GUIDELINES ON PROGRAMMATIC MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS IN INDIA

2017

REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME
Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhavan, New Delhi
GUIDELINES
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Ministry of Health & Family Welfare, Nirman Bhavan, New Delhi
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Acknowledgements

The Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India (2017) have been developed as the end-product of a series of meetings and deliberations with national experts from the Government of India (GoI), WHO Country Office for India (WHO India) and key technical and developmental partners. These deliberations and workshop were organized by the Central TB Division (CTD), Ministry of Health and Family Welfare (MoHFW), GoI with technical and organizational support from WHO India over 2016 and 2017.

The deliberations and workshop involved discussions with several stakeholders, extensive review of literature and aligning with current and emerging evidence to address the prevailing epidemiology of drug-resistant TB (DR-TB) in India from initiatives such as:

- the recently concluded first national drug resistance survey (2014-16);
- lessons learnt from the roll-out of Bedaquiline containing regimen in 6 sites in 2016;
- revised technical and operational guidelines for TB;
- WHO PMDT Guidelines (2016) updates that recommend shorter multidrug resistant TB (MDR-TB) regimen with second line – line probe assay and other evidence based updates on management of DR-TB; and
- National Strategic Plan for TB elimination in India (2017-25) which in turn is aligned with the WHO End TB Strategy.

In October 2016, the National Experts Committee on Diagnosis and Treatment of TB recommended adoption of the updated WHO PMDT Guidelines (2016) along with geographical expansion of access to Bedaquiline with active drug safety monitoring in India.

We express our gratitude to Smt. Preeti Sudan, Union Secretary, MoHFW, GoI; Dr. Soumya Swaminathan, Deputy Director General – Programmes, WHO Geneva (former Secretary, Department of Health Research, GoI & Director General (DG), Indian Council for Medical Research (ICMR)); Dr. Jagdish Prasad, Director General Health Services (DGHS), GoI; Shri Manoj Jhalani, Additional Secretary & Mission Director, National Health Mission (NHM), MoHFW, GoI; Shri Arun Kumar Jha, Economic Advisor, MoHFW, GoI; Dr. B D Athani, Special DG, DGHS, GoI; Dr. G N Singh, Drug Controller General of India (DCGI), DGHS, GoI; Dr. Henk Bekedam, WHO Representative to India; Dr. Prakin Suchaxaya, Coordinator Health Programmes (WHO India); Dr Nicole Seguy, Team Leader Communicable Diseases Surveillance (WHO India) and Dr. Sunil D Khaparde, Deputy Director General (DDG), TB, CTD, GoI for providing leadership, encouragement and support to the core team as they updated the guidelines for PMDT in India (2017). This will play a major role in contributing to the rapid and effective control of (DR-TB) in the country.
We would like to place on record efforts of the core team from the Central TB Division and WHO India who took the lead in this process. Premier institutions, namely the National Institute of TB and Respiratory Diseases (NITRD), New Delhi; National TB Institute (NTI), Bangalore; National Institute for Research in TB (NIRT), Chennai; BJ Medical College, Ahmedabad, Rajan Babu Institute for Pulmonary Medicine & Tuberculosis (RBIPMT), New Delhi, King Edward Memorial (KEM) Hospital, Mumbai, Guwahati Medical College, Assam and Pharmacovigilance Programme of India (PVPI) as well as experts from technical agencies and developmental partners like The UNION, FIND, PATH, Clinton Health Association of India (CHAI) and the United States Agency for International Development (USAID) who contributed significantly to the process.

Eminent experts from the World Health Organization South East Asia Region Office (WHO SEARO) and the Global TB Programme, Geneva provided technical inputs in developing this document. WHO India ensured funding support through their developmental partners, the Lilly MDR-TB Partnership supported by Eli Lilly and Company. Further, Johnson and Johnson Co. India (Janssen & Janssen Co.) and USAID agreed to donate 10,000 courses of Bedaquiline through the Global Drug Facility with facilitation by WHO India.

The valuable contribution of prominent experts and officials from the above institutes and organizations and also those experts who reviewed this document, providing inputs for its finalization are well acknowledged. Special appreciation is due for the medical consultants of WHO–RNTCP technical assistance network for their inputs, particularly in aligning the content with the new DR-TB epidemiological knowledge, emerging evidence, national and global guidelines and the National Strategic Plan for TB elimination (2017-25). Special thanks to the communications team at WHO India for their crucial support in editing, formatting and designing this document.

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The guidelines were reviewed, edited and further enriched by Dr. A Sreenivas, Dr. A Dalal, Dr. C Lienhardt, Dr. D Falzon, Dr. E Jaramillo, Mr. E Thanaraj, Dr. H Sawhney, Dr. K Rade, Dr. M Gupta, Dr. P Darshini, Dr. P Kumar, Dr. P Mandal, Dr. R Sarin, Dr. V Oswal, Dr. V Bhatia, Dr V Kalaiselvan and Dr. V S Salhotra. Our special thanks to each one of them.
These guidelines are consistent with the WHO PMDT guidelines (2016), Companion Handbook to WHO Guidelines on PMDT (2014). The technical and operational aspects listed herein are intended to complement the existing RNTCP technical and operational guidelines and the National Strategic Plan for TB Elimination (2017-25) in India. These guidelines will now be implemented across India to gain and document experiences on feasibility, safety monitoring and enhancement in treatment outcomes of DR-TB patients to further guide the country in its refinement as national and global evidence emerges in future.
Foreword

The emergence of resistance to drugs used to treat tuberculosis (TB), particularly multidrug-resistant TB (MDR-TB), has become a significant public health problem in a number of countries and an obstacle to end TB. In India, available information from several drug resistance surveillance studies conducted in the past and the recently concluded national drug resistance survey 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 RNTCP 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.

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

These Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India (2017) are an advancement over the RNTCP Technical & Operational Guidelines, 2016 and the Guidelines for use of Bedaquiline under conditional access through RNTCP PMDT in India, 2016 and would now supersede those. They have been duly updated and aligned with the WHO End TB Strategy, Sustainable Development Goals (SDG) and WHO PMDT Guidelines, 2016 in order to cover advancing the country to scaling-up universal access to drug susceptibility testing for all diagnosed and notified TB patients. As part of the national strategic plan (NSP) 2017-25, decentralization of diagnosis and treatment of MDR-TB to district level, the recently endorsed WHO recommended second-line probe assay (SL-LPA), rapid molecular drug susceptibility test (DST) for second-line drugs, shorter MDR-TB regimen, DST guided regimen to cover all variety of DR-TB including Isoniazid (H) mono-poly DR-TB, use of newer drugs like Bedaquiline, revised recording reporting systems, e-NIKSHAY and pharmacovigilance systems for active drug safety monitoring and management (aDSM) have been outlined. As global evidence evolves, in future, these guidelines will be updated based on the revision of WHO DR-TB guidelines.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>aDSM</td>
<td>Active drug safety monitoring and management</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AFB</td>
<td>Acid Fast bacilli</td>
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<tr>
<td>AIC</td>
<td>Airborne infection control</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>Am</td>
<td>Amikacin</td>
</tr>
<tr>
<td>AMC</td>
<td>ADR monitoring center</td>
</tr>
<tr>
<td>Amx/Clv</td>
<td>Amoxicillin/clavulanate</td>
</tr>
<tr>
<td>ART</td>
<td>Anti-retroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Anti-retroviral</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>Bdq</td>
<td>Bedaquiline</td>
</tr>
<tr>
<td>BPL</td>
<td>Below poverty line</td>
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<tr>
<td>CAP</td>
<td>Conditional Access Programme</td>
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<tr>
<td>CBNAAT</td>
<td>Cartridge Based Nucleic Acid Amplification Test</td>
</tr>
<tr>
<td>CEM</td>
<td>Cohort event monitoring</td>
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<tr>
<td>Cfz</td>
<td>Clofazimine</td>
</tr>
<tr>
<td>Clr</td>
<td>Clarithromycin</td>
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<tr>
<td>Cm</td>
<td>Capreomycin</td>
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<tr>
<td>CMO</td>
<td>Chief Medical Officer</td>
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<tr>
<td>CP</td>
<td>Continuation phase</td>
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<tr>
<td>CPT</td>
<td>Co-trimoxazole preventive therapy</td>
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<tr>
<td>Cs</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>CTD</td>
<td>Central TB Division</td>
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<tr>
<td>CUP</td>
<td>Compassionate Use Programme</td>
</tr>
<tr>
<td>C-DAC</td>
<td>Centre for Development of Advanced Computing</td>
</tr>
<tr>
<td>C-DST</td>
<td>Culture and Drug Susceptibility Test</td>
</tr>
<tr>
<td>CL-HIV</td>
<td>Children living with HIV</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of AIDS</td>
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<tr>
<td>DBT</td>
<td>Direct Beneficiary Transfer</td>
</tr>
<tr>
<td>DCGI</td>
<td>Drugs Controller General of India</td>
</tr>
<tr>
<td>DDG</td>
<td>Deputy Director General</td>
</tr>
<tr>
<td>DDS</td>
<td>District drug store</td>
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<tr>
<td>DDR-TBC</td>
<td>District DR-TB Centre</td>
</tr>
<tr>
<td>DG</td>
<td>Director General</td>
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</table>
DGHS
Directorate General of Health Services
Dlm
Delamanid
DMC
Designated microscopy centre
DOT
Directly observed treatment
DOTS
Core approach underpinning the Stop TB strategy for TB control
DRT
Drug resistance testing
DR-TB
Drug-resistant tuberculosis
DR-TBC
Drug-Resistant Tuberculosis Centre
DSMC
Drug Safety Monitoring Committee
DST
Drug susceptibility testing
DTO
District TB officer
DVDS
Drug vaccine distribution management system
E
Ethambutol
ECG
Electrocardiogram
ECO
Extension of Community Health Care Outcomes
EP-TB
Extra-pulmonary tuberculosis
EQA
External quality assurance
Eto
Ethionamide
EU
European Union
FDA
Food and Drug Administration
FEFO
First expiry first out
FL-LPA
First line-line probe assay
FQ
Fluoroquinolone
GLC
Green Light Committee
GFATM
Global Fund for AIDS, Tuberculosis & Malaria
Gfx
Gatifloxacin
GMSD
General Medical Stores Depot
GoI
Government of India
H
Isoniazid
H^h
High dose isoniazid
HRCT
High resolution CT scan
ICH
International Conference on Harmonization
ICT
Information communication technology
ICMR
Indian Council for Medical Research
IP
Intensive phase
Ipm
Imipenem
IPAQT
Initiative for promoting affordable & quality TB test
IQC
Internal Quality Control
IRL
Intermediate reference laboratory
ISO
International Standard Organization
Km
Kanamycin
LC  Liquid culture
LFT  Liver function test
Lfx  Levofloxacin
LJ   Lowenstein Jensen
LPA  Line probe assay
LT   Laboratory technician
LTFU Lost to follow up
Lzd  Linezolid
MAC  Mycobacterium avium complex
MDR-TB Multidrug-resistant TB
Mfx  Moxifloxacin
Mfx^h High dose Moxifloxacin
MGIT Mycobacteria growth indicator tube
MIS  Management information system
MO   Medical Officer
MoHFW Ministry of Health and Family Welfare
MO-DMC Medical Officer-designated microscopy centre
MO-PHI Medical Officer- peripheral health institute
MO-TC Medical Officer TB control
MOTT Mycobacterium other than tubercle bacilli
MoU  Memorandum of understanding
Mpm  Meropenem
MPR  Mixed pattern resistance
MR   Mono resistance
MSS  Monthly stock statement
NAAT Nucleic Acid Amplification Test
NABL National accreditation board for laboratories
NDRS National Drug Resistance Survey
NDR-TBC Nodal DR-TB Centre
NGO  Non-Government Organization
NGS  Next-Generation Sequencing
NHPS National health protection scheme
NHM  National Health Mission
NIRT National Institute for Research in Tuberculosis
NITRD National Institute for Tuberculosis and Respiratory Diseases
NRL National reference laboratory
NSP  National strategic plan
NTI  National TB institute
NTM  Non-Tuberculous Mycobacterium
OBR  Optimized background regimen
Ofx  Ofloxacin
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>OPD</td>
<td>Out Patient Department</td>
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<tr>
<td>PAS</td>
<td>p-aminosalicylic acid</td>
</tr>
<tr>
<td>Pdx</td>
<td>Pyridoxine</td>
</tr>
<tr>
<td>PDR</td>
<td>Poly drug resistance</td>
</tr>
<tr>
<td>PHI</td>
<td>Peripheral health institute</td>
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<tr>
<td>PK/PD</td>
<td>Pharmacokinetic/pharmacodynamics</td>
</tr>
<tr>
<td>PL-HIV</td>
<td>People living with HIV</td>
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<tr>
<td>PMDT</td>
<td>Programmatic management of drug-resistant tuberculosis</td>
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<tr>
<td>PP</td>
<td>Private Provider</td>
</tr>
<tr>
<td>PQC</td>
<td>Product quality compliance</td>
</tr>
<tr>
<td>PSM</td>
<td>Procurement and supply management</td>
</tr>
<tr>
<td>PT</td>
<td>Previously treated</td>
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<tr>
<td>PTE</td>
<td>Pre-treatment evaluation</td>
</tr>
<tr>
<td>Pto</td>
<td>Protonamide</td>
</tr>
<tr>
<td>PvPI</td>
<td>Pharmaco-vigilance programme of India</td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>QSE</td>
<td>Quality System Elements</td>
</tr>
<tr>
<td>R</td>
<td>Rifampicin</td>
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<tr>
<td>RNTCP</td>
<td>Revised National Tuberculosis Control Programme</td>
</tr>
<tr>
<td>RR-TB</td>
<td>Rifampicin-resistant tuberculosis</td>
</tr>
<tr>
<td>R&amp;R</td>
<td>Recording &amp; reporting</td>
</tr>
<tr>
<td>RT-MERM</td>
<td>Real time medication event reminder monitor device</td>
</tr>
<tr>
<td>S</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>SA</td>
<td>Statistical Assistant</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SDG</td>
<td>Sustainable Development Goals</td>
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<tr>
<td>SDS</td>
<td>State drug store</td>
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<tr>
<td>SLD</td>
<td>Second line anti-TB drugs</td>
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<tr>
<td>SLDST</td>
<td>Second line drug susceptibility testing</td>
</tr>
<tr>
<td>SLI</td>
<td>Second line injectable</td>
</tr>
<tr>
<td>SL-LPA</td>
<td>Second line-line probe assay</td>
</tr>
<tr>
<td>SME</td>
<td>Supervision, Monitoring &amp; Evaluation</td>
</tr>
<tr>
<td>SoP</td>
<td>Standard operating procedures</td>
</tr>
<tr>
<td>SPC</td>
<td>Specimen Processing Control</td>
</tr>
<tr>
<td>STLS</td>
<td>Senior TB Laboratory Supervisor</td>
</tr>
<tr>
<td>STO</td>
<td>State TB Officer</td>
</tr>
<tr>
<td>STR</td>
<td>Standardized treatment regimen</td>
</tr>
<tr>
<td>STS</td>
<td>Senior treatment supervisor</td>
</tr>
<tr>
<td>TALFU</td>
<td>Treatment after lost to follow up</td>
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<tr>
<td>TAT</td>
<td>Turn-around time</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>TBHV</td>
<td>TB Health Visitor</td>
</tr>
<tr>
<td>Thz</td>
<td>Thioacetazone</td>
</tr>
<tr>
<td>ToR</td>
<td>Terms of reference</td>
</tr>
<tr>
<td>Trd</td>
<td>Terizidone</td>
</tr>
<tr>
<td>TU</td>
<td>TB Unit</td>
</tr>
<tr>
<td>UDST</td>
<td>Universal Drug Susceptibility Testing</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>UPT</td>
<td>Urine pregnancy test</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>USFDA</td>
<td>United States Food &amp; Drug Administration</td>
</tr>
<tr>
<td>WCO India</td>
<td>World Health Organization Country Office for India</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extensively-drug resistant TB</td>
</tr>
<tr>
<td>Z</td>
<td>Pyrazinamide</td>
</tr>
</tbody>
</table>
Chapter 1: Background and framework for effective control of drug-resistant tuberculosis

Globally, the first WHO endorsed PMDT services began in the year 2000. At that time, the Green Light Committee (GLC) was established to promote access to high quality second-line drugs for appropriate use in TB programmes. In 2002, the Global Fund to Fight AIDS, TB and Malaria (GFATM) started financing TB programmes, including DR-TB, thus greatly reducing the economic barrier to countries for DR-TB services. Since then, PMDT services have expanded rapidly. Based on data and experience from these projects and practices, further scientific evidence continues to evolve with respect to services for DR-TB.

1.1 History of PMDT in India

After successfully establishing RNTCP services across the country in 2006, the PMDT services were introduced in 2007 and complete geographic coverage was achieved by 2013. [1] To begin with, DR-TB services were offered to the subset of TB patients with the highest risk to develop drug resistance i.e., treatment failures. This was followed by a horizontal and vertical scale-up. Definite criteria were set to assess the risk and eligibility for the drug susceptibility test (DST). The DST was thus offered to TB patients who remained smear positive during follow-up; to previously treated patients; those who were HIV positive and people who had contact with a known DR-TB patient. [2] This would then lead to universal DST, i.e., DST to all diagnosed and notified TB patients. To conduct this, huge laboratory capacity in terms of geographic coverage, DST technology, trained laboratory personnel, quality assurance and certification were required. From a few national reference laboratories (NRL), and state level Intermediate reference laboratories (IRL) with solid or liquid culture and DST facilities, the country expanded its capacity to a wide network of state and regional level intermediate reference laboratories with solid and liquid culture DST and Line Probe Assay (LPA) and district level network of Cartridge Based Nucleic Acid Tests (CBNAAT). [1] [3]

Providing treatment to diagnosed DR-TB patients is extremely important. To begin with, only MDR-TB patients were offered treatment with a standard second-line regimen. Later, treatment with standard regimen was offered to extensively drug resistant (XDR) TB patients and MDR-TB with additional resistance to quinolone or second-line injectable. Procurement and supply chain management of second-line drugs is complex, since no standardized patient-wise boxes are manufactured, shorter shelf-life of some drugs and drugs do need temperature regulated storage and repacking. [2]

During 2011-12, there was a massive scale-up of all these facilities with concerted efforts of multiple stakeholders, resulting in countrywide coverage by 2013. Later in 2014, baseline
second-line DST facilities were established in a few intermediate reference laboratories, which also got scaled-up to the entire country in 2015. The progress of DR-TB treatment coverage is shown in Figure 1.1 below [1]:

Detection of DR-TB through RNTCP has been progressively rising with increased access to various forms of DST. In 2016, RNTCP was detected and treatment initiated in about 34016 patients of MDR-TB and 2476 patients of XDR-TB. [1]

In 2016, new drugs Bedaquiline (Bdq) was made accessible to DR-TB patients through a conditional access programme (CAP) under RNTCP. [4] In 2016, with the release of the revised Technical and Operational Guidelines, regimens to treat other forms of drug resistance, such as mono and poly resistance to first and second-line drugs were also included. [5]

Offering treatment to DR-TB patients was far more complex than today due to limited capacity of diagnosis and treatment. However, it still requires multidisciplinary drug resistant TB centres (DR-TBC) for pretreatment evaluation, observation and management of adverse drug reactions (ADR), where trained specialists, supportive human resources, efficient management information systems and AIC facilities are assured.
1.2 Magnitude of the DR-TB problem in India

Drug-resistant TB has been known from the time anti-TB drugs were first introduced for the treatment of TB. Currently, the WHO estimated incidence of Rifampicin (R) and MDR-TB in India is estimated to be around 147000. This translates to around 11 patients per 100 000 population annually as per the Global TB Report, 2017 [6]. Newer and higher quality information from various sources helped update the estimates of DR-TB. This revision in estimates has resulted in a rise of the perceived burden of DR-TB. However, this is not indicative of the problem of drug resistance being on the rise. The first national anti-TB drug resistance survey for 2014-16 (NDRS) concluded recently.[7] The following are the key findings of the NDRS report:

- under the survey 526 (92.5%) designated microscopy centres (DMC) participated and the quality of specimens collected was good, with >97% specimens accepted;
- 95% patient enrolments were completed within the planned period; and
- recovery rate for cultures was 94.6% in new and 92.8% in previously treated patients.

Table 1.1 Summary of DST patterns from the National Drug Resistance Survey

<table>
<thead>
<tr>
<th>DST pattern</th>
<th>New</th>
<th>Previously treated</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DST results available</td>
<td>3065</td>
<td>1893</td>
<td>4958</td>
</tr>
<tr>
<td>Sensitive to all drugs</td>
<td>2374 (77.46 %)</td>
<td>1196 (63.18 %)</td>
<td>3570 (72.01 %)</td>
</tr>
<tr>
<td></td>
<td>(75.93-78.92%)</td>
<td>(60.96-65.36%)</td>
<td>(70.73-73.25%)</td>
</tr>
<tr>
<td>Any drug resistance</td>
<td>691 (22.54 %)</td>
<td>697 (36.82 %)</td>
<td>1388 (28.00 %)</td>
</tr>
<tr>
<td></td>
<td>(21.10-24.10%)</td>
<td>(34.64-39.04%)</td>
<td>(26.77-29.29%)</td>
</tr>
<tr>
<td>MDR</td>
<td>87 (2.84%)</td>
<td>220 (11.62 %)</td>
<td>307 (6.19%)</td>
</tr>
<tr>
<td></td>
<td>(2.28-3.49%)</td>
<td>(10.21-13.15%)</td>
<td>(5.54-6.90%)</td>
</tr>
<tr>
<td>MDR with second-line anti-TB (SLI) resistance</td>
<td>6 (6.90 %)</td>
<td>5 (2.27 %)</td>
<td>11 (3.58 %)</td>
</tr>
<tr>
<td></td>
<td>(2.57-14.41%)</td>
<td>(0.74-5.22%)</td>
<td>(1.80-6.32%)</td>
</tr>
<tr>
<td>MDR with fluoroquinolone (FQ) resistance</td>
<td>21 (24.14 %)</td>
<td>46 (20.91 %)</td>
<td>67 (21.82 %)</td>
</tr>
<tr>
<td></td>
<td>(15.60-34.50%)</td>
<td>(15.73-26.89%)</td>
<td>(17.33-26.87%)</td>
</tr>
<tr>
<td>XDR</td>
<td>2 (2.30 %)</td>
<td>2 (0.91 %)</td>
<td>4 (1.30 %)</td>
</tr>
<tr>
<td></td>
<td>(0.28-8.06%)</td>
<td>(0.11-3.25%)</td>
<td>(0.36-3.30%)</td>
</tr>
</tbody>
</table>
any drug resistance among new patients is 22.54%, among previously treated (PT) patients is 36.82% and among all patients 28.02%;

- further, any H resistance (16% in all with 11.6% in new and 25.09% in previously treated patients) being the driver for R resistance;
- almost all RR-TB patients are resistant to H with/without other first or second-line drugs;
- MDR-TB is 6.19% in all patients (2.84% among new and 11.6% among previously treated patients);
- among MDR-TB patients, additional resistance to other first-line drugs is high at 74.3%. The drug specific resistance in combination with MDR-TB includes:
  - any Streptomycin resistance – 70% in new and 59.09% in PT;
  - any E resistance - 45.98% in new and 46.36% in PT; and
  - any Z resistance – 31.03% in new and 20.45% in PT.
- among MDR-TB patients, additional resistance to other second-line drugs includes:
  - any FQ (Ofx, Lfx, Mfx) is 21.82% (24.14% in new and 20.91% in previously treated patients);
  - any SLI drugs (Km, Am, Cm) is 3.58% (6.9% in new and 2.27% in previously treated patients); and
  - XDR-TB is only 1.3% in all MDR-TB patients (2.3% in new and 0.91% in previously treated patients).

