloserine is not absolutely contraindicated for the psychiatric patient.
- Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders
- Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patient being a danger to oneself or others
- Treatment with psychiatric medication, individual counselling and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication.

8.10 Treatment of DR TB with CNS involvement

- Extra pulmonary drug-resistant TB is treated with longer regimens. Adjustments may be required depending upon the specific location of the disease.
- If the patient has symptoms suggestive of central nervous system involvement and is infected with drug-resistant TB (rifampicin-resistant or multidrug-resistant TB), then the regimen should use drugs, which have adequate penetration into the central nervous system.
- Fluoroquinolones (Levofloxacin and moxifloxacin) is recommended as they penetrate the central nervous system (CNS) well as do ethionamide (or prothionamide), cycloserine (or terizidone) linezolid and imipenem–cilastatin. Seizures may be more common in children with meningitis treated with imipenem–cilastatin (meropenem is preferred for meningitis cases and in children).
- High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the cerebrospinal fluid and may be useful if the strains are susceptible. (Caution should be exercised as a large percentage of MDR-TB strains may be resistant).
- PAS and ethambutol do not penetrate the CNS well and should not be counted upon among the number of effective drugs to treat MDR-TB meningitis.
- Amikacin and streptomycin penetrate the CNS only in the presence of meningeal inflammation
- There are little data on the CNS penetration of capreomycin, clofazimine, bedaquiline or delamanid

CHAPTER 9

Initial Evaluation and Preparing the Patient for Treatment

9.1 Flow of Patients into Treatment

Patients considered for DR TB screening are described in Chapter 5. 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 (5.2).

9.2 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 an initial medical evaluation:

- Malnutrition
- Diabetes mellitus
- Hypertension
- Renal insufficiency
- Acute or chronic liver disease
- Thyroid disease
- Mental illness
- Pregnancy
- 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.

9.3 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.

Sl. No	Pre-treatment evaluations	Shorter MDR-TB regimen	Longer Regimen
1	Detailed history (including screening for mental illness, seizure disorder, drug/alcohol abuse, etc.)	+	+
2	Previous history of ATT taken especially SLI/FQ	+	+
3	Weight & height	+	+
4	Thorough clinical examination	+	+
5	Complete blood count with hemoglobin & platelets count	+	
6	Blood sugar to screen for Diabetes Mellitus	+	+
7	Blood urea and S. Creatinine to assess renal function	+	
8	Urine examination – routine and microscopic	+	+
9	UPT (for all women in the child-bearing age)	+	+
10	Chest X-ray	+	+
11	HIV counselling and testing	+	+
12	Audiogram	+	+
13	Liver function tests	+	+
14	TSH levels to assess the thyroid function	+	+
15	Mental health evaluation	+	+
16	Surgical evaluation	+	+
17	ECG (if Mfx^{h}, Dlm, Bdq, Cfz used)	+	+
18	Serum electrolytes – potassium, magnesium, calcium	+	+
19	Serum proteins, lipase, amylase		+

CHAPTER 10

Monitoring Treatment Progress

This chapter focuses on monitoring the progress of treatment and identifying failure of treatment that indicates the need for a change in treatment strategy. While monitoring treatment progress, it is also important to proactively detect and manage adverse effects to drugs.

10.1 Monitoring the progress

- All patients on second-line treatment should be monitored closely for 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. 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.
- 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.
- Sputum Follow-up Examinations
  - The most important evidence of improvement 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 up to the completion of treatment. Sputum culture monthly throughout the treatment
- 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.
- Laboratory screening: 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).
- 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 is 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.

- DST may be repeated for patients who remain smear and culture positive or who are suspected for treatment failure
- A key component of monitoring the progress of treatment is patient-centered DOT. All treatment should be given under direct observation and DOT providers should be trained on the signs of treatment failure.

10.2 Activities for monitoring treatment response

Monitoring & Evaluation	Recommended frequency
Evaluation by clinician	There will be clinical follow up with a doctor, monthly until treatment completion. During the continuation phase: Monthly assessments unless there is a medical necessity to see the patient more often. The DOT provider sees the patient daily between consultations and signals any concerns to the clinician.
Treatment adherence & tolerance	Daily at every DOT encounter by the DOT provider.
Sputum smears & culture	Monitoring smears and culture monthly throughout treatment.
Weight	At baseline, then monthly.
Height	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
Drug susceptibility testing	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four
Chest radiograph	At baseline, and then every six months.
ECG	At baseline, after 2 weeks and then monthly throughput the treatment
Audiometry	At baseline and then monthly during injectable phase
Clinical blood testing	See table 10.4

10.3 Monitoring after treatment

All patients will be followed up until 12 months after the STR treatment and 24 month after LTR has ended. A follow-up visit will be planned at 6 months after treatment completion (or at any time earlier in case of re-occurrence of symptoms) for clinical assessment and a final visit will take place at month 12 and 24 post-completion.

10.4 Monitoring schedule (Clinical, bacteriologic and laboratory) during M-/XDR-TB treatment with all oral longer/shorter regimen

	Evaluation/Test	Baseline	Intensive phase (IP)	Continuation phase (CP)	Follow-up after treatment completion
CLINICAL	Clinical evaluation (symptoms, side effects &PE)	√	Daily during DOT and monthly by physician	Monthly	For STR: post treatment month 6 & 12 For LTR: : post treatment month 6,12,18&24
	Weight	√	Monthly	Monthly	
	Audiometry	√	Monthly while on injectable		No needed
	Visual (Snellen's and Ishihara chart)	√	Monthly while on Lzd	Monthly while on Lzd	
	12-lead ECG	√	Week 2,4, then monthly, and ad hoc[1]	Monthly, and ad hoc if on Bdq or Dlm, Mfx and Cfz[1]	Post treatment month 6
			Note: Special attention in patients receiving more than one QT prolonging drugs (Bdq, Dlm, Mfx,Lfx, Cfz) or with low albumin (<3,4g/dl)		
	Chest X-ray	√	Month 4 and ad hoc in STR Every 6 month, and ad hoc in LTR	Every 6 month, and ad hoc in LTR	For STR: post treatment month 6 & 12 For LTR: : post treatment month 6,12,18&24
BACTERIOLOGIC	Xpert® MTB/Rif	√			
	Smear	√	Monthly	Monthly	For STR: post treatment month 6 & 12 For LTR: : post treatment month 6,12,18&24
	Culture	√	Monthly	Monthly	
	SL-LPA	√	In case of + (ve) Culture after conversion		If Culture + (ve)
	DST (H, R, Mfx, Lfx, Km, Am, Cm, Bdq, Dlm), if culture positive	√	In case of + culture by month 3 of treatment, or reversion	In case of reversion	If Culture + (ve)

	Evaluation/Test	Baseline	Intensive phase (IP)	Continuation phase (CP)	Follow-up after treatment completion
LABORATORY	Complete Blood Count (CBC)	√	Monthly or If indicated Note: If on Lzd, monthly or if indicated	Monthly or If indicated	If indicated
	Creatinine	√	Monthly while on injectable Note: Special attention for diabetics and other high-risk patients		If indicated
	Potassium	√	Monthly while on injectable Note: Repeat if any ECG abnormalities develop while on Bdq or Dlm Every 1-3 weeks in HIV-infected, diabetics and other high-risk patients		If indicated
	Liver function tests (LFTs) include AST, ALT, alk phos, bilirubin, GGTP	√	Monthly and as clinically indicated for DM	At least quarterly and as clinically indicated for DM	If clinically indicated
	Glucose	√	Monthly if elevated at baseline and patient is Diabetic		If indicated
	Thyroid-stimulating hormone (TSH)	√	At months 3 and 6, if with Eto (with or without PAS), then if clinically indicated		If indicated
	HbsAg and anti-HCV	√	If risk factors are present		If clinically indicated
	HIV	√	Repeat, if indicated		If clinically indicated
	CD4 count (if HIV +)	√	At month 6		
	Pregnancy test (for childbearing women)	√	Repeat, if indicated		
	Serum magnesium and calcium	If hypokalemia is present If on Bdq or Dlm	If hypokalaemia is present. Monthly if on Bdq or Dlm. Repeat if any ECG abnormalities develop		When indicated
	Albumin	√	Every 2 months if on Dlm		When indicated
	Serum Lipase/amylase	Special attention to patients receiving Bdq, Lzd and based on risk factors			
	Lactic acid	When indicated	For work up of lactic acidosis in patients on Lzd and ART or Lzd and Metformin		

CHAPTER 11

Active TB drug-safety monitoring and management (aDSM)

aDSM is defined as the active and systematic clinical and laboratory assessment of patients on treatment with all 2nd line TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.

While all detected adverse events (AEs) need to be managed, the core package of aDSM requires the reporting of serious AEs (SAEs) only. MDR/XDR-TB treatment sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the programme as part of comprehensive aDSM.

11.1 Objectives of aDSM

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

aDSM includes t**hree essential activities** to achieve these objectives:

1. Patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.
2. All AEs detected should be managed in a timely manner in order to deliver the best possible patient care.
3. Standardized data should be systematically collected and reported for any detected SAE

11.2 Definitions of terms in aDSM

aDSM	aDSM is defined as the active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.
Adverse event	Any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.
Adverse drug reaction	A response to a TB medicine that is noxious and unintended, and which occurs at doses normally used in humans.
Causality assessment	The evaluation of the likelihood that a TB medicine was the causative agent of an observed adverse reaction.
Serious adverse event:	An AE which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. SAEs that do not immediately result in one of these outcomes but which require

	an intervention to prevent it from happening are included. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event.
Adverse event of clinical significance	an AE that is either a) serious, b) of special interest, c) leads to a discontinuation or change in the treatment, or d) is judged as otherwise clinically significant by the clinical management committee. The centers that offer the advanced package of aDSM will include all AEs of clinical significance in their reporting.
AE of special interest	An AE documented to have occurred during clinical trials and for which the monitoring programme is specifically sensitized to report regardless of its seriousness, severity, or causal relationship to the TB treatment. The center that offers intermediate and advanced package of aDSM will include all AEs of special interest in their reporting.

11.3 Levels of aDSM monitoring

There are **three levels of monitoring** aDSM, namely

- Core package: requiring monitoring for and reporting all SAEs
- Intermediate package: including SAEs as well as AEs of special interest
- Advanced package: including all AEs of clinical significance.

The NTP in Bangladesh will implement t**he core package of aDSM** and, therefore, will monitor and report only SAEs. However, as resources become available and as the NTP decides, aDSM may be expanded to include monitoring of other AEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM.

11.4 aDSM Components

There are three components in aDSM. These are

A. Clinical monitoring (active and systematic clinical safety monitoring and management (aDSM) and laboratory assessment during treatment to detect drug toxicity and AEs)
B. Management of AEs in a tie manner guided by ADR grading
C. Systematic and standardized recording and reporting of AEs which includes data collection to include safety data; SAEs and AEs to be reported to the PV center and assessed for causality; and regular meeting between National PMDT Coordination committee and the PV Center,

A. Clinical monitoring

AEs should be monitored in a systematic and timely manner. At every DOT encounter, health workers should ask the patient about clinical symptoms of common AEs including skin rashes, gastrointestinal disturbances, psychiatric disturbance (headache, anxiety, depression, irritability, behavior change), jaundice, vestibular toxicity (nausea, vertigo, ataxia), peripheral neuropathy and symptoms of electrolyte wasting (muscle cramping, palpitations), etc. Ototoxicity (hearing loss) needs particular attention.

Timely recognition and management of AEs are important for adherence, treatment outcome, overall treatment tolerance and well-being of patients. In order to detect AEs, it is important to always be observant of the patient, and be diligent in performing clinical and laboratory assessments:

- Observe and listen: detection of AE is primarily dependent upon reporting from patient, nurses, doctors, counsellors, etc. All healthcare professionals involved must be trained on adverse event screening. And patients should be counseled early and often about AEs.
- Perform routine clinical assessments
- Schedule regular laboratory screening, even if the patient has no specific complaints (e.g. ECG, liver function tests) to detect occult adverse effects. As Mfx, Cfz, and the new drugs used in individualized regimens, Bdq and Dlm, may induce QT prolongation, monitoring of ECG is essential and required.
- There will be clinical follow-up with a doctor for all patients at a minimum at 2 weeks after DR-TB treatment initiation and then monthly until treatment completion. At each visit, clinical assessment with evaluation of treatment efficacy and AEs will be conducted. Treatment safety will be assessed by the doctor and/or nurse with a specific data collection form.
- Any relevant clinical event (adverse events or reactions) and any required additional diagnostic testing and/or therapy will be recorded

B. Management of AEs

The appropriate and timely management of all AEs and ADRs is an integral component of aDSM and patient care. Further details on the management of ADRs are included in chapter 12. Early detection of signs and symptoms is key to proper management of adverse drug reactions that significantly impacts the patient's well-being, overall treatment acceptance, and adherence.

The clinical monitoring and management of AEs should ensure patient access to diagnostics and treatment for AEs, including ancillary drugs, implement baseline examinations at initiation of treatment and monitoring during treatment for all MDR-TB patients, assess availability of clinical examinations and tools required; seek funds to procure, if not available, and ensure quick test results feedback, to allow for timely clinical decision-making.

C. Recording and reporting of AEs

The recording and reporting of aDSM primarily target serious adverse events (SAEs) as a core requirement. Treatment initiation sites with additional resources may also monitor other AEs, which are of clinical significance or of special interest to the NTP programme, as part of an extended aDSM approach.

Following information will be recorded using WHO Adverse Reactions Terminology (WHO-ART):

- Type of SAE (congenital anomaly or birth defect; persistent or significant disability; death; required hospitalization; prolonged hospitalization; life threatening)
- Type of AE of special interest
- Onset date of adverse event
- Clinical action taken (including provision of ancillary drugs, rechallenge), and
- Result of the causality assessment (whether the SAE is attributable to one or more anti-TB or concomitant drugs).

11.5 Causality categories definition

Category	Description
Related	There is a reasonable possibility that the AE may be related to the drug(s). Elements in favor of a reasonable causal relationship includes: • A favorable temporal relationship, • A positive dechallenge and/or rechallenge, • A plausible pharmacological/biological mechanism of action (whether proven or potential), • Previous knowledge of similar reaction with the drug(s), or • No other evident cause (e.g. previous disease, other drugs). *There is insufficient information to evaluate the causal relationship between the AE and the exposure. Conservatively, the AE should be considered*
Not related	There is no reasonable possibility that the AE is related to the drug(s). This implies that there is a plausible alternative cause for the AE that better explains the occurrence of the AE or that highly confounds the causal relationship between the drug(s) and the AE.

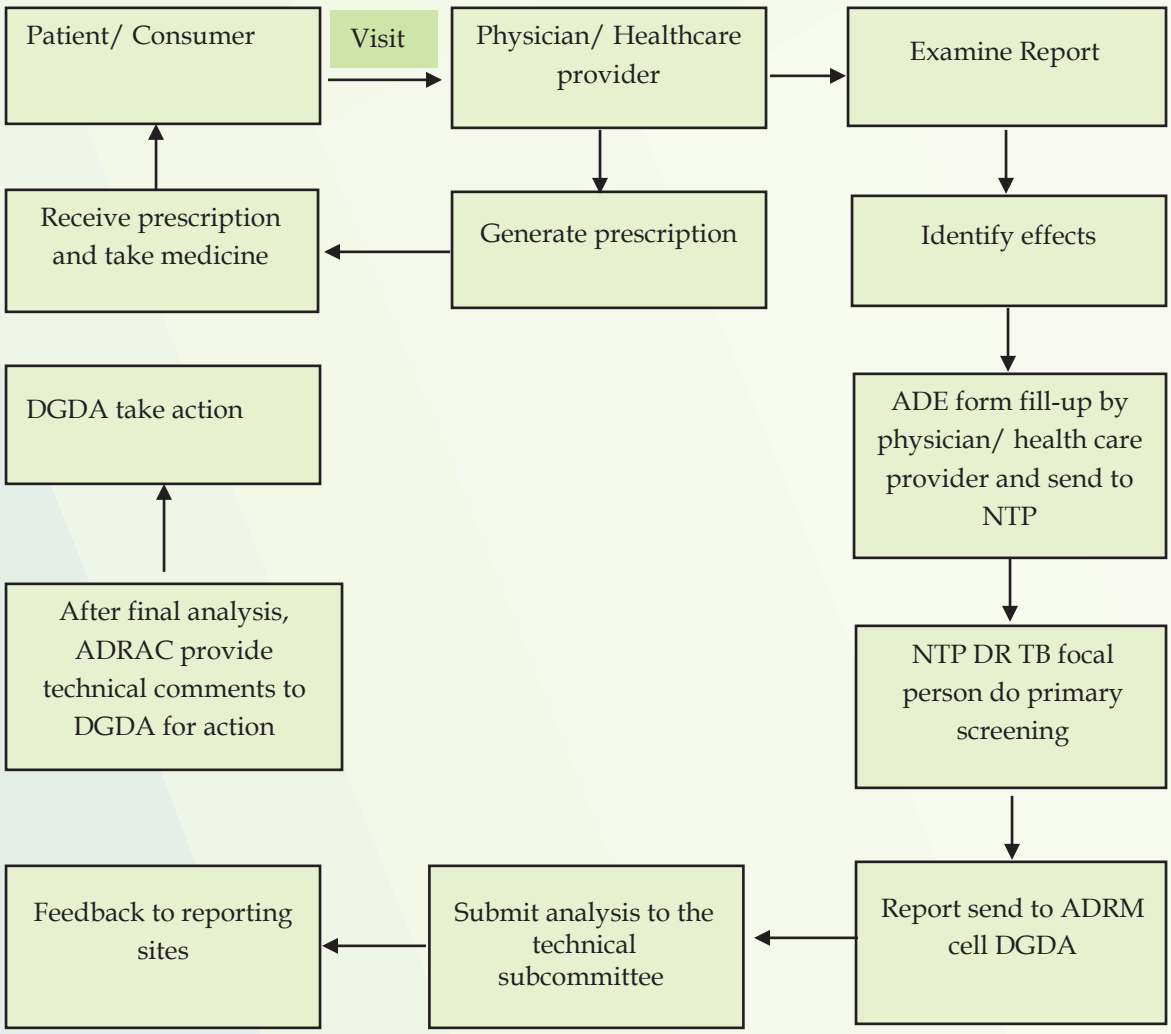
11.6 Adverse events of clinical significance or special interest

- All serious adverse events (SAEs).
- All AEs of special interest (suggested list):
  - Peripheral neuropathy (paraesthesia)
  - Psychiatric disorders and central nervous system toxicity (e.g. depression, psychosis, suicidal intention, seizures)
  - Optic nerve disorder (optic neuritis) or retinopathy Ototoxicity (hearing impairment, hearing loss)
  - Myelosuppression (manifested as anaemia, thrombocytopenia, neutropenia or leukopenia)
  - Prolonged QT interval (Fridericia correction)
  - Lactic acidosis
  - Hepatitis
  - Hypothyroidism
  - Hypokalaemia
  - Pancreatitis
  - Phospholipidosis
  - Acute kidney injury (acute renal failure).
- Adverse events leading to treatment discontinuation or change in drug dosage.
- Adverse events not listed above but judged as otherwise clinically significant by the clinician.