- state level and cluster-wise variations clearly indicate that although the national DR TB situation is well within the range of previous state level surveys, there exist focal epidemics of DR TB in some states.

Programmatically, MDR-TB (at-least to H & R), Rifampicin resistance (RR-TB) and XDR-TB (at-least H, R, second-line injectable [SLI] and fluoroquinolones [FQ]) received priority. As facilities for detecting other varieties of resistance became increasingly available, making available regimens for their treatment also became a programmatic priority.

While prevention of development of drug resistance is of paramount importance for ending TB, early detection and immediate enrolment as well as completion of an effective treatment regimen are keys to interrupt on-going transmission, to prevent death and reduce chances of sequelae post-treatment. The programme has so far been able to successfully treat 46% of the cohorts of patients initiated on treatment 30-33 months ago. However, treatment outcomes vary from state-to-state. While few states were able to achieve more than 70% treatment success rate among the diagnosed MDR/RR-TB patients, others could achieve less than 40%, suggesting the variability of the health system to deliver treatment, care and cure. Main reasons attributed for the attrition were death and lost to follow-up (LTFU) during treatment. [1]
1.3 Causes of drug-resistant tuberculosis

Drug-resistant TB, like TB is a disease of poverty, expressed through microbial, clinical and programmatic channels. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. In clinical settings, an inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB. Clinical characteristics of patients have also been recognized where appropriately administered drugs have not achieved necessary drug levels to deal with all populations of mycobacteria. From a programmatic perspective, weak TB services lead to delay in detection and effective treatment of drug resistance and are unequipped to support patients to keep adherence to treatment and prevent ongoing transmission.

1.4 Prevention of drug-resistance

The problem of DR-TB cannot be addressed completely by standalone systems for detection and treatment of drug-resistance. Strong systems to detect, successfully treat and ensure long term disease-free status of TB patients, are required to prevent emergence of resistance. Thus, basic TB diagnostic and treatment services should receive priority and systems for early detection and treatment of drug-resistant forms of TB which should be integrated into existing TB services.

Improperly treated patients with resistant strains of TB will constitute a source of ongoing transmission of resistant strains. Health care facilities and congregate settings lacking of proper infection control measures as recommended by WHO contribute to maintain transmission. The interruption of transmission and not only rapid detection and immediate enrolment on effective regimens are therefore necessary to prevent the emergence of new DR-TB patients. Measures to prevent incidence and transmission of TB are also effective in prevention of drug-resistance. The framework for PMDT presented in this document is to be considered along with management of drug susceptible TB patients as a continuum of care.

1.5 Move to patient-centric care

Successful treatment and care can only result when patient preferences, values and needs are satisfactorily addressed along with PMDT services. This includes ensuring that the diagnosis of DR-TB is early, accurate and affordable; and the most effective treatment is delivered early and provided in a manner that is easily accessible to the patient, affordable and socially acceptable. At the same time it must ensure that the confidentiality and dignity of the patient is protected. It is the responsibility of the health system to make sure that the patient is treated successfully within the society s/he belongs to, enjoying all support which the community would otherwise provide to its members so that the new chain of infection is arrested at source and the cured member enriches his/her material, social and cultural
Prevention, management and mitigation of stigma and discrimination are essential elements of a patient-centered care approach to TB management.

1.6 Universal drug susceptibility testing

The programme is committed to providing Universal Drug Susceptibility Testing (UDST) for all diagnosed and notified TB patients. Depending upon resource availability, this service is progressively being made available throughout the country. A range of rapid molecular tests are available for UDST, such as Cartridge Based Nucleic Acid Amplification Test (CBNAAT) and Line Probe Assay (LPA).

In the past, patients were offered DST based on their risk of developing drug resistance. Over time, DST has been increasingly made available to the patient to lower levels of risk. Currently, all patients of TB apart from those not previously exposed to anti-TB treatment (ATT) are routinely offered at least the R resistance test. The revised algorithm for presumptive TB in the RNTCP Technical and Operational Guidelines, 2016 gives provision for testing presumptive patients for TB on CBNAAT for reliable and early microbiological confirmation and in these patients, R resistance information is available as a byproduct.

There are several additional DST technologies in the development pipeline. These tests will be made available progressively as they are endorsed for use by WHO. Recently, WHO endorsed LPA for use for DST of FQ class and SLI class. Currently, LPA labs are in preparation for rolling out this facility while DST on CBNAAT is offering more accurate and wider testing of resistance to R which is also in various phases of development.

1.7 DST guided treatment

The 2012 PMDT Guidelines were largely prioritized for dealing with RR, MDR and XDR types of drug resistant TB. This version will address management of all variants of DR-TB, including H mono/poly resistance (R sensitive) and various types of poly-drug resistance (mixed patterns beyond MDR/RR and XDR).

1.8 Decentralized DR-TB management

Previously, guidance was largely provided for centralized PMDT treatment initiation in inpatient settings. This version provides guidance on both inpatient and outpatient based treatment initiation for providing increased access to PMDT services. Inpatient-care for those who require it on medical grounds and drug supply chain management have been decentralized down to the district level.
1.9 Customized treatment supervision and patient support

Traditionally, treatment supervision methods were limited to direct observation of therapy (DOT) by a trained person other than family members. Move to a patient-centric approach would mean giving more priority for patient’s needs and preferences in view of better adherence in such a way that ethics and standards for DOT are met. In some patients, a family member might be able to ensure better treatment supervision and adherence as compared to an external individual visiting the home. With the development of information communication technology (ICT), there are options by which patients can reliably self-report drug consumption, be monitored and supported by various levels simultaneously. [3] The newer guideline favours the principle of adherence monitoring which has to be applied logically and judicially. These also provide options, whereby, the most appropriate modality of adherence monitoring may be used as a collective decision for the patient, treatment supporter and the Medical Officer (MO).

The necessity for supporting patient needs related to TB care in addition to treatment is increasingly being recognized. This version of the PMDT Guidelines includes a section on treatment support.

1.10 Newer drugs and regimen

There are newer drugs like Bedaquiline (Bdq) and Delamanid (Dlm) currently approved for conditional use by stringent drug regulatory authorities and for which WHO has provided interim guidance for their use under programmatic settings. These drugs, still under development, are expected to improve treatment outcomes among selected populations. [10] [11] Similarly, some of the earlier drugs like clofazimine and linezolid are being repurposed and recommended for use in the management of DR-TB. A few shorter MDR-TB regimens are being studied worldwide using combination therapy with newer drugs. However, till further evidence is available, WHO has recommended a shorter MDR-TB regimen for use for MDR/RR-TB patients without any additional resistance to FQ/SLI class based on available evidence. [12]

This version of the guidelines on the Programmatic Management of Drug-Resistant TB (PMDT) in India, 2017, integrates use of the shorter MDR-TB regimen and newer drug containing regimen under RNTCP with a DST guided regimen design.
Chapter 2: Structure and responsibilities

This chapter describes the structure and responsibilities for PMDT at various levels and the service cascade for DR-TB.

Diagnosis of DR-TB starts with identification of patients presumed to have DR-TB. This will keep on changing with availability of new technologies to detect resistance and the availability of resources to detect resistance and the prevalence of various types of resistance in the background population. Thus, every newly diagnosed TB patient could be a presumptive DR-TB in a population with a high background prevalence of resistance to the most potent anti-TB drugs. [13] Similarly, even the treatment failures may be presumed to fail due to reasons other than drug resistance in a population with very low background prevalence of resistance.

When PMDT (erstwhile DOTS Plus) was rolled-out in India in 2007, failures after treatment with Category 1 (2[HREZ]3 + 4[HR]3 for new TB patients or Category 2 (2[HREZS]3 + 1[HREZ] + 5[HRE]3 for previously treated TB patients only were considered as presumptive MDR-TB patients. Later, patients remaining smear positive during any follow-up, patients with history of previous TB treatment, people living with HIV (PLHIV) with TB and TB patients who are close contacts of DR-TB were added to the presumptive list (erstwhile Criteria C). [2] These vertical expansions were aligned with the horizontal geographic expansion since 2010. By 2013, the entire population had access to rapid molecular DRT (CBNAAT/LPA) at least for R and by 2014 all districts initiated DST as per Criteria C.

However, all eligible presumptive DR-TB patients may not be subjected to DST if the patients are not closely monitored and health service staff and Medical Officers are not keen. The key adjectives to ‘identification’ of presumptive DR-TB patients are ‘early’ and ‘complete’. From identification of presumptive DR-TB patients to initiating treatment of confirmed DR-TB patients, there are a chain of events that are prone for loss of patients. The first event is the patient becoming presumptive DR-TB as per the prevailing criteria. This is followed by identification, referral, passive reporting/active tracking of referred presumptive patients, collection and transportation of biological specimen, rejection and retesting of specimens if it occurs, reporting of results, referral of confirmed patients for treatment and patients reaching DR-TB appropriate service delivery sites for initiating treatment. At each point, a proportion of patients are lost.

The “WHO End TB Strategy” recommends every country to advance towards knowing at-least the RR-TB status of all TB patients at the time of diagnosis to guide appropriate treatment decisions.
2.1 State-level structure and responsibilities

While a national expert technical working group has developed national policies, technical and operational guidelines, the state-level is where the majority of planning activities, implementation and monitoring occur. The overall structures and roles are summarized in Figure 2.1 below. The State PMDT Committee is responsible for developing the plan of action for implementation, expansion, maintenance, supervision, monitoring and quality enhancement of PMDT services in the respective state. The composition and terms of reference of the State PMDT Committee are detailed in Annexure 1.

![Figure 2.1 Overall PMDT structures and roles]

- Diagnose RR-TB patients at district level
- Maintain records & NIKSHAY

- Identify presumptive case, refer specimens
- Support, supervise, manage DR-TB patients
- Communicate results to patients

- Identify suspects, refer specimens
- Coordinate for test results
- Refer patients to N/DDR-TBC
- Coordinate care & drug flow from district drug store to field level
- Maintain records, NIKSHAY, monitor & supervise

- Manage minor adverse effects
- Refer patient for the treatment initiation
- Collect and refer follow-up specimens

2.2 Drug resistant-tuberculosis centre

Programmatic and clinical management of DR-TB is complex but feasible when the health system is strengthened to effectively integrate what is necessary. Treatment of drug-resistant TB is not completely based on centralized and institutionalized care for the entire duration. In fact, clinical care needs the presence of a clinical and patient support expert resource centre. This is the DR-TB Centre which is a 20-30 bedded tertiary care facility established to serve a population of approximately 10 million, with an airborne infection...
control compliant ward, facilities for pretreatment evaluations, treatment initiations, follow-up monitoring and management of adverse drug reactions, prevention and relief of physical and social suffering caused by the disease and its treatment, complications and comorbidities. [2] All these activities are supported by the programme staff in addition to having counselling for patients and undertaking data management.

Currently, 147 DR-TBCs are established across India (2017), one for approximately every 10 million population, including some in private institutes partnering with RNTCP. [1] About 5 to 10 districts are attached to each centre. DR-TB patients are admitted for a short period and once stabilized on treatment, discharged with advance intimation to the districts and referred back to their districts for continuation and completion of treatment. During treatment, they are referred back to DR-TBCs for change of regimens and management of ADRs. [2]

However, periodic monitoring and review by the programme revealed that many challenges are currently being faced by the programme. These relate to delayed initiation of treatment, inadequate bed capacity, compromised follow-up, insufficient and untimely relief of suffering and poor accessibility. In most situations, patients have to travel long distances, including loss of work hours and family income, resulting in catastrophic expenditures. Further, the travel poses additional risk of transmitting infection in transit.

Since March 2016, 500 CBNAAT machines have been made functional in addition to 128 existing machines to cover access to most of the districts in India. [1] These machines are currently utilized at the district level for testing presumptive DR-TB patients and presumptive TB patients among key populations to detect presence of M. Tb in the biological specimen with concomitant detection of RR-TB if present. A 35% rise in MDR/RR-TB patients notified was observed in Q2 2016 against Q1 2016 which is expected to further increase in future. [1] This is likely to increase the demand for treatment significantly. Treatment and care capacity needs to be enhanced to meet with this diagnostic capacity in every district in India. This will empower districts to enable the “test and treat approach” to eliminate delays in diagnostic and treatment initiation pathways for all MDR/RR-TB patients within the district. However, until initiation of treatment, infection control services and advice need to be available for all diagnosed DR-TB patients.

Hence, to decentralize the pretreatment evaluation, treatment initiation of RR-TB or H mono/poly DR-TB and follow-up processes, two distinct types of DR-TBCs will be accordingly established. The existing nodal DR-TB centre (NDR-TBC) will continue for approximately 10 million populations. District DR-TB centre (DDR-TBC) should be established for at least every district. Some of the states have already established these centres. Additionally, DDR-TBC that could function on an outpatient department (OPD) basis are considered to manage DR-TB patients on OPD basis. Structure and function of these centres and provisions under
RNTCP to upgrade them to function as RNTCP designated DDR-TBC and NDR-TBC are detailed below.

Decentralization is necessary to ensure prompt treatment initiation with scale-up to universal DST, shorter MDR-TB regimen and DST guided regimen with/without newer drugs, and delivery of patient care including nutritional assessment and support, palliative and end-of-life care and management of co-morbidities.

2.2.1 District DR-TB centre

The DDR-TBC is responsible for the initiation and management of uncomplicated DR-TB patients like RR-TB or H mono/poly DR-TB in a district, not only on inpatient basis, but also on outpatient basis, wherever advisable and possible.

**Rationale for setting up District DR-TB centres**

The advantages of decentralized “test and treat approach” are:

- early and faster initiation of treatment of all diagnosed DR-TB patients;
- bringing care closer to the residence of majority of the DR-TB patients;
- significant reduction in catastrophic expenditure including loss of work hours and family income;
- rationally minimizing the need and duration for hospitalization;
- minimizing travel of patients, thereby transmission risks during travels;
- accountability of the district programme management units; and
- rationalizing utilization of existing DR-TBCs to enable them to concentrate in more complex clinical decisions and ensuring quality assurance of treatment and research.

The 147 existing DR-TBCs will be designated as NDR-TBCs, serving as referral centres for DDR-TBCs. The NDR-TBC located at a district may also serve as DDR-TBC for the same district based on the work load as well as a referral centre for other districts.

**Process of establishing DDR-TB centres**

The DDR-TBC can be established at institutes in a certain order of preference, namely, medical colleges, district hospitals, TB hospitals and NGO/private/corporate institutes/other sector hospitals with the availability of required clinical expertise.

It must be ensured that the DDR-TBC is in close proximity of the CBNAAT site/ LPA lab in the district. There should be atleast one DDR-TBC available in the district which should be identified by the State TB officer (STO) in consultation with the District TB Officer (DTO) and Chief Medical Officer (CMO) of the district. However, more than one DDR-TBC can be
established wherever needed to improve access. The district authorities may take a decision to establish more than one centre based on the workload of the first centre and the distance taken by patients to travel. This should be in consultation with CTD. The composition and terms of reference of the DDR-TBC Committee is detailed in Annexure 1 and a checklist to guide preparation of DDR-TBC is enclosed at Annexure 2.

Each DDR-TBC should preferably have an airborne infection control (AIC) compliant indoor facility to accommodate at least 4 DR-TB patients with male and female separation (wherever indoor DDR-TBC is proposed) outdoor facilities and specialists trained in clinical management of DR-TB patients. Patients who are ambulatory can be managed on an OPD basis. DDR-TBCs could operate in public or private sector institutions, linked with appropriate schemes for private sector engagement under National Partnership guidelines of RNTCP.

The DDR-TBC should be established preferably under auspices of the Department of Respiratory Medicine/General Medicine. The committee may be formed with members of various clinical specialties in the same institution if available or through other public/private sector institutions. This committee should meet every month or whenever required. The DDR-TBCs will continue to be attached to concerned NDR-TBCs for referral and expert consultations.

The DDR-TBC would leverage upon as well as strengthen the capacity of the health system to respond not only to DR-TB but also to its most common comorbidities, which have a significant country burden as well (e.g. HIV, diabetes, hepatitis C, mental health) and other clinical and public health services such as nutritional assessment and management of undernutrition, respiratory infection control, patient-centered care, pharmacovigilance, digital health, palliative/end-of-life care services.

**Requirements from institute and provision from RNTCP for establishing DDR-TBCs**

Requirements from the institute:

- should preferably be a tertiary/secondary care institute;
- wherever indoor DDR-TBC is proposed, at least 2 beds each, for male and female separated structurally or temporally within existing wards/ separate isolation areas if available or necessary;
- for indoor and outdoor DDR-TBC, an outpatient clinic and a separated well ventilated waiting area in an open-air and shaded area to be made available;
- administrative, environmental and personal protective measures for airborne infection control to be in place in all indoor and outdoor facilities; [14]
- all PMDT services to be provided free of cost to the patient;
- DDR-TBC Committee to be formally established with minimum set of experts available at the district level as per Annexure 1;
• relevant specialties like physician (Nodal Officer), psychiatrist, dermatologist, ENT specialist, nutritionist, anesthesiologist or palliative/end of life care specialist, cardiologist and gynaecologist etc., to be made available. This can be direct or through honorary visits mainly to provide specialist consultations;

• State-level training of DDR-TBC committee doctors (including Chairperson), where trainers including from NDR-TBC committee members can serve as facilitators;

• routine clinical, radiological, audiological, biochemical investigation and ECG facility to be made available for pretreatment evaluation and follow-up monitoring at no cost to patient;

• ancillary drugs to be provided as per DDR-TBC Committee’s advice at no cost to patients;

• doctors, nursing and support staff should be available from the institute;

• records and reports to be maintained for PMDT;

• NIKSHAY entries to be done on real time basis with regular electronical updates; and

• financial requirements to be availed through institute/state budgets or National Health Mission (NHM).

Provision under RNTCP:

• Existing MO DTC/ 2ndMO of DTC/ MO Medical College will provide support to the physician in-charge serving as nodal officer of the DDR-TBC;

• DR-TB Counsellor for counselling patients as per RNTCP NSP 2017-25;

• District DR-TB TB-HIV Supervisor to maintain all records and reports including NIKSHAY entry and coordination with all PHI and TB Unit staff;

• training concerned staff and availability of formats and registers for PMDT;

• Ensuring availability of second-line anti-TB drugs; and

• Computer, internet facility and NIKSHAY login ID for the institute.

Functions of the DDR-TB centres

The package of services at these DDR-TBCs would include:

Pre-treatment evaluation (PTE): All investigations (detailed in the relevant section) would be done within the district, at no cost to the patients. If there are some investigations which are not available within the district, then adequate linkages will be established with the private laboratories with proper memorandum of understanding (MoU) mechanism as per schemes available under the National Partnership Guidelines. Since the drugs used for the treatment of DR-TB patients are known to produce adverse effects, a proper pretreatment evaluation is essential to identify patients who are at increased risk of developing such adverse effects.
Providing counselling to patient and family members: Counsellor at the DDR-TBC will provide counselling and health education, an essential part of the social support to the DR-TB patient and his/her family members about the disease, necessity of taking regular and adequate treatment, possible adverse events and memorandum of understanding (steps to be taken, mechanisms of TB transmission, prevention and mitigation of stigma and discrimination, nutritional counselling and assistance to avail social support and social protection schemes. Health education and counselling is provided to all patients and family members at different levels of health care, right from one at the periphery to those at the DR-TB facility. It is started at the initial point of contact and carried out on a continuous basis during all visits by the patient at the health facility. The continuous counselling and motivation is essential, not only for the patient but also family members and caregivers to ensure treatment adherence.

Treatment initiation of RR-TB or H mono/poly DR-TB patients: Treatment initiation based on results of first-line DST with CBNAAT or LPA will be done by the DDR-TBC committee. Treatment of the patient can be initiated by the nodal person of DDR-TBC with post facto approval of other committee members after pretreatment evaluation of the patient is completed. PMDT treatment card and patient treatment booklet are opened; first dose is given under supervision and registration of patients done at the DDR-TBC using the revised PMDT treatment register. Before starting treatment, the patient should be instructed in detail about potential adverse effects that could be produced by the prescribed drug regimen and if and when they occur, to notify the treatment supporter or healthcare provider.

Referral of patients to NDR-TBC for regimen change: The regimen may have to be changed in any of the following circumstances:
- additional laboratory confirmed resistance to second-line drugs;
- severe adverse events known before treatment or during follow-up treatment;
- seriously ill patient with very low general condition or as evaluated by DDR-TBC any time before or during treatment; and
- patient with failing regimen or returning after treatment interruption of >1 month or emergence of any exclusion criteria for standard regimen.

Providing travel enablers: This will be provided to the patient and one attendant during PTE, initiation of treatment and follow-up visits as per RNTCP guidelines.

Follow-up monitoring: DDR-TBC committee would ensure timely follow-up for all DR-TB patients initiated on treatment as per the follow-up schedule for clinical, biochemical and
culture including audiometry, mental health monitoring and ECG monitoring for QTC interval as applicable.

**Management and monitoring of adverse drug reactions:** The DDR-TBC committee doctors, nurses, treatment supporters and supervisory staff, will prevent, monitor, manage, document all the adverse events routinely and the doctor will report them as per the aDSM framework. The PTE serves to establish a baseline and may identify patients who are at increased risk for adverse effects or poor outcomes. Laboratory investigation including audiometry and periodic ECGs will be done as per the follow-up schedule. These are invaluable for detecting certain adverse effects that are more occult and before serious harm is done. Most of the ADRs can be prevented and managed by the DDR-TBC. If required, the patients may be referred to the NDR-TBC for the management of the serious ADRs after providing initial management.

**Recording and reporting:** All records and reports for DR-TB patients managed at the DDR-TBC will be maintained by the respective DDR-TBC staff at the district level.

**NIKSHAY:** Real time entries, periodic updating of patient information and analysis for corrective actions need to be ensured from each DDR-TBC.

**Airborne infection control measures:** These would be implemented as per the National infection control guidelines. [14] During routine household visits, patient and family members will be advised on measures needed for infection control by the concerned health staff.

**Nutritional assessment:** Nutritional assessment will be undertaken for all patients and the corresponding nutritional advice and support will be provided, according to guidelines for nutritional assessment and support for TB patients in India.

**Mental health:** Assessment of mental health is essential in all patients at the time of diagnosis and regularly monitored in all patients especially those receiving cycloserine.

**Palliative care:** Palliative/end-of-life care with priority for patients with XDR-TB and other MDR-TB patients with poor prognosis will be provided in consultation with the NDR-TBC.

### 2.2.2 Nodal DR-TB centre

Patients with additional resistance to second-line drugs, drug intolerance, contraindications, failing regimen, patients returning after treatment interruption of >1 month, emergence of any exclusion criteria for standard regimen for RR-TB or H mono-poly DR-TB regimen, non-TB *mycobacterium* (NTMs) and those needing palliative care would be managed at NDR-TBC.
Process of establishing the NDR-TB centre

The existing DR-TBC must be upgraded to function as NDR-TBC. Additional NDR-TBC as required must be established under the auspices of the Department of Respiratory Medicine or Department of Medicine (if the former department does not exist). NDR-TBC Committee is a clinical committee where the Head of Department (HoD) or a senior faculty member of the department of Respiratory Medicine (General Medicine) is the Chairperson and HoDs or senior faculty members of other specialties are members. Clinical function of these committees should be adequately supported by the administrative or management committees of the institution in which the STO must be ex-officio member. (composition and terms of reference of NDR-TBC Committee are detailed in Annexure 1).

The requirements from the institute (listed below) must be provided by the Government medical college/ institutes, including free laboratory investigations and ancillary drug supply as part of their commitment for which no reimbursement will be available from the programme. To manage paediatric DR-TB, a specific AIC compliant isolation area in the paediatric ward in the institute of NDR-TBC must be designated. However, government medical colleges/ institutes will be eligible for all provisions from RNTCP listed above along with one-time provision for upgradation of the ward to incorporate AIC measures as per norms of costing.

Private and NGO hospitals are considered to serve as NDR-TBC at places where a government medical college is not available. A scheme is available for such engagement under National partnership guideline of RNTCP.

Requirements from the institute and provision from RNTCP to establish Nodal DR-TB centres

Requirements from the institute:

- should preferably be a tertiary care institute;
- separate ward for male and female patients should be available with at least 10 beds in each;
- all PMDT services (beds, investigations, ECG and ancillary drugs for management of adverse drug reactions) to be provided free of cost to the patient;
- relevant specialties including respiratory medicine, general medicine, psychiatry, dermatology, ENT, ophthalmology, gynaecology, paediatrician, anaesthesiologist and cardiologist should be available directly or through linkages;
- NDR-TBC committee to be formed;
- national training of NDR-TBC committee members (including Chairperson);
- National AIC Guidelines to be implemented in DR-TB wards and outpatients setting. (Annexure 3); and
• routine clinical laboratory investigation facility to be made available for pretreatment evaluation and monitoring;
• ancillary drugs should be available;
• management of adverse drug reactions (ADR) as per PMDT guidelines;
• doctors, nursing and support staff should be available from the institute;
• records and reports to be maintained for PMDT; and
• quarterly reports to be submitted electronically.

Provision under RNTCP

• remuneration of Senior Medical Officer & Statistical Assistant and Counsellor;
• training, formats and registers for PMDT;
• second-line anti TB drugs; and
• computer, internet and NIKSHAY ID for the facility.

Functions and responsibilities of Nodal DR-TB Centres

The package of services at these NDR-TBCs would include:

Pretreatment evaluation: Patients should be examined by specialist members. The pretreatment investigations should be done free of cost. If there are some investigations which are not available within the public sector, then adequate linkages need to be established with the private sector with proper MoU mechanism as per schemes available under the National Partnership Guidelines. Pretreatment evaluation should include a thorough clinical evaluation by a physician, chest radiograph, haematological and biochemical tests detailed below. Since the drugs used for treatment of DR-TB are known to produce adverse effects, a proper pretreatment evaluation is essential to identify patients who are at increased risk of developing such adverse effects. A thorough clinical examination should be done during pretreatment evaluation (details of pretreatment evaluation are given in relevant sections);

Counselling to patient and family members: As detailed in DDR-TBC section;

NIKSHAY: As detailed in DDR-TBC section;

Travel enablers: These will be provided to the patient and one attendant during PTE, initiation of treatment and follow-up visits as per RNTCP guidelines;

Follow-up monitoring and management of adverse drug reactions: As detailed in DDR-TBC section, patients referred from DDR-TBC will be appropriately managed;

Providing clinical decision, referral, management support and training to districts;
**Airborne infection control measures:** As detailed in DDR-TBC section;

**Nutritional assessment:** As detailed in DDR-TBC section;

**Mental health:** As detailed in DDR-TBC section; and

**Palliative care:** Palliative/end-of-life care with priority for patients with XDR-TB and other MDR-TB patients with poor prognosis will be provided. In addition, guidance will be provided by NDR-TBC to the DDR-TBC and concerned health staff for palliative care at community level.

### 2.3 DR-TB services for patients seeking care in the private sector

The programme recognizes the fact that although free quality diagnostic and treatment services are available in the public sector, a significant number of patients are seeking health services from the large unorganized private/other sector. Reaching out to these patients is equally important, especially to deliver essential public health services to prevent the spread of disease, emergence of drug-resistance, to support TB patients on treatment and address comorbidities which adversely affect treatment outcomes. Patients seeking care in private/other sectors are equally eligible for diagnostics, drugs and all supportive services offered to patients seeking care in the public sector.

Screening for presence of drug resistance, access to quality diagnosis of DR-TB, access to second-line anti-TB drugs including newer drugs and shorter regimen for the patient diagnosed with drug-resistance TB available under RNTCP can be systematically offered to patients seeking care in the private/other sector. This includes all treatment support services like pretreatment investigations, counselling, treatment adherence support, management of adverse drug reaction etc., as part of public health actions to be taken by the public sector after any TB patient is notified.

A strong and sustainable partnership between the programme and providers is necessary to establish linkages to ensure availability of all services for any DR-TB patient irrespective of where the patient chooses to seek care. One of the options for such linkages available within the programme currently is the National Guidelines for Partnership (2014). [15] The Guideline provides options for purchasing services for diagnosis, specimen transportation, DR-TB centres and treatment support to all type of TB patients. It also provides some programme management options like packaging of anti-TB drugs which may be used based on the requirement for repackaging second-line anti-TB drugs at the State drug store.

States can innovate and use flexibility of budget options provided under the NGO-PP head (H.9) under RNTCP to extend services in private sector. As per norms of existing budget, the
State can use 10% of the NGO-PP head budget to involve NGOs or private providers and use 30% of the NGO-PP head budget for innovative interventions for patients who seek care in private/other sectors. PMDT services for patients seeking care in the private/other sectors can be accessed from RNTCP at all levels. However, this would be guided by the willingness on part of the patient as well as provider and hence there needs to be flexibility and choices for the provider and patients to avail these services in various situations. Access to DST must be ensured in consultation with providers. With expansion of CBNAAT services up to district level, states need to arrange for DST of notified TB patients as per eligibility criteria followed under the programme.

As states advance DST coverage to universal DST, they need to ensure that all notified TB patients undergo DST at least for R. To avail services available under RNTCP, efficient specimen collection and transport system should be established from the private/other providers to the nearby CBNAAT laboratory. Cost of such specimen transportation system should be borne from the relevant budget head of the patient support system. As an option, the NGO/any other agency may be engaged for specimen collection and transport using partnership options under the National Partnership Guidelines. Laboratory services for C-DST of first-second-line drugs as well as DR-TB treatment services can also be purchased from the private/other sector as per the National Partnership Guidelines, if required.

For patients diagnosed as DR-TB patients in the private sector, efforts should be made to put in place patient-friendly and provider-convenient system of referral to DR-TBCs. For such patients, the DR-TBC should provide public health action which includes contact investigation, family counselling, treatment adherence support, comorbidity testing, follow-up investigation, reporting of treatment outcomes, pharmacovigilance and social protection linkages.

For increasing capacity of DR-TB treatment services and utilizing experts/health institutes in expanding access, the State should consider engaging private health institutes or provider for DR-TB Centres. There are three options available under National Partnership Guidelines. namely, DR-TB centres with wards/ on outpatient basis/ private specialist to be provided honorarium for supporting public sector DR-TB patients in clinical management.

If the provider has the capacity to initiate an appropriate DR-TB treatment regimen as per WHO recommended principles of designing a regimen and is willing to avail treatment support services including second-line drugs from RNTCP, efforts should be made to partner with such institutes to serve as a DR-TB Centre as per National Partnership Guidelines.

A strong and sustainable partnership between the programme and providers is necessary to establish linkages to ensure availability of all services for any DR-TB patient irrespective of where the patient chooses to seek care.
Access to PMDT services including newer drugs to patients seeking care in private/other sector

PMDT services including newer drugs like Bedaquiline would be available through regulated access from RNTCP and can be provided to the patient seeking services in private/other sector. Again, priority providers should be mapped by every state for partnership. The mechanism for access to PMDT services including newer drugs for patient seeking care in the private sector are detailed in Chapter 7.

2.4 Preparation for introduction of newer regimen and drugs

In India, RNTCP has introduced a new drug Bedaquiline (Bdq) as per WHO interim recommendations in 2016 through conditional approval of DCGI. [4] Bdq is currently available through RNTCP under the conditional access programme and is not available to the open market in India. There are few prerequisites proposed for states to expand access under the RNTCP programme:

- availability or linkage with a laboratory with expanded second-line DST;
- establishment of district DR-TB centre in every district as per guidelines;
- availability of a nodal DR-TB centre with all requisite specialists as per guidelines;
- availability of human resources trained for introduction of newer drugs and regimen including staff at DR-TB centres, labs, drug stores, state, districts and field level;
- availability or access to all requisite laboratory investigations for pre-treatment evaluation and follow-up monitoring including electrocardiography (ECG) as per technical specifications (Annexure 4);
- mechanism for active drug safety monitoring and management (aDSM) [17]; and
- updated recording and reporting systems with NIKSHAY readiness.

2.5 Coordination

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

**Central TB Division (CTD), MoHFW, GoI:** The CTD is the central coordinating body for activities described in the framework. Commitment of necessary resources, particularly towards a strong central management team, ensures all aspects are in place from the procurement of second-line anti-TB drugs to appropriate implementation and monitoring of PMDT service. As needed, partnerships with all relevant health care providers can be built. The CTD is supported by a National PMDT Committee, comprising members from CTD, the three central TB institutes (NTI, NIRT and NITRD), medical colleges and WHO.
**Local health system:** RNTCP PMDT activities will be tailored to fit into the respective state and district levels’ infrastructure. The exact organizational structure of RNTCP PMDT services may vary between different settings depending on how local health care is provided. Transfer between hospitals to outpatient settings or between Treatment centres requires great care, advance planning and good communication. Given the type of care required in the treatment of DR-TB, a team of health workers including physicians, nurses and social workers (wherever available) should be used.

**Community level:** Community involvement and communication with community leaders can greatly facilitate implementation of PMDT and may respond to needs that cannot be met by medical services alone. Community education, involvement and organization around TB issues can encourage a feeling of community ownership of TB programmes and reduce stigma. In some circumstances, communities can help address the patient’s interim needs including provision of treatment support, food and/or housing, vocational support etc.,

**2.6 Overview of model of care**

Integration of PMDT services will require multiple care levels to work in coordination. No longer can the field level unit be totally self-sufficient. The care at the field level is supported by the laboratory and the DR-TB, coordinated by the district and supported by the State. This is depicted in the Figure 2.2.
Supportive services for DR-TB patients are an essential component of comprehensive DR-TB care. Core strategies like screening for drug resistance, DST guided treatment, treatment regimen containing newer drugs, ensuring uninterrupted supply of diagnostics and second line drugs, ancillary drugs for management of adverse drug reactions, treatment adherence support, patient education and counseling are essential, however, these need to be supplemented by appropriate nutritional support, linkage to various social protection measures like direct benefit transfers to make it more comprehensive. Prevention of DR-TB transmission through adequate infection control as well as averting amplification by appropriate treatment of drug sensitive TB, remains the top priority to fight with DR-TB problem. Strategies for DR-TB management are depicted in figure 2.3 and included in the NSP (2017-25). [3]

![Figure 2.3 Strategies for DR-TB management](image)
Chapter 3: National strategic plan for universal access to quality diagnosis and treatment of DR-TB

This chapter provides a brief overview of the RNTCP PMDT vision under the National Strategic Plan (2017-25) for Tuberculosis elimination by 2025. The National Strategic Plan (NSP) sets out the strategic direction and key initiatives that MoHFW, GoI will undertake in the period, 2017 to 2025 for working towards achieving the goals of eliminating TB by 2025. This includes the strategy for prevention and management of DR-TB; strategy to strengthen laboratory capacity and treatment services; and nationwide scale-up of new interventions under PMDT. [3]

3.1 PMDT expansion plans and progress

RNTCP expanded PMDT services to all districts in the country by March 2013. The systematic participatory planning undertaken by CTD with all states for phased scale-up of PMDT services in 2010 keeping available/planned resources with secured funding in mind and intensive regional review for course correction over the last five years have enabled the programme to successfully scale-up PMDT services as per the national PMDT and lab scale-up plans (2009-2014). The enormous efforts put in and cooperation extended to CTD by every state is well appreciated. However, states since 2011 were expected to strive to consolidate the current policy of offering DST to presumptive DR-TB and CBNAAT to presumptive TB among PLHIV, children and EP-TB with baseline second line DST to RR-TB patients.

The National Strategic Plan (2012-17) for RNTCP set the goal of universal access to quality diagnosis and treatment for all TB patients (including DR-TB and TB HIV). [18] The year 2014 saw large strides being undertaken with many new initiatives and policy changes in RNTCP-PMDT. Some examples include the launch of the first nationwide anti-TB drug-resistance survey of India and formulation of guidelines on DST guided treatment for drug-resistant TB patients.

The national PMDT and lab scale-up plans were accordingly updated for the next five years (2015-20) to align them with this goal with part-funding secured through the Global Fund NFM. The revised RNTCP Technical and Operational Guidelines 2016 [5] (updated in accordance to the WHO End TB Strategy [13]), guidelines for use of Bedaquiline under conditional access in RNTCP PMDT [4] and expansion of CBNAAT services were launched by the Hon’ble Health Minister of India in March 2016. [1]
3.2 National Strategic Plan (2017-25) and PMDT

PMDT is one of the thrust areas of the RNTCP National Strategic Plan. India’s achievements in the TB programme over the past decade have been remarkable. India achieved complete geographical coverage for diagnostic and treatment services for MDR-TB in 2013, with a remarkable 139369 persons with MDR-TB diagnosed and 126136 put on treatment till 2016.

The National PMDT scale-up plan for 2017-2020, an operational plan, was developed by consolidating state-wise PMDT micro-plans developed during the series of regional PMDT review meetings with 35 states organized by CTD at north, south, west, east and northeast zone in the year 2015-2016. Outputs included clarity and transparency on national training and district appraisal needs, laboratory scale-up requirements, national/state/district responsibilities understood by all and scale-up plan of Bedaquiline, shorter MDR-TB regimen and DST guided treatment.

Specific objectives for PMDT under NSP are:

- by end 2017, complete nationwide geographical coverage of access to baseline second-line DST using SL-LPA, access to shorter MDR-TB regimen and newer drugs like Bedaquiline;
- by 2025 ensure Universal access to rapid molecular DRT for all diagnosed TB patients; Universal access to DST guided treatment and expands access to newer drug; and management of NTM.

3.3 RNTCP strategy & intervention for prevention and management of DR-TB under NSP (2017-25)

The RNTCP response to DR-TB revolves around strategy to prevent emergence and stop transmission of DR-TB. These are enumerated below:

Prevention of DR-TB

- sustain the highest quality care for drug sensitive TB patients;
- promote rational use of anti-TB drugs; and
- implement infection control measures.

Stopping transmission of DR-TB

- ensure early diagnosis, respiratory isolation (segregation of active TB patients in waiting rooms, wards, fast tracking) and prompt effective treatment initiation of all forms of DR-TB;
- improve laboratory capacity for rapid diagnosis of DR-TB (expanded below);
- initiate and rapidly scale-up services to all types of DR-TB patients (expanded below);
- ensure effective DST guided treatment of DR-TB patients; and
- evaluate the extent of second-line anti-TB drug resistance and management strategies.
- ensure full implementation of infection control guidelines

The specific strategies laid down in the NSP for early diagnosis, prompt and appropriate treatment as well quality care, social support and protection for DR-TB patients are enlisted below:

**Laboratory systems for drug-resistant TB:**

- universal DST to at least R for all diagnosed TB patients through offer of rapid molecular tests will be rolled out in a phased manner starting 2017;
- introduce and scale-up diagnostics for NTM detection and DST;
- strengthen surveillance systems including introduction and scale-up of next generation sequencing (NGS) platforms;
- scale-up effective mechanisms of affordable diagnostics for TB in private sector will be done including provision of services by the programme, giving diagnostics to the private sector or reimbursement of the cost;
- have the programme empanel accredited laboratories for diagnostics; get NABL accreditation for public sector laboratories as per the lab scale up plan; maintain linkages with NABL for providing proficiency panels to private and corporate sector laboratories for quality assured diagnostics; and have DST expand capacity and accessibility;
- implement a laboratory information management system and link it to e-NIKSHAY during this plan period; and
- purchase and ensure notification through laboratories from the private sector and link them to laboratory surveillance.

**Treatment of DR-TB**

- Decentralize DR-TB treatment: As RNTCP moves to universal DST with rapid molecular tests available at every district, second-line DST testing, shorter MDR-TB treatment and DST guided treatment with or without newer drugs, volume of patients to be managed at centralized DR-TB centres will delay treatment initiation and increase numbers lost to follow-up. To mitigate this anticipated loss and promote DR-TB treatment initiation within 24-48 hours, RNTCP will decentralize DDR-TBC to initiate standard regimen for H mono-poly DR-TB and MDR/RR-TB regimen (shorter/ conventional longer) at every district level established within close proximity of CB-NAAT site. Patients with additional resistance to second-line drugs, drug intolerance or those seriously ill will need regimen modification and will be managed at the NDR-TBC;
• Manage the H mono/poly DR-TB patients: H mono/poly resistance is known to be around thrice as prevalent as RR-TB. A specific 9-12 month treatment regimen has been initiated to manage H mono-poly resistance with available first-line drugs strengthened with a fluoroquinolone and a second-line injectable. This regimen will be scaled-up across the country as per expansion of diagnostic and treatment capacity;

• scale-up shorter MDR-TB regimen across the country by the end of 2017 for all RR-TB patients that meet criteria for this regimen;

• Finalize the regimens containing newer drugs: Access to Bedaquiline will be expanded across India by the end of 2017. RNTCP will also introduce another new drug Delamanid by the end of 2017, after conditional approval from DCGI and undertake research with support of ICMR to evaluate the use of these newer drugs in combination therapy to reduce the duration of DR TB regimens to 4-6 months;

• Ensure DST guided DR-TB regimen and manage XDR TB patients with or without resistance to any other first or second-line drugs, who do not consent or are not eligible for newer drugs. Do this with an appropriate regimen design based on their DST results. This approach will be scaled-up along with Bedaquiline expansion across India by the end of 2017; and

• RNTCP to initiate addressing non TB *Mycobacteria* and scale-up along with NTM diagnosis and treatment across India by the end of 2018.