Setting up aDSM for patients on treatment for drug-resistant TB implies additional responsibilities and resource needs. In contrast to the surveillance of drug resistance and treatment outcomes, the active systematic monitoring of the occurrence of SAEs is relatively new

to TB programmes. Implementation, management and supervision necessary for aDSM should be systematically built into the Treatment initiation sites component of the TB programme and conducted in step with other activities related to patient care and monitoring.

11.7 Reporting flow of AEs from the DR-TB treatment Initiation Centre



Note: Any SAEs should be reported within 24 hours

11.8 The WHO-UMC Classification System for causality assessment

Causality term	Definition	Assessment criteria*
Certain	**Clearly caused by the exposure** There is **clear** evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	• Event or laboratory test abnormality, with **plausible time** relationship to drug intake • **Cannot** be explained by disease or other drugs • Response to withdrawal **plausible (pharmacologically, pathologically)** • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge **satisfactory**, if necessary
Probable/Likely	**Likely to be related to the exposure** There is evidence to suggest a **likely** causal relationship and the influence of other factors is unlikely.	• Event or laboratory test abnormality, **with reasonable time** relationship to drug intake • **Unlikely** to be attributed to disease or other drugs • Response to withdrawal **clinically reasonable** • Re-challenge **not required**
Possible	**May be related to the exposure** There is **some** evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	• Event or laboratory test abnormality, with **reasonable time** relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	**Doubtfully related to the exposure** There is **little** evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study regimen). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	• Event or laboratory test abnormality, **with a time to drug intake that makes a relationship improbable** (but not impossible) • Disease or other drugs provide **plausible explanations**
Conditional or Unclassified	**There is insufficient information** about the ADRs to allow for an assessment of causality.	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Un assessable or Unclassifiable	There is insufficient information about the ADRs to allow for an assessment of causality and **NO MORE is expected**.	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

CHAPTER 12

Adverse effects, suspected agents and suggested management strategies

MDR-TB can be deadly but the drugs used to treat the disease can be harmful in many ways.

This chapter focuses on the measures to promote patient safety that contribute to improving quality of care during the treatment of multidrug-resistant TB (MDR-TB), relieving unnecessary suffering.

- Adverse events (AEs) are more frequent in patients on second-line TB treatment than with first-line drugs and are the main cause of treatment interruption.
- Good counselling at the beginning of the treatment and careful monitoring and management are the basis of patient adherence.
- During the first baseline visit, comorbidities that are associated with a high risk of AEs, such as diabetes, kidney and liver failure, malnutrition, HIV infection, excessive alcohol and drug use, etc., should be identified and recorded.

12.1 AEs are classified according to their severity

Grade	Description
Grade 1: Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; no medical intervention or corrective treatment required.
Grade 2: Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL) *.
Grade 3: Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4: Life-threatening or permanent injury	Life-threatening consequences; urgent intervention indicated.

*DMID Nov 2007 and *CTCAE v.4.03 14-Jun-2010

*Division of Microbiology and Infectious Diseases and *Common Terminology Criteria for Adverse Events

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.2 Management of adverse effects

12.2.1 Dermatological disorders

Itchiness, Rash, allergic reaction and anaphylaxis

Suspected drugs: all

Steps to take:

- Symptoms generally resolve spontaneously in the first few weeks.
- In case of dryness of the skin, use moisturising cream.
- For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include
  - Antihistamines (diphenhydramine 25–50 mg or cetirizine 5–10 mg before medication)
  - Hydrocortisone cream for localized rash
  - Prescribe oral prednisolone in low doses (10–20 mg/day) if there is no improvement.
- Identify and discontinue the drug in case of serious AEs (e.g., Stevens Johnson syndrome and Lyell's syndrome).
- Once the rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause.

- Dry skin may cause itching (especially in diabetics), liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with Clofazimine.
- Eliminate other potential causes of allergic skin reactions (like Scabies or other environmental agents).

12.2.2 Gastro-intestinal disorders

Nausea and vomiting

Suspected drugs: Eto, Pto, PAS, Bdq, H, E, Z, Amx/Clv, Cfz, Dlm

Steps to take:

- Assess for danger signs including dehydration, electrolyte disturbances and hepatitis. Initiate rehydration therapy if indicated and correct any electrolyte disturbances. If there is blood in the vomit, check haemoglobin and treat for possible bleeding ulcers.
- Recommend taking a light meal before medication.
- Prescribe metoclopramide 10-20 mg 30 min before drug intake.
- If vomiting persists, prescribe ondansetron 2–8 mg 30 min before drug intake.
- Divide Pto/Eto dose into morning and evening provided DOT is ensured (dose-dependent effect; higher doses better tolerated by most patients in the evening).
- For patients concerned about possible nausea, prescribe diazepam 5 mg 30 min before medication.

Step-wise approach to manage nausea and vomiting

Phase 1: Adjust medications and conditions without lowering the overall dose:

- ❖ Give Eto/Pto at night
- ❖ Give Eto or PAS twice or thrice daily
- ❖ Give a light snack (biscuits, bread, rice, tea) before the medications
- ❖ Give PAS two hours after other anti-TB drugs

Phase 2: Start antiemetic(s):

- ❖ Metoclopramide 10 mg, 30 minutes before anti-TB medications.
- ❖ Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used.) For refractory nausea give 24 mg, 30 minutes before the dose can be tried.

Phase 3:

- ❖ Decrease dose of the suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.

Gastritis and abdominal pain

Suspected drugs: PAS, Eto, Pto, Cfz, FQs, H, E and Z

Steps to take:

- Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent.
- If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) prescribe omeprazole 20-40 mg in the evening (2 hours before or 3 hours after medication).
- Avoid the use of antacids as they decrease absorption of fluoroquinolones.
- For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days).
- Lower the dose of the suspected agent, if this can be done without compromising the regimen.
- Discontinue the suspected agent if this can be done without compromising the regimen.

Diarrhoea and/ or flatulence

Suspected drugs: PAS, Eto/Pto

Steps to take:

- Encourage patients to tolerate mild diarrhoea..
- Encourage fluid intake.
- Treat uncomplicated diarrhoea (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.
- Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe.

- Fever and diarrhoea and/or blood in the stools indicate that diarrhoea may be secondary to something other than the simple adverse effect of anti-TB drugs.

Hepatotoxicity

Suspected drugs: Z, H, Cfz, PAS, Eto/Pto, Bdq, FQ, Amx/Clv.

Hepatitis is characterized by nausea, vomiting, jaundice, scleral icterus, pale stool, and diminished appetite in the setting of elevated liver function tests.

Steps to take:

- Eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis being the two most common causes) and treat any that is identified.
- If ALT, AST ≤5 times the upper limit of normal and there is no jaundice, continue treatment and treat nausea and vomiting.
- If ALT, AST >5 times the upper limit of normal and/or jaundice (bilirubin>3 mg/dl), stop all drugs and assess the transaminases every week; if they return to 2 times the upper limit of normal, reintroduce the least hepatotoxic drugs (Am, E, Mfx, Cfz) and check transaminase levels. Then, reintroduce hepatotoxic drugs in the following order: Pto/Eto, H and Z and monitor transaminase levels every 3 days. Check transaminase values after introducing each drug.
- Reintroduce anti-TB drugs once liver enzymes return to baseline. Anti-TB drugs should be reintroduced in serial fashion by adding a new medicine every three to four days. The least hepatotoxic drugs should be added first, while monitoring liver function tests after each new exposure.
- If drug reintroduction leads to the return of hepatotoxicity, remove the culprit drug from the treatment and replace it by another if this is an essential drug. Do not replace H and Z.

- Mild elevation of liver enzymes, especially at baseline, may be related to TB rather than an adverse effect of treatment.
- Generally hepatotoxicity due to medications resolves upon discontinuation of suspected drug.
- In HIV coinfection, cotrimoxazole can be a cause of hepatotoxicity

Clinical management of elevated liver enzymes according to severity grading

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT (SGPT)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST (SGOT)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.

* NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

12.2.3 Osteoarticular disorders

Arthralgia

Suspected drugs: Z, Bdq, Fluoroquinolones

Steps to take:

- Initiate therapy with nonsteroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day).
- Lower the dose of the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen.
- Discontinue the suspected agent if this can be done without compromising the regimen.

Tendonitis (Achilles' tendon) and tendon rupture

Suspected drugs: Fluoroquinolones

Steps to take:

- If significant inflammation of tendons or tendon sheaths occur:
  - Consider stopping fluoroquinolones
  - Give a non-steroidal anti-inflammatory drug (ibuprofen 400 mg four times daily)
  - Rest the joint.
- If treatment failure is likely without the fluoroquinolone
  - Reduce dose if possible
  - Ensure joint is strictly rested
  - Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the fluoroquinolone.

12.2.4 Kidney disorders

Nephrotoxicity

Suspected drugs: Km, Am, Cm, E, Z, Cs.

Steps to take:

- Monitor serum creatinine and electrolytes frequently in patients receiving injectable. Patients with pre-existing kidney disease, diabetes, or HIV are at high risk of injectable nephrotoxicity and may be monitored more frequently.
  - Any increase of serum creatinine above normal limits should be considered acute renal insufficiency.
  - A doubling of serum creatinine above baseline, even if within normal limits, should be considered worrisome for acute renal insufficiency and monitored carefully.
- Repeat electrolytes if necessary.
  - Injectable nephrotoxicity may be associated with injectable-induced electrolyte wasting. For example, it is possible to see elevated creatinine and severe hypokalemia/hypo magnesemia at the same time.
  - The etiology of this phenomenon is unclear, but it may occur more often in HIV co infected patients.

- Discontinue the suspected drug (usually the injectable). If the acute renal failure is severe, then stop all drugs.
  - Nephrotoxicity due to the injectable is frequently reversible after the injectable is stopped, but permanent damage can result if it is not detected early.
  - If the acute renal insufficiency is severe or resolving slowly, the dose of other renally excreted drugs should be adjusted.
- Consider other contributing etiologies (prerenal, intrinsic renal, and postrenal).
- Follow serum creatinine and electrolytes closely until the creatinine has returned to baseline or has stabilized.
- Consider reintroducing the injectable with an intermittent dosing schedule (two or three times a week) if the drug is essential to the regimen.
  - Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen.
  - Consider strict weight-based dosing of the injectable if the patient's weight is less than 50 kg.
  - Suspend the injectable permanently if the nephrotoxicity recurs despite intermittent dosing, and add additional anti-TB drugs to reinforce the regimen

- Acute kidney injury is characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).
- The injectable (aminoglycosides and capreomycin) are the most common cause of acute renal failure in MDR-TB patients. Capreomycin may be less nephrotoxic than the aminoglycosides.
- Injectable nephrotoxicity is often asymptomatic in the early stages and can only be diagnosed with routine laboratory monitoring. End-stage renal failure may present with oliguria/anuria or signs of volume overload including peripheral edema and shortness of breath. Mental status changes due to uremia or electrolyte abnormalities are a late symptom.

Clinical management of acute kidney injury according to severity grading

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Acute Kidney Injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5- 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated
Action	Consider stopping injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF).	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF) or substitute with a non-nephrotoxic drug.	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF) or substitute with a no nephrotoxic drug.	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF) or substitute with a non-nephrotoxic drug.

* NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

Electrolyte disturbances (hypokalaemia and hypomagnesaemia)

Suspected drugs: Cm, Km, Am, S

- Hypokalemia and hypomagnesemia are often asymptomatic.
  - Moderate cases may present with fatigue, myalgia, cramps, paresthesia, lower extremity weakness, behavior or mood changes, somnolence, and confusion.
  - Severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias.
- Hypokalemia and hypomagnesemia are common in patients receiving MDR-TB treatment. Common causes in MDR-TB patients are:
  - Vomiting and diarrhea.
  - Renal tubular toxicity from the injectable (probably more common in capreomycin than the aminoglycosides).
  - The injectables can cause a syndrome of electrolyte wasting, including potassium, magnesium, calcium, and bicarbonate.
  - This syndrome is more common and severe in HIV coinfected patients; hospitalization and aggressive serum electrolyte monitoring and correction may be necessary.

Steps to take:

- Monitor serum potassium, magnesium, and calcium frequently in patients with vomiting/diarrhea and patients receiving injectables.
- Check for signs of dehydration in patients with vomiting and diarrhea. Start oral or intravenous rehydration therapy immediately until volume status is normal
  - Dietary intake of potassium should be encouraged. Bananas, oranges, tomatoes are good sources of supplementation.
  - Oral potassium and magnesium should be administered either two hours before or four to six hours after fluoroquinolones as they can interfere with fluoroquinolone absorption.
  - Oral potassium can cause nausea and vomiting. Oral magnesium can cause diarrhea.
  - Amiloride 5 to 10 mg PO daily or spironolactone 25 mg PO daily may decrease potassium and magnesium wasting due to the injectable and may be useful in severe cases that are refractory to replacement therapy.
- Replete potassium and magnesium.
  - Hypokalemia may be refractory if concurrent hypo magnesemia is not also corrected.
  - If unable to check serum magnesium, give empiric oral replacement therapy in all cases of hypokalemia with magnesium gluconate 1000 mg twice daily.
- In all cases of detected serum electrolyte disturbances (Grade 1-4) obtain an electrocardiogram as soon as possible and then weekly until potassium and other electrolytes return to normal.
- Drugs that prolong the QT interval should be discontinued in patients with evidence of QT interval prolongation.
- Electrolyte abnormalities are reversible upon discontinuation of the injectable. Even after suspending the injectable, it may take weeks or months for this syndrome to disappear, so electrolyte replacement therapy should continue for several months after completion of the injectable phase of MDR-TB treatment.

Clinical management of hypokalemia according to severity grading

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Hypokalemia	3.4 - 3.0 mmol/L	2.9 - 2.5 mmol/L	2.4 - 2.0 mmol/L or intensive replacement therapy or hospitalization required	< 2.0 mmol/L or abnormal potassium with paresis, ileus or life threatening arrhythmia
Action	Continue injectable. Start oral potassium replacement therapy. Check serum magnesium and replace if necessary.	Continue injectable. Start aggressive oral potassium replacement therapy. Replace magnesium.	Consider stopping the injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Clinical management of hypo magnesemia according to severity grading

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Hypomagnesemia	0.70-0.60 mmol/L	0.59-0.45 mmol/L	0.44-0.30 mmol/L	<0.30 mmol/L
Action	Start oral magnesium replacement therapy.	Start aggressive oral magnesium replacement therapy.	Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.	Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Potassium replacement therapy

Potassium level (mmol/L)	**Dosing**	**Monitoring frequency**
>3.4	None	Monthly
3.3-3.4	40 mmol PO in 2-3 divided doses daily	Monthly
2.9-3.2	60-80 mmol PO in 3 divided doses daily	Weekly
2.7-2.8	60 mmol PO every eight hours	One to two days
2.5-2.6	80 mmol PO every eight hours	Daily
< 2.5	10 mmol/hour IV and 80 mmol PO every six to eight hours	One hour after infusion, every six hours with IV replacement

Note: The normal preparation of a potassium chloride infusion is 40 mmol (3 ampoules) in 1L of NaCl 0.9% infused over 4 hours. Do not exceed an infusion rate of 10 mmol/hour (250 mL/hour). Potassium chloride 10% (100mg/ml) ampoules = 1g per ampoule = 13.4 mmol. Potassium chloride controlled release tablets of 600mg = 8mmol/tablet.