**Social protection & supportive systems**

• patients with drug resistance in whom an appropriate regimen cannot be formed, even with addition of newer drugs, as per the WHO recommended regimen, will be offered palliative care through the nodal DR-TB centres or at the community level under guidance of the nodal DR-TB Centre. Necessary palliative services including pain relief, surgery, prosthesis, psychosocial support and respiratory physiotherapy will be provided;

• any additional cost incurred by patients for diagnosis, treatment, other social determinants, palliative care and rehabilitation will be covered under existing insurance schemes like National Health Protection Scheme (NHPS) that provides health insurance cover of up to Rs. 1 lakh to the poor. The scheme is projected to benefit about 10 crore families in the first phase. The main beneficiaries of the scheme would be families belonging to the below poverty line (BPL) category or those in the list of deprivations as per the socioeconomic caste census data; and

• the guidance document for nutritional assessment and supplementation for TB patients in India (2016) provides technical and operational guidance to states to establish systems of nutritional assessment and linkages with various social welfare schemes and public distribution systems to provide nutritional supplementation to the family of patients suffering from TB and DR-TB in India with successful models being implemented by some states like Kerala, Chhattisgarh etc.,
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<td>25%</td>
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<td>50%</td>
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<td>80%</td>
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<td>95%</td>
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<td>53460</td>
<td>66000</td>
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<td>92000</td>
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<td>78250</td>
<td>69000</td>
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<td>59400</td>
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<td>82800</td>
<td>82800</td>
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<td>13144</td>
<td>16038</td>
<td>79200</td>
<td>189540</td>
<td>276000</td>
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<td>No. of H mono-poly resistant TB patients initiated on treatment</td>
<td>100</td>
<td>200</td>
<td>14434</td>
<td>71280</td>
<td>170586</td>
<td>248400</td>
<td>248400</td>
<td>211275</td>
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<td>No. of pre XDR TB patients notified</td>
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<td>1785</td>
<td>13365</td>
<td>22500</td>
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<td>No. of pre XDR TB patients initiated on treatment</td>
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<td>Treatment success rate for MDR/RR TB</td>
<td>46%</td>
<td>46%</td>
<td>48%</td>
<td>48%</td>
<td>56%</td>
<td>65%</td>
<td>70%</td>
<td>72%</td>
<td>73%</td>
<td>74%</td>
<td>75%</td>
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<td>Proportion of notified TB patients (including DR-TB) using ICT supported adherence systems</td>
<td>1%</td>
<td>2%</td>
<td>10%</td>
<td>30%</td>
<td>50%</td>
<td>80%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
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<td>90%</td>
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<tr>
<td>Proportion of notified TB patients (including DR-TB) receiving financial support through DST</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
<td>50%</td>
<td>70%</td>
<td>80%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
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<tr>
<td>Proportion of tertiary and secondary facilities with budgeted action plan for AIC in TB facilities</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>40%</td>
<td>60%</td>
<td>80%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Number of District DR-TB Centre established</td>
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<td>143</td>
<td>250</td>
<td>700</td>
<td>750</td>
<td>790</td>
<td>810</td>
<td>820</td>
<td>830</td>
<td>840</td>
<td>850</td>
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<tr>
<td>No. of rapid molecular laboratories established</td>
<td>123</td>
<td>628</td>
<td>835</td>
<td>1335</td>
<td>1835</td>
<td>2335</td>
<td>3335</td>
<td>4335</td>
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<tr>
<td>No. of first-line DST (Phenotypic) laboratories established</td>
<td>62</td>
<td>66</td>
<td>80</td>
<td>95</td>
<td>110</td>
<td>125</td>
<td>125</td>
<td>125</td>
<td>125</td>
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<tr>
<td>No. of first-line DST (Genotypic) laboratories established</td>
<td>44</td>
<td>46</td>
<td>54</td>
<td>54</td>
<td>54</td>
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<tr>
<td>No. of second-line DST (Genotypic) laboratories established</td>
<td>0</td>
<td>0</td>
<td>54</td>
<td>54</td>
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<td>54</td>
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<td>54</td>
</tr>
<tr>
<td>No. of second-line DST (Phenotypic) laboratories established</td>
<td>18</td>
<td>26</td>
<td>40</td>
<td>55</td>
<td>70</td>
<td>85</td>
<td>100</td>
<td>115</td>
<td>130</td>
<td>145</td>
<td>160</td>
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<tr>
<td>Percentage of districts covered for call center support for treatment adherence (including ICT intervention districts)</td>
<td>4%</td>
<td>4%</td>
<td>18%</td>
<td>50%</td>
<td>80%</td>
<td>100%</td>
<td>100%</td>
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Chapter 4: Laboratory services for programmatic management of drug-resistant TB

This chapter describes the concept of certification of laboratories for quality-assured results, case definitions for different drug-resistant TB (mono-resistant, poly-resistant, MDR-TB, XDR-TB), laboratory services needed to diagnose and treat DR-TB patients. In addition, the section elaborates the process of liaising with the NRL for setting up and maintaining the entire gamut of laboratory services across the health sector.

4.1 Vision

The vision of the programme is to provide Universal DST to all diagnosed TB patients, while offering an upfront CBNAAT to all presumptive TB patients among key populations. Revised diagnostic algorithm for DR-TB will ensure comprehensive diagnostic and drug susceptibility testing of patients to enable timely treatment decision with appropriate regimen. Towards this end, a staggered testing algorithm utilizing newer rapid diagnostic technologies such as CBNAAT, first and second-line LPA in line with WHO guidelines and expert committee meetings is detailed.

The programme must strive to provide every TB patient with access to at least R susceptibility testing i.e., UDST.

4.2 Laboratory services required for PMDT

Optimal management of DR-TB requires both Mycobacterial and clinical laboratory services. At a minimum, the state level Intermediate Reference Laboratory (IRL) or any other RNTCP-certified Culture & DST laboratory should provide diagnostic culture on liquid and/or solid media; testing for resistance/susceptibility to at least R by RNTCP approved genotypic or phenotypic methods; and confirmation of the species as M. tuberculosis by Immuno-chromatographic assay.

Clinical laboratory services are required for proper evaluation and monitoring of patients, including basic haematology, biochemistry, serology, and urine analysis. These would also be available at the DR-TBCs identified by the state through public or private facility. Refer to pretreatment evaluation for details in Chapter 6.

4.3 Definition of accreditation and certification

Laboratory accreditation means third-party certification by an authorized agency using internationally approved standards for evaluating competence of laboratories to perform
specific type(s) of testing and is a formal recognition of competent laboratories. It includes all aspects of the laboratory such as physical infrastructure, biosafety, competencies of staff, processes, procedures and quality system elements (QSE) as per National Accreditation Board for Testing and Calibration Laboratories (NABL) standards (ISO 15189)

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

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

4.4 Definitions and classification of DR-TB patients

The following are the definitions and classification for DR-TB patients. [5][19]

**Presumptive DR-TB:** It refers to the following patients in order of their risk:

- TB patients found positive on any follow-up sputum smear examination during treatment with first line drugs including treatment failures;
- paediatric TB non-responders;
- TB patients who are contacts of DR-TB;
- previously treated TB patients;
- new TB patients with HIV co-infection;
- all notified new TB patients.

A patient is confirmed to have drug resistant TB, only when the results are from a RNTCP quality-assured Culture & DST Laboratory and by a RNTCP-endorsed testing method. Such patients are classified according to the following definition:

**Mono-resistance TB (MR):** A TB patient, whose biological specimen is resistant to one first-line anti-TB drug only.

**Poly-drug resistance TB (PDR):** A TB patient, whose biological specimen is resistant to more than one first-line anti-TB drug, other than both H and R.

---

1States to advance in phased manner as per PMDT scale-up plan for universal DST based on lab capacity and policy on use of diagnostics. Although new TB patients from above mentioned categories are at the lower risk of drug resistance, testing them further for presence of drug resistance at the time of diagnosis is a necessary standard of care.
**Rifampicin resistance (RR):** A TB patient, whose biological specimen is resistant to R, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R, in the form of mono-resistance, poly-resistance, MDR or XDR.

**Multidrug resistance TB (MDR):** A TB patient, whose biological specimen is resistant to both H and R with or without resistance to other first-line anti-TB drugs. MDR-TB patients may also have additional resistance to any/all FQ OR any/all SLI anti-TB drug.

**Extensive drug resistance (XDR):** A MDR-TB patient whose biological specimen is additionally resistant to at least a FQ (Ofx, Lfx Mfx) and a SLI anti-TB drug.

It is to be noted that R resistance is quite rare without H resistance. Majority of DST results with R resistance will also be H resistant, i.e., MDR-TB. This has been substantiated in the National Drug Resistance Survey (2014-16). Therefore, RNTCP has taken the programmatic decision that patients, who have any R resistance, should be managed as if they are an MDR-TB patient and this is in line with WHO global guidelines for PMDT.

### 4.5 Methods for drug susceptibility testing

Presently drug resistance detection using the following technologies is available for diagnosis of Drug Resistant TB through rapid molecular diagnostic testing:

- Line Probe Assay (LPA) for detection of MTB complex and resistance to first line drugs R, H and second-line drugs class FQ and class SLID [20] [8]; and
- Cartridge Based - Nucleic Acid Amplification Test (CBNAAT) Xpert MTB/Rif testing using the Gene-Xpert platform for now [20].

**Growth-based phenotypic drug susceptibility testing:** Culture though a highly sensitive and specific method for TB diagnosis, requires 2-8 weeks to yield results and hence does not help in early detection. However culture will be used for long-term follow-up of patients on Drug Resistant TB treatment and help detect early recurrence in both drug sensitive and drug-resistant TB. The growth-based phenotypic culture methods include automated Liquid culture systems *e.g.*, BACTEC MGIT 960, BacAlert or Versatrek etc., and solid (*Löwenstein* Jensen) media.

**Rapid molecular Drug Resistance Testing:** Line Probe Assay (LPA) provides rapid diagnosis of R and H resistance as well as resistance to class FQ and class SLID. LPA can yield results in 72 hours. Nucleic Acid Amplification Test (NAAT) provides accurate and rapid diagnosis of TB by detecting *M.tb* and R resistance conferring mutations. [20] The test can be performed on both respiratory and non-respiratory specimens and yields results in 2 hours. Presently, under RNTCP, its use is recommended for diagnosis of DR-TB in presumptive DR-TB patients
and TB in children, EP TB and in Key Population such as PLHIV, socially and clinically vulnerable groups and for active case finding efforts.

Drug resistance status is determined by either of the following methods:

**Drug Resistance Tests (DRT) using molecular methods:** This can be performed on sputum specimen (direct) or on culture isolates (indirect) for diagnostic purpose. The methods are PCR-based and cannot be used for determining response to treatment. The tests that belong to this group include:

- CBNAAT: can be performed on smear positive, smear negative and extra pulmonary specimen. The test detects TB and resistance to R; and
- Line Probe Assay (LPA): is performed on smear positive specimen. The test detects TB and resistance to R and H (FL- LPA) as well as class FQ and class SLI (SL-LPA)

**Drug Susceptibility Test (DST):** These are growth based tests and can be performed on L J culture isolates or in Liquid culture system Mycobacteria growth indicator tube (MGIT) for both pulmonary and EP specimen. Most commonly used method for testing is the economic variant of the proportion sensitivity. MGIT is preferred method for DST and both first and second-line anti-TB drugs can be tested. Following drugs can be tested for susceptibility by liquid culture:

- first-line drugs: R, H, Z*
- second-line drugs: Lfx, Mfx, Km, Cm, Am
- other drugs: Lzd, Cfz*, Bdz*, Dlm* etc.,

*when standardized, WHO endorsed and approved for use in programme

### 4.6 Organization and development of the laboratory network

RNTCP has a three-tier laboratory network. The first is the designated microscopy centres (DMCs) providing sputum smear microscopy services. The second tier includes the Intermediate Reference Laboratories (IRL) and other C-DST laboratories. IRL has 3 main functions namely imparting trainings, ensuring quality assurance [QA] and providing TB Culture and DST services. The third-tier is the National Reference Laboratories (NRL). The overall quality assurance of IRL and other C-DST laboratories (medical colleges, NGO, private etc.,) is the responsibility of the designated NRL to which the State is linked. NRLs are also responsible for all training activities and EQA for C-DST as well as molecular diagnostics (LPA & CB-NAAT) for state level staff. [21]
4.7 Choice of diagnostic technology

The programme has substantially scaled-up the laboratory capacity of various C-DST laboratories. The choice of technology to be used for diagnosis of DR-TB has been determined as per recommendations of the National Laboratory Committee. The choice of technologies is given below.

<table>
<thead>
<tr>
<th>DR diagnostic technology</th>
<th>Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBNAAT/LPA</td>
<td>First</td>
</tr>
<tr>
<td>Liquid culture isolation and LPA DST</td>
<td>Second</td>
</tr>
<tr>
<td>Liquid culture isolation and liquid DST</td>
<td>Third</td>
</tr>
</tbody>
</table>

All the follow-up cultures will be done through the liquid culture. If the state is facing challenges, with respect to follow up culture by LC, this may be communicated to the Central TB Division for facilitation.

4.8 Specimen collection and transportation to C-DST laboratories

Obtaining good quality specimens of adequate volume is critical to ensuring correct diagnosis. The Laboratory technician needs to explain the process of collecting “a good quality sputum specimen” while adhering to AIC measures. Programme recommends collection of sputa one spot and one morning, OR 2 spot specimens collected within a gap of at least one hour (if the patient is coming from a long distance OR s/he is unlikely to return to give the second specimen). Ideally, a sputum specimen should have a volume of 2-5 ml and preferably be mucopurulent. Care should be taken to ensure that specimens sent for molecular testing are not heavily blood stained or contaminated. It is advisable to let the haemoptysis subside before collecting the specimen. The patient must be advised to collect the specimen in a sterile container (50 ml conical tube) after thorough rinsing of the mouth with clean water. Specimens should be transported to the laboratory as soon as possible after collection. In case of leakage or spillage of specimen during transportation leading to non-testing of specimen, special care should be taken to ensure recollection of specimen.
As per the diagnostic algorithm, two fresh specimen need to be collected at designated collection centres (DMC or PHI level) by trained LT and transported in a cool chain on the same day to the nearest CBNAAT lab for all eligible patients. At the CBNAAT site, the test is performed. For all results reported as TB (RS and RR), the second specimen need to be repacked by the CBNAAT LT and transported to the RNTCP C-DST laboratory on the same day in cool chain. The request form (RNTCP request form for examination of biological specimen for TB) updated with the CBNAAT result should be sent along with the transported specimen. Simultaneously, the result of CBNAAT test is to be communicated to the patient and provider. At the C-DST laboratory, SL-LPA is performed for RR-TB and FL-LPA for RS-TB. All specimens need to be delivered to the RNTCP C-DST laboratory within 48-72 hours of collection. Ideally, an agency (courier/speed post) should be identified for this purpose by the concerned DTO. NGOs may be engaged as per partnership guidelines for specimen transportation in cool chain. If none is available, transporter need to be identified from the health system/ community to transport the specimen in bio safe conditions with appropriate enablers. Models for packaging specimens are given in Figure 4.1 above. The following points are critical for the collection of fresh sputum specimens at designated collection points:

- 50-ml conical bottom tubes (made of polypropylene material) and the 3 layer packing materials like thermocol box, ice gel pack (pre-freezed at -20 degree for 48 hours), request form for examination of biological specimen for TB, polythene bags, tissue paper
roll as absorbent, parafilm tapes, brown tape for packaging box, permanent marker pen, labels, BIO-HAZARD sticker, scissors, spirit swab etc. should be supplied to the DMCs for collection of sputum through the DTO;

- 50-ml conical tubes should carry a label indicating the date of collection of the specimens along with patient’s details like name, date of specimen collection, name of DMC/DTC, Lab. No:- XYZ, specimen A or B;
- LT at DMCs should be trained to carefully to pack the sputum specimens in the cool box to avoid spillage of the specimens;
- LT of DMC issuing the conical tubes to the patients should give clear instructions to the patients on correct technique of collection of the sputum. Also the date of issue of the conical tubes to the patient should be recorded;
- LT of DMC should ensure that the request form for examination of biological specimen for TB is packed in a separate plastic zip pouch and placed in the cool box before sealing the lid of the box. Also, the BIO-HAZARD symbol should be pasted on the external side of the cool box along with the label indicating the postal address of the C-DST Lab assigned;
- LT of DMC should promptly inform the specimen transport agency like a courier/ speed post service to collect and transport the specimens;
- as per national guidelines on biomedical waste management (Annexure 5) the containers used for transporting sputum specimens to the C-DST laboratory should be labelled with a “BIO-HAZARD” sticker;
- for every presumptive DR-TB patient referred by MO-DMC, date of referral and transport of sputa specimens to C-DST laboratory should be entered in “Remarks” column of the respective DMC lab register and TB notification register and in the referral for C-DST register held at the DTC. Alternatively, presumptive DR-TB patient referred to nearby DMC selected for specimen collection and transport for C-DST maybe provided two conical tubes by the concerned DMC LT/MO and instructed on collecting two specimens (one early morning and one supervised spot);
- these specimens will be taken by the patient/relative to the DMC selected for specimen collection from where these will be packed in cool boxes and transported to the C-DST laboratory; and
- once the sputum has been transported to the C-DST laboratory, the presumptive DR-TB patient should return to continue their RNTCP first-line treatment.

The specimen collection and transportation from EP-TB sites and children need to be done as per the SOP under RNTCP (Annexure 6) [22]
4.9 Certification and quality assurance for C-DST laboratories

The components of Quality Assurance for C-DST include Internal Quality Control (IQC) and External Quality Assessment (EQA) mechanisms. IQC of LJ media is performed as a routine laboratory protocol and involves testing each batch of media for contamination as well as the use of control strain (H37RV) for growth parameters. IQC for MGIT is instrument guided. EQA is not performed for culture. IQC of DST involves use of control strain (H37RV) as well as mono resistant strains (R mono and H mono) with every batch of DST performed.

EQA for both LJ as well as MGIT is performed in two stages, initial retesting as one time activity where the NRL retests 10 strains out of 100 performed by the participating laboratory. This is assessment of the laboratory in real time. As a second stage, the participating laboratory is required to perform DST for 30 panel strains received annually from the NRL. This is the actual test of performance. For further details refer to Guidance for accreditation of laboratories under RNTCP for *Mycobacterial* culture & DST.
Quality assurance for LPA: Initially, the NRL retests DNA extracts of 20 strains out of 50 performed in duplicates at the participating laboratory. This is followed by annual proficiency with panel strains. Panel Testing benchmark includes:

- invalid LPA results – less than 10%;
- contamination of negative control – clean in all runs;
- internal concordance – greater than 95%; and
- external concordance – greater than 95%.

Quality assurance for CBNAAT: Each CBNAAT cartridge contains internal controls, Specimen Processing Control (SPC) and Probe Check Control. If the probe check fails, then the test is stopped and an error result is obtained. Troubleshooting is required based on the error code generated. Error rates higher than 5% should be investigated. Meanwhile, SPC must be positive when the result is MTB not detected. It can be negative/positive when the result is MTB detected. The test result is considered invalid if the SPC is negative when the test result is found negative.

Visits to CBNAAT sites should be planned at regular intervals to assess laboratory performance by district, state, IRL, NRL, CTD using the available standardized supervisory checklist for CBNAAT. CBNAAT sites in the districts should also be visited by IRL/NRL during
their visits for EQA of sputum smear microscopy. Poorly performing sites should be prioritized for onsite visits. All newly inducted laboratory staff members must undergo an induction training and periodic refresher training, as prescribed under RNTCP.

4.10 Initiative for Promoting Affordable and Quality TB Test (IPAQT) for private sector

TB diagnosis in the private sector was driven by extensive use of unreliable serological test and high cost of WHO endorsed diagnostics tests. IPAQT (Initiative for Promoting Affordable and Quality TB Tests) is an initiative which started in 2013 to bring RNTCP or WHO-approved TB tests at affordable prices to patients in the private sector. IPAQT brought together various private labs with the support of test manufacturers and other major stakeholders to cut down the cost for quality TB tests by up to 50% in the private sector. IPAQT is an initiative of nonprofit stakeholders and over 100 private sector labs/hospitals (more than 5000 collection centres) with a pan-India presence that have come together to provide WHO approved tests for TB. Each patient diagnosed by these IPAQT labs must notify to the programme surveillance system (further details available at [http://www.ipaqt.org/](http://www.ipaqt.org/)) and appropriate public health action must be offered for all noticed TB & DR-TB patients. [23]

4.11 Non Tuberculous Mycobacteria (NTM)

A large number of Mycobacteria other than Mycobacterium tuberculosis are being increasingly recognized as a cause of human disease. Commonly referred to as non-TB Mycobacteria (NTM), they are also known as atypical mycobacteria, anonymous mycobacteria or mycobacteria other than tubercle bacilli (MOTT). NTM are ubiquitously distributed in the environment and hence also known as environmental mycobacteria. They are distinct from M.tb in their characteristics that they can survive outside the human or animal host. They are generally nonpathogenic or opportunistic pathogens and most commonly causes disease when there is immunosuppression or injury, except for few species which infect immune-competent humans.

Often these bacteria inhabit the respiratory passages in the form of commensal organisms. Pulmonary infection from NTM though rare, can cause disease similar to TB. They more commonly infect the skin, soft tissue, lymph nodes, implant devices, wounds, bones and joints. Disseminated NTM disease is mostly seen in patients who are immunosuppressed or who have Acquired Immunodeficiency Syndrome (AIDS).

Though NTM are widely distributed in the environment, the clinical infection is rare. They may be falsely recovered from clinical specimens due to laboratory contamination or contamination of medical instruments. Chronic pulmonary infection due to M. avium complex and M. Kansasi generally occurs in elderly persons especially males who are smokers or who have preexisting lung lesions. Cervical lymphadenopathy occurs in children...
due to *M. Scrofulaceum*, while skin and soft tissue infections may develop from *M. Fortuitum, M. Chelonei, M. Xenopi* and *M. Ulcerans*. Exposure of humans to NTM may occur while bathing, swimming and drinking and the organism can also gain entry through cuts and abrasions. However, the risk of infection is generally less. Disseminated lesions are found in immunocompromised patients due to infection from *M. Avium* complex. Sometimes, *M. Chelonei* may cause very indolent pulmonary infection.

**Diagnosis of NTM**

Because of their omnipresence in our environment, isolation of NTM from non-sterile body sites does not imply true infection or disease, per se. Repetitive isolation, signs of clinical disease, radiological abnormalities, the exact species isolated and predisposing conditions of the patient involved, are all helpful in determining whether the isolated *mycobacteria* are to be considered causative agents of the patient’s disease. In normally sterile sites, isolation of NTM, preferably backed up by histological evidence of granulomatous inflammation, suffices for the diagnosis of NTM disease. [24][25]

**Table 4.1: Most frequently isolated Non TB Mycobacteria and their sites of infection**

<table>
<thead>
<tr>
<th>Species</th>
<th>Main site of infection</th>
<th>Growth rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. Avium complex</em></td>
<td>Pulmonary, lymph nodes,</td>
<td>Slow</td>
</tr>
<tr>
<td><em>(M. Avium, M. Intracellulare, minor species)</em></td>
<td>disseminated disease</td>
<td></td>
</tr>
<tr>
<td><em>M. Kansasii</em></td>
<td>Pulmonary, disseminated disease</td>
<td>Slow</td>
</tr>
<tr>
<td><em>M. Xenopi</em></td>
<td>Pulmonary</td>
<td>Slow</td>
</tr>
<tr>
<td><em>M. Malmoense (NW Europe)</em></td>
<td>Pulmonary</td>
<td>Slow</td>
</tr>
<tr>
<td><em>M. Ulcerans</em></td>
<td>Skin</td>
<td>Slow</td>
</tr>
<tr>
<td><em>M. Marinum</em></td>
<td>Skin</td>
<td>Intermediate</td>
</tr>
<tr>
<td><em>M. Abscessus</em></td>
<td>Pulmonary, skin</td>
<td>Rapid</td>
</tr>
<tr>
<td><em>M. Cheloneae</em></td>
<td>Skin, soft tissues, disseminated</td>
<td>Rapid</td>
</tr>
<tr>
<td><em>M. Fortuitum</em></td>
<td>Skin, soft tissues, pulmonary</td>
<td>Rapid</td>
</tr>
<tr>
<td><em>M. Scrofulaceum</em></td>
<td>Lymph nodes</td>
<td></td>
</tr>
<tr>
<td><em>M. Haemophilum</em></td>
<td>Disseminated disease</td>
<td></td>
</tr>
</tbody>
</table>

The minimum evaluation of a patient presenting with features suggestive of non-TB *Mycobacterial* (NTM) lung disease should include the following:

- chest radiograph or chest high-resolution computed tomography (HRCT) scan. HRCT may be done in settings where access to this technology is available. However, it is not mandatory for evaluation and decision to treat the patient;
- three or more sputum specimens for acid-fast bacilli (AFB) analysis;
- exclusion of other disorders, such as TB;
• expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination. Patients suspected of having NTM lung disease but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded; and
• making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.

Clinical, radiological and microbiological criteria are equally important and all must be met to make a diagnosis of NTM lung disease. The following criteria apply to symptomatic patients with radiographic opacities, nodular or cavitary or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules. These criteria best fit with *Mycobacterium avium complex* (MAC), *M. Kansasi* and *M. Abscessus*.

**Clinical**

• pulmonary symptoms include cough, hemoptysis, fever, weight loss or organ specific signs and symptoms *etc.*; and
• exclusion of any other etiologies.

**Radiological**

• radiological findings pertain to nodular or cavitary opacities on chest radiograph; and/or
• HRCT scan that shows multifocal bronchiectasis with multiple small nodules.

**Microbiological**

**Table 4.2: Microbiologic criteria for diagnosis of NTM lung disease**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least three results available with OR</td>
<td>Two positive cultures regardless of the results of AFB smear</td>
</tr>
<tr>
<td>Single available bronchial wash or lavage with OR</td>
<td>One positive culture regardless of the results of AFB smear</td>
</tr>
<tr>
<td>Tissue biopsy with:</td>
<td>Compatible histopathology- (granulomatous inflammation) and a positive biopsy culture for NTM</td>
</tr>
<tr>
<td></td>
<td>and a positive sputum or bronchial wash culture for NTM</td>
</tr>
</tbody>
</table>

**Guidelines for making the diagnosis of NTM-pulmonary disease**

• clinical features of an indolent, respiratory disease include cough, expectoration, fever and other constitutional symptoms;
- positive smear for AFB and/or heavy growth of NTM (at least 1+ on solid media) on culture in respiratory specimens with the same species being identified repeatedly;
- histopathological features of mycobacterial/granulomatous disease or culture of NTM from biopsy specimens;
- radiological features of nodular infiltrates with or without cavitation and/or bronchiectasis lesions;
- underlying host conditions include immunosuppression, AIDS, alcoholism, COPD, cystic fibrosis, diabetes, malignancies, prior TB, esophageal motility disorders etc.;
- absence of other causes of pulmonary lesions, such as TB, aspergillosis, etc.;
- persistence of AFB after anti-TB treatment for two weeks or more with CBNAAT or LPA report not detecting M.tb; and
- smear positive, CBNAAT negative, LPA-TUB band absent with or without R resistance in patients of presumed DR at diagnosis also need to be evaluated.

The diagnostic processes for NTM to be followed at C-DST laboratories are detailed in Annexure 7. The laboratory staff would be separately trained in these standard operating procedures for laboratory confirmation of NTM. For more information on NTM including extra-pulmonary NTM, microbiologists are encouraged to refer to the latest American Thoracic Society (ATS) guideline.
Chapter 5: Case-finding

This chapter describes the RNTCP strategy for timely case-finding and confirmation of diagnosis among presumptive DR-TB patients as well as vulnerable groups. Early identification and prompt initiation of treatment will prevent the patient from spreading the disease to others, developing a resistant strain to more drugs and progressing to a chronic state of permanent lung damage.

5.1 Case-finding strategy

Vulnerable groups to be offered upfront CBNAAT. A vulnerable group is any group of people in which the prevalence or incidence of TB is significantly higher than in the general population. The recommended vulnerable groups to be considered for intensified case finding may be classified as follows [5]:

Table 5.1: Classification of vulnerable groups

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Social</th>
<th>Geographical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clients attending HIV care settings</td>
<td>Prisoners</td>
<td>Urban slums</td>
</tr>
<tr>
<td>Substance abuse including smokers</td>
<td>Occupations with risk of developing TB (enumerate from TOG)</td>
<td>Hard-to-reach areas</td>
</tr>
<tr>
<td>Comorbidities like diabetes mellitus, malignancies, patients on dialysis and on long term immunosuppressant therapy</td>
<td>People in congregated settings – night shelters, de-addiction centres, old age homes</td>
<td>Indigenous and tribal populations</td>
</tr>
<tr>
<td>Health care workers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household &amp; workplace contacts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with past history of TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnourished</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antenatal mothers attending antenatal /MCH clinics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Medical Officer, Peripheral Health Institute (MO PHI) along with DMC LT will be responsible for identification of all diagnosed and notified TB patients and other key and vulnerable patient. This will be in addition to presumptive DR-TB patients who have failed treatment with first-line drugs, paediatric TB non-responders, TB patients who are contacts of DR-TB, TB patients who are found positive on any follow-up sputum smear examination during treatment with first line drugs, previously treated TB patients and/or TB patients with HIV co-infection. It should be ensured that detailed history is elucidated for every patient. The testing of new TB patients from non-key/vulnerable groups would be initiated after ascertaining the available CBNAAT capacity in the districts/ states.
A patient who is identified for testing with CBNAAT should be referred by the respective MO-PHI to the nearby sputum collection centre for diagnosis by the rapid molecular method. CBNAAT is the preferred rapid molecular diagnostic test under RNTCP. At the CBNAAT site, two specimens will be collected as detailed earlier. In certain patients, second specimens may need to be tested for confirming R Resistance (in case of invalid, indeterminate, error or no results reported by CBNAAT machine). With availability of X-pert ultra-cartridges in the near future, the reconfirmation of RR-TB among new TB patients will no longer be required. Patient’s results will be available within a day and the decision of starting the patient on the appropriate regimen can be taken after results are available.

**Figure 5.1 Operational process of specimen referral**

![Operational process of specimen referral](image)

**Turnaround time:** Genotypic testing is much faster than phenotypic methods. As these are not growth based tests, timely diagnosis and prompt treatment initiation is possible. DST results on Solid LJ media have a turnaround time (TAT) of up to 84 days, liquid culture (through MGIT) up to 42 days, LPA up to 72 hours and CBNAAT by 2 hours.

Once the MO PHI confirms that the patient belongs to presumptive DR-TB, s/he should arrange for sending two sputa specimens, one of which is an early morning specimen and the other a “supervised” spot specimen, from the patient to the assigned C-DST laboratory along with the RNTCP request form (Request for examination of biological specimen for TB). For specimens to be collected and transported from the DMC, all necessary materials for specimen collection and transport need to be made available at the DMC identified by the DTO as specimen collection centre for C-DST.

Empty 50-ml conical tubes can be provided by the LT/ MO to the patient with guidance to collect fresh sputum specimen. The patient is to be advised to go on the next day with the early morning specimen and relevant medical records to the nearest specimen collection center for C-DST. The spot specimen can be collected in such cases when the patient arrives to submit the early morning specimen. Alternately, specimens can be collected at such DMCs and PHIs and transported in cool boxes by the staff on the same day to the nearest DMC identified as specimen collection centre. The specimen is further packed and transported in cool boxes through courier or speed post to the C-DST. If there is likely to be a delay in transporting the specimens, these should be stored in a refrigerator at the peripheral DMC/PHI with biosafety precautions.
5.2 Integrated DR-TB diagnostic algorithm

The vision of the programme is to offer DST to TB patients at the earliest time in their diagnostic process. The integrated diagnostic algorithm starts with two groups of patients who are either presumptive TB or diagnosed TB. The main objective of this algorithm is to segregate people based on risk assessment for DR-TB and offer DST guided treatment based on drug resistance status at least for R resistance at the time of diagnosis of TB *i.e.*, Universal DST. The subsequent time points when DST is offered if any of the following events occur during the course of a TB treatment schedule:

- bacteriologically positive after intensive phase of a course of TB/DR-TB treatment;
- failure to respond to treatment as per RNTCP definitions;
- recurrence of TB diagnosed after a course of TB treatment;
- for patients who are retrieved after lost to follow-up;
- for patients found to be HIV positive before or anytime during the course of TB treatment and
- any other reason as per treating physicians advice.

Two diagnostic specimens would be collected from the patients one early morning and one spot specimen wherever possible, but if there is a likelihood of the patient not returning for the second collection or travelling from long distance then 2 spot specimens may be collected with a gap of at least one hour. The DR-TB diagnostic algorithm is as given in Figure 5.2.

The left arm of the algorithm starts with persons presumed to have TB. From this group those belonging to the paediatric age group, PLHIV, EP group or with a smear negative chest X-ray suggestive of TB will be offered CBNAAT test. By virtue of using CBNAAT as the TB diagnostic test, the R status is also available simultaneously along with TB detection.
Figure 5.2 DR-TB Diagnostic Algorithm

**Offer molecular testing for H mono/poly resistance to TB patients prioritized by risk as per the available lab capacity**

**LC DST (Mfx 2.0, Km, Cm, Lzd)** will be done only for patients with any resistance on baseline SL-LPA. DST to Z, Cfx, Bdq & Dlm would be considered for policy in future, whenever available, standardized & WHO endorsed.

$^5$ States to advance in phased manner as per PMDT Scale up plan for universal DST based on lab capacity and policy on use of diagnostics.

Key/Vulnerable populations
- Paediatric age group
- People living with HIV
- EPTB sites
- Smear negative/NA with X-ray suggestive of TB

Presumptive TB

All diagnosed TB patients

- Non responders to treatment
- DR-TB contacts
- Previously treated TB
- TB-HIV co-infection
- New TB patients $^5$

CBNAAT

RR TB

For discordance on LPA for RR-TB – repeat CBNAAT at LPA lab

RS TB

FL-LPA*

SL - LPA**

FQ and SLI Sensitive

FQ and/or SLI Resistance

H Resistant

H Sensitive

For discordance on LPA for RR-TB – repeat CBNAAT at LPA lab

*Offer molecular testing for H mono/poly resistance to TB patients prioritized by risk as per the available lab capacity
Patients other than key/vulnerable population would be evaluated for TB as per the RNTCP technical and operational guidelines. The right arm begins with offer of CBNAAT to all diagnosed or notified TB patients who are at risk of DR-TB as per risk group criteria and districts will transition to testing all patients diagnosed or notified as TB. Based on the result obtained on the CBNAAT, the patient would be classified as R resistant (RR TB) or R susceptible (RS TB) to guide decision of the appropriate treatment. As soon as the CBNAAT results are available, the reports must be immediately updated in Nikshay by the CBNAAT lab and communicated to the DDR-TBC, DTO, MO PHI and the patient.

For patients with CBNAAT result as M.tb detected (RR-TB & RS-TB), the second specimen will be reflexly transported in cool chain from the CBNAAT lab to the C-DST lab. In rare circumstances when CBNAAT may reveal R indeterminate or no result on the first specimen, the second specimen will be used at CBNAAT lab itself to repeat the test. In such cases, a fresh specimen is to be collected from the patient and transported in cool chain to the concerned C-DST lab. However, this may not be always possible for EP specimen.

At the C-DST laboratory (for all smear positive specimen) FL- LPA test will be performed for RS-TB and SL- LPA will be performed for RR-TB (Base line SL DST). DST to Mfx (2.0), Km, Cm and Lzd will be set up on liquid culture using the decontaminated deposits only for patients who are found to be resistant to FQ and/or SLI class. The results of the LC-DST for individual FQ and second line SLI will be provided based on a single breakpoint concentration and decisions on modification of regimen will be made by the NDR-TBC committee based on the results of LC-DST for each individual patient as detailed in the guidelines later.

It is to be noted that for the individual FQs the cross resistance between Ofx (2.0), Lfx (1.5) and low level Mfx (0.5) is almost complete as observed in NDRS and thus not useful for clinical management except for higher concentration of Mfx (2.0) DST [7][8] which then guides to take a decision to use it at a higher dose if sensitive or to move to a FQ free regimen if resistant.

For patients with discordant results of R resistance between CBNAAT and LPA, another CBNAAT test is performed in the C-DST lab using the decontaminated deposit. The final result will be on consensus of the 3 tests (2 CBNAAT and 1 LPA). If 2 of 3 are R resistant then the final result will be R resistant; if 2 of 3 are sensitive, then the final result will be sensitive to R.

If the specimen is found to be smear negative at C-DST lab, a culture would be set up and LPA will be indirectly conducted on the culture isolate.

If the result is H resistant, the SL-LPA will be reflexly performed on available specimen (DNA) and if any class resistance (FQ/SLI) detected on SL-LPA, DST to Mfx (2.0), Km, Cm and Lzd will be done as per the algorithm.
DST to Z, Cfz, Bdq and Dlm would be considered for policy in future, whenever available, standardized and WHO endorsed. Z LC-DST though standardized is not being performed in line with the recent WHO recommendations (2016) and will be reviewed later based on in-country evidence after evaluating the Nipro LPA, sequencing and LC-DST concordance or agreement studies.[12] [26] [27] [28]

5.3 Laboratory recording and reporting

Results of the smear, culture and DST / LPA/ CBNAAT results are entered in the culture and DST register as annexed, held at the laboratory. All results must be communicated to the concerned DTO, DR-TBC/ private provider through Nikshay as soon as results are available so that patient treatment decisions can be smoothly managed. However, for providers without access to Nikshay, alternative means (email, SMS etc.,) for communicating the results must be utilized. If the culture result shows early contamination (within 4 days), the same is informed to the DTO within 24 hours and s/he is expected to arrange sending a repeat specimen (one early morning and one spot) to the laboratory within 3 days.

If LPA is found to be invalid or the sputum is smear negative, the sputum specimen is inoculated on solid or liquid culture immediately. If the culture result is found to be positive, the culture isolate is subjected to LPA test for confirming MDR-TB / RR-TB.

5.4 Management of patients while DST results are awaited

Any TB patient whose RR-TB result is awaited, would be initiated on first-line anti-TB treatment and continued on the same if found to be RS-TB. If RR-TB is detected, the patient is immediately referred for pretreatment evaluation and treatment initiation for DR-TB. However, the first-line treatment should be stopped as applicable. Moreover, all presumptive TB among key/vulnerable population would be initiated on RR-TB or RS-TB regimen based on the results of CBNAAT. Patients must be counselled to practice covering the cough and other infection control measures like provision of personal protective equipment and support to prevent the transmission of infection.

5.5 Diagnosis of DR-TB in children

Very limited data is available for DR-TB in children. It is mainly due to primary transmission of drug-resistant TB to the child and less likely to be acquired from exposure to TB treatment. Paediatric DR-TB is likely to reflect DR-TB in adults, so DR-TB is common in children in settings with higher prevalence, mortality and morbidity of DR-TB in adults compared to drug-sensitive TB.

Children with recurrent TB, treatment after lost to follow-up and treatment after failure are presumed patients of DR-TB. Children usually have pauci-bacillary disease and are sputum
negative. So, these definitions are to be used in conjunction with clinico-radiological picture. Additionally, other children who are at high risk of DR-TB could be contacts of DR patients, children living with HIV (CLHIV) and paediatric non-responders. With recent experience gained in India through a multi-city project involving paediatrician, there is now a policy to use CBNAAT for diagnosis of TB in children that gives the opportunity of simultaneous diagnosis of RR-TB using an appropriate biological specimen.

**Approach to diagnose DR-TB in children:** Careful history of patients, in particular, history of contact with DR-TB patients is critical information, as also considering child failing first-line TB treatment despite adherence. Clinical examination and investigations that are relevant for presumptive TB or EP-TB patients need to be carried out. It is important to try and get appropriate specimens from children. Failure to respond to TB treatment must rule out HIV-related lung disease which may not be TB. Bacteriological confirmation and drug susceptibility testing should be carried out whenever possible. For this, sputum (or other relevant specimens e.g. lymph node aspiration) must be collected from children with presumed DR-TB for CBNAAT (Xpert MTB/RIF) or LPA or culture and drug sensitivity testing.

Microbiological confirmation should always be done to ensure correct diagnosis, all effort must be made to get appropriate clinical specimens from affected site. Sputum, gastric lavage, BAL, pleural tap, lymph-node aspiration, excision, cerebrospinal fluid (CSF) and laparoscopic tissue biopsy can be considered. Diagnosis of DR-TB in absence of microbiological confirmation must be thoroughly reviewed as it may be untenable. In presumptive DR-TB, if there is no microbiological confirmation, bacteriologically negative clinically diagnosed DR-TB can be considered after ruling out alternative diagnosis. [20] [29] [30]

**Probable MDR-TB among children:** The case definitions of presumptive DR-TB and variety of DR-TB patients used for adults in section 4.4 of the previous chapter, would also apply to children. However, the term probable MDR-TB in children would be applied to children wherein bacteriologic confirmation is not available and the decision regarding diagnosis and initiation of treatment is taken by the NDR-TBC committee. Criteria for diagnosis of “probable MDR-TB” include children with signs and symptoms of active TB disease who in addition have the following risk factors. They should be considered as having “probable” MDR-TB and started on MDR-TB treatment, even in the absence of bacteriological confirmation. They include children who have:

- close contact with a known case of MDR-TB;
- close contact with a person who died whilst on TB treatment;
- close contact with a person who failed TB treatment;
- failure of a first-line regimen, recognizing that both bacteriological and clinical definitions of failure should be used; and
- previous treatment with second-line medications.
The algorithmic approach to diagnose DR-TB in children is shown in Figure 5.3. If an appropriate specimen is available from the child, the specimen processing will be in accordance to the integrated DR-TB diagnostic algorithm shown in Figure 5.2.

All patients considered to have ‘probable’ MDR-TB should be presented to and discussed with a NDR-TBC Committee followed by a decision to treat which ought to be made in consultation with the paediatrician. This consideration of initiation of appropriate DR-TB regimen without bacteriological confirmation does not replace the need for a thorough and ongoing diagnostic evaluation, including consideration of non-TB causes, prior to initiation of DR-TB treatment. Children with a central nervous system disease and/or those with other life-threatening manifestations who meet the criteria for ‘probable’ MDR-TB should be initiated on therapy immediately, in consultation with the paediatrician in the NDR-TBC committee, given the high risk of mortality.
Chapter 6: Pretreatment evaluation

The chapter provides the process of referral for pretreatment evaluation and pretreatment evaluation process.

6.1 Referral for pretreatment evaluation

It is crucial that patients with DR-TB be referred for treatment as soon as possible. If RR-TB/H mono-poly DR-TB is confirmed, the DTO will trace the patient, with help of Medical Officers – TB Control (MO-TC) & PHI, Senior DR-TB TB-HIV Supervisor and Senior Treatment Supervisor (STS) and bring the patient to the DDR-TBC where s/he will be counselled by the counsellor. Counselling should include the following:

- information on lab results and reliability of lab results from CBNAAT/RNTCP certified C-DST laboratories;
- need for additional treatment;
- importance of rapid initiation of treatment and adherence to prescribed treatment;
- services RNTCP offers for PMDT;
- what the patient should do next;
- necessary infection control precautions;
- re-assurance to the family against panic or unnecessary stigmatization of the patient; and
- patient support system

After counselling, the patient is referred to the DDR-TBC with its DST result and PMDT referral for treatment form, for pretreatment evaluation and initiation of standard regimen for DR-TB as appropriate. In addition to those patients diagnosed as RR-TB or MDR-TB, patients with H mono/poly DR-TB, will also be referred to the DDR-TBC for pretreatment assessment. Those patients, who have RR-TB, will also be treated with a regimen for MDR-TB.

While the RR/MDR-TB/H mono/poly DR-TB patient is undergoing pretreatment evaluation, the Senior DR-TB TB-HIV Supervisor, STS and DTO should ensure an initial home visit to verify the address and meet the family members. A Treatment supporter (who can either be a health care worker, community worker/volunteer or private practitioner) should be identified in consultation with the patient. The Treatment centre can either be at the sub centre of the health system or in the community. The family member, if identified as Treatment supporter should be trained to give medication under supervision at the residence, under close monitoring by TBHV/STS. The Treatment supporter should also be given training for drug administration, identification of adverse effects during treatment,
frequency of follow-up and record keeping. During IP, appropriate arrangement for injections should be done by the DTO.

6.2 Pretreatment evaluation for DR-TB patients

In majority of MDR/RR TB and H mono/poly DR-TB patients, pretreatment evaluation can be done on an outpatient basis, under intensive supervision. The DTO can arrange pretreatment evaluation at DDR-TBC or at sub-district level health facility, wherever possible. The patient should be fast-tracked for pretreatment evaluation and for infection control purposes and a separate space for specimen and blood collection should be identified.

Patients will be referred to the DDR-TBC/NDR-TBC with pretreatment evaluation results for initiation of treatment. The physician may decide for admission to DDR-TBC/NDR-TBC for pretreatment evaluation and initiation of treatment or get it done on an outpatient basis. Pretreatment evaluation should include, a thorough clinical evaluation by a physician. A specialist consultation along with reports of pre-treatment evaluation tests can be arranged, if required. Since the drugs used for the treatment of DR-TB have significant adverse effects, a pretreatment evaluation is essential to identify patients at increased risk of developing such adverse effects. This evaluation will vary as per the regimen class and is detailed in Table 6.1.[31]

Each of the DR-TBCs (DDR-TBC/NDR-TBC) must ensure that laboratory capacity and consultancy services from various specialists are available, either in-house supported under institutional/state government mechanism or through an outsourced mechanism. Tie up with private facility under Partnership Guidelines (innovation option) should be undertaken for investigations that are not available.

Pretreatment evaluation and treatment initiation must be done at the DR-TBC (DDR-TBC/NDR-TBC). The concerned DR-TBC committee provides counselling, initiates activities related to active drug safety monitoring (aDSM) like, assessing the baseline history of known adverse/serious adverse events (AE/SAE), biochemical investigations, ECG etc., and initiates him/her on an appropriate treatment regimen. Care must be taken to correct any electrolyte imbalance before treatment initiation.