Magnesium replacement therapy

Magnesium level (mmol/L)	Total daily dose	Monitoring frequency
>0.7.0 or more	None	Monthly
0.60-0.70	1,000 mg-1,200 mg	Monthly
0.45-0.59	2,000 mg	One to seven days
< 0.45	3,000 mg-6,000 mg	Daily

Note: Quantities greater than 2,000 mg are usually given IV or IM. The normal preparation is magnesium sulfate 2 g in 100 mL or 4 g in 250 mL of normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 mL administered over one to two hours, 4 g in 250 mL administered over two to four hours).

12.2.5 Thyroid disorders

Hypo-thyroidism

Suspected drugs: Eto/Pto, PAS

- Ethionamide (or prothionamide) and PAS have a direct toxic effect on the thyroid that interferes with thyroid hormone synthesis. The exact incidence of hypothyroidism is unknown, but it is probably more common than traditionally thought.
- Patients may develop symptoms as soon as a few weeks after exposure to offending medications.
- Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as depression and inability to concentrate. Thyromegaly and delayed deep tendon reflexes may be encountered on exam

Steps to take:

- Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner:
  - Young healthy adults can be started on 75–100 mcg daily
  - Older patients should begin treatment with 50 mcg daily
  - Patients with significant cardiovascular disease should start at 25 mcg daily.
- Children clear thyroxine faster than adults, so daily replacement doses may be higher.
  - Children (4-15 years): 4 mcg/kg/day (maximum dose is 200 mcg).
  - Infants (1-3 years): 10-15 mcg/kg/day (maximum dose is 200 mcg).
- Monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions.
- Hypothyroidism is reversible upon discontinuation of ethionamide/prothionamide or PAS. As a result, thyroid hormone replacement may be stopped several months after completion of MDR-TB treatment.

Clinical management of hypothyroidism according to severity grading

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL hospitalization	Life-threatening consequences; urgent intervention indicated

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Action	Continue anti-TB drugs.	Continue anti-TB drugs. Start thyroxine.	Continue anti-TB drugs. Start thyroxine.	Stop all anti-TB drugs. Start thyroxine.

*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

12.2.6 Haematological disorders

Myelosuppression (anemia, thrombocytopenia, or neutropenia)

Suspected drugs: Lzd (Possible other causes: AZT, Cotrimoxazole.)

- The mean corpuscular volume (MCV) may be helpful to assess whether anemia is normocytic versus microcytic versus macrocytic. Macrocytic anemia is more likely to be due to AZT, but AZT can also induce a normocytic anemia.
- If the patient has thrombocytopenia or neutropenia, this is more likely to be due to linezolid. AZT can do this, but it is rarer.
- Acute blood loss (occult GI bleeding from a peptic ulcer) can cause anemia.
- Other causes of anemia (TB, iron-deficiency, etc.) are possible, but less likely to occur in the middle of treatment, especially if the patient is clinically improving.

Steps to take:

- Stop linezolid if myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs. Consider restarting with a lower dose of linezolid (300 mg instead of 600 mg) if myelosupression resolves and if linezolid is considered essential to the regimen.
- Monitor full blood counts regularly.
- Hospitalize the patient and consider transfusion or erythropoietin (EPO) if the myelosuppression is severe.

Clinical management of myelosuppression according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL
Platelets decreased	99,999 - 75,000 /mm^3	74,999 - 50,000 /mm^3	49,999 - 20,000 /mm^3	< 20,000 /mm^3
Action	Monitor carefully, and Consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly).	Monitor carefully, and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly); in case of Grade 2 neutropenia, Stop Lzd immediately. In case of Grade 2 Anemia, consider EPO. Restart at reduced dose once toxicity has	Stop Lzd immediately. In case of Grade 3 Anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd Immediately. Consider hemotransfusion or EPO. Restart at reduced dose once toxicity has decreased to Grade 1.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007

12.2.7 Neurological disorders

Peripheral neuropathy

Suspected drugs: Cs, Lzd, H, S, Km, Amk, Cm, H, Fluoroquinolones, rarely Pto/Eto, E

Steps to take:

- Peripheral neuropathy is a common side effect of MDR-TB treatment caused by drug toxicity to the nerves of the peripheral nervous system.
- Check for possible comorbidities: diabetes, HIV, alcohol abuse, hypothyroidism, malnutrition (no contraindications to anti-TB treatment in case of comorbidities).
- All patients taking isoniazid should receive 50 mg of pyridoxine daily; all patients taking Cs should receive 50 mg of pyridoxine daily for every 250 mg of Cs
- Many patients experience improvement when offending drugs are suspended, especially if the symptoms are mild.
- Symptomatic relief:
  - Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
  - Tricyclic antidepressants have also been used successfully. Start amitriptyline 25 mg at bedtime. The dose may be increased to a maximum of 150 mg daily for refractory symptoms. If possible, the co-administration of amitriptyline and Lzd should be avoided due to potential risk of serotonergic syndrome.
  - Carbamazepine may also be effective in relieving pain and other symptoms of peripheral neuropathy. Carbamazepine is a strong inducer of CYP3A4 and should not be used with bedaquiline or delamanid.
- The neuropathy associated with linezolid is common after prolonged use and often extremely painful and irreversible. For this reason, linezolid should be immediately stopped and not reintroduced when symptomatic neuropathy develops (grade 2 or above). Consider additional anti-TB drugs to reinforce the regimen.

Optic neuritis

Suspected drugs: Lzd, E, Eto/Pto, Rifabutin, Cfz, H, S.

- Optic neuritis is inflammation of the optic nerve eventually resulting in permanent vision loss. The first sign of optic neuritis is usually the loss of red-green color distinction. This is best tested using the Ishihara test. Other symptoms include central scotomas.
- Linezolid is by far the most common cause of optic neuritis amongst all of the TB drugs
- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention. Patients with advanced kidney disease are also at increased risk for optic neuritis.

Steps to take:

- Do not restart the suspected causative drug (linezolid or ethambutol).
- Refer patient to an ophthalmologist for immediate evaluation and management.
- Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.
- Consider additional anti-TB drugs to reinforce the regimen.

Seizures

Suspected drugs: Cs, H, Fluoroquinolones

Steps to take:

- Discontinue Cs, the drug likeliest to be responsible.
- Always check creatinine levels in patients with sudden onset of seizures. Compromised renal function may cause increased serum concentrations of Cs.
- Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride
- Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used).
- Increase pyridoxine to the maximum daily dose (200 mg per day).
- When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.
- Replace Cs by Pto/Eto (or PAS) if not previously used in a failed regimen

12.2.8 Psychiatric disorders

Depression

Suspected drugs and condition: Psychological and socio-economic conditions, Cs, H, FQs.

Steps to take:

- Assess psychological and socio-economic conditions.
- Initiate individual counselling (or group counselling if the patient is sputum smear and culture negative).
- When depression is more significant, initiate antidepressant therapy (amitryptiline, fluoxetine or similar). Tricyclic antidepressants and selective serotonin reuptake inhibitors should be given together and should not be given to patients on linezolid.
- Lower the dose of the suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and ethionamide to 500 mg daily to see if the depression is lessened is a common strategy).
- Discontinue the suspected agent if this can be done without compromising the regimen.

Psychosis

Suspected drugs: Cs, H, fluoroquinolones

Steps to take:

- Stop the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high dose isonizaid.
- If moderate to severe symptoms persist, initiate antipsychotic therapy (haloperidol).
- Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others.
- Increase pyridoxine to the maximum daily dose (200 mg per day).
- Lower the dose of the suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising the regimen.

- Discontinue the suspected agent if this can be done without compromising the regimen.
- Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered off. If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist trained in the adverse effects of second-line anti-TB drugs.

Suicidal ideation

Suspected drugs: Cs, H, Eto/Pto

Steps to take:

- Hospitalize the patient and put under 24-hour surveillance.
- Discontinue cycloserine.
- Request psychiatric consultation.
- Initiate antidepressant therapy.
- Lower the dose of Eto/Pto to 500 mg daily until the patient is stable.

12.2.9 Ototoxicity

Hearing impaired

Suspected drugs: S, Km, Am, Cm

- Hearing impaired is a disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures
- The injectables can cause damage of the hearing apparatus of the inner ear, including the cochlea, vestibule, semicircular canals, and cranial nerve VIII. Symptoms include hearing loss and tinnitus, as well as vestibular symptoms such as disequilibrium and vision problems.
- Hearing loss and vestibular dysfunction are generally not reversible upon discontinuation of therapy.

Steps to take:

- Document hearing loss and compare with baseline audiogram if available
- Perform a monthly assessment of hearing loss and balance. Audiometry is helpful in detecting early high-frequency hearing loss that the patient may not even be aware of.
- If the patient is experiencing hearing loss, stop the injectable and replace it with a non ototoxic drug (consider the use of new (BDQ or Dlm) and repurpose (Lzd) drugs
- If there is no other non-ototoxic drug available or effective, consider decreasing the dosing frequency of the injectable to two to three times a week. Even when non-ototoxic drugs are not available, stopping the injectable can be considered based on the patient's desire to maintain hearing.
- If moderate or severe vertigo, tinnitus (ringing in the ears) or vestibular disturbances arise, with or without significant hearing loss, consider decreasing frequency or stopping the injectable agent.

12.2.10 Cardiac disorders

Prolonged QT interval

Suspected drugs: Cfz, Bdq, Mfx, Dlm, Lfx.

Steps to take:

- Stop all QT prolonging drugs immediately.
- Hospitalize and consider continuous electrocardiac monitoring for Grade 3. Hospitalization should occur in a facility capable in the management of Torsades de Pointes arrhythmia.
- Check potassium, calcium and magnesium levels. Electrolyte levels should be maintained in the normal range in any patients with an elevated QT interval.
  - It is suggested to maintain potassium levels of more than 4 mEq/l and magnesium levels of more than 1.8 mg/dl.
- Check a TSH and treat any hypothyroidism found.
- Once stable (QTcF interval below 450 and normal electrolytes), critical QT prolonging anti-TB drugs can be added back:
  - If the patient was on moxifloxacin consider using levofloxacin instead.
  - If the patient was on clofazimine consider suspending it permanently if not critical to the regimen.
  - If the patient is on bedaquiline and it is considered critical to the regimen, consider adding the drug back to the patient's regimen while suspending all other QT prolonging drugs (with the exception of stopping ART, which should not normally be suspended in the management of QT prolongation).
  - If the patient is on delamanid and it is considered critical to the regimen, consider adding the drug back to the patient's regimen while suspending all other QT prolonging drugs (with the exception of stopping ART, which should not normally be suspended in the management of QT prolongation).

Clinical management of prolonged QT interval according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Electrocardiogram QT Corrected Interval Prolonged	QTcF 450 – 480 ms	QTcF interval 481 – 500 ms	QTcF ≥ 501 ms on at least two separate ECGs.	QTcF ≥ 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes

* NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

when multiple ECGs are recorded on a same day, average of the QTcF measures should be used to determine the grade.

12.2.11 Metabolic and Hormonal disorders

Lactic acidosis

Suspected drug: Lzd.

Steps to take:

- Symptoms: abdominal pain, nausea, vomiting, rapid deep breathing, general weakness.
- Stop Lzd and replace with another drug

Gynaecomastia

Suspected drug: Eto/Pto

Steps to take:

- Breast enlargement can be a troublesome side effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported.
- Encourage patients to tolerate this side effect.

CHAPTER 13

Treatment Delivery and Adherence

Multidrug-resistant TB (MDR-TB) often affects the poorest and most marginalized members of a society. Their quality of life and financial situation are further aggravated by the disease, due to the adverse drug reactions produced by its treatment, the catastrophic costs they incur while seeking care and adhering to treatment, and the stigma attached to the disease and subsequent discrimination. Treatment support of patients using a patient-centred approach is needed to maximize treatment adherence and enable early detection of patients who are not responding to treatment.

DOT administered by trained providers or health care workers is conditionally recommended over DOT administered by family members or unsupervised treatment. Video (virtual) observed treatment (VOT) can replace DOT when the technology is available, and can be appropriately organized and operated by health care providers and patients. Apart from DOT, several other interventions are considered important to promote treatment adherence and a patient-centred approach (e.g. nutritional support, financial incentives and reimbursement of transport fees), psychological support, home visits, use of information technology, treatment monitoring. Moreover, counselling and patient education on the disease and on treatment.

In this chapter, the patient-centred care approach to direct observation of therapy and the social support framework for programmatic management of drug-resistant TB, both aimed at improving quality of life of DR-TB patients and enabling their adherence to treatment, are discussed.

13.1 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 and poor treatment outcomes. 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 conditions to be screened for are listed in below. Conditions to be screened for an initial medical evaluation:

- Malnutrition
- Diabetes mellitus
- Hypertension
- Renal insufficiency
- Acute or chronic liver disease
- Thyroid disease
- Hearing/visual disturbance
- Mental illness
- Drug or alcohol dependence
- Pregnancy
- Breast feeding/Lactating women
- Seizures

- Bowel disorder e.g. IBS
- HIV infection (option of HIV testing)

13.2 Treatment initiation

Once, the most appropriate treatment regimen has been decided,

- The patient will be provided with comprehensive counseling and education on the treatment duration, potential side effects and whom to consult, TB infection control, etc.
- At baseline, i.e., before initiation of treatment, a clinical evaluation will be done including symptoms, physical examination, weight, and examinations including audiometry, visual acuity, ECG and chest x-ray (CXR).
- Bacteriologic examinations will include baseline smear, culture, SL-LPA and phenotypic SL DST.
- Other laboratories will include a complete blood count, potassium, renal and liver functions tests, TSH, etc. (See chapter 11)

13.3 Hospital Based Care

- The delivery of DR TB treatment may start with a short hospitalization. Patients started on the STR or LTR are hospitalized to do baseline assessment and initiating an appropriate regimen.
- Criteria and duration of hospitalization will follow the clinical conditions, and physical weakness, severe co-morbidities such as heart disease, diabetes mellitus, HIV, renal failure, hepatitis, severe anemia, etc., moderate to severe side-effects, or treatment adherence problems.

Patients may also start ambulatory treatment or initiate at home for some special conditions with comprehensive treatment and care by an experienced DR-TB team and an appropriate follow-up and care system in place. Patient will receive daily DOT from a well-trained Drug-Resistant TB DOT Provider (DR TB DOT Provider).

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.

During the period of hospitalization, the patient is closely monitored and for any drug reactions. Smear microscopy should be done weekly and then move to ambulatory care following below criteria:

Criteria for Discharge of Patients from DR TB treatment Initiation Center

- The patient is smear negative (at least two consecutive smears negative one week apart) and clinically improving
- The patient is tolerating drugs well (no major adverse drug reactions observed)
- The patient has completed at least 2-4 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 center 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 outpatient DR TB team)

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

- Discharge certificate from the facility.
- DR TB Identity Card.
- Second Line Anti TB drugs (SLD), required ancillary drugs (if available) with "Chalan"
- Copy of the Treatment Card.
- Patient Education Material on DR TB.
- 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 needs to be in place to deliver comprehensive home-based care to the patient.

13.4 Community Based Care

After the hospitalization period, the patient will be prepared for decentralization.

- DR TB treatment initiation center will convey information to relevant outpatient DR TB team regarding the discharge of patient to take necessary action for smooth transfer and continuation of community based PMDT care (cPMDT).
- The upazila outpatient DR TB team will identify the community DR TB DOT provider and provide necessary training for patient care.
- DR TB DOT provider will receive the patient along with necessary documents and logistics (e.g. discharge certificate, copies of the Treatment Card and ID card, Chalan of medicine, follow up documents, patient education materials) and need to submit the documents and logistics to the team at upazila.
- Daily supervised treatment be done by the assigned DR TB DOT Provider, with monthly evaluations by the clinical officer in-charge at the DR TB Treatment Initiation Center or at the trained Upazila Health Complex (UHC).

- DOT will take place at the patient's home.
- Essential medications for other medical conditions, including ART, will be given together with the DR-TB drugs as far as medically possible and practically feasible.

- The patient will visit the DR-TB treatment Initiation Center or UHC monthly, at which time tests will be conducted and adverse events will be monitored and documented.
- After each visit, the patient will be reminded about the next visit schedule, the tests due,

and will be given a sputum cup for specimen collection early morning prior to the next visit.

- When a patient's condition demands in-patient care after discharge, he will be hospitalized. He will again resume ambulatory treatment upon discharge, as described above.

13.5 Patient Education during discharge

Patient education will start from the beginning of the treatment and should be repeated when the patient starts community based care. Some patients will start treatment in the community and will need a number of sessions with members of the Outpatient DR-TB Team. Ongoing education will be continued in every visit. The hospital or outpatient team member will prepare the patient for community-based care

13.6 Out-patient DR-TB Team (see the annex 3)

Out-patient DR-TB Team should be set up at the respective center when a patient gets discharged from the hospital/ treatment initiation center to the community to continue the treatment. There will be –

- One Divisional supervisory DR TB Team
- One District based supervisory DR-TB team
- Upazila out Patient DR TB Team

Training the Out-patient DR-TB Team

The National PMDT Committee is responsible for planning and organizing training for Out-patient DR-TB Teams. The trainings are of

- Three-days intensive training for all members of the Outpatient DR TB Team
- One-day orientation for the members of supervisory DR-TB team.

13.7 DR-TB DOT Providers

DR-TB DOT providers may be selected from existing pool of community workers. This pool has already received some training in health and TB. The choice in order of preference is:

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

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

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

Selection criteria for DR-TB DOT provider: Criteria for selection of DR TB DOT provider:

- is acceptable to the patient;

- is active, not too old, and able to work hard;
- is available to support the patient at any time during the day or night;
- has a stable living situation near the patient's house;
- has basic literacy skills at least to read and write Bangla and English
- has received DR-TB specific training;
- is motivated to care for DR-TB patients;
- is willing to do a home visit every day
- is committed to support the patient for the full length of treatment;
- Should not be immune-suppressed. (eg: HIV AIDs, Diabetes mellitus etc.)
- Should have a mobile phone for easy communication

Note: It is not recommended to use family members as DR-TB DOT provider. The family relationship may interfere with the ability to monitor DR-TB treatment. For DR-TB Patients the DOT will be given at the patient's home daily by the DR-TB DOT provider. If necessary, he/she may need to go patient's house twice a day.

13.8 Responsibilities of DR-DOT Providers

- Supervise all doses of drugs and keep records on DR-TB treatment card.
- Report any side-effects.
- Accompany patient to all medical consultations.
- Attend refresher training.
- Collect and transport follow up sputum specimen (For STR: monthly throught the whole treatment period and for LTR: monthly in the initial phase and every three months in the continuation phase) to the respective reference laboratory through UHC/DOTS Centers
- Provide health education to the family members about cPMDT patients

13.9 Training of DR-TB DOT Providers

Specific training for DR-TB DOT Providers to provide DOT can be done in a few days. The followings are based on the WHO's Training plan for a new community DR-TB DOT Provider which will be used as the foundation training for DR-TB DOT Providers.

- Review basic information about TB
- Review role and responsibilities of the DR-TB DOT Provider
- Teach how to read the treatment card
- Teach how to fill up the treatment card
- Teach about adverse drug effects (ADR)
- Teach how to encourage the patient to continue TB treatment.
- Teach what to do if a patient missed a scheduled treatment.
- Teach how to obtain a resupply of drugs.
- Teach what to do if the patient or the DR TB DOT Provider is away for a few days.
- Teach when to send the patient back to the health facility for follow-up.
- Teach how to control TB Infection

13.10 Psychosocial support

The delivery of psycho social support services is essential in any programmatic management of drug-resistant TB that is grounded in the consideration of human rights, ethical standards, financial risk protection, and that pursues high effectiveness in efforts to prevent and treat MDR-TB. Social support may also contribute to improving the quality of life of patients. In many cases it also makes a difference to enable the patient and family to access health care.

- Patients who received education or educational counselling had better rates of treatment success, treatment completion, cure and treatment adherence, and had lower rates of loss to follow up.
- Patient education could include oral or written education via health-care workers or pharmacists. The education could be during hospitalize period/ time at discharge from the intensive phase of therapy or at each presentation for follow-up care.
- The educational session might include only the health-care worker or it might involve the patients' social network and family members. It is important to make sure that education and counselling are done in a culturally appropriate manner. Additionally, specific marginalized populations may require special educational efforts.

Although treatment of DR TB is completely free of cost, isolation from the family during initial hospitalization and adverse events of drugs make their mental health condition very poor. Patients suffer considerable distress to deal with the disease and adhere to long treatment course that increase risks of morbidity and mortality

Since tuberculosis is a long-term medical condition affecting personal, family and social life, a multidimensional psychological (e.g. patient and family counseling, mental health first aid training to caregivers, and life skill training), social (e.g. group activities), and medical (i.e. proper medication) intervention approach is likely to benefit patients most.

Psychological support includes:

- Proper counseling of DR TB patients throughout the treatment duration
- Assessment of patients' psychological (i.e. depression, anxiety, self-esteem, changing attitudes to disease and life), behavioral (i.e. adaptation to illness behavior), and sociological dimensions (i.e. gaining social support)
- Training of health service providers (i.e. nurses) on mental health to become more sensitive to (e.g. changes in knowledge and attitude) and better able to support DR-TB patients' psychosocial needs.
- Vocational training on income generation activities (preparing handicrafts through paper craft, clay art and glass paints etc.).

13.11 Socio-economic support to DR TB patient

While taking medicines regularly is the most important part of DR-TB treatment, a nutritional diet also plays a vital role to cure DR-TB patients. The DR-TB DOT Provider and Outpatient DR-TB Team should educate the patient what are the foods to eat as nutritious diet. The monthly socio-economic support is meant to allow the patient to take nutritious diet. If use of the monthly nutritional allowance is found being abused, providing food basket can be considered.

Every patient on DR-TB treatment will receive the following socio-economic support and transportation allowance:

- Socio-economic package will be provided to the patient while patient will be in the community and monthly nutritional support should start from the day of enrolment even if the patient is in hospital.
- DR TB patient along with accompanied health personnel will receive actual transportation cost when he/she goes to reference NTRL/ RTRL/ Xpert sites/ DR-TB hospitals for follow-up
- Every DR TB patient will receive support for treatment monitoring investigations (eg. CBC, RBS, Audiometry, ECG, TSH, S. Creatinine, S Bilirubin, SGPT, Electrolyte etc.)

13.12 Social support to DR TB DOT provider

During the monthly evaluation of the patient, a member of the UHC Team will evaluate each DR-TB DOT Provider. If performance is acceptable, the DR-TB DOT Provider will receive the monthly incentive.

- DR-TB DOT Providers will not be paid unless he/she performance is satisfactory.
- If performance is not acceptable for consecutive two months, the Out-patient DR-TB Team will immediately find an alternate DR-TB DOT Provider for the patient.
- The incentive per month to the designated DR-TB DOT Provider for each patient under his/her supervision
- It is recommended that one DR-TB DOT Provider should not be responsible for more than two patients.
- The incentive and transportation cost will be distributed during the monthly visit by a member of the respective NGO.
- If a DOT center (UHC/Urban) sends sputum sample of presumptive DR TB to NTRL/ RTRL/ Xpert sites for diagnosis or follow-up, in that case respective DOT center will receive actual courier cost.

CHAPTER 14

Drug Resistance and Infection Control

Infection control is of paramount importance in the management of DR-TB. The best infection control is treatment. Early diagnosis and rapid initiation of treatment should be the priority for any TB control program. All facilities treating DR TB patients must comply with adequate infection control measures. Ensuring implementation of infection control policy in all healthcare facilities, at public/ private/ household level and in congregate settings (correctional facilities, military barracks, homeless shelters, refugee camps, student dormitories and nursing homes, among others) is essential. This will help prevent transmission before diagnosis up to initial stages of treatment till the patient has culture converted and turned noninfectious.

Risk factors for TB transmission:

- The infectiousness of the patient (smear positivity, presence of cavitation, intensity and frequency of cough).
- Absence of treatment or non-supervised treatment.
- Individual and acquired predisposition: HIV, malnutrition, diabetes, children etc.

Transmission depends on:

- The number of bacilli produced by the patient.
- The number of persons in the exposed area (poor circulation of air).
- The degree of ventilation in the exposed area.
- The duration of exposure.

Infection control measures: Generally the infection control measures are divided into

1. Administrative control,
2. Environmental control
3. Personal protective equipment

Priority	Type of measure	Objectives
First	Administrative control	Reduce exposure of all people within the area where there may be exposure to TB.
Second	Environmental control	Reduce concentration of infectious particles.
Third	Individual respiratory protection	Protect health personnel in areas where the concentration of particles cannot be reduced.

14.1 Administrative controls

Administrative controls are comprised of policies and procedures that are intended to promptly identify, separate and treat infectious cases. 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.

Outpatient settings:

- Screen for respiratory symptoms as early as possible upon patient' arrival at the health

care facility.

- Separation and triaging of patients with cough
- Well ventilated waiting area - preferably through an open corridor/s
- Provide face mask (surgical) to the patient with respiratory symptoms
- Fast-track patients with respiratory symptoms
- Sensitization of staff, patients and their families, visitors.
- Monitoring for TB among health care workers involved in TB care.

Inpatient settings:

- Establish separate rooms, wards or areas within wards for patients with infectious respiratory diseases, such areas should promote minimum mixing with other patients.
- Educate inpatients on cough hygiene
- Instruct the patient to stay in the ward and not to roam around and mingle with other patients
- Train the health workers on respiratory protection
- Educate patients on respiratory hygiene and the importance of covering their mouth

At home:

- Advise patients to minimize contact with infants, children and immunocompromise family members (if any) in the initial months of treatment.
- Advise the patient to use surgical mask and about cough etiquette
- Advise patients to sleep in a separate room in the initial months of treatment if at all possible.
- When possible, patient should stay outside, to avoid infection
- When the patient is inside any room, windows should be open to allow for maximum ventilation
- Provide N-95 masks to DR TB DOT Providers to use while visiting the patient in the initial months of treatment
- Contact tracing of family members

Facility Risk Assessment

Health-care and congregate settings should conduct an annual evaluation of the risk for transmission of M. tuberculosis. The risk assessment determines the type of administrative, environmental, and respiratory-protection controls needed by examining the

- Number of patients with TB disease in the setting;
- Promptness of detection, isolation, and evaluation of patients with suspected or confirmed TB disease;
- Evidence of transmission of M. tuberculosis in the setting; and
- Community rate of TB disease

Health-care and congregate settings should conduct an annual evaluation of the risk for transmission of M. tuberculosis.

Risk Classification

Risk Classification	Need for Testing	Frequency of Testing
Low risk	Should be used for settings in which persons with TB disease are not expected to be encountered	Exposure to M. tuberculosis in these settings is unlikely, and further testing is not needed unless exposure has occurred.
Medium risk	Should be used for facilities in which the risk assessment has determined that HCWs will possibly be exposed to persons with TB disease.	Repeat testing should be done annually.
Potential ongoing transmission	Should be temporarily assigned to any setting where there is evidence of person-to-person transmission of M. tuberculosis in the past year.	Testing should be repeated every 8 to 10 weeks until there is no evidence of ongoing transmission.

14.2 Environmental controls

The second level of hierarchy is the use of environmental controls to prevent the spread and reduce the concentration of droplet nuclei. In order to reduce the number of infectious airborne droplets in health facilities, it is necessary to ensure good ventilation of waiting and consultation rooms and hospital wards. Environmental controls consist of engineering technologies that are designed to prevent the spread and reduce the concentration of infectious TB droplet nuclei in ambient air. The technologies include

Ventilation technologies:

- Natural ventilation: Natural ventilation relies on cross ventilation in a building designed for good air exchange open windows on opposite walls, interior hallways designed so that air is not trapped and waiting areas are open at least on three sides.
- Mechanical ventilation: Mechanical ventilation refers to the use of equipment to circulate and move air in a building. Mechanical ventilation should be used by hospitals, TB clinics, and other health-care and congregate setting. Mechanical ventilation consists of
  - Local exhaust ventilation: External hoods; Booths; and Tents.
  - General ventilation: Dilution of contaminated air, Removal of contaminated air, Control of airflow patterns
  - High efficiency particulate air filtration (HEPA)
  - Ultraviolet germicidal irradiation (UVGI)

14.3 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.

Respiratory protection controls

- Implementing a respiratory-protection program;
- Training HCWs on respiratory protection; and
- Educating patients on respiratory hygiene and the importance of cough etiquette

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 attendant's 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, presumptive and documented cases of XDR TB
Implement home-based infection control protocols
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 Equipment
Wearing of respirator (e.g: N 95, FFP2 etc) by the healthcare provider while seeing DR TB patients who are smear positive and presumptive DR TB cases and UVGI fixtures

Airborne Infection Control -recommendation for DR-TB Wards

Located away from the other wards, with adequate facilities for hand washing and good maintenance and cleaning.
Adequate ventilation (natural and/or assisted ventilated) to ensure>12ACH at all times.
Adequate space between 2 adjacent beds, at least 6feet
Cough hygiene should be promoted and practice should be ensured through patients and staff training, on-going reinforcement by staff
Adequate sputum disposal, with individual container with lid, containing 5% phenol, for collection of sputum
All staff should be trained on standard precautions, airborne infection control precautions, and the proper use of personal respiratory protection.

Airborne Infection Control -recommendation for Outpatient Department

Reduce overall duration of staying outpatient department by screening, separation and fast tracking of coughing patients and other means.
Location of OPD should be properly ventilated. Adequate ventilation (natural and/ or assisted ventilated) to ensure >6ACH at all times.
Education on cough etiquette and respiratory hygiene in waiting area
Training of institutes staff to identify symptomatic and provide mask and segregate them if fast tracking is not possible

CHAPTER 15

Management of contacts of DR-TB patients

Close contacts' of DR-TB patients are people living in the same household as the index patient, or spending many hours a day together with the patient in the same indoor space since the patient became symptomatic with cough (or within the last three months if this is not known). These include:

- People spending nights in the same room with DR TB patient e.g. spouses, children, caretakers, etc.
- People spending time in common living areas with DR TB patient.

A person who shared the same fixed living space with surrounding for one or more nights or for frequent or extended periods during the day with the index case during the three months before commencement of the current treatment episode

Casual contacts would include work places, school and social contacts. These may not require routine screening unless they are thought to be susceptible (< 5 years old, immune compromised) or the contacts spends a lot of time with them.

15.1 Managing DR TB Contacts

Adult: Symptomatic contacts should receive:

- An evaluation by a doctor, preferably a member of the Outpatient DR-TB Team. The evaluation should include history and physical examination.
- Sputum smear, culture and DST. Every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a person with suspected DR-TB.
- A chest X-ray examination if possible.
- HIV counseling and testing (if suspected to be, HIV-infected)

Child: Children who live with MDR-TB patients, particularly young children, have a high risk of Infection with MDR-TB and of development of active MDR-TB

Child contacts of MDR-TB patients should include the following:

- an evaluation by a physician, including history and physical examination;
- sputum investigations (ideally a rapid diagnostic method such as Xpert MTB/RIF, or if not available, sputum smear microscopy, culture and DST); and
- a chest radiograph examination;
- tuberculin skin testing with purified protein derivative;
- HIV testing (if either parent is known to be HIV-positive).

However, if any of the above recommended investigations are not present or are inconclusive, the diagnosis of MDR-TB can still be made clinically in a child contact.

Since young children are often unable to produce good sputum samples gastric aspiration using a nasogastric tube is the classic way to obtain sputum samples. Sputum induction is another method that has been shown to be safe and effective in young children

According to Guidance for national tuberculosis programs on the management of tuberculosis in children, the presence of three or more of the following should strongly suggest a diagnosis of TB

- Symptoms suggestive of TB
- Physical signs highly suggestive of TB
- A positive tuberculin skin test
- Chest radiograph suggestive of TB.

15.2 Treatment of MDR-TB contacts

Close contacts of MDR-TB patients who develop active TB almost always have MDR-TB themselves. Household close contacts of MDR-TB patients should be directly start empirically DR-TB treatment when rapid DST is not available.

Close contacts of MDR-TB patients; who do not have TB should be under preventive therapy after evaluation of active TB disease

- **Contacts with bacteriologically confirmed TB, but without confirmation of MDR-TB.**

If rapid molecular DST is not available, confirmation of drug resistance by culture-based methods may take weeks or months. These patients should be empirically treated with the same regimen as the index patient while DST is pending.

- **Contacts with extra pulmonary TB**

Close contacts with evidence of extra pulmonary TB should be started on empiric treatment with the same regimen as the index patient, with the possible addition of isoniazid and rifampicin. This is particularly important for HIV-positive contacts who are at risk for developing severe forms of extra pulmonary TB that are rapidly fatal.

- **Contacts with culture negative TB**

Children, who are often unable to produce good sputum samples but once a child contact of MDR-TB meets the criteria for diagnosis with active TB, he/she should be started empirically on treatment with the same regimen as the index patient. Isoniazid and rifampicin can be added to the regimen as described above.

CHAPTER 16

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:

- Short shelf life of some of the second-line anti-TB drugs, e.g: Cap Cycloserine and
- Long lead time required between placing the order and the arrival of the order.

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

The management cycle of second-line anti-TB drugs and consumables is of comprised of six elements:

- Drug selection
- Assessment of drug requirements/quantification
- Management of procurement (order placement, shipment, port-clearance, receiving)
- Distribution including storage and inventory control
- Assurance of drug quality
- Ensuring rational use of drugs following early warning system (EWS)

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 usually no SLDs are kept in stockpile by the 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:** In this method, the all the treatment regimens and the number of patients to be treated in respective regimens are predicted based on the best projection considering all local factors. This approach is recommended for the initial phase of the PMDT or when rapid scale-up from a pilot project is underway. NTP Bangladesh is following this approach for quantification using QuanTB tool.

The selection on second-line anti-TB drugs is based on the drugs used in different regimen (Shorter, Longer, Individualized, Pre-XDR and XDR-TB). Ordering second-line TB drugs is a very important activity conducted at the central level. Below the guidance that can be used to calculate second-line drug orders.