MDR/RR-TB patients (without additional resistance) and H mono/poly DR-TB patients can be initiated on a standard treatment regimen at DDR-TBC. The DDR-TBC should refer those patients to NDR-TBC for management of patients with additional drug resistance, drug intolerance, contraindication, failing regimen, return after treatment interruption of >1 month, emergence of exclusion criteria for standard regimen, for expert opinion, management of any complications warranting regimen change for consideration of newer drug containing regimen or DST guided regimen based on a detailed assessment.
Table 6.1 Pretreatment evaluation of DR-TB patients by regimen class

<table>
<thead>
<tr>
<th>SN</th>
<th>Pretreatment evaluations</th>
<th>Regimen for H Mono / poly DR-TB</th>
<th>Conv. MDR-TB regimen</th>
<th>Shorter MDR-TB regimen</th>
<th>Regimen for RR-TB with FQ/SLI ± Lzd resistance (without newer drugs)</th>
<th>Newer drugs containing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Detailed history (including screening for mental illness, seizure disorder, drug/alcohol abuse, etc.)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>2</td>
<td>Previous history of ATT taken especially SLI/FQ</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3</td>
<td>Weight &amp; height</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4</td>
<td>Thorough clinical examination</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5</td>
<td>Complete blood count with hemoglobin &amp; platelets count</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>6</td>
<td>Blood sugar to screen for Diabetes Mellitus</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>7</td>
<td>Blood urea and S. Creatinine to assess renal function</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>8</td>
<td>Urine examination – routine and microscopic</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>9</td>
<td>UPT (for all women in the child-bearing age)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>10</td>
<td>Chest X-ray</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>11</td>
<td>HIV counselling and testing*</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>12</td>
<td>Audiogram</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>13</td>
<td>Liver function tests*</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>14</td>
<td>TSH levels to assess the thyroid function</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>15</td>
<td>Mental health evaluation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>16</td>
<td>Surgical evaluation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>17</td>
<td>ECG (if Mfx*, Dlm, Bdq, Cfzused)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>18</td>
<td>Serum electrolytes – potassium, magnesium, calcium</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>19</td>
<td>Serum proteins, lipase, amylase</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Ophthalmologist opinion to rule out chorioretinitis / uveitis</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*All DR-TB patients will be offered referral for HIV counselling and testing at the nearest centre if the HIV status is not known or HIV test result is negative with results more than 6 months. If patient is HIV positive, refer to ART centre (if not on ART)
# Including HBsAg at baseline
6.3 Providing health education/ counselling to patient and family members

Providing counselling and health education to the MDR/RR-TB patient and family members about the disease, the mechanism of transmission and necessity of taking regular and adequate treatment, is of utmost importance. Health education and counselling is provided to all patients and family members at different levels of health care, from the periphery to the DDR-TBC facility. It is started at the initial point of contact and continued during all visits by the patient to a health facility. Confidentiality and informed decision making process according to sound ethics standards is paramount when performing education and counselling to patients and their family members.

DDR-TBC/NDR-TBC counsellors to provide counselling for all DR-TB patients on the following:

- nature and duration of treatment;
- importance of adherence to treatment and need for complete and regular treatment;
- possible side effects of drugs;
- mechanism of transmission; and
- consequences of irregular treatment or premature cessation of treatment.

It is advisable to involve close family members during the counselling, since family support is an essential component in the management. Patients should be advised to report any side effects immediately. Female patients should receive special counselling on family planning. The treatment must be presented as an option and include information on any uncertainty about the adverse effects of drugs as detailed in the patient education booklet.

The counsellors would be trained exclusively with a counsellors training module on an e-learning platforms by RNTCP. This covers the various approaches, steps involved in counselling, tools, activities to be undertaken as well as the records and reports to be maintained by the counsellors. A patient-based counselling register must be maintained for all patients for recording information about patients’ situation and counselling services provided from the time of diagnosis till post-treatment follow-up period.

Pretreatment counselling must serve as an informed decision-making process that enables patients to make a duly informed decision regarding the use of all anti-TB drugs including newer drugs like Bdq. This activity must be recorded in the counsellor’s register, PMDT treatment card and treatment book of the patient before initiating treatment.
Chapter 7: Treatment of drug-resistant TB

This chapter provides guidance on the treatment of all forms of DR-TB patients.

7.1 Classes of anti-TB drugs recommended for treatment of DR-TB patients

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 PMDT Guidelines 2016. The same is explained in the table below. [12]

Table 7.1: Grouping of anti-TB drugs

<table>
<thead>
<tr>
<th>New grouping of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Fluoroquinolones</td>
</tr>
<tr>
<td>Levofoxacin</td>
</tr>
<tr>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Gatifloxacin</td>
</tr>
<tr>
<td>B. Second-line injectable agents</td>
</tr>
<tr>
<td>Amikacin</td>
</tr>
<tr>
<td>Capreomycin</td>
</tr>
<tr>
<td>Kanamycin</td>
</tr>
<tr>
<td>(Streptomycin)</td>
</tr>
<tr>
<td>C. Other second-line agents</td>
</tr>
<tr>
<td>Ethionamide / Prothionamide</td>
</tr>
<tr>
<td>Cycloserine / Terizidone</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
<tr>
<td>Clofazimine</td>
</tr>
<tr>
<td>D. Add-on agents (not part of the core MDR-TB regimen)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Ethambutol</td>
</tr>
<tr>
<td>High-dose isoniazid</td>
</tr>
<tr>
<td>Bedaquiline</td>
</tr>
<tr>
<td>Delamanid</td>
</tr>
<tr>
<td>p-aminosalicylic acid</td>
</tr>
<tr>
<td>Imipenem-cilastatin</td>
</tr>
<tr>
<td>Meropenem</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
</tr>
<tr>
<td>(Thioacetazone)</td>
</tr>
</tbody>
</table>

Note: E = Ethambutol, H = High-dose isoniazid.
7.2 Newer anti-TB drugs

After almost five decades of discovery of Rifampicin, the first new drug named Bedaquiline with anti-TB effect was approved for treatment of multidrug resistant TB by US FDA in late 2012. [10] This was followed by the approval of another new drug Delamanid by the stringent regulatory authority of various countries. [11] The drug development pipeline of new and repurposed drug has gained momentum in the recent past and more new molecules are expected to be approved in the future.

Bedaquiline is a new class of drug, diarylquinoline that specifically targets mycobacterial ATP synthase, an enzyme essential for the supply of energy to Mycobacterium TB. Strong bactericidal and sterilizing activities against M.tb have been shown in pre-clinical, laboratory and animal experiments. The drug has a high volume of distribution, with extensive tissue distribution, highly bound to plasma proteins and is hepatically metabolized. The drug has an extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping BDQ. The dosing schedule has been established after extensive pharmacokinetic/ pharmacodynamic (PK/PD) studies in animals and humans and hence need to be administered as per the manufacturer’s advice. BDQ has shown significant benefits in improving the time to culture conversion in MDR-TB patients. [10]

Delamanid as per an interim policy guidance document released by WHO in 2014, may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB. [11] The process for introduction of Dlm under RNTCP is ongoing and guidance for the same will be released subsequently as an addendum to these guidelines.

In June 2013, WHO published an interim policy guideline for use of BDQ in conjunction with WHO recommended MDR TB treatment that recommends that BDQ may be added to a WHO recommended regimen in adult patients with pulmonary MDR TB when an effective treatment regimen containing at least four second-line drugs in addition to Z cannot be designed or when there is documented evidence of resistance to any FQ and/or SLI in addition to MDR TB. In 2015, WHO published an implementation plan for introduction of BDQ for treatment of MDR TB at country level to support country efforts towards implementation of recommended new drugs or treatment regimens with particular emphasis on aDSM in absence of Phase III results on safety and efficacy of the drug. [10]

7.2.1 Regulatory approvals for Bedaquiline in India

After a thorough review of available evidence from various phased trials up to phase IIb; evidence emerging from several of the early implementing countries; WHO interim guidelines for use of Bdq; regulatory processes adopted by United States Food Drugs Administration (US FDA), European Union (EU) and stringent regulatory authorities of various countries was undertaken by the national expert committee on regulation of newer
anti-TB drugs in India. On 24 December 2014, the Apex Committee under the MoHFW, GoI for supervising clinical trials on new chemical entities in the light of directions of the Supreme Court of India approved the use of BDQ (100 mg) in adults aged 18 and above as part of a combination therapy of pulmonary TB due to MDR-TB.

Considering MDR-TB as a serious condition with high mortality and a disease of special relevance in the Indian health scenario, the committee recommended waiver of local clinical trials at this stage and approved BDQ with restriction that it shall be used under the RNTCP framework for conditional access through the PMDT programme for treatment of MDR-TB patients only. Soon after this, on 04 January 2015, the Drug Controller General of India (DCGI) granted an import license to Janssen (M/s. Johnson & Johnson Limited, India) that is guided by apex committee approval. The drug was approved for conditional access. This means, it shall be used under RNTCP PMDT framework for treatment of MDR-TB patients only with aDSM systems. [4] In March 2016, RNTCP introduced BDQ through a conditional access programme at six DR-TBCs in the country. Based on the lessons learnt from these initial sites, preparation for expansion of access to BDQ was initiated in all states in 2017.

7.2.2 Criteria for patients to receive Bedaquiline

**Inclusion criteria**
The criterion for patients to receive BDQ as approved by the Apex Committee is: adults aged > 18 years having pulmonary MDR-TB.

**Additional requirements**
- non-pregnant females or females not on hormonal birth control methods are eligible. They should be willing to continue practicing birth control methods throughout the treatment period or have been post-menopausal for past 2 years; and
- patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation.

**Exclusion criteria**
- currently having uncontrolled cardiac arrhythmia that requires medication;
- having any of the following QT/QTc interval (Annexure 8) characteristics at screening:
  - marked prolongation of QT/QTc interval, e.g. repeated demonstration of QTcF (Fredericia correction) interval > 450 ms; and
  - history of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalaemia, family history of long QT syndrome;

BDQ is provided along with a background regimen based on DST results. Certain conditions as listed below should be taken into consideration while choosing the drugs for the background regimen in patients who:
• have evidence of chorioretinitis, optic neuritis or uveitis at screening which precludes long-term Lzd therapy;
• have the following laboratory abnormalities (DAIDS grading of adverse events):
  - creatinine grade 2 or greater, i.e., >1.5 times the upper limit of normal (ULN);
  - haemoglobin grade 4 (<6.5 gm/dL);
  - platelet count grade 3 or greater (≤ 49 999/mm³);
  - absolute neutrophils count grade 3 or greater (≤ 749/mm³);
  - aspartate aminotransferase (AST) grade 2 or greater (>2.5 times ULN);
  - alanine aminotransferase (ALT) grade 2 or greater (>2.5 times ULN);
  - total bilirubin grade 2 or greater (>1.6 times ULN); and
  - lipase grade 2 (with no signs or symptoms of pancreatitis) or greater (>1.5 times ULN).

**Note:** If results of the serum chemistry panel, haematology or urinalysis are outside the normal reference range (including above listed parameters), the patient may still be considered if the physician judges abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable. Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to a patient receiving BDQ.

Patients who are not found to be eligible for a BDQ containing regimen would have DST results for the key first line and second line drugs and managed with DST guided regimens.

BDQ is indicated in adult MDR-TB patients not eligible for the newly WHO-recommended shorter regimen. [32] These may include:

- MDR/RR-TB patients with resistance to any/all FQ OR to any/all SLI;
- XDR-TB patients;
- mixed pattern resistant TB patients;
- treatment failures of MDR-TB + FQ/SLI resistance OR XDR-TB; and
- MDR/RR-TB patients with extensive pulmonary lesions, advanced disease and others deemed at higher baseline risk for poor outcomes. [32]

Caution must be exercised that BDQ is not added to a failing regimen in any patient already on DR-TB treatment.

### 7.3 Integrated drug-resistant TB algorithm

The integrated DR-TB algorithm (Figure 7.1) clearly indicates the management strategies to be followed right from the day the results of CBNAAT test are available. These management strategies are described in subsequent sections of this document. The programme is improving laboratory capacity to offer DST for all TB patients (Universal DST). An integrated algorithm offers FL-LPA for the presumptive DR-TB found R sensitive on CBNAAT. The LPA will be primarily utilized to do DST for second-line drugs and to test FL-LPA to detect H mono resistance as per the available laboratory
Figure 7.1 Integrated Drug Resistant TB Algorithm

Presumptive TB

Key/Vulnerable populations
- Paediatric age group
- People living with HIV
- EPTB sites
- Smear negative/NA with X-ray suggestive of TB

All diagnosed TB patients

- Non responders to treatment
- DR-TB contacts
- Previously treated TB
- TB-HIV co-infection
- New TB cases

CBNAAT

RR TB
- For discordance on LPA for RR-TB – repeat CBNAAT at LPA lab

RS TB
- FL-LPA

First line treatment

Shorter MDR TB Regimen (9-11 m)#

SL - LPA**
- FQ and SLI Sensitive
  - Continue same regimen (shorter MDR or H mono/poly regimen)
- FQ and/or SLI Resistance
  - Newer Drugs & DST guided treatment

H Resistant
- H mono/poly resistant TB regimen

H Sensitive
- Continue First line treatment

In case of addl resistance, failing regimen, drug intolerance, return after interruption (>1 m) or emergence of any exclusion criteria

# Conventional MDR TB Regimen (24 m) for pregnant women or for EP TB patients those who are not eligible for shorter MDR/RR regimen

*Offer molecular testing and treatment for H mono/poly resistance to TB patients prioritized by risk as per the available lab capacity

**LC DST (Mfx 2.0, Km, Cm, Lzd) will be done only for patients with any resistance on baseline SL-LPA. DST to Z, Cfx, Bdq & Dlm would be considered for policy in future, whenever available, standardized & WHO endorsed.

§ States to advance in phased manner as per PMDT Scale up plan for universal DST based on lab capacity and policy on use of diagnostics
capacity. The programme would continue building capacity of the laboratories to eventually test all R sensitive patients on LPA to detect H mono resistance that would serve as a surrogate for poly drug resistance. These patients would be managed as per the algorithm. Within the first 2-3 months, patients would receive the LC DST results, reach their final classification and treated with the appropriate regimen.

7.4 Treatment initiation

If CBNAAT reveals RS-TB, the patient is initiated on the first-line treatment at the PHI level.

At DDR-TB Centres

If the CBNAAT/ LPA reveal RR/ MDR-TB or if LPA reveals H mono resistance, the patient must be counselled by the PHI staff to visit the DDR-TBC with a family member for further management without further delay. The treatment initiation of the patients following results of CBNAAT and FL LPA on standard regimens i.e., either shorter MDR-TB regimen or conventional MDR-TB regimen or H mono/poly DR-TB regimen could be undertaken by the physicians at the DDR-TBC. The first-line treatment will be stopped and the appropriate standard DR-TB regimen will be initiated at the DDR-TBC.

For all laboratory confirmed RR-TB patients, the DDR-TBC will initiate the standard shorter MDR-TB regimen (9-11 months) after careful assessment ensuring SL-LPA is conducted and management of pregnancy or if the patient has EP-TB through specialist consultation if required. Such patients, if after assessment, are found to be not eligible for shorter MDR-TB regimen will be initiated on standard conventional MDR-TB regimen (24-27 months). Less severe forms of EP-TB patients like those with lymph node TB or pleural effusion who are drug resistant and eligible based on the DRT/DST and SL-LPA, would also be offered the shorter MDR-TB regimen. Similarly, a laboratory confirmed H mono resistant TB patient is initiated on a standard regimen for H mono/poly DR-TB.

The DDR-TBC Committee can decide on a case-to-case basis, the need for admission for DR-TB patients for initiation of treatment. The patient is initiated on standard regimen at DDR-TBC on indoor or outpatient basis. The first dose is given under supervision at DDR-TBC for ambulatory patients. In patients who are admitted, the duration of indoor management would be decided by DDR-TBC committee as clinically indicated. On discharge, the patient will be provided with a maximum seven days of drug supply for the transit.

In both scenarios, DTO refers the patient to the identified treatment supporter with advance information to MO-PHI to identify and prepare the treatment supporter and provide drugs and records to the treatment supporter. The results of SL-LPA are expected to be available within a week of specimen submission. The LPA laboratory must report whether the specimen is resistant to all SLIs (i.e., rrs mutation) or only Km (eis mutation). The results of LC DST are expected to be available after 6-8 weeks of specimen submission. Based on
results, if no additional resistance is detected, the patient will be continued on the same regimen at the district level.

**At NDR-TB centres**

If additional resistance to FQ and/or SLI is reported, the patient is counselled by the PHI staff and referred to the NDR-TBC immediately. The pretreatment evaluations and baseline aDSM assessment done at the DDR-TBC would be considered valid for assessment of the patient and further management, only if additional resistance is reported on the basis of SL-LPA received within a week. However, these would be repeated if the additional resistance is reported on the basis of LC-DST. The standard DR-TB regimen will be stopped and the NDR-TBC committee would re-design the regimen based on the DST pattern with or without newer drugs as appropriate. As the patient would still be in early IP, the patient would be re-classified and re-registered for a new episode of treatment and updated on Nikshay on the same ID. For monitoring the treatment outcome, the patient would be accounted for the most recent episode of treatment. However, patients who need regimen change in CP will be declared with outcome as “Treatment failed” and re-registered for the next episode of an appropriate treatment.

Apart from this, in case of emergence of additional resistance, failing regimen, drug intolerance, return after interruption (>1 months) or emergence of any exclusion criteria, the patient must be immediately referred by N/DDR-TBC. S/he should have a copy of all records or baseline pretreatment evaluation, baseline aDSM assessment and PMDT treatment book to the NDR-TBC for the committee to consider redesigning the DST guided regimen with or without newer drugs for managing the patient as applicable.

The patient will be reclassified as per DST pattern and date and type of patient’s re-classification will be specified in the remarks column of the PMDT treatment register of DDR-TBC and NDR-TBC as well as updated on Nikshay. The duration of treatment, follow-up timelines, interim and final outcomes of the patient would be considered from the date of most recent reclassification. All modifications in regimens or change of the regimen class would be undertaken by NDR-TBC.

Patients eligible for newer drugs need to be offered counselling along with a patient education booklet (Annexure 9) which will give details of the nature and duration of treatment including information on the new drug Bdq; need for regular treatment; possible side-effects of these drugs; drugs to be avoided with Bdq and the consequences of irregular treatment or premature termination of treatment. Female patients will receive special counselling on family planning. The informed decision making process and its documentation is detailed in Chapter 6.
Cohort Event Monitoring (CEM) treatment initiation form needs to be completed and uploaded on Nikshay for all DR-TB patients at the time of initiation of each new regimen. All patients eligible for newer drugs containing regimen would be managed in an in-patient setting for a period of two weeks (15 days) to complete the initial two weeks of Bdq doses. The final decision of further duration of in-patient management rests with the NDR-TBC Committee and must be well-documented for every patient. After discharge, treatment will be continued on ambulatory basis with strict adherence to treatment and follow-up schedule. All measures for AIC must be implemented as per the national AIC guidelines while managing all TB patients. In exceptional patients who are not seriously ill, it is important to have all pretreatment evaluations within normal limit and for those who are ambulatory or residing close to the NDR-TBC and are willing to visit NDR-TBC for periodic ECG and clinical monitoring, the NDR-TBC Committee may decide to manage the patient on an ambulatory basis.

7.5 Regimen type (with or without newer drugs)

Principles of designing a WHO recommended DR-TB regimen

In patients with RR or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including Z and four core second-line TB medicines - one chosen from group A, one from group B and at least two from group C. If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five. In patients with MDR/RR-TB, it is recommended that the regimen be further strengthened with H₈ and/or E.[12]

Newer drugs containing regimen would contain the new drug as one of at-least four core second-line drugs considered to be effective (choice of drugs should be based on DST pattern) and Z as per the above principles. Because of GI side effects of PAS, as far as possible, will be avoided in Bdq containing regimen.

Designing a regimen is the prerogative of the DR-TBC committee. The regimen may be with or without inclusion of new drugs like BDQ and would be classified into the following types:

**At DDR-TB centres:**

- H Mono/Poly drug resistant TB
- MDR/RR-TB
  - shorter MDR-TB regimen; and
  - conventional MDR-TB regimen.

**At NDR-TB centres:**

- MDR/RR-TB with additional resistance to any/all FQ or SLI
- XDR-TB
- Mixed pattern drug resistant TB
- with H mono + FQ/SLI/Lzd resistance;
- with MDR/RR-TB + FQ/SLI+ Lzd resistance; and
- other patients who need careful regimen designing detailed later.

- Non - TB *Mycobacterium* (NTM)

### 7.5.1 H Mono/Poly drug-resistant TB

On receiving the reports showing H mono resistance on LPA that serves as a surrogate for first-line drugs mono & poly DR-TB (excluding R), the patient and their family members should be counselled and referred to the nearest DDR-TBC. Baseline SL DST will be performed as detailed above. The DDR-TBC will undertake the pretreatment evaluation (including clinical and radiological evaluation) and initiates the patient on the standard treatment regimen as in Table 7.3

### 7.5.2 MDR/RR-TB

All lab confirmed MDR/RR-TB patients will be initiated on the shorter MDR-TB regimen with special precautions in pregnant women and EPTB patients (see sections later).

#### Shorter MDR-TB regimen

The shorter MDR-TB regimen is recommended for patients in whom the diagnosis of MDR/RR-TB has been reliably confirmed by molecular (e.g. CBNAAT/ LPA) or phenotypic DST method and are found to be sensitive to both FQ and SLI by SL-LPA. All patients with confirmed R-resistant disease are treated as for MDR-TB and the shorter MDR-TB regimen could be used in these patients too. Children and PLHIV on antiretroviral therapy (ART) could receive the shorter MDR-TB regimen. [12][26] The following are the features of shorter MDR-TB regimen:

- standardized shorter MDR-TB regimen with seven drugs and a treatment duration of 9-11 months;
- indicated conditionally in MDR-TB or RR-TB, regardless of patient age or HIV status;

#### Exclusion criteria

- Second-line drug resistance (FQ and/or SLI drugs), previous exposure for >1 month to a FQ or a second-line injectable medicine which is not in the shorter MDR-TB regimen but which may generate cross-resistance is considered an exclusion criterion. However, if resistance to both of these two agents has been excluded by a reliable drug-susceptibility test (DST), then the shorter MDR-TB regimen can be used.
- It is not recommended to base treatment decisions on the DST to any other drug in the regimen (Z, H⁹, E, Eto, Cfz) apart from those mentioned, owing to the unreliable nature of the tests.
Pregnancy.
• Extra-pulmonary TB (Other than plural effusion & lymph node TB)

Justification for shorter MDR-TB regimen

It has been observed from pooling individual patient data (n=1116) of observational studies from Bangladesh, Uzbekistan, Swaziland, Cameroon, Niger and nine countries of sub-Saharan Africa that patients who met specific inclusion criteria for receiving the shorter MDR-TB treatment regimens had a statistically-significant higher likelihood of treatment success than those who received longer conventional regimens (89.9% vs. 78.3% respectively when success was compared with treatment failure/relapse/death (Table 7.3) and 83.4% vs. 61.7% when compared with treatment failure/relapse/death/lost to follow-up). The number of relapses was very low, although this may have been as a result of the relatively small number of patients followed up. As expected, the treatment success was lower in patients with additional resistance to Z and/or FQ on shorter MDR-TB regimens, even if in general it remained high and exceeded that in the patients on individualized, conventional regimens (although the differences were not statistically significant).[12]

Table 7.2: Treatment success in patients treated with shorter MDR-TB regimen vs conventional MDR-TB regimens*

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Shorter MDR-TB regimen</th>
<th>Conventional MDR-TB regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>All patients regardless of pyrazinamide and fluoroquinolone susceptibility</td>
<td>1008/1116</td>
<td>90.3% (87.8%-92.4%)</td>
</tr>
<tr>
<td>Pyrazinamide resistant; fluoroquinolone resistant</td>
<td>19/28</td>
<td>67.9% (47.6%-84.1%)</td>
</tr>
<tr>
<td>Pyrazinamide resistant; fluoroquinolone susceptible</td>
<td>90/100</td>
<td>88.8% (47.3%-98.6%)</td>
</tr>
<tr>
<td>Pyrazinamide susceptible; fluoroquinolone resistant</td>
<td>12/15</td>
<td>80.0% (50.0%-94.1%)</td>
</tr>
<tr>
<td>Pyrazinamide susceptible; fluoroquinolone susceptible</td>
<td>121/125</td>
<td>96.8% (77.3%-99.6%)</td>
</tr>
</tbody>
</table>

*Treatment success (cured or treatment completed) versus failure/relapse/death in patients not previously treated with second-line TB medications; percentages shown have been adjusted when possible.