Table: 1 Ordering Anti-TB Drugs to Treat DR TB

Drug (Unit)	Quantity Needed
Pyrazinamide (500 mg tab)	Q*D*P
Amikacin (500 mg vial)	Q*D*P
Ethionamide (250 mg tab)	Q*D*P
Prothionamide (250mg tab)	Q*D*P
Cycloserine (250 mg tab)	Q*D*P
Levofloxacin (250 mg tab)	Q*D*P
Moxifloxacin (400 mg tab)	Q*D*P
Clofazimine (100 mg Tab)	Q*D*P
Linezolid (600 mg tab)	Q*D*P
Bedaquiline (100 mg tab)	Q*D*P
Delamanid (50 mg tab)	Q*D*P
Ethambutol (400mg tab)	Q*D*P
Isoniazid (300 mg tab)	Q*D*P
Syringe & needle (Auto-disabling) 5ml	Q*D*P

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

16.2 Distribution, inventory management and Storage of DR TB Drugs and Consumables

16.2.1 Distribution

- 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 and should coincide with the first line drugs transportation. Note, lab consumables (including Xpert cartridges) should also coincide with first line drug and transportation with the help of respective implementing partners.
- In special cases where the volume is too high or sudden increase of demand a separate transportation can be arranged. This is also true for lab consumables and Xpert cartridges.

16.2.2 Inventory Management:

- The inventory management of the drugs in DR TB store is very important as stock out of second line drugs may eventually lead to resistance to second line drugs and poor treatment outcome. The inventory should be maintained every time a store receives or issues any item. At the end of every month the inventory should be recorded as month end

balance and should be verified through physical count. The inventory data should be shared with NTP PSM at the end of each month.

- While in the peripheral drug stores the inventory, management is manual/paper based, the Shyamoli central TB warehouse uses electronic tool named "TB WIMS" for inventory management.
- Patients while admitted in designated hospital/inpatient facility for MDR/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 MDR/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.

16.2.3 Storage:

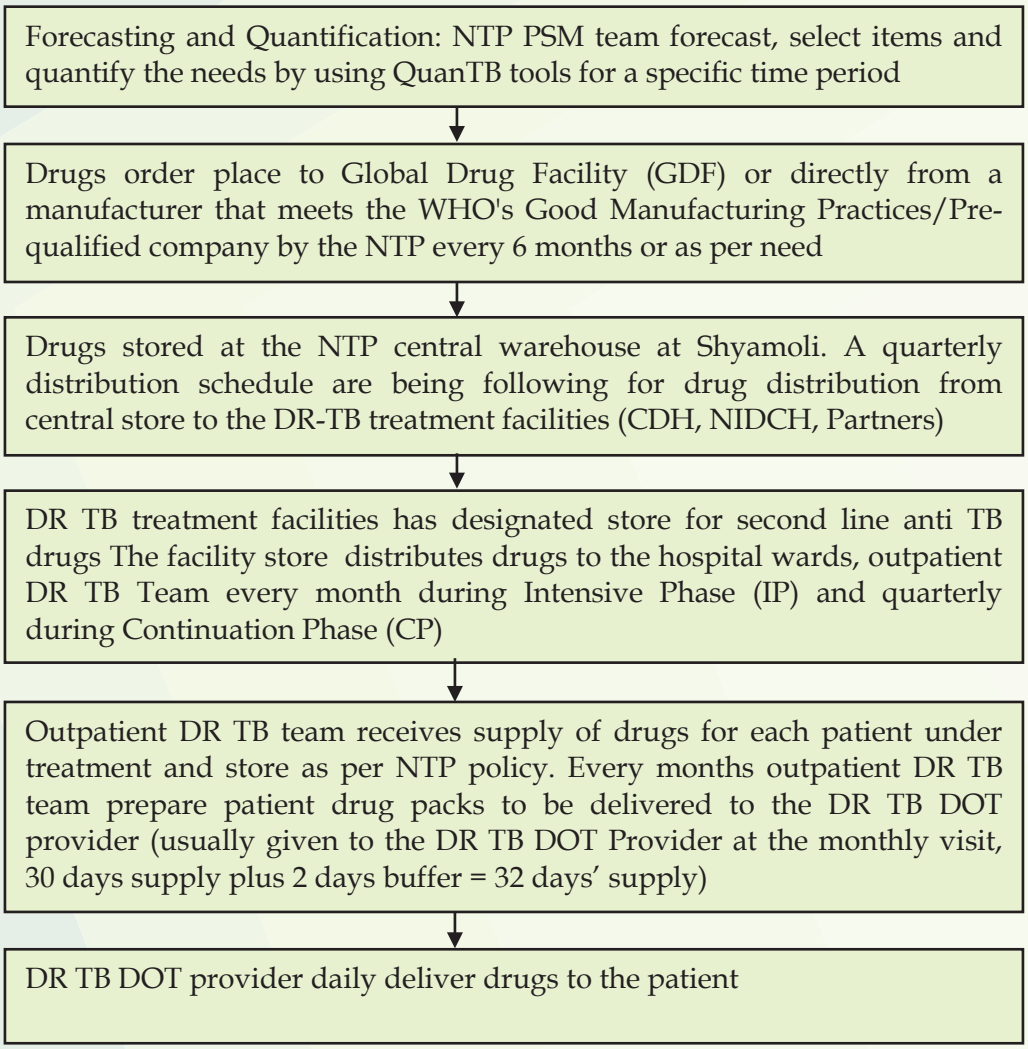
The respective DOTS centre will store the received drugs in their drug store and should maintain proper record as first line drugs. For storage, GOB facility will be preferred but NGO facility can also be an option where GOB facility is not available.

- The storage site should be cool, dry, away from direct sunlight, well ventilated and secured. Moreover, the storage facility should also ensure the optimal temperature condition for drugs or lab items (cartridges) those require maintenance of specific temperature range for efficacy. Temperature should be measured thrice a day and recorded in the temperature chart.

16.3 Requisition form for second line anti-TB drugs/ Ancillary drugs/ other logistics and consumables are in (DRTB-07)

- Signing of the requisition will be similar to that of first line i.e. superintendent of CDH to civil surgeon to NTP.
- Requisition may also include N-95 respirator, surgical mask, syringe, needles, recording and reporting formats etc.
- Selected second line TB drug 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 outpatient 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.
- Xpert cartridges are issued to Xpert sites. Controlled environment (especially temperature) should be maintained during the transportation. The calculation of requirement is based on Quarterly consumption data. One-month buffer should be added with the quarterly requirement.

16.4 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.

16.5 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.

CHAPTER 17

Supervision, Monitoring and Evaluation

This section describes the supervisory, monitoring and evaluation 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 DOT Supervisor of DR TB will regularly monitor and evaluate the DOT Provider.

17.1 Supervisory Activities

Supervisory visits involve six main units:

- The laboratory facility including GeneXperts
- The drug store and supply management
- Inpatient wards
- The DR TB outpatient treatment facility
- Patients data and Records corners and
- Patient residence.

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-job 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 outpatients DR TB team is expected.

A key aim of the supervisory 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;
- Review and analyze the referral of presumptive DR TB cases, diagnosis and enrollment.
- 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 including social support (investigation, nutrition, travel etc.) then taking the necessary corrective actions.

17.2 Monitoring activities

The PMDT monitoring is part and parcel of overall monitoring of National TB control programe. This monitoring for a rapid managerial assessment of input, process and output to ensure overall DR-TB service quality and keeping performances of each facility, institution, district, and division on track in order to attain ultimate goal of the program. Monitoring at every stage, like presumptive identification, detection, enrollment to treatment, follow up and treatment outcome of DR-TB to be done routinely. Monitoring visits will be paid from different levels – central, divisional, local (district & upazila) and community level. At each level both independent and/or joint monitoring by NTP & implementing partner will be done. (Patient Monitoring checklist are attached as annex.)

Recording and Reporting is described in Chapter 19 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.

Programmatic indicators on effectiveness

The programmatic indicators on effectiveness – to be reported based on routine patient data recorded- are:

- Proportion of DR-TB patients among total TB cases diagnosed
- Average time taken from diagnosis of DR TB to initiation of treatment
- Treatment outcomes by DR-TB regimen group: interim (6-month culture conversion) and final treatment outcomes including the number and proportion of patients requiring a change of regimen due to the occurrence of adverse drug reactions or lack of efficacy of the regimen
- Frequency of relapse at 6 and 12 months after successful treatment completion by DR-TB regimen group

Note: For patients diagnosed with RR-/MDR-TB who are not started on any DR-TB treatment regimen, the reasons for not starting DR-TB treatment will be registered in their patient file, e.g., critical condition, death, drugs not available to form an appropriate regimen, etc.

Programmatic indicators on safety

The programmatic indicators on safety – to be reported based on routine patient data recorded- are:

- Frequency of serious adverse events (SAE),by DR-TB regimen group
- Frequency of adverse events of special interest, by DR-TB regimen group.

Evaluation:

Evaluation will be done annually by analyzing the program data and reports, and periodic evaluation will be done through DRS after every 5 years. Moreover, external evaluation from WHO and development partners would be appreciated.

CHAPTER 18

DR TB Recording and Reporting System

18.1 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.

18.2 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 Programe.

18.3 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 center (mainly at chest disease 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 center (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
  - 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 MDR/XDR 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 center.
- Signature of the PMDT coordinator of the DR TB treatment initiation center

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 (P) 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 center: Signature of assigned authority of DOTS center where patient referred after discharged from the DR TB treatment initiation center

Pages 5 & 6:

- Brief information on adverse effects, date of onset, suggestive intervention taken and outcome should be recorded in page-5 & 6.

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 Extra pulmonary.
- Registration group: Code needs to be mentioned as per written as 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 than 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 entered 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.

Registration group: Code needs to be mentioned as per written as foot

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 center (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 center should use this form to collect SLDs, ancillary drugs and necessary logistics from respective treatment initiation center and DR TB DOT provider should also use this form. Outpatient DR TB center 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 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 09 is completed for shorter regimen both for 12 and 24 month longer regime both for 24 and 36 months after the last patient starts treatment in the cohort.

Example: **For shorter regimen:** The outcome report of the patients registered during 1st quarter 2016 (January- March, 2016) should be completed in 7 April 2017 and 7 April, 2018.

For longer regimen: The outcome report of the patients registered during 1st quarter 2016 (January- March, 2016) should be completed in 7 April 2018 and 7 April, 2019.

Most of the patients will have finished treatment by 12 month for shorter regimen and 20 months for longer regimen and this allows preliminary assessment of cure rates. Since a few patients may be on treatment for longer than 20 months in longer regimen, the form is completed again at 36 months after the last patient in the cohort starts treatment. The 24 month evaluation in shorter regimen and 36-month evaluation in longer regimen 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 provides culture and DST information done by L-J media, LPA and Liquid culture method

Annexes

Annex-1: 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 programe 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 programe at all levels • Coordinate with in country governmental and nongovernmental organization partners • Coordinate with National and International technical 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 programe (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 programe • Review policy and guideline as needed
National Tuberculosis Control Programme (NTP)	Focal Person for DR-TB	• 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 supervision and monitoring system at all level • Ensure establishment of TB IC in all treatment centers
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
DR TB treatment initiation centers/CDH/ Hospitals	Head of the DR TB treatment initiation centers /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

Annex-2: Prepare the patient for community-based care

A. Assess patient's knowledge and ability to take the MDR-TB treatment:

- How he/she was infected with a drug resistant strain.
- His/her understanding of MDR-TB therapy
- Ability to adhere with treatment.
- Whether he/she can comply with DOT

B. Advises and teaches:

- Drug-resistant TB:
  - o Is created when TB patients do not take anti-TB drugs regularly
  - o Can be transmitted to family and friends
  - o Can be easily transmitted to people living with HIV.
- Duration of treatment
- Every single dose must be taken under direct supervision (DOT provider). If not, there is every chance of treatment failure and development of XDR-TB.
- There is no other treatment for MDR-TB.
- During treatment he/she may adverse drug effect, but these can be managed. The clinical team must communicate closely with the DR-TB DOT provider about adverse drug effect and vice- versa.
- The patient is most infectious during the first few months when he/she is still smear positive. During this period, patients need to use surgical mask. Windows and doors should be left open in the home to increase ventilation. Usually most of the day time patient should stay at open space.

C. Return to Work

Patients should be encouraged to resume work as soon as sputum smear and culture-negative. This allows patients to reintegrate into society and earn money for his/her family. Those without skills/jobs may be encouraged to engage in income generating activities, such as:

- Sewing
- Gardening
- Raising chickens or cows
- Operating phones etc.

D. Reminders for the Patient on each visit

The Patient	Advice
If the patient has not yet Brought symptomatic household contacts for examination or testing	All household members with > 2 weeks cough should be tested
If the patient is unfamiliar with the drugs, or a change occurs in the regimen	Describe the type, colour, and number of drugs to be taken by showing the drugs to the patients. Describe how often drugs should be taken and for how long
If the patient feels better	Even after you feel better, you must continue taking drugs for the entire treatment period
If the patient is planning to travel or move	If you plan to travel or move from the area, Please inform me. We can make arrangements so that you will not miss any dose treatments
If the patient has missed a dose	To be cured, you must take all of the Recommended drugs daily until completion of treatment. Together for the entire duration with completion of entire dose. If you do not take all of the drugs, you will continue to spread TB to others and develop almost incurable TB
If the patient is not willing to continue and complains about continuing the treatment	Taking only some of the drugs, or taking them irregularly, is dangerous and can make the disease impossible to cure

Annex-3: out-patient DR-TB Team

A. Divisional supervisory DR TB Team

- Director Health (Division) – Chair Person
- Civil Surgeon(Central) - Co Chair Person
- Medical Superintendent - CDH/ Senior or Junior Consultant (CDH or CDC)/Consultant Medicine (District hospital) if no CDH or CDC – PMDT Coordinator and Member secretary
- NTRL/RTRL Coordinator
- 1 Medical Officer (MOCS/MO-CDC/CDH)
- 1 Divisional Consultant (NTP)
- 1 Program organizer-CS office, if available (trained in MDR-TB care)
- 1 Statistical Officer for recording and reporting.
- 1 Representative of NGO Partner

Responsibilities of divisional supervisory DR TB Team

- Provide assistance to NTP in implementation of PMDT expansion and maintain regular liaison with NTP
- Supervise and Monitor the activities, and provide guidance to District/ UHC based team
- Provide support for proper functioning of RTRL
- Ensure proper management of the complicated referred cases or if there is any emergency.
- Ensure availability and proper storage and distribution of SLDs.
- Provide medical consultation when required.
- Update of mother register and treatment card regularly.
- Collect report from District and submit to NTP.
- Link the routine DOTS program to refer suspect for DR-TB diagnosis.

B. District based supervisory DR-TB team:

District based supervisory DR-TB team should be set up in each district. A district Out-patient DR-TB Team can be based at any of the following set up as per convenience:

- Civil Surgeon's Office
- Chest Disease Hospital (CDH)
- Chest Disease Clinic (CDC)
- District Hospital

District based supervisory DR-TB team consists of:

- Civil Surgeon-Team Leader
- Senior or Junior Consultant (CDH or CDC)/Consultant Medicine (District hospital) if no CDH or CDC –Member secretary
- Medical Officer (MO TB/MOCS/MO-CDC)
- Public Health Nurse
- Program organizer-CS office/ TLCA sadar, if available (trained in MDR-TB care)
- Statistical Officer/Asst. for keeping all records
- Medical Officer/ any responsible officer from NGO Partner

Responsibilities of the Supervisory DR-TB team

- Assist in organizing training for the UHC/DOTS center-based DR- TB team

- Monitor the patient on scheduled visit
- Supervise the activities, and provide guidance to outpatient DR TB team
- Ensure proper management of the complicated referred cases or if there is any emergency.
- Link the DOTS program to refer presumptive DR-TB cases for diagnosis.
- Over all supervision and monitoring of PMDT programme

C. Upazila outpatient DR-TB Team consists of:

For UHC

- UH&FPO- Team Leader.
- Medical Officer Disease Control (MODC)-Member Secretary
- RMO/ Medical Officer (for back up, if MODC is not available or gets transferred out)
- TB and Leprosy Control Assistant (TLCA) will act as the DR-TB DOT Supervisor (and can also be a DR-TB DOT Provider if patient lives near-by)
- Medical technologist –Lab (GO/NGO).
- Representative from Partner NGO

Note: If TLCA acts as DR-TB DOT provider, he/she will be supervised by the MO or MODC

For Urban/ Peri-Urban:

- Medical Officer – Team Leader
- Center Manager – Member Secretary
- Paramedic/ Nurse
- Medical Technologist
- MIS/ M&E officer/ M&E Asst.
- Counselor

Note: 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).

Responsibilities of UHC based Out-patient DR-TB Team

1. General responsibilities:
   - Ensure enrollment of the DR-TB patient
   - Select DR-TB DOT provider
   - Collection, storing and recording of second line drugs and logistics
   - Ensure regular supply of the drugs and logistics to the DR-TB DOT provider
   - Calculate appropriate drug doses and modify as per requirement for patient
   - Ensure proper recording and reporting
   - Ensure TB IC measures at the community level
   - Ensure regular communication with respective treatment initiation center/hospital
   - Training of the DR-TB 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 DR-TB DOT provider regularly
   - Proper distribution of incentives to DR-TB DOT Providers and Patients.