Hence, there is merit in immediately adopting the shorter MDR-TB regimen (9-11 months) based on the advantage of being substantially less expensive than the conventional regimen and its potential to improve treatment success and decrease deaths when compared to conventional MDR-TB regimens (24-27 months) with poor treatment outcomes in MDR-TB of about 46% in India (2013 cohort). [1][6] It should be noted the value and guidance for implementing the shorter regimen will be updated as soon as the results of the phase 3
STREAM clinical trial evaluating this regimen are reviewed by WHO, according to well established process. The shorter MDR-TB regimen is detailed in Table 7.3.

A recently published meta-analyses of individual patient data and aggregate data from five studies on effectiveness and safety of standardized shorter regimens for MDR-TB revealed 669/796 lab confirmed MDR/RR-TB patients not previously exposed to second-line drugs. They were successfully treated (83%, 95% CI 71.9-90.3%) while failure/relapse was associated with fluoroquinolone resistance (crude OR 46, 95% CI 8–273), pyrazinamide resistance (OR 8, 95% CI 2–38) and no culture conversion by month 2 of treatment (OR 7, 95% CI 3–202). The major implications for the programmatic use of shorter MDR-TB regimens are highlighted in the box below.

The study has revealed few major implications for the programmatic use of shorter MDR-TB regimens

- The observation that resistance to fluoroquinolones or resistance to pyrazinamide were risk factors for failure/relapse and that acquired drug resistance occurred among failures underscore that programmes implementing shorter regimens should simultaneously strive to scale-up DSTs for component drugs. Others recently suggested alternate regimens available for patients identified to have strains that are resistant at baseline or that acquire resistance during treatment. This is supported by evidence from other studies showing that successful MDR-TB treatment is determined, in part, by the number of drugs used against which the infecting strain is susceptible, including pyrazinamide.
- All shorter regimen studies used intensive treatment adherence systems along with social support. They provided ART to all PLHIV. Hence, such interventions should be considered essential components of shorter regimens.
- Programmes should ensure proper screening and management of adverse events
- Successfully treated patients should be followed for relapse for at least 1 year after completion of therapy.[27]

All these recommended strategies are well adopted in this guideline

The NDRS results revealed concerns around resistance to component first and second-line drugs included in shorter MDR-TB regimen as detailed in Chapter 1 and was discussed extensively among the national experts.[7] However, the meta-analysis detailed above with high treatment success rates excluded RR-TB patient susceptible to H, implying that H resistance do not affect the treatment success observed in shorter MDR-TB regimen. Resistance to E was not significantly affecting the treatment outcomes with shorter MDR-TB regimen. The treatment success rate was still observed to be as high as 92% in patients treated with shorter MDR-TB regimen with Z resistance but FQ susceptible.[27]
WHO recommended regimens always have Z without counting it with the other effective drugs which still remains a practice globally with inconclusive evidence.\[12][26][31] With SL-LPA simultaneously introduced across India, patients with FQ and/or SLI class resistance will be clearly excluded. However, the programme would continue to simultaneously strive to scale-up DSTs for component drugs in future and help generate evidence around the use of Z, \( H^h \) as component drugs are included in shorter MDR-TB regimen. Till such time that it gets accepted, the programme would continue implementing the standard shorter MDR-TB regimen as recommended by WHO.

**Conventional MDR-TB regimen**

Those patients who are not considered eligible for shorter MDR-TB regimen (particularly after assessment in pregnant women, EP-TB except patients with lymph node TB and pleural effusion) should be initiated on conventional MDR-TB regimen as in Table 7.3

As the above three regimen for treatment of MDR/RR-TB or H mono-poly DR-TB are standard regimen, these would be initiated at the DDR-TBC based on results of CBNAAT or FL-LPA. The regimen designs adhere to the principles of designing a WHO recommended DR-TB regimen \[12\] detailed in Table 7.3

**Table 7.3: Standard regimen for initiating treatment of MDR/RR-TB or H mono-poly DR-TB at district DR-TB centre based on CBNAAT or FL-LPA**

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Regimen class</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Principle of regimen design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen for H mono/poly DR-TB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H mono/poly DR-TB (R susceptible H resistant TB &amp; DST of SEZ not known)</td>
<td>H Mono-poly DR-TB regimen</td>
<td>(3-6) Lfx Km R E Z</td>
<td>(6) Lfx R E Z</td>
<td>REZ + augment with 1 GpA + 1 GpB drug</td>
</tr>
<tr>
<td><strong>Shorter MDR-TB regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R resistant + H sensitive/ unknown or MDR–TB</td>
<td>Shorter MDR-TB regimen</td>
<td>(4-6) Mfx(^h) Km* Eto Cfz Z H(^h) E</td>
<td>(5) Mfx(^h) Cfz Z E</td>
<td>As per WHO recommendation</td>
</tr>
<tr>
<td><strong>Regimen for MDR/RR-TB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R resistant + H sensitive/ unknown or MDR–TB</td>
<td>Conventional MDR-TB regimen</td>
<td>(6-9) Lfx Km Eto Cs Z E</td>
<td>(18) Lfx Eto Cs E</td>
<td>1 GpA + 1GpB + 2 GpC + Z + add on 1 GpD1</td>
</tr>
</tbody>
</table>

*If the intensive phase is prolonged, the injectable agent is only given three times a week in the extended intensive phase.*
7.5.3 MDR/RR-TB with additional resistance to any/all FQ or SLI

All patients with additional resistance to FQ class or SLI class on SL-LPA would be assessed for eligibility for newer drug containing regimen. Patients who have consented and are found to be eligible would be initiated on newer drugs containing the regimen while rest of the patients would be initiated on a DST guided regimen and reclassified. The regimen design is detailed in Table 7.4. If a patient is resistant to either FQ or SLI class on SL-LPA, is found to be resistant to any of the drugs of the other class, in LC-DST, the patient will be reclassified as XDR-TB.

7.5.4 XDR-TB

All XDR-TB patients identified with SL-LPA or LC-DST would be assessed for eligibility for the newer drug containing regimen and reclassified as above. The regimen design is detailed in Table 7.4.

7.5.5 Mixed pattern drug resistant TB

Following patient/s would be operationally re-classified into mixed pattern drug-resistant TB:

- H mono-poly DR-TB patients with additional resistance to FQ and/or SLI and/or Lzd based on LPA and/or LC-DST will be reclassified as mixed pattern DR-TB. All such patients should be subject to consultation by a thoracic surgeon for consideration of surgery at tertiary centres with surgical facilities. These patients would be initiated on a DST guided regimen as detailed in Table 7.4;
- Similarly, RR-TB patients with additional resistance to FQ and/or SLI with Lzd resistance detected on LC-DST will also be reclassified as mixed-pattern DR-TB; and
- Apart from this, MDR/RR-TB patients would also be managed with the regimen for mixed-pattern DR-TB if the following events prevent them to be managed with any of the above regimen classes:
  - patients who are failing any DR-TB regimen or
  - patients who have drug intolerance or contraindications or
  - patients who return after interruption (>1 months) or
  - patients who have emergence of any exclusion criteria
  - patients with extensive pulmonary lesions, advanced disease and others deemed at higher baseline risk for poor outcomes.

All such patients would be re-evaluated for eligibility for newer drug containing regimen and re-classified as above. The regimen design is detailed in Table 7.4. In patients who have failed an M/XDR TB regimen, the regimen proposed for mixed pattern regimen should be
designed using drugs considered to be effective-based on previous use. It is also advised to use a minimum of 5 drugs and maximum 8-9 drugs in the regimen. [9]

The regimen design will start with appropriate modification of the regimens proposed for XDR-TB with or without newer drugs as per the eligibility/consent of the patient using the guidance in the footnotes as detailed in Table 7.4.

In future, whenever standardized, WHO endorsed DST methods for Z, Ctz, Bdq, Dlm etc., are available and included as programme policy, patients found to be resistant to any of the above drugs would be managed with the regimen for mixed pattern DR-TB.[12][26] [27][28]

**Replacement drugs in sequence of preference**

In case of an adverse drug reaction, poor tolerance, contraindication or non-availability of any component drug of the combination regimen warranting replacement, the following drugs would be added to replace that drug in the order of sequence, if not already used: Cs, H\(^{\text{H}}\) E, Bdq* (*in RR-TB patients also where a WHO recommended regimen could not be formed), PAS, Amx-clv.[12]

If more than one drug is required to be replaced but this replacement is just a modification and does not change the regimen class, the patient would continue to be reported on the same regimen. However, if the replacement of drugs affects the regimen class, then these patients would need to be re-classified as mixed pattern DR-TB. This decision would be based on the judgment of the NDR-TBC Committee. As far as possible, patients need not be unnecessarily asked to travel to NDR-TBC while required changes may be carried out at DDR-TBC or at field-level as per modifications recommended in the regimen by NDR-TBC.
Table 7.4: DST guided regimen with or without newer drugs for initiating treatment of DR-TB patients with additional resistance to FQ class and/or SLI class, at NDR-TBC based on SL-LPA

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>DST guided regimen class</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Principle of regimen design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen with new drugs for MDR-TB + FQ / SLI resistance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR/RR + resistance to FQ class / SLI class</td>
<td>MDR/RR + res to FQ class</td>
<td>(6-9) Km Eto Cs Z Lzd³Cfz + (6) Bdq</td>
<td>(18) Eto Cs Lzd³Cfz</td>
<td>0 GpA + 1GpB + 2 GpC + Z + add on 2 GpC + 1 GpD2</td>
</tr>
<tr>
<td></td>
<td>MDR/RR+ res to SLI¹ class</td>
<td>(6-9) Lfx Cm¹ Eto Cs Z Lzd³Cfz + (6) Bdq</td>
<td>(18) Lfx Eto Cs Lzd³</td>
<td>1 GpA + 1 GpB¹ + 2 GpC + Z + add on 2 GpC + 1 GpD2</td>
</tr>
<tr>
<td><strong>Regimen MDR-TB + FQ / SLI resistance: (without new drugs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR/RR + resistance to FQ class / SLI class</td>
<td>MDR/RR + res to FQ class</td>
<td>(6-9) Mfxʰ² Km Eto Cs Z Lzd³Cfz</td>
<td>(18) Mfxʰ² Eto Cs Lzd³Cfz</td>
<td>1 GpA² + 1GpB + 2 GpC + Z + add on 2 GpC</td>
</tr>
<tr>
<td></td>
<td>MDR/RR+ res to SLI¹ class</td>
<td>(6-9) Lfx Cm¹ Eto Cs Z Lzd³Cfz</td>
<td>(18) Lfx Eto Cs Lzd³</td>
<td>1 GpA + 1 GpB¹ + 2 GpC + Z + add on 2 GpC</td>
</tr>
<tr>
<td><strong>Regimen with new drugs for XDR-TB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XDR-TB (res to both FQ and SLI¹ class)</td>
<td>XDR-TB</td>
<td>(6-12) Cm¹ Eto Cs Z Lzd³Cfz E + (6) Bdq</td>
<td>(18) Eto Cs Lzd³Cfz E</td>
<td>0 GpA + 1 GpB¹ + 2 GpC + Z + add on 2 GpC + 1GpD1 + 1 GpD2</td>
</tr>
<tr>
<td><strong>Regimen for XDR-TB: (without new drugs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XDR-TB (res to both FQ and SLI¹ class)</td>
<td>XDR-TB</td>
<td>(6-12) Mfxʰ² Cm¹ Eto Cs Z Lzd³Cfz E</td>
<td>(18) Mfxʰ² Eto Cs Lzd³Cfz E</td>
<td>1 GpA² + 1 GpB¹ + 2 GpC + Z + add on 2 GpC + 1GpD1</td>
</tr>
<tr>
<td><strong>Regimen with new drugs for mixed pattern DR-TB:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed pattern DR-TB</td>
<td>MDR/RR-TB + res to FQ / SLI¹ + Lzd³ or more</td>
<td>Modify the regimen with new drugs for XDR-TB as per the footnotes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Regimen for mixed pattern DR-TB: (without new drugs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed pattern DR-TB</td>
<td>H mono-poly + res to FQ/SLI¹/ Lzd³</td>
<td>(3-6) R E Z Cm¹ Eto Lzd³</td>
<td>(6) R E Z Eto Lzd³</td>
<td>REZ + augment with 1 GpB¹ + 2 GpC drug</td>
</tr>
<tr>
<td></td>
<td>MDR/RR-TB + FQ / SLI¹ with Lzd³ or others.</td>
<td>Modify the regimen for XDR-TB (without new drugs) as per the footnotes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Foot note:

1. if only Km resistant (at eis mutation), then add Cm in IP upfront in the regimen design;
2. in patients with MDR/RR + FQ class resistance, XDR-TB and mixed pattern resistance where a new drug is not considered in the regimen for any reason, Mfx\(^h\) would be added upfront in the regimen design and the decision to continue or replace it would be taken based on LC-DST results to Mfx (2.0) by NDR-TBC; and
3. Lzd to be replaced with a suitable drug if found to be resistant on LC-DST. In such situation the patient must be reclassified as mixed pattern DR-TB.

Once the baseline LC-DST results are available, the decision to modify the regimen in patients with FQ or SLI class resistance by adding individual drugs in FQ or SLI groups in the above DST guided regimen would be considered. This would be done as below, based on LC-DST results:

- if Mfx (2) is susceptible, then add Mfx\(^h\) and increase the frequency of ECG monitoring if used in a regimen containing other cardio toxic drugs like Bdq, Cfz, Dlm etc.;
- if Mfx (2) is resistant, then remove all FQ;
- if any of the SLI are susceptible, then add one susceptible injectable in the order of Km, Cm; and
- if all SLI are resistant, then do not add the SLI.

However, the susceptible drug added from the FQ or SLI class would not be counted as an effective drug in the regimen but rather considered as an add-on drug to substantiate the strength of the regimen.

7.5.6 Non-TB *Mycobacterium* (NTM)

**Treatment of NTM:** [24][25]

NTM are uncommonly encountered clinical pathogens; some species, in fact, are much more likely to be isolated as a result of specimen contamination than as a result of disease. It can also be isolated from patients with lower respiratory infections especially from patients who live in areas of higher density of environmental NTM presence. This is a transient carriage and usually does not meet the criteria for NTM disease. However, even these species can, under some circumstances, cause clinical disease. The clinician, therefore, must always know the context in which an NTM isolate was obtained to assess accurately the clinical significance of that isolate. Given these complexities, the treatment of NTM will be the prerogative of the NDR-TBCs. When questions about the clinical significance of an NTM isolate arise, expert consultation is strongly encouraged. In this context, important points to note would be:
treatment recommendations for infrequently encountered NTM are made on the basis of only a few reported patients. With that limitation in mind, unless otherwise stated, the duration of therapy for most pulmonary NTM pathogens is based on treatment recommendations for more frequently encountered species such as MAC and M. kansasii (e.g., continue therapy for at least 12 months after the last negative sputum culture). For disseminated disease, treatment duration for most NTM pathogens is the same as for disseminated MAC infection;

- treatment of NTM disease is generally not directly analogous to the treatment of TB. In vitro susceptibilities for many NTM do not correlate well with clinical response to antimycobacterial drugs. Recommendations for routine in vitro susceptibility testing of NTM isolates are limited. The clinician should use in vitro susceptibility data with an appreciation for its limitations;

- empiric therapy for suspected NTM lung disease is not recommended; and

- there are not widely accepted criteria for choosing patients with NTM lung disease for resectional surgery. In general, the more difficult an NTM pathogen is to treat medically, the more likely surgery should be considered from a risk/benefit perspective. Expert consultation is strongly encouraged at NDR-TBC.

**Suggested treatment regimen covering maximum NTMs mainly MAC**

- Rifampicin 450-600 mg OD;
- Ethambutol 800 – 1200 mg OD;
- Clarithromycin 1gm OD (split into two doses); and.
- Add injection Amikacin 750mg-1gm thrice weekly for the first 2-3 months.

Intensive phase is for 3 months and can be extended to a maximum of 6 months with all four drugs. Continuation phase of treatment will be with the same drugs except injectable. This should be continued for 12 months after sputum culture conversion. Drugs will be given as per the standard weight bands. If the patient does not culture covert by end of 3 months, then species identification and DST is required for further management by the NDR-TBC committee based on expert consultations.

*Note:- As the proportion of the patients estimated is very low, drugs will not be available through RNTCP but will have to be made available through the general health system.*

**Points to note for treatment of NTM**

- recommended initial regimen for most patients with nodular/bronchiectatic MAC lung disease is a thrice-weekly regimen including Clarithromycin 1000 mg or Azithromycin 500 mg, E 25 mg/kg, and R 600 mg administered three times per week;

- recommended initial regimen for fibro-cavitary or severe nodular/bronchiectatic MAC lung disease includes clarithromycin 500–1000 mg/day or azithromycin 250 mg/day, E
15 mg/kg/day, and R 10 mg/kg/day (maximum, 600 mg). An initial 2 months of E at 25 mg/kg/day is no longer recommended;

- intermittent drug therapy is not recommended for patients who have cavitary disease, or patients who have been previously treated or patients who have moderate or severe disease;
- primary microbiologic goal of therapy is 12 months of negative sputum cultures while on therapy; therefore, sputum must be collected from patients for AFB examination throughout treatment on monthly basis in IP and quarterly basis in CP after culture conversion is achieved;
- macrolides should not be used as monotherapy for MAC because of the risk for developing macrolide-resistant MAC isolates;
- macrolide with a single companion drug, E, may be adequate for nodular/bronchiectatic MAC disease but should not be used in patients with fibro-cavitary disease because of the risk of emergence of macrolide resistance;
- patients respond best to MAC treatment regimens the first time they are administered; therefore, it is very important that patients receive recommended multidrug therapy the first time they are treated for MAC lung disease; and
- expert consultation should be sought for patients who have difficulty tolerating MAC treatment regimens or who do not respond to therapy.

For further details on management of individual NTMs including EP NTMs, the physicians of NDR-TBC are encouraged to refer to the latest ATS guidelines.

### 7.6 Drug dosage and administration

The dosage of drugs would vary as per weight of the patients. Patients would be classified in weight bands of <16 kg, 16-29 kg, 30-45 kg, 46-70 kg and >70kg. All drugs in the regimen are to be given on a daily basis under observation. Injectable will be administered for six days/week (excluding Sundays). All morning doses are to be supervised by the treatment supporter. After taking the morning doses on Saturday, next day’s oral drugs would be given to the patient to be taken at home on Sunday. Empty blisters of medicines taken unsupervised in the evening and on Sundays are to be collected by treatment supporter. In cases of drug intolerance – E, Cs and Na-PAS can be given in divided doses (twice a day).

The dosage for drugs used in various DR-TB regimens by weight bands for adults are enumerated in Table 7.5. These are in accordance to the WHO recommended doses of anti-TB drugs for adults and paediatric patients. [31](Annexure 10)
### Table 7.5: Dosage of DR-TB drugs for adults

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drugs</th>
<th>16-29 kg</th>
<th>30-45 kg</th>
<th>46-70 kg</th>
<th>&gt;70 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rifampicin (R)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>300mg</td>
<td>450mg</td>
<td>600mg</td>
<td>600mg</td>
</tr>
<tr>
<td>2</td>
<td>High dose H (H&lt;sup&gt;h&lt;/sup&gt;)</td>
<td>300 mg</td>
<td>600 mg</td>
<td>900 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>3</td>
<td>Ethambutol (E)</td>
<td>400 mg</td>
<td>800 mg</td>
<td>1200 mg</td>
<td>1600 mg</td>
</tr>
<tr>
<td>4</td>
<td>Pyrazinamide (Z)</td>
<td>750 mg</td>
<td>1250 mg</td>
<td>1750 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>5</td>
<td>Kanamycin (Km)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>6</td>
<td>Capreomycin (Cm)</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>7</td>
<td>Amikacin (Am)</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>8</td>
<td>Levoflaxacin (Lfx)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>250 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>9</td>
<td>Moxifloxacin (Mfx)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>200 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>10</td>
<td>High dose Mfx (Mfx&lt;sup&gt;h&lt;/sup&gt;)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>400 mg</td>
<td>600 mg</td>
<td>800 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>11</td>
<td>Ethionamide (Eto)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>375 mg</td>
<td>500 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>12</td>
<td>Cycloserine (Cs)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>250 mg</td>
<td>500 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>13</td>
<td>Na-PAS (60% weight/vol)&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>10 gm</td>
<td>14 gm</td>
<td>16 gm</td>
<td>22 gm</td>
</tr>
<tr>
<td>14</td>
<td>Pyridoxine (Pdx)</td>
<td>50 mg</td>
<td>100 mg</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>15</td>
<td>Clofazimine (Cfz)</td>
<td>50 mg</td>
<td>100 mg</td>
<td>100 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>16</td>
<td>Linezolid (Lzd)</td>
<td>300 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>17</td>
<td>Amoxyclov (Amx/Clv) (In child: WHO 80mg/Kg in 2 divided doses)</td>
<td>875/125 mg BD</td>
<td>875/125 mg BD</td>
<td>875/125 mg (2 morning +1 evening)</td>
<td>875/125 mg (2 morning +1 evening)</td>
</tr>
<tr>
<td>18</td>
<td>Bedaquiline (Bdq)</td>
<td>Week 0–2: Bdq 400 mg daily</td>
<td>Week 3–24: Bdq 200 mg 3 times per week</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>For H mono/poly resistant TB;

<sup>2</sup>For adult more than 60 yrs of age, dose of SLI should be reduced to 10mg/kg (max up to 750 mg)

<sup>3</sup>In patient of PAS with 80% weight/volume the dose will be changed to 7.5gm (16-29Kg); 10 gm (30-45 Kg); 12 gm (46-70 Kg) and 16 gm (>70 Kg)

<sup>4</sup>Drugs can be given in two divided doses in a day in the event of intolerance

**Bedaquiline:** All patients eligible for Bdq will receive Tab. Bdq400 mg once daily for the first 2 weeks and 200 mg 3 times a week (with at least 48 hours between doses) for the following 22 weeks, in combination with an optimized background regimen (OBR) as detailed above. The OBR will be continued beyond 24 weeks of Bdq administration for the RNTCP recommended duration of treatment. As mentioned above, OBR will be designed as per RNTCP PMDT guidelines and WHO recommendations for designing an OBR for concomitant use with Bdq for avoiding drugs like Mfx and Cfz that are likely to cause increased toxicity when administered in combination with Bdq.
**Week 0–2**: Bdq 400 mg (4 tablets of 100 mg) daily (7 days per week) + OBR;  
**Week 3–24**: Bdq 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses) for a total dose of 600 mg per week + OBR; and  
**Week 25 (start of month 7) to end of treatment**: Continue other second-line anti-TB drugs only as per RNTCP recommendations.