2. Cares for patients

- Assesses the home and family at the beginning of treatment at home
- Visits the patient in case of medical emergencies
- Screens family members for HIV and TB if indicated
- Educates the family and community about TB and DR-TB
- Provide counseling and helps patient to receive monthly social support
- Tracks lost to follow up

3. Supervises DR TB DOT Providers

- Finds an acceptable DR TB -DOT Provider for each patient
- Trains the DOT Provider (initial and refresher training)
- Communicates with the DOT Provider in case of emergencies
- Monitor the DOT Provider (either at the facility or on a home visit)
- Spot visits to the patient's home to assess quality of DOT

4. Manages at the Outpatient facilities

- Screens new patients, such as those who are referred as DR-TB presumptive
- Makes sure that all scheduled patients have come for follow up visit
- Ensures that cards and registers are filled out correctly
- Organizes distribution of social support, transportation reimbursements, and MDR-DOT Provider incentives
- Makes sure that patients are given the right follow-up appointments

5. Coordinates with clinical data, and pharmacy staff

- Arranges for hospital admission in case of medical emergencies
- Coordinates transition from the hospital to community-based care
- Coordinates the next follow-up visit
- Manages Out-patient clinic schedules with the data team
- Works with pharmacist and/or UM to deliver medications to DOT provider

In addition, TLCA or any other person from partner NGO has a special role in assisting the Out-patient DR-TB Team:

- Trace lost to follow up patients by arranging home visits.
- Ensure proper recording and reporting at community level and submitting report regularly to district supervisory team.
- Link the DOTS program to refer presumptive DR-TB cases for diagnosis.

Annex-4: Supervising the DR-TB DOT Provider (and monthly performance evaluations)

The TLCA or NGO representative should evaluate the DR-TB DOT Provider on a monthly basis. This can be done by using the following checklist

Does the DR-TB DOT Provider understand?	**Circle the appropriate number 1=poor, 2=average, 3=good, 4=very good, 5=excellent**	**Tick if not applicable**
The patient's TB treatment regimen (names and number of medicines to be given)	1 2 3 4 5	
Common adverse drug reaction of the Second line anti TB drugs	1 2 3 4 5	
All other drugs taken by the patient and why	1 2 3 4 5	
Whether the patient is infectious (smear or culture positive)	1 2 3 4 5	
Knowledge of/about Sputum follow up schedule	1 2 3 4 5	
Performance	**Circle the appropriate number: 1=poor, 2=average, 3=good, 4=very good, 5=excellent**	**Tick if not applicable**
Performance (during the past month)	1 2 3 4 5	
Treatment card filled properly and in good condition	1 2 3 4 5	
Medicines are kept in good condition	1 2 3 4 5	
Provided DOT correctly (if on home visit and able to observe the provider giving the medicines, otherwise check not applicable)	1 2 3 4 5	
Referred DR-TB Team in case of any problems	1 2 3 4 5	
Addressed any social problems	1 2 3 4 5	

Spot visits are done by any member of the UHC/DOTS center DR-TB Team or District Supervisory team to the patient's home at any time during the day for the purpose of evaluating and supervising the DR-TB DOT Provider. The supervising visit should make an unannounced visit to the patient's home first in order to ask the patient and his/her family about the DR-TB DOT Provider. The DR–TB DOT Provider should then be called to discuss any issues and reinforce teaching points.

Drug counts can be done at monthly evaluations or during spot visits. The remaining drugs are counted and compare to the number of drugs that should be remaining based on the number of days since the medication bag was replenished. If there are any extra or missing drugs, this needs to be explained by the DR-TB DOT Provider.

The treatment card (photo copy) should always be kept by the DR-TB DOT Provider (Main copy kept in UHC). The DR-TB DOT Provider should read the exact treatment regimen listed on the card and tick immediately after observing the morning or evening dose. Adverse drug reactions, prophylaxis, and ART if any, should be recorded in the remark column of treatment card

Annex-5: Factors contributing to poor TB treatment outcomes

Anti-TB drug resistance is said to be present if growth of M. tuberculosis isolates is 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. Below table summarizes the common causes of inadequate treatment.

Health Care Providers: Inappropriate Treatment	Drugs: Inadequate Supply/Quality	Patients: Inadequate Drug Intake or Treatment Response
• Inappropriate guidelines • Non-compliance with guidelines • Absence of guidelines • Poor training • Financial disincentives • Poor patient education • No monitoring of treatment • Poor management of adverse • drug reactions • Poor treatment support • Poorly organized or funded TB control programmes	• Poor quality medicines • Unavailability of certain medicines (stock-outs or delivery disruptions) • Poor storage conditions • Wrong dose or combination • Poor regulation of medicines	• Lack of information • Lack of means to adhere to treatment (transportation, food, etc.) • Adverse effects • Social barriers • HIV • Diabetes mellitus • Under nutrition • Malabsorption • Substance abuse/dependency • Psychiatric condition

*adapted from Companion Hand Book to the WHO Guidelines for the Programmatic Management of Drug Resistant Tuberculosis 2014

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.

Annex-6: Contraindication and Overlapping toxicity of New and Repurpose Drugs

Contraindications for new and repurposed drugs

There are no absolute contraindications for the use of any drug in the treatment of MDR- and XDR-TB, a disease that poses serious risk of death or debilitation to the patient if treated inadequately. However, there are relative contraindications for the use of the new and repurposed drugs. If the clinician judges that the potential benefits outweigh the potential risk, treatment may proceed with caution.

Contraindications for new and repurposed drugs*

Drug	Relative contraindications	Remarks/Precautions
All drugs	Known hypersensitivity to the drug	History of anaphylaxis or severe drug reaction like Stevens-Johnson syndrome is an absolute Contraindication.
Bdq, Dlm	Baseline ECG demonstrating a QTcF > 500 ms (repeated); **or** History of syncopal episodes, ventricular arrhythmias or severe coronary artery disease	Use with caution if QTcF > 450/470 ms in Male/Female patients. Weekly ECG monitoring and serum electrolyte screening should be performed if Bdq or Dlm is being used despite a cardiac contraindication. Dlm may prolong the QT interval less than Bdq.
Bdq	Severe hepatic failure	Caution in patients with severe hepatic impairment.
Bdq, Dlm, Lzd	Severe renal failure	Caution in patients with severe renal impairment.

Possible drug-drug interactions with the new TB drugs*

	Drugs	Examples/notes

Avoid use with Bdq	Strong/moderate **inducers** of cytochrome P450 may decrease blood levels of Bdq	• Efavirenz*
		• Rifamycins:
		  ➢ Rifampicin
		  ➢ Rifapentine
		  ➢ Rifabutin
		• Phenytoin
		• Carbamazepine
		• Phenobarbital

	Strong/moderate **inhibitors** of cytochrome P450 may increase blood levels of Bdq	• Ritonavir-boosted PIs*
		• Oral azole antifungals (can be used up to two weeks):
		  ➢ Itraconazole
		  ➢ Fluconazole
		• Macrolide antibiotics other than azithromycin
		  ➢ Clarithromycin

Avoid use with Dlm	First-line standard anti-TB therapy (isoniazid, rifampicin, ethambutol, pyrazinamide)	• First line anti-TB therapy with fixed dose combination of HREZ appears to decrease levels of Dlm in early studies. The mechanism is not clear.

*For a more comprehensive list of drugs that affect and are affected by the cytochrome P450 system, seeThe Drug Interactions webpage of the Department

Possible drug-drug interactions between antiretroviral and the new TB drugs

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

Possible drug–drug interactions of linezolid with other medicines

	Interaction	Medicine
Avoid use with Lzd	Increasing serotonin levels that may result in serotonergic syndrome	• Serotonin re-uptake inhibitors (SSRIs): fluoxetine and paroxetine • Tricyclic antidepressants: amitriptyline and nortriptyline • Serotonin 5-HT1 receptor agonists • Monoamine oxidase inhibitors (MAO): phenelzine and isocarboxazid • Other serotoninergic agents: meperidine and bupropion or buspirone and quetiapine

Overlapping toxicities

- Every effort should be made to avoid the use of drugs with overlapping toxicities. However, there may be circumstances where no other option is available and the potential benefits outweigh the risks. For example, a fragile mental health patient with a high risk of suicide that must have linezolid in the regimen (no other anti-TB drug options) could require a serotoninergic medication.
- Psychiatric drugs are commonly used in MDR-TB patients for the treatment of cycloserine induced psychosis or reactive depression. The anti-psychotics in particular are well-known to prolong the QT interval. It is the responsibility of the TB physician to understand the effects and side effects of psychiatric drugs, and to monitor MDR-TB patients taking these drugs carefully, even if the patient is referred to a psychiatrist.
- Finally, a number of cardiac drugs are listed in this table. Cardiac drugs are used in MDR-TB patients for a number of incorrect reasons, such as to "prevent" arrhythmia, to treat cardiac symptoms, or to decrease the QT interval. In fact, there is no cardiac drug that can counteract or

"protect" from QT prolongation. Cardiac rhythm-controlling and rate-controlling drugs should therefore only be used for clear indications. Sinus tachycardia is often a physiologic response to other pathologies. It should be viewed as a symptom, not as a cardiac disorder. For example, beta-blockers should not be used to treat sinus tachycardia in TB patients.

Non-TB drugs that have potential overlapping toxicities with the new TB drugs

	Drugs	Examples/notes
Avoid with Bdq, Dlm	Drugs that cause QT prolongation or affect the heart rhythm*	• Oral azole antifungals (can be used up to two weeks): ➢ Ketoconazole ➢ Itraconazole ➢ Fluconazole • Macrolide antibiotics: ➢ Azithromycin ➢ Clarithromycin ➢ Erythromycin • Antipsychotics (all have some risk), including: ➢ Haloperidol ➢ Risperidone • Many anti-nausea drugs, for example: ➢ Ondansetron ➢ Granisetron ➢ Domperidone ➢ Chlorpromazine • Methadone • Cardiac drugs that may affect the heart rhythm, for example: ➢ Amiodarone ➢ Beta-blockers ➢ Digoxin ➢ Quinidine
Avoid with Lzd	Medicines that increase serotonin levels	• Serotonin re-uptake inhibitors (SSRIs): fluoxetine, paroxetine • Tricyclic antidepressants: amitriptyline, nortriptyline • Serotonin 5-HT1 receptor agonists • MAO inhibitors: phenelzine, isocarboxazid • Other serotoninergic agents: meperidine, bupropion, or buspirone, quetiapine

* This is not a comprehensive list. Doctors should inform themselves about potentially QT-prolonging drugs that their MDR-TB patients may be taking (see CredibleMeds.org).

Government of the People's Republic of Bangladesh
National Tuberculosis Control Programme
Programatic Management of Drug Resistant Tuberculosis (PMDT)
DR TB Treatment Card (Page 01 of 06)

Form DR TB 01

Name of Initial Treatment Center:.....
Address of Initial Treatment Center:.....
Name of Patient:.....
Father's/Husband's Name:.....
Mother's Name:.....
Address of the Patient:.....
.....
Mobile No:.....
Sex: ☐ M ☐ F ☐ T Age:.....
Initial Weight (kg):..... Initial Hight (cm):.....
*DR TB Registration Number:.....
Previous TB/DR TB Registration Number (if any):.....
Date of DR TB Registration...../...../.....
Date of DR TB Treatment Started:...../...../.....
e-TB Manager Number:...../...../.....
Site: ☐ Pulmonary ☐ Extra pulmonary (Specify):.....
Comorbid Disease (if any).....
History of Contact With TB/DR TB Patients: ☐ Yes ☐ No
Relation and Duration (If Yes):.....
Date of Discharge from Hospital to the Local Tratment/Dots Center:.....

	Registration Group (Put√ Mark at left)		Type of Patient (Put√ Mark at left)		
			Treatment after loss to follow up- Standard MDR TB Regimen		
	CAT I Non Converter (Remain positive at month of 2)		Faliure of Standard MDR TB Regimen		
	CAT I Failure (Remain pos. at 5 m or later/ Neg. Patient Positive at month 2)		Relapse after Standard MDR TB Regimen		
	Treatment after loss to follow up-CAT I		Intolarence on Standard MDR TB Regimen		
	CAT I Relapse		Treatment After loss to follow up- Shorter Regimen		
	Retreatment Reg. Non Converter (Remain positive at month of 2)		Faliure of Shorter Regimen		
	Retreatment Reg. Failure (Remain pos at 5 or 6 month/Neg patient positive at month 2)		Relapse after Shorter Regimen		
	Treatment after loss to follow up- Retreatment Reg.		Intolarence on Shorter Regimen		
	Retreatment Reg. Relapse				
	Close Contact of DR TB with S/S	Unknown History	New	Previously Treated	
	HIV infected patient with TB S/S	Unknown History	New	Previously Treated	
	Others (Specify):				
	i) Pulmonary-Clinically diagnosed	Unknown History	New	Previously Treated	
	ii) Extra Pulmonary	Unknown History	New	Previously Treated	
	iii) Pulmonary-Bacteriologically Confrimed	Unknown History	New		

Previous Tuberculosis Treatment History Including DR TB:

No	Start Date (if Unknown, Year)	TB Registration Number With Date	Regimen (Write Regimen In Drug Abbreviations)	Outcome

Outcome:

Outcome:	Date
Cured	
Completed	
Died	
Failed	
Lost to follow up	
Transferred Out	

Drug Abbreviations:

First line Drugs
H= Isoniazid
R= Rifampicin
E= Ethambutol
Z= Pyrazinamide
S= Streptomycin

Second Line drugs
Am= Amicacin
Lfx= Levofloxacin
Mfx= Moxifloxacin
Eto= Ethionamide
Pto= Prothionamide
Cfz= Clofazimine
Cs= Cycloserine
Lzd= Linezolid
Trd= Terizidone
Bdq= Bedaquiline
Dlm= Delamanid
Ipm-cin= Impenem cilastatin
Mpm= Meropenam

Name and Address of Local Treatment/DOTS Center:.....
Shorter treatment Regimen (Oral): Intensive Phase: (4-6)Bdq-Lfx-Pto-Mfx-Z-H-E Continuation Phase: 5 LFX-Cfz-Z-E
Shorter treatment Regimen (Injectale): Intensive Phase: (4-6) Amk-Lfx-Pto-Cfz-Z-H-E Continuation Phase: 5 Mfx-Cfz-Z-E
Longer Treatment Regimen: .....
XDR treatment Regimen: .....
Other Regimen (if any):

Regimen and Drug Doses

**Date	Am(mg)	Mfx/Ifx (mg)	Pto/Eto (mg)	Cs (mg)	H (mg)	E (mg)	Cfz (mg)	Trd (mg)	Lzd (mg)	Z (mg)	PAS (mg)	Bdq (mg)	Dlm (mg)	Others	Comments

*write 'STR' if patient started on shorter treatment regimen; Example:*STR/Sl#/Yr/Centre/Dist/Div. ** Date of treatment started and doses, Change of doses (if any)

.....
Signature of the Authority of the DR TB Treatment Initiation Center
Name and Designation.....
Contact Number:.....

.....
Type of Resistance:
RR/MDR TB/Pre XDR TB/ XDR TB/
Poly Resistance (Specify).....

Microscopy Resut:

DR TB Treatment Card (Page 02 of 06)

Form DR TB 01

Month	Week	Sputum Smear Microscopy			
		Date of sample colleciton	Lab ID.	Date of report received	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					
22					
23					
24					

Month	Culture Result			
	Date of sample colleciton	Lab ID.	Date of report received	Result
0				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				

Post Treatment Follow-Up**				
Month	Sputum Smear Microscopy			
	Date of Sample collection	Lab ID.	Date of report received	Result
Month	Culture Result			
	Date of Sample collection	Lab ID.	Date of report received	Result

Comments on Post Treatment Follow-Up:

Relapse Yes ☐ No ☐ Unknown ☐

Date.....
Others.....

HIV Status:

Date:

Pos ☐ Neg ☐ Unknown ☐

Meeting Dates and Decision of Clinical Management/ PMDT Committee:

Day	Decision	Next date

Drug Susceptibility Test (DST) Results:

*Method	Date	S	H	R	E	Km/Amk	Ofx/Lfx/Mfx	Eto/Pto	Bdq	Lzd	Dlm	Cfz	Others

Notation:
symbol for DST
R = Resistant
S = Susceptible
C = Contaminated

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

** Up to 12 Months for Shorter Rgimen and 24 months for Standard MDR-TB Regimen After Treatment Completion Date

DR TB Treatment Card (Page 04 of 06)

Form DR TB 01

Administration of Drug (One row per month):

Patient's Name:.....

Month/Year	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

Laboratory and Radiological Investigation: Patient's Name:.....

Month	Date	Chest X-ray	Hb(g/dl)	ESR	Blood Glucose	HBA1C	S. Creatinine	S. Electrolyte	Serum Bilirubin	SGPT	Alkaline Phosphate	TSH	Audiometry	ECG	Pregnancy Test	Other	

DR TB Treatment Card (Page 06 of 06)

Form DR TB 01

Adverse Effects (AEs)

Patient's Name:.....

Averse Effect	Suspected Product/s	Brief description of Adverse Effect	Date of onset (dd-mm-yy)	Intervention/action taken*	Outcome of Adverse Effect after Intervention with Date (dd-mm-yy)**

*Intervention/Action taken may be one or two of the following: a) reassurance, b) provision of ancillary drug, c) dose adjustment, c) drug discontinuation, d) shift from shorter to longer regimen

** Out Come: a) Resolved, b) Resolved with sequel, c) Ongoing, d) Not resolved, e) Became an SAE, f) Unknown

Name of the DOT Provider:.....

Designation:.....

Organization:.....

Address:.....

Mobile:.....

Comments:.....

Remarks:

.....

Name and Signature of Assigned Authority of DOTS Center

Date:

Form DR TB 02

National Tuberculosis Control Programme
DT TB Register (Page 1 of 4)

Unique DR TB Registration No. Sl/Yr/ Center/ Dist./Div* / e-TB Manager	DR TB Registration Date / Treatment Starting Date	Name (in Full)	Sex M/F/ T	Age	Address and Mobile No.	TB/DR TB Registration Number and Date or at least Year (Recent and previous if any)	Site of Disease (P/EP)	**Registration group (see code below) / *** Type of Patient(if Applicable)	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 / **** Method of DST	HIV status with date (Yes/No/ Unknown) / If Yes, on ART (Y/N) and Date / On CPT (Y/N) and Date
									R	H	E	S	Km/ Cm	Ofx/ Lfx/ Mfx	Eto/ Pto	Others (Specify)		

* Write 'STR' if patient started on shorter treatment regimen; Example:*STR/Sl#/Yr/Centre/Dist/Div.
** Registration Group (Code):
1. Failure of Cat-1
2. Relapse
3. Treatment after loss to follow-up
4. Non-Converter (remain positive at month 2 of treatment follow-up)
5. Close contacts of DR TB patients with symptoms
6. HIV Infected person, with /without TB S/S
7. Pulmonary smear negative or extra pulmonary TB patient clinically not improved in spite of treatment as per NTP guideline

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

***Type of Patient
1. Treatment after loss to follow up- Longer MDR TB Regimen
2. Failure of Longer MDR TB Regimen
3. Relapse after Longer MDR TB Regimen
4. Intolerance of Longer MDR TB Regimen
5. Treatment after loss to follow up- Shorter Regimen
6. Failure on Shorter Regimen
7. Relapse after Shorter Regimen
8. Intolerance on Shorter Regimen

Form DR TB 02

National Tuberculosis Control Programme
DT TB Register (Page 2 of 4)

Smear (s) and culture (s) results during treatment (If more than one smear or culture done in a month, enter the most recent positive result)																														
Reason for entering in DR TB Register					Week	*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	
RR TB	MDR TB Confirmed)	Pre-XDR TB Confirmed	XDR TB Confirmed	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*
						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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DR TB= Drug Resistant TB, MDR TB= Resistant to Rifampicin (R) and Isoniazid (H), XDR Tb= MDR TB + Resistant to Inj Amikacin/Kanamaycin/Capriomycin (Amk/Km/Cm) and one of the Fluoroquinolones (Ofx/Lfx/Mfx etc),

RR TB= Rifampicin Resistant with or without resistant to other anti Tb drug except Isoniazid (e.g: R, REZ, RES etc). DR Tb (Others): Other then M/X DR/Pre-XDR and RR (e,g: HES, etc)

Form DR TB 02

National Tuberculosis Control Programme
DT 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)																						Post Treatment Follow Up (Upto 12 months for Shorter Regimen and 24 month for Longer treatment regimen)									
Unique DR TB Register No. Sl/Yr/.Center/ Dist./Div	Month 14		Month 15		Month 16		Month 17		Month 18		Month 19		Month 20		Month 21		Month 22		Month 23		Month 24		Month		Month		Month		Month		Month	
	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		d/m/y	
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Form DR TB 02

National Tuberculosis Control Programme
DT TB Register (Page 4 of 4)

Labroratory and Radiological Investigation:															Final Outcome			
Chest X-ray	Hb/g/dl	ESR	Blood glucose	S.Creatinine	Serum Potassium	Serum Bilirubin	SGPT	Alkaline Phosphate	TSH	Pregnancy Test	Audiometry	ECG	Others		Unique DR TB Registration No.	Outcome Cured/Treatment Completed/Treatment Failed/Died/Lost to follow up/ Transferred out	Comments: Post treatme nt Follow-up	Comments (if any)
													Specify	Specify				
Date And Result																		
																	Relapse: Y ❑ N ❑ Unknown ❑ Date: Others	
																	Relapse: Y ❑ N ❑ Unknown ❑ Date: Others	

FORM DR TB 03

গণপ্রজাতন্ত্রী বাংলাদেশ সরকার
জাতীয় যক্ষ্মা নিয়ন্ত্রণ কর্মসূচি, বাংলাদেশ
প্রোগ্রামেটিক ম্যানেজমেন্ট অব ড্রাগ রেজিস্টেন্ট টিউবারকুলোসিস
ডিআর টিবি রোগীর পরিচয় পত্র

নাম:

ডি আর টিবি রেজি: নং :.....

e-TB Manager No:-.....

পূর্ণ ঠিকানা: .....

মোবাইল নং:.....

লিঙ্গ : ❑ পুরুষ ❑ মহিলা বয়স :

চিকৎসা শুরুর স্থান :.....

স্থানীয় চিকিৎসা কেন্দ্র/স্থান :.....

রোগের শ্রেণী বিন্যাস ❑ ফুসফুস ❑ ফুসফুস বহির্ভুত স্থান :.....	চিকিৎসা শুরুর তারিখ: দিন মাস বছর

Type of Patient

Specify.....

Type of Resistance

❑ **RR** ❑ **MDR TB** ❑ **Pre-XDR** ❑ **XDR TB** ❑ **Poly resistance**

❑ Other resistance .....

Treatment regimen:

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

.....
কর্তৃপক্ষের নাম, পদবী এবং স্বাক্ষর

গণপ্রজাতন্ত্রী বাংলাদেশ সরকার
জাতীয় যক্ষ্মা নিয়ন্ত্রণ কর্মসূচি, বাংলাদেশ
প্রোগ্রামেটিক ম্যানেজমেন্ট অব ড্রাগ রেজিস্টেন্ট টিউবারকুলোসিস
ডিআর টিবি রোগীর পরিচয় পত্র

পরবর্তী উপস্থিতির তারিখ:

DOT প্রদানকারীর তথ্যাবলী:

নাম: .....

পদবী: .....

সংস্থা:.....

কর্মস্থল ঠিকানা: .....

.....

মোবাইল: .....

অফিস: .....

ব্যক্তিগত: .....

১। আপনার কার্ডের যত্ন নিন।

২। নিয়মিত, পরিমিত ও ক্রমাগত ঔষধ সেবন করুন।

৩। অসম্পূর্ণ চিকিৎসা এবং অনিয়মিত ঔষধ গ্রহণ উভয়েই রোগ নিরাময় না হওয়ার কারণ। এর ফলে রোগের পরিণতি জটিলতর হয় এবং রোগের জীবানু সমাজের অন্যান্য সুস্থ্য ব্যক্তির দেহে ছড়িয়ে পড়তে পারে।

৪। যেখানে সেখানে কফ ও থুথু ফেলবেন না ।

৫। হাঁচি ও কাশির সময় নাক-মুখ ঢেকে রাখুন।

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 1 of 3)

Laboratory serial number / e-TB number	Date of specimen received / Date of specimen collected	Local lab ID	Type of specimen inoculated	Name & address of referring health authority with cell phone number	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)/ e-TB no. (if any)

*Type of Patient (Code): 1. Non converts of Category I (remain positive at month 2), 2. Failure of Category 1 (remain positive at month 5 or later and/ smear negative patients who become smear positive at month 2), 3. Treatment after loss to follow up Category I, 4. Relapse Category I, 5. Non converts of Retreatment regimen(remain positive at month 2), 6. Failure of Retreatment regimen (remain positive at month 5 or 6), 7. Treatment after loss to follow up Retreatment regimen, 8. Relapse Retreatment regimen, 9. Close contacts of DR TB patient with symptoms, a) Unknown history b) New c) Prev. treated, 10. HIV infected person with TB S/S, a)Unknown history b)New c)Prev. treated, 11. Other (Specify) i. Pulmonary, clinically diagnosed, a) Unknown history b) New c) Prev. treated ii)Extra Pulmonary, a) Unknown history b) New c) Prev. treated, iii) Pulmonary, Bacteriologically Confirmed a) Unknown history b) New

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 2 of 3)

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 and designation of person reporting results	Signature	Date of result sent to Referring health facility	Comments
Diagnosis	**Follow-up	[a]Xpert MTB/RIF	[b]Culture (specify method) L-J/LC							
	Month	DR TB Reg. No. / e-TBm No.								

aXpert MTB/Rif test 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

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

bCulture result reported as follows: (L-J)
0=No growth
(1-9) =<20 colonies (report number of colonies) 1+=20-100 colonies
2+=>100-200 colonies
3+=>200, innumerable or confluent growth

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)

cResults of Drug Susceptibility Testing (DST)										***Method of DST	Date of results reported	Date of report sent back to refining health facility	Name and designation	Signature	Comments
H	R	E	S	Amk	Cm	FQ	Others (Specify)	Others (Specify)	Others (Specify)						

cReport 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

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

Lab ID	e-TB Manager Number	TB Registration Number (Current) - if any	Date of sample Collected / Received	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)	*Criteria for presumptive DR TB	Microscopy Result and Method (ZN/LED)	** Xpert Result	Date of Result/ Report	Date of Report send back to the referring health facility	DR TB 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

* Criteria for presumptive DR TB/Reason for Xpert MTB/RIF test (Code):

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 Retreatment Regimen (remain positive at month 5 and smear negative patients who become smear positive at month 2)
3. Non converters of Retreatment Regimen (remain positive at month 2)
4. Non converters of Category I (remain positive at month 2)
5. Relapses- a) Caregory I, b) Retreatment Regimen
6. Treatment after loss to follow up- a) Category I, b) Retreatment Regimen
7. Close contacts of DR TB patient with symptoms, a) Unknown history b) New c) Prev. treated
8. HIV infected person with TB S/S, 1) Unknown history b) New c) Prev. treated
9. Others (Specify) i. Pulmonary, clinically diagnosed, a) Unknown history, b) New, c) Prev. treated ii. Extra Pulmonary, a) Unknown history, b) New, c) Prev. treated, iii. Pulmonary, Bacteriologically COnfirmed a) Unknown history b) New
10. Presumptive Pulmonary Smear Negative TB Cases, a) Unknown history b) New c) Prev. treated. ☐ ☐
11. Presumptive TB- a) Unknown history, b) New

** 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 (code no)

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

DR TB 06

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: _____

e-TB registration No: _____ Name of patient: _____ Age (yrs):____ Sex:____ *HIV-status: Pos / Neg / Unknown

Address of patient: _____

_____Cell Phone #:_____

B. TB Disease Type and Treatment History

Type : A) Pulmonary B) Extra Pulmonary (Specify Site).....

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 Retreatment regimen (remain positive at month 5)
3) Non converters of Retreatment regimen (remain positive at month 2)
4) Non converters of Category I (remain positive at month 2)
5) Relapses- a) Category I b) Retreatment regimen
6) Treatment after loss to follow up- a) Category I b) Retreatment regimen
7) Close contacts of DR TB patient with symptoms, a) Unknown history ☐ b) New ☐ c) Prev.treated ☐
8) HIV infected person, with TB S/S a) Unknown history ☐ b) New ☐ c) Prev.treated ☐
9) Others (Specify) i. Pulmonary, clinically diagnosed, a) Unknown history ☐ b) New ☐ c) Prev.treated ☐
   ii) Extra Pulmonary, a) Unknown history ☐ b) New ☐ c) Prev.treated ☐
   iiii) Pulmonary, Bacteriologically Confirmed a) Unknown history ☐ b) New
10) Presumptive Pulmonary Smear Negative TB Cases a) Unknown history ☐ b) New ☐ c) Prev.treated ☐
11) Presumptive TB-a)Unknown histroty ☐ b)New ☐

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 test at the reference laboratory: NTRL /RTRL _____ / X-Pert MTB/RIF Site: _____

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

Specimen: Sputum ☐ Sputum in preservative, type ☐ specify _____ 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/Collected in the reference laboratory: NTRL / RTRL _____ / X-Pert MTB/RIF Site: _____

Reference laboratory specimen ID:_____

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

ID #	Neg	Scanty	1+	2+	3+

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

3. Culture result: Method used: Solid (LJ) ☐ Liquid (MGIT) ☐ 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) Line Probe Assay (LPA) ☐ X-Pert MTB/ Rif

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

Name:
Designation:
Cell Number:

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 .....

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 (Number of Doses x Number of Days)	Stock in Hand = c	Quantity Required = **d= (ax4xb)-c	Actual Quantity Supplied	Remark
	MDR	XDR	Other DR					
Pyrazinamide (Z) (500 mg tab)								
Amkl gm (Km) vial (only for IP)								
Ethionamide (Eto) (250 mg tab)								
Cycloserine (Cs) (250 mg tab)								
Levofloxacin (Lfx) (250 mg tab)								
Moxifloxacin (Mfx) (400 mg tab)								
Clofazimine (Cfz) (50 mg tab)								
PAS (4 gm sachet)								
Bedaquiline Bdq (200 mg tab)								
Delaminid Dlm (50 mg tab)								

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 (Number of Doses x Number of Days)	Stock in Hand = c	Quantity Required= **d= (ax4xb)c	Actual Quantity Supplied	Remark
	MDR	XDR	Other DR					
Omeprazole (20 Mg)								
Domperidone (10 Mg)								
***pyridoxine (25 Mg)								
Multivitamin								
Alprazolam (0.5mg)								
Others*****								

*b = Average number of drugs needed per day per patient x No of Days (follow National PMDT guideline of NTP)
**d=This column is not required to fill up when supplying drugs and logistics to DOT Provider
***Linozolid (600 mg) =Two tab daily for one month and calculate rest of the months as one tab daily
****Pyridoxine (25 mg) =50 mg Pyridoxine for every 250 mg of Cycloserine
*****Others=Example: N-95 respirator, surgical mask, syringe, needles, water for injections, recording and reporting for mats etc.
❑ Pediatric drugs should be calculate as per guidelines

Signature:……

Name and Designation of the treatment cantre authority…….....

……

Cell/Phone Number:…….....Date:…….....

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

From DR TB 08

Name of the Treatment Center:
Name of PMDT Coordinator:
Designation: Organization
Phone Number:

Nomber of Patients Registered in the DR TB Register:
During Quarter of Year

Date of Completion of the Form:

Signature:

Block 1: Patient Registered in DR TB Register and Started on DR TB Regimen (Age and Sex Distribution)

Types of DR TB		0-4		5-9		10-14		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	**M**	**F**	**Total**
(i) RR	Shorter Regimen																			**0**	**0**	**0**
	Longer Regimen																			**0**	**0**	**0**
(ii) MDR	Shorter Regimen																			**0**	**0**	**0**
	Longer Regimen																			**0**	**0**	**0**
(iii) Pre-XDR																				**0**	**0**	**0**
(iv) XDR																				**0**	**0**	**0**
(v) Other DR																				**0**	**0**	**0**
Grand Total	**Shorter Regimen**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Longer Regimen	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Total	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Comment if any:

From DR TB 08

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

Block 2: DR TB Cases (RR+MDR) Registered During the Quarter

Bacteriologically confrimed (Pulmonary)																								Others (Specify) (13)						Total (14)
CAT I Non Convertor (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	Non Converter Retreatment Regimen (Remain positive at the month of 2).	Failure Retreatment Regimen (Remain pos at 5 or 6 month/negative patient positive at month 2).	Treatment after loss to follow up-Retreatment Regimen	Relapse Retreatment Regimen	Relapse after MDR-TB treatment	Transform in (form another DR TB treatment initiation center).	Close Contact of DR TB With S/S			HIV infected patients with TB S/S			Pulmonary-Clinically diagnosed			Extra pulmonary			Pulmonary Bacteriologically confirmed							
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)			(12)			(i)			(ii)			(iii)							
										a) Unknown History	b) New	c) Previously Treated	a) Unknown History	b) New	c) Previously Treated	a) Unknown History	b) New	c) Previously Treated	a) Unknown History	b) New	c) Previously Treated	a) Unknown History	b) New	a) Unknown History	b) New	a) Unknown History	b) New	a) Unknown History	b) New	0

Block 3: HIV status among DR-TB patients

	<15 years		15 years and above		Total	
	Male	Female	Male	Female	Male	Female
HIV +ve					0	0
HIV -ve					0	0
Unknown					0	0
Total	0	0	0	0	0	0

Block 4: Category of DR TB /HIV Patient Registred During the Quarter

Age Group	Types of patient												Number of Patient on ART	Number of patient on CPT
	Pulmonary						Extra Pulmonary							
	Bacteriologically Confirmed			Clinically diagnosed			Bacteriologically Confirmed			Clinically diagnosed				
	a) Unknown History	b) New	c) Previously Treated	a) Unknown History	b) New	c) Previously Treated	a) Unknown History	b) New	c) Previously Treated	a) Unknown History	b) New	c) Previously Treated		
< 15 years														
15 years and above														
Total	0			0			0			0			0	0

Comment if any

Name of the Person Filled the Form:

Organization: Government/Non Government (Specify):

Designation:

Phone no:

Signature:

Date:

Government of the People's Republic of Bangladesh

Form DR TB 09

National Tuberculosis Control Program

Programmatic Management of Drug Resistant Tuberculosis (PMDT)

Treatment Outcome Report of DR TB patients (Longer Regimen)

To be Filled in 24 & 36 Months after Treatment initiation (Page 1 of 2)

Name of the Treatment Center: NIDCH

Name of PMDT Coordinator: Dr. Md. Wahiduzzaman Akhanda

Designation: Senior Consultant Organization

Phone Number: 01711322414

Signature: Date

Patients Registered: During 4th Quarter of Year 2017

Date of Completion of the form: 12.02.2019

Block 1: Treatment Outcome According to the Types of DR TB Patients

Patient group			Total number of DR TB patients registered during the quarter	Outcome								Total	Shifted to longer regimen (Other than failure)
				Cured	Treatment completed	Treatment Failed	Died	Lost to follow up	Transferred out	Still on treatment	Not evaluated		
(i) RR	<15 years	M										0	
		F										0	
	≥15 years	M										0	
		F										0	
(ii) MDR	<15 years	M										0	
		F										0	
	≥15 years	M										0	
		F										0	
Total	**<15 years**	**M**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
		F	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	≥15 years	**M**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
		F	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Grand Total			**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Comment if any:

Form DR TB 09

Government of the People's Republic of Bangladesh
National Tuberculosis Control Program
Programmatic Management of Drug Resistant Tuberculosis (PMDT)
Treatment Outcome Report of DR TB patients (Longer Regimen)
To be Filled in 24 & 36 Months after Treatment initiation (Page 2 of 2)

Name of the Treatment Center:
Name of PMDT Coordinator:
Designation: Organization:
Phone Number:
Signature: Date:

Reprting month: ☐ 24 Month ☐ 36 Month
Patients Registered: During Quarter of Year
Date of Completion of the 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	Shifted from shorter regimen	Outcome								Total
					Cured	Treatment completed	Treatment Failed	Died	Lost to follow up	Transferred out	Still on treatment	Not evaluated	
(i) RR	<15 years	M											0
		F											0
	≥ 15 years	M											0
		F											0
(ii) MDR	<15 years	M											0
		F											0
	≥ 15 years	M											0
		F											0
(iii) Pre-XDR	<15 years	M											0
		F											0
	≥ 15 years	M											0
		F											0
(iv) XDR	<15 years	M											0
		F											0
	≥ 15 years	M											0
		F											0
(v) Other DR	<15 years	M											0
		F											0
	≥ 15 years	M											0
		F											0
Total	**<15 years**	**M**	0	0	0	0	0	0	0	0	0	0	0
		F	0	0	0	0	0	0	0	0	0	0	0
	≥ 15 years	**M**	0	0	0	0	0	0	0	0	0	0	0
		F	0	0	0	0	0	0	0	0	0	0	0
Grand Total			0	0	0	0	0	0	0	0	0	0	0

Comment if any:

Government of the People's Republic of Bangladesh **DR TB 10 A**

National TB Control Programme

Programmatic Management of Drug Resistant Tuberculosis (PMDT)

Monthly Report on Xpert MTB/RIF Results

National

Reporting period : ..... Month ..... Quarter of year **2018**

Block 1:

Number of total Cases Tested	Presumptive DS-TB Cases(Total)	
	Presumptive DR TB Cases(Total)	
	Total	

Results:	Presumptive DS-TB	Presumptive DR-TB	Total
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):

Presumptive DS-TB			Presumptive DR-TB			Total

Block 2:

Number of :	Type of Patient : Presumptive DS-TB Cases			Type of Patient : Presumptive DR TB Cases													Total (Column 3- Column 13)
	Unknown History	**New**	**Total** (Column 1- Column 2)	Failures of CAT I (remain positive at month 5 or later/ Smear negative patients become smear positive at month 2)	Failures of CAT II (remain positive month 5 or 8) at	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 DR TB patient with symptoms		HIV infected person with TB S/S		Others (Specify)* i) Pulmonary clinically diagnosed ii) Extra Pulmonary iii) 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)	
Presumptive cases tested by Xpert MTB/RIF												Unknown history:		Unknown history:			
												New:		New:			
												Prev. treated:		Prev. treated:			
MTB detected												Unknown history:		Unknown history:			
												New:		New:			
												Prev. treated:		Prev. treated:			
RR TB detected												Unknown history:		Unknown history:			
												New:		New:			
												Prev. treated:		Prev. treated:			

Block 3:

Number of Presumptive smear negative TB cases				
	Unknown History	New	Prev. Treated	Total
Presumptive Sm. Neg cases tested by Xpert				
MTB Detected				
RR TB Detected				

*Others (Specify)

Type of Patient	Presumptive DR TB cases			MTB detected			RR TB detected		
	Un. His.	N	Prev. Tr.	Un. His.	N	Prev. Tr.	Un. His.	N	Prev. Tr.
i) Pulmonary clinically diagnosed									
ii) Extra Pulmonary									
iii) Pulmonary bacteriologically confirmed									

Un. His. = Unknown History, N = New, Prev. Tr. = Previously Treated

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 Category I (remain positive at month 5 or later and smear negative patients who become smear positive at month 2), 2. Failures of Retreatment Regimen (remain positive at month 5 and smear negative patients who become smear positive at month 2), 3. Non converters of Retreatment Regimen (remain positive at month 2), 4. Non converters of Category I (remain positive at month 2), 5. Relapses- a) Caregory I, b) Retreatment Regimen, 6. Treatment after loss to follow up- a) Category I, b) Retreatment Regimen, 7. Close contacts of DR TB patient with symptoms, a) Unknown history b) New c) Prev. treated, 8. HIV infected person with TB S/S, 1) Unknown history b) New c) Prev. treated, 9. Others (Specify) i. Pulmonary, clinically diagnosed, a) Unknown history, b) New, c) Prev. treated ii. Extra Pulmonary, a) Unknown history, b) New, c) Prev. treated, iii. Pulmonary, Bacteriologically COnfirmed a) Unknown history b) New, 10. Presumptive Pulmonary Smear Negative TB Cases, a) Unknown history b) New c) Prev. treated., 11. Presumptive TB- a) Unknown history, b) New

**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.

Annex 7: Recording Form for Adverse Effect (AE)

Averse Effect	Brief description of Adverse Effect	Date of onset (dd-mm-yy)	Intervention/action taken*	Outcome of Adverse Effect after Intervention with Date (dd-(dd-mm-yy)

**Intervention/Action taken may be one or two of the following: a) reassurance, b) provision of ancillary drug, c) dose adjustment, c) drug discontinuation, d) shift from shorter to longer regimen*

*** Out Come: a) Resolved, b) Resolved with sequel, c) Ongoing, d) Not resolved, e) Became an SAE, f) Unknown*

Annex 8: Serious adverse Event Reporting Form

Government of the People's Republic of Bangladesh
National Tuberculosis Control Programme
Directorate General of Health Services
Mohakhali, Dhaka-1212

Case number:		
Initial report: ☐	Follow-up report: ☐	Date of report:

Patient information		
Name:		DR TB registration number:
Age:	Sex: M ☐ F ☐	Treatment center:
Weight:	Height:	Phone number:
Diagnosis: RR ☐ MDR ☐ Pre-XDR ☐ XDR ☐		
Date of diagnosis		Date of treatment started:

Serious adverse event(s) information			
	SAE 1	SAE 2	SAE 3
Adverse event term			
Event onset date			
Date event became serious			
Event end date			
Seriousness criteria			
Death	☐	☐	☐
	In case of death:	Death date:	
Life-threatening	☐	☐	☐
Hospitalization required / prolonged	☐	☐	☐
	Hospitalization dates:	Admission:	Discharge:
Persistent or significant disability / incapacity	☐	☐	☐
Congenital anomaly / birth defect	☐	☐	☐
Otherwise medically important	☐	☐	☐
Severity	Grade 1☐ 2☐ 3☐ 4☐	Grade 1☐ 2☐ 3☐ 4☐	Grade 1☐ 2☐ 3☐ 4☐
Event outcome			
Fatal	☐	☐	☐
Not resolved	☐	☐	☐
Resolved	☐	☐	☐
Resolved with sequelae	☐	☐	☐
Resolving	☐	☐	☐
Unknown	☐	☐	☐

Suspected drug(s)	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
Suspected drug name							
Daily dose & route							
Treatment start date							
Treatment stop date							
Action taken in response to the event							
Dose maintained	☐	☐	☐	☐	☐	☐	☐
Dose reduced	☐	☐	☐	☐	☐	☐	☐
New daily dose On (dd/Mmm/yyyy)							
Drug permanently withdrawn On (dd/Mmm/yyyy)	☐	☐	☐	☐	☐	☐	☐
Druginterrupted From (dd/Mmm/yyyy)To (dd/Mmm/yyyy)	☐	☐	☐	☐	☐	☐	☐
Not applicable	☐	☐	☐	☐	☐	☐	☐
Event diminished after drug stopped/dose reduced?	Yes ☐ No ☐ N/A☐	Yes ☐ No ☐ N/A☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A☐	Yes ☐ No ☐ N/A☐
Event reappeared after drug/dose reintroduction?	Yes ☐ No ☐ N/A☐	Yes ☐ No ☐ N/A☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A☐	Yes ☐ No ☐ N/A☐

Causality assessment	SAE 1							SAE 2							SAE 3						
Related to Drug No.	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Not related to Drug No	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other causal factors (incl. medical history, procedure, etc.)																					

Concomitant medications

Drug name	Daily dose and route	Indication	Treatment start date	Treatment stop date	Continued

Name of reporter: Address:	Designation: Signature:

Annex 9: DR TB Patient Supervision Checklist

Government of the People's Republic of Bangladesh
National Tuberculosis Control Programme
Directorate General of Health Services
Mohakhali, Dhaka-1212

Name of Person Visited:	Date:

PART-A: PATIENT

DR TB registration No:	Patient Name:	Age: ……Years	Sex: ❑ M ❑ F
Patient Address:		Contact No:	
Diagnosis: ❑ RR ❑ MDR ❑ Pre -XDR ❑ XDR ❑ Other			
Medical diagnosis other than TB: ❑ DM ❑ Chronic renal insufficiency ❑ Chronic liver Disease ❑ Cardiovascular disease ❑ Psychiatric problem ❑ HIV/AIDS			
Date of Treatment started:	Date of Discharge from hospital:		

Name of prescribed drugs:	❑ Z ❑ E ❑ H high dose ❑ Mfx ❑ Lfx ❑ Cfz ❑ Lzd ❑ Pto ❑ Amk ❑ Cs ❑ Bdq ❑ Dlm ❑ PAS
Do patient know how long s/he has to continue the treatment and its importance	❑ Yes ❑ No
Does patient have any complain:	❑ Yes ❑ No
If Yes , what is/are the complain/s	❑ Fever ❑ Cough ❑ Hemoptysis ❑ Dyspnea ❑ Chest Pain ❑ Breathlessness ❑ Palpitation ❑ Yellow Eyes ❑ Swelling of Face ❑ Hearing Problem ❑ Visual Problem ❑ Other symptoms:
Measures taken (if any):	❑ Counselled ❑ Discussed with MO ❑ Referred to Hospital
Pregnancy status:	Pregnant: Yes ❑ No ❑ Uncertain ❑
Breast feeding:	Yes ❑ No ❑

Adverse effect if any:

Side Effect	Question to Ask Patient	Patient Response	Action Taken
Hearing loss	Are you having trouble hearing?	Yes ❑ No ❑	
Tinnitus and dizziness	Do you have any ringing in your ears or dizziness?	Yes ❑ No ❑	
Nausea	Have you had nausea the last week?	Yes ❑ No ❑	
Vomiting	Have you vomited in the last month?	Yes ❑ No ❑	
	Have you vomited up your medications?	Yes ❑ No ❑	
Diarrhea	Have you had diarrhea in the last month?	Yes ❑ No ❑	
Abdominal Pain	Have you had abdominal pain?	Yes ❑ No❑	
	Have you had black stools or vomited blood?	Yes ❑ No ❑	

Anorexia	Do you have a poor appetite?	Yes ❑ No ❑	
Neuropathy	Have you had pain or numbness or burning in your legs?	Yes ❑ No ❑	
Low Potassium	Have you had leg cramping?	Yes ❑ No ❑	
	Do you feel weak?	Yes ❑ No ❑	
Depression	Do you feel sad?	Yes ❑ No ❑	
	Do you have thoughts of committing suicide?	Yes ❑ No ❑	
Anxiousness	Do you feel anxious or agitated?	Yes ❑ No ❑	
Psychosis	Do you hear voices or see things that may not be there?	Yes ❑ No ❑	
Hepatitis	Have you noticed yellowing of your eyes or your skin?	Yes ❑ No ❑	
Allergy	Do you have any rashes?	Yes ❑ No ❑	
Joint Pain	Do you have any joint pain?	Yes ❑ No ❑	

Laboratory Result

Sodium		**Chloride**		**Potassium**		**Creatinine**	
Date		Date		Date		Date	
Glucose		**ALT (SGPT)**		**AST (SGOT)**		**Bilirubin**	
Date		Date		Date		Date	
WBC		**HB**		**Platelet**		**Ca**	
Date		Date		Date		Date	
Albumin		**Uric acid**		**TSH**		**Serum Lipase/amylase**	
Date		Date		Date		Date	
Microbiology Results:		Most recent sputum smear		Date:		Negative ❑ Positive ❑	
		Most recent sputum culture		Date:		Negative ❑ Positive ❑	
Electrocardiogram		Routinely done ❑ Yes ❑ No, If **Yes**, Most recent Date: If **No**, what are the reason?					
Audiometry (during injectable phase):		Done routinely ❑ Yes ❑ No If No, at are the reason?					

PART – B: DOT PROVIDER

DOT Provider name:	Designation:

Knowledge of the disease	Satisfactory ❑ Unsatisfactory ❑
Does the DOT provider visits patient daily? (feedback from patient)	Yes ❑ No ❑ If No, Reason: What action taken:
Record Keeping-Perfect	Yes ❑ No ❑
Does the DOT provider know about the FU schedule?	Yes ❑ No ❑
Does the DOT provider have enough knowledge on AEs?	Yes ❑ No ❑ If No, what steps taken?
Does the DOT provider count the drugs and cross check with the DOT record? (Physical verification)	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 ❑

Overall Comments:

Annex 10: Contact Investigation (CI) Form for DR TB

Government of the People's Republic of Bangladesh
National Tuberculosis Control Programme
Directorate General of Health Services
Mohakhali, Dhaka-1212

Date of Visit:

Block-A

Information of Index Patient		Name of the DOTS Corner	
Name		Treatment Initiation Centre	
Village/Ward		DR TB registration number	
Union		Name of the Contact Investigator	
Upazila		Phone number of contact investigator	
District		Name of the DOT provider	
Division		Designation of the DOT provider	
Phone number		Phone number of the DOT provider	

Block-B

Sl. No.	Contact Name	Age (Y/M	Sex M/F/Other	Relation Code *	Symptoms Code**	Refer Yes/No	Outcome Code***	Remarks

*Relation Code: 1. Household member, 2. Workplace member, 3. Neighbour, 4. Others
**Symptoms code: 1. Cough for 2 weeks, 2. Fever, 3. Weight loss, 4. Cough with blood
For Child: 1. Cough for 2 weeks, 2. Fever, 3. No significant weight gain, 4. Cough with blood, 5. Lethargy
***Outcome code: 1. Presumptive DR TB, 2. DS TB, 3. DR TB, 4. Did not come

Signature

Annex 11: Interim guidance for management of DR TB services during COVID-19 pandemic

Government of the People's Republic of Bangladesh
National Tuberculosis Control Programme
Directorate General of Health Services
Mohakhali, Dhaka-1212

Management of Drug Resistant TB (DR-TB):

a. For newly diagnosed DR-TB patients:

- All newly diagnosed multidrug-resistant and rifampicin-resistant TB (MDR/RR-TB) patients are preferred to start the treatment in DR-TB treatment hospitals according to the national guidelines.
- If a DR-TB patient cannot move to the hospital due to the lockdown, ambulatory treatment can be started at the community level.
- Sputum sample should be sent to the NTRL for second line LPA through sputum transport mechanism. If not possible, the patient will be preferred to start all oral longer regimen.
- MODC/ MO of the respective upazilla will advise for the baseline investigations according to the national guidelines and will communicate with nearby DR-TB treatment center over telephone and send the short history of the patient with the investigation reports through email. Alternatively, the list of baseline investigations can also be advised by the respective chest disease hospital through email where the patient will be registered. Any of the options can be opted which is feasible in the local context.
- The DR-TB treatment center will register the patient and provide a registration number, prepare the regimen and doses for the patient and send it back to the upazilla to start the treatment.
- Respective partner NGO will be responsible to collect the drugs from the CDH for one month.
- Upazilla outpatient DR-TB team will identify a suitable DOT provider who lives close to the patient's residence and can push injection. If any suitable DOT provider is not found, it is advised to start all oral longer regimen instead of shorter regimen and family DOTS will be encouraged. The TLCA or representative of partner NGO will train the family member on DOT and will also supervise DOT and adverse events over the phone.
- Sputum for monthly culture follow up should be sent to the NTRL/ RTRLs through the sputum transportation mechanism. If courier service is not available to send sample for culture, microscopy should be ensured at local level and further decisions should be taken after consultation with focal person of respective CDH over phone.

b. For the DR-TB patients already under treatment:

- Provide maximum one-month supply of drugs to DR DOT provider for the patients who have already started the DR-TB treatment either on the shorter or longer regimen.
- If the patient is in the intensive phase of shorter regimen and requires injection, the upazilla outpatient DR-TB team will identify a suitable DOT provider who lives close to the patient's residence and can push injection.
- If the patient is in the continuation phase of shorter regimen or receiving longer regimen who does not require injection, family DOTS can be encouraged. The TLCA or representative of partner NGO will supervise the DOT and adverse events over the phone.
- Sputum for monthly culture follow up should be sent to the NTRL/ RTRLs through the sputum transportation mechanism.

World Health Organization
Bangladesh