If taking a light meal with Bdq and other anti-TB drugs, patients should not consume milk-containing products at the same time, as the calcium in these can decrease the absorption of FQs. Also, large fatty meals should be avoided, as these can impair absorption of some of the other anti-TB drugs (Cs, H, etc.). [4][10][32]

The following medications are disallowed during the 24-week administration of Bdq and up to one month after the last dose of Bdq because of potential drug–drug interactions:

- systemic use of moderate and strong CYP3A4 inhibitors, e.g. azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolides such as telithromycin and macrolide antibiotics other than azithromycin for more than 2 consecutive weeks;
- systemic use of strong CYP3A4 inducers, e.g. phenytoin, carbamazepine, phenobarbital, St. John’s wort and rifamycins (rifampin, rifabutin, rifapentine); and
- cholesterol lowering medications of the “statin” class.

Bdq should be used with caution in PLHIV infection treated with ARVs that exhibit drug-drug interactions with Bdq (efavirenz) or prolong the QT interval (lopinavir/ritonavir) as well as in patients with comorbidities (such as diabetes) or persons with drug or alcohol use, due to limited or no information. Bdq has been used in large cohorts of patients. While experience is growing and drug monitoring is still required, concern is less, due to cohort data reviewed from South Africa.[32] However, frequent clinical and cardiac evaluation is required in these patients.

Bdq will be provided through RNTCP once the patient has been confirmed as eligible by the DR-TBC Committee and has consented for the same. The dosage of BDQ would apply to all weight bands while the dosage of other drugs in the OBR would be as per weight bands in accordance to guidelines.

### 7.7 Patient counselling for DR-TB patients

Counselling offers an opportunity to explore and heal past and present difficulties faced by patients in a confidential and supportive environment, especially while dealing with life issues. The role of counselling in the management of DR-TB is significant. A competent counsellor can sensitize patients in several key aspects of TB with particular emphasis on DR-TB care and control. It is important to understand the mode of disease transmission and its prevention.
A counsellor can help the patient to better understand importance of regular treatment as well as consequences of deviation from the treatment. His/her role is to empower patients with disease related information and enable him to take informed decision related to treatment adherence. Treatment duration of any DR-TB regimen is long enough for the patient which needs multiple sessions of counselling, preferably more frequently in the initial phase of treatment.

Documentation is an essential part of counselling. It helps the counsellor in being aware about the progress of the sessions and targets achieved in the process. It informs about the efforts made by the clients to make desired changes. It also gives space for the counsellor to record his/her observations. In case of any legal issue cropping up, the documentation stands as proof of the work done with the client. The DR-TB counselling register that is available with the counsellor serves the purpose of documentation (formats are discussed in Chapter 12). RNTCP provides a counsellor at every NDR-TB centre for this purpose.

7.8 Treatment duration for various DR-TB regimen

The treatment is administered in two phases, namely intensive phase (IP) and continuation phase (CP). The treatment duration for DR-TB patients would depend upon the classification of the patient and regimen designed.

7.8.1  H mono-poly DR-TB regimen

Total duration of H mono-poly DR-TB regimen is 9-12 months, depending on IP duration. The IP should be given for at least three months. After the third month of treatment, if the result of microscopy is negative, then CP should be initiated. If the third month smear result is positive then, IP is extended by one month. If the IP is prolonged, the injectable agent is only given three times a week. IP should be extended for a maximum of three months (i.e., total duration of IP is not more than six months). Duration of CP is fixed for six months. [5]

7.8.2  Shorter MDR-TB regimen

Total duration of shorter MDR-TB regimen is for 9-11 months, depending on IP duration. IP should be given for at least four months. After fourth month of treatment, if the result of sputum microscopy is negative then CP should be initiated. If sputum smear does not become microscopy negative by the fourth month of treatment, the IP should be prolonged until sputum smear converts. If the intensive phase is prolonged, the injectable agent is only given three times a week. IP should be extended for a maximum of two months (i.e., total duration of IP is not more than six months). Duration of CP is fixed for five months. [12] [26]
7.8.3 Conventional MDR-TB regimen

Total duration of conventional MDR-TB regimen is 24 – 27 months, depending on IP duration. IP should be given for at least six months. After the sixth month of treatment, the patient must be reviewed and the treatment changed to CP if the fourth or fifth month culture result in solid or liquid culture is negative. If the fourth or fifth month culture result remains positive, the treatment is extended by one month. Extension of IP beyond one month is decided based on the results of subsequent culture results and the clinical/radiographic response. If the result of the fourth month culture is still pending after six months of treatment, IP is extended until the result is available, with further treatment being decided, based on the culture result. IP should be extended for a maximum of three months (i.e., total duration of IP is not more than six months).

The recommended duration for CP is 18 months and if the patient continues to remain culture positive or reverts back to culture positive after the extended IP up to a maximum of three additional months. After this, the patient is declared as “Treatment failed”, re-evaluated as per integrated DR-TB algorithm, reclassified as mixed pattern DR-TB and initiated on an appropriate DST guided regimen.

7.8.4 XDR-TB regimen

Total duration of regimen for XDR-TB would be of 24-30 months duration with 6-12 months IP and 18 months CP. The change from IP to CP will be done only after achievement of culture conversion (two consecutive negative cultures taken at least one month apart with no subsequent positive cultures). In case of delay in culture conversion, the IP can be extended on monthly basis from 6 months up to a maximum of 12 months. In case of extension, the NDR-TRC committee, which will be responsible for initiating and monitoring the regimen for XDR-TB, can decide on administering Cm injection intermittently (3 times/week) for the months 7 to 12.

7.8.5 Regimen for mixed pattern resistant TB

**H mono-poly + resistance to FQ/SLI with Lzd (without newer drugs):** Total duration of regimen for mixed pattern resistant TB - H mono with FQ/SLI resistance (without newer drugs) is 9 - 12 months. The duration of IP is for a minimum of three months. If sputum smear does not become microscopy negative by the third month of treatment, the initial phase should be prolonged until sputum smear converts. IP can be extended on a monthly basis for a maximum period of three months. Total duration of IP is not more than 6 months. Duration of continuation phase (CP) is fixed for 6 months. [9]

**MDR/RR-TB + resistance to FQ / SLI³ with Lzd³ or failure of DR-TB regimen or patients who do not fit in any of the above regimen (with or without newer drugs):** This will be the same as for XDR-TB patients detailed above. [9]
7.9 Patient flow for DR-TB patients

- DDR-TBC and NDR-TBCs should be involved actively in management of all DR-TB patients;
- DDR-TBC will be the reporting unit for the respective district and will register all MDR/RR-TB and H mono/poly DR-TB patients of respective districts initiated on standard regimen based on CBNAAT or FL-LPA or culture DST results in PMDT treatment register with issue of unique PMDT number. Patient details will be entered and regularly updated on Nikshay;
- NDR-TBC will be the reporting unit for catering districts and re-register all DR-TB patients of respective districts (who need DST guided regimen redesigning with or without new drugs) in PMDT treatment register with issue of unique DR-TB number. Patient details would be entered and regularly updated on Nikshay. Overall accountability of all such patients will be shared by the concerned DDR-TBC and DTO;
- PMDT treatment card of DR-TB patients managed at the concerned DR-TBC for pretreatment evaluation will be opened by responsible staff of DR-TBC at district or nodal level;
- after pretreatment evaluation and initiation of treatment, the patient should be referred back to the PHI with up to a maximum of one week’s supply of drugs, arrangements for injections in transit and a copy of the PMDT treatment book and referral form under intimation of the DTO. The respective DTO/ MO-PHI should be informed by the concerned DR-TBC on referral of patients for ambulatory care in advance, by means of the RNTCP PMDT referral for treatment form via email or mobile phone;
- drugs provided to the patients to cover for transit period may be counted as unsupervised doses. However, as much as possible, efforts should be made by the district staff to restrict these transit doses;
- DTO arranges for availability of the monthly IP drug box to the treatment supporter (via the TU staff like STS/TBHV) and the patient records at the identified treatment support centre with timely information to the respective Medical officer peripheral health institution (MO-PHI);
- MO-PHI is responsible for supplying patient records and drugs to the designated treatment supporter. The MO-PHI will need to make suitable arrangements during intensive phase of the treatment for daily injections, including free sterile needles and syringes; and
- patient’s information as per PMDT treatment book and CEM treatment review form in patient on newer drugs as detailed later must be regularly updated on Nikshay (at least weekly) by the concerned field staff responsible.
Overall responsibility of monitoring the patient’s progress on treatment, including follow-up is with the MO-PHI where patient is being treated with support of the respective TU team.

**7.10 Management of DR-TB patients with treatment interruptions and lost to follow-up**

All efforts must be made to ensure that DR-TB patients do not interrupt treatment or are lost to follow-up. Action should be taken to promptly retrieve patients who fail to come for their daily dose by the treatment supporter as discussed in Chapter 11. The following strategies are applicable for patients who interrupt treatment:

**Patients in IP/CP who miss doses:** All missed doses during IP must be completed prior to switching the patient to CP. Similarly, all missed doses during CP must be administered prior to ending treatment.

**Patients who interrupt treatment for less than one month during IP:** When the patient returns to resume treatment, IP will be continued. However, the duration of treatment will be extended to complete IP. The follow-up cultures will be done as per the schedule.

**Patients who interrupt treatment for less than one month during CP:** When the patient returns to resume treatment, the CP will be continued, however the duration of treatment will be extended to complete CP. The follow-up cultures will be done as per the schedule.

**Patients who are “lost to follow-up” (interrupt treatment continuously for one month or more) and return back for treatment:** Such patients will be given an outcome of “lost to follow-up”. The patient would be subjected to repeat CBNAAT & FL-SL LPA and LC as per the diagnostic algorithm to restart with appropriate DST guided regimen with or without newer drug for a fresh episode of treatment.

**MDR-TB patients who do not respond to the shorter MDR-TB regimen or who interrupt treatment:**

- patients on the shorter MDR-TB regimen who do not respond need to be assessed to decide whether they need to be switched to an appropriate DST guided DR-TB regimen;
- if there are signs of impending treatment failure (no sputum smear conversion by 6 months or deterioration of clinical condition despite treatment) while the patient is on a shorter MDR-TB regimen, s/he should be considered for an appropriate DST guided DR-TB regimen;
- if patients interrupt shorter MDR-TB treatment continuously for one month or more, the outcome is lost to follow-up;
- if a patient has received the shorter MDR-TB regimen for more than one month and returns for treatment after an interruption of one month or more, s/he is not restarted.
on a shorter MDR-TB regimen. Rather s/he is put on an appropriate DST guided DR-TB regimen. Patients need to be made aware of this; and

- if there are interruptions of less than one month (medical indication in the patient of adverse events, patient decision) then the shorter MDR-TB regimen can be continued and missed doses added to the rest of the treatment.

**DR-TB patients on Bdq containing regimen who interrupt treatment or are “lost to follow-up” or recurrent DR-TB [4]**

**BDQ:** If a dose is missed during the first 2 weeks of treatment, one should not make up for the missed dose but continue the usual dosing schedule. From the third week onwards, if a 200 mg dose is missed, one should take the missed dose as soon as possible and then resume the three-times-a-week regimen.

**Patients who interrupt treatment during the first two weeks of Bdq course and returns to resume the treatment:**

- if interruption is up to 7 days, Bdq containing regimen will be continued to complete the doses and the duration of treatment will be extended to complete IP. Follow-up cultures will be done as per the revised schedule; and
- if interruption is more than 7 consecutive days, Bdq course will be reloaded (started afresh) and a fresh specimen collected for culture. The culture isolate must be stored for Bdq DST in future.

**Patients who interrupt treatment during 3-24 weeks of Bdq course and return to resume treatment:**

- if interruption is up to one month, Bdq containing regimen will be continued to complete the doses and duration of treatment will be extended to complete IP. Follow-up cultures will be done as per revised schedule; and
- if interruption is more than one month, Bdq will be permanently discontinued. Such patients will be given an outcome of “Lost to follow-up” (LTFU) based on duration of LTFU and managed as per DST guided treatment and registered afresh. A sputum specimen will be collected for culture. The culture isolate must be stored for Bdq DST in future. In addition, the serum sample will be collected and transported to the concerned lab within 6 hours for Bdq levels for correlation with outcomes, wherever feasible and lab capacity is available.

Where further treatment is concerned, if the patient has any indication of a treatment failure or recurrence, the NDR-TBC Committee will be contacted to discuss whether s/he should be retreated. The decision will be made on a case-to-case basis, using all available bacteriological and clinical data.
7.11 Transfers of DR-TB patients

It is important to note the patient’s address (current residence), native place, occupation and place of work to get a fair idea about the possible places that s/he could move to. If a DR-TB patient on treatment decides to move and informs the health care worker, the patient can be transferred out to the district where s/he wishes to migrate. Transfer out should be brought to the notice of the DDR-TBC by the concerned DTO. Transfer module of Nikshay redirects a patient to the receiving district while referring district is still able to fetch the patient details through their district/TU login.

If the patient is migrating to an adjoining TB Unit being served by the same DDR-TBC as the current district of residence, then s/he may be shifted with 7 days of drugs for the transit period to a suitable treatment supporter. This would be at that place where s/he proposes to move, in consultation with the DTO of that district and under intimation of the DDR-TBC. The patient will continue treatment on the same PMDT TB number and same patient records, including a referral for treatment form and copies of the PMDT treatment book with a transfer note sent to the district receiving the patient. Further, details of the patient will be updated in the PMDT treatment register at the DR-TBC and on Nikshay.

If the patient is migrating to any other district that is not being served by the same DR-TBC, s/he may be formally transferred out with 7 days of drugs for transit period to a suitable treatment supporter at that place where s/he proposes to move. During transfer to other N/DDR-TBC, the patient should be referred along with the referral for treatment form, the PMDT treatment card and the PMDT treatment booklet. This would be in consultation with DTO of that district and under intimation of DDR-TBC. This patient will be registered at the DDR-TBC catering to the receiving district with a new PMDT TB number mentioning the old PMDT TB number in the remarks column for future reference. However, the Nikshay ID of the patient would remain the same and transfer details with the new PMDT TB number updated online. The patient will be continued on the same treatment on the new PMDT TB number. The patient records including the referral for treatment form, copies of PMDT treatment cards with a transfer note, copy of CEM treatment initiation and review forms as applicable, pre-treatment and follow-up investigations from the concerned DR-TBC transferring the patient, will be sent to the DDR-TBC and DTO of the district receiving the patient, by the DTO who initiated the transfer-out process.

The patient must be motivated to carry the PMDT treatment book to the receiving DDR-TBC. The details of the patient will be updated in the PMDT treatment register at both the DR-TBCs for future reference. It is the responsibility of the receiving DTO and DDR-TBC to send feedback about the patient with the new PMDT TB number to the former DDR-TBC to establish a link for future exchange of information about interim reports, culture conversion and treatment outcomes of the patient.
7.12 Managing referrals from private/other sectors of patients for DR-TB evaluation and treatment

Some patients with previous diagnosis of DR-TB and/or treatment with second-line anti-TB drugs will wish to avail RNTCP services. RNTCP has a policy against empirical treatment of DR-TB without microbiological confirmation. Microbiological confirmation is required before initiation of treatment for DR-TB. DST results from private laboratories will be considered acceptable under the following situations:

- CB-NAAT results from labs that regularly undertake annual calibration of machines; and
- C-DST labs who participate in the annual proficiency testing through NRLs under RNTCP for the respective DST technology.

For patients who do not have results in accordance to the above, DST would be offered under RNTCP as per the integrated DR-TB algorithm. Similarly, even though some patients may have consumed variable amounts of second-line anti-TB drugs, such prior anti-TB treatment is not likely to be uniformly reliable in quality of drugs, or quantity and duration consumed. Given that uncertainty, the basic principle is that duration of the regimen for DR-TB offered under RNTCP will not be reduced. There may be exceptional circumstances that the DR-TBCs may consider where prior treatment is very well-documented, adequate and effective. The DDR-TBC/NDR-TBC committee can exceptionally adjust the duration after detailed patient review, approval and documentation of decisions taken.

7.13 Access to PMDT treatment services including newer drugs for the patient seeking care in private/other sector

To expand access of PMDT services including newer drugs for patients seeking care in the private sector, the following mechanisms are applicable:

- interested and potential providers/institutions are expected to fulfill the requirement to serve as a NDR-TBC and establish an MoU with state as per the partnership guidelines to avail access to PMDT services including newer drugs. The collaboration will be implemented as per conditions detailed under the MoU; [15] and
- for providers not in a position to fulfill such requirement, their patients can still be provided access to PMDT services including newer drugs, through a mechanism that entails engaging with the programme. They can approach the concerned district TB Officer for linkage with the concerned DDR-TBC for access to standard regimen (H mono/poly DR-TB, RR/MDR-TB) or the concerned NDR-TBC for access to newer drugs and DST guided regimen as per guidelines. The provider needs to consult the concerned N/DDR-TBC with an understanding to be a responsible partner with the programme for complete patient care throughout the treatment course, including decisions around patient eligibility, treatment initiation, follow-up schedule, ADR monitoring and
management, treatment outcomes and long term follow-up as per programme guidelines. To locate the nearest DTO or NDR-TBC, providers can refer to the list of all NDR-TBC in India with contact details of the nodal physician available at [www.tbcindia.gov.in](http://www.tbcindia.gov.in). For assessing eligibility for specific regimens, all relevant medical records and reports of the patient should be shared with N/DDR-TBC to facilitate a decision on the regimen design that would suit the patient’s condition.

Based on mutual understanding between patient, provider and N/DDR-TBC, initial hospitalization to patients will be offered at N/DDR-TBC or private institute with requisite monitoring. After discharge, the provider can continue to be the treatment supporter and monitor the patient in close coordination with N/DDR-TBC. The monthly drug supply and follow-up investigations need to be undertaken as per guidelines. Moreover, patients would be enrolled under RNTCP, recording and reporting the system for monitoring, including long term follow-up. The state/district TB officers should provide public health support to all notified TB patients seeking care from private/other sector for DSTs, pretreatment investigations, drugs, follow-up investigations, counselling and social support.

### 7.14 Palliative care

Palliative care is a multidisciplinary approach to medical care for people with serious illnesses. It focuses on providing patients with relief from symptoms, pain, physical and mental stress of a serious illness, whatever the diagnosis. WHO defines palliative care as an approach that improves quality of life of patients and their families facing the problem associated with life-threatening illness, through prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. The goal of such therapy is to improve quality of life for both patient and family. [33]

#### Need of palliative care in DR-TB

While high cure rates of TB are being reported by majority of the programmes across the globe, in many countries DR-TB remains a life-threatening condition with high mortality and poor cure rates. There is significant suffering associated with DR-TB illness and its treatment. This kind of burden adds to the possibility of TB patients not being able to adhere to treatment and resultantly, the treatment failing to cure them. The life-threatening nature of DR-TB and the burden of disease management in terms of symptoms, adverse treatment effects, adherence, stigma and subsequent discrimination and social isolation, clearly show the need for care that addresses physical, social and emotional suffering by patients. Thus, the need for palliative and end-of-life care is being increasingly recognized as an important part of the continuum of care for DR-TB patients. Improvement in availability of diagnostic services, have led to increased detection of people with DR-TB. Therefore, the demand for treatment and need for palliative care has also grown.
Challenges in palliative care

Current TB treatment strategy is based on a patient-centered approach to treatment and care and international guidelines have identified practices resulting in better treatment outcomes. However, alleviation of the patient’s suffering associated with disease and its management has been restricted mostly, to physical aspects and not adequately too. Difficulties faced by patients and families affected by life-threatening diseases span across physical, psychological, social and spiritual aspects. Neither trained health workers nor local community-based palliative care resources are usually available in the settings that are most in need. Although, clinical expertise in palliative care for patients who die in respiratory distress has developed considerably, individuals with DR-TB are yet to see the benefits.

Services under palliative care for DR-TB

Palliative care would be necessary for care of patients who are chronically ill, with extensive drug resistance, with extensive fibro-cavitary or disseminated bilateral lung disease, who have failed regimen for XDR-TB or mixed pattern resistance and for whom a WHO recommended regimen could not be designed even with new drugs. They would be required in some patients when there are symptoms or other suffering during the treatment process. All measures to relieve the patient of suffering caused by the disease and its treatment begins at the time of diagnosis and continues, regardless of whether or not s/he is expected to be cured of or will fail the treatment.

Services under palliative care include addressing pain and symptom control (including respiratory insufficiency), nutritional support, need for medical intervention after treatment cessation (including management of psychological morbidity), ensuring appropriate place of care, preventive care, infection control and end-of-life care.

Supportive measures in palliative care

The details on palliative care supportive measures are summarized below:

**Respiratory rehabilitation:** Relief from dyspnoea with oxygen may be used to alleviate shortness of breath in some patients but there is no significant evidence to generalize its practice. Physiotherapy, evaluation for surgery, respiratory rehabilitation including yoga etc., need to be considered in such patients. An example of pulmonary rehabilitation is placed at Annexure 11. Morphine provides significant relief from respiratory insufficiency and should be offered according to established clinical protocols available in the medical literature.

**Relief from pain and other symptoms:** Paracetamol or Tramadol with paracetamol gives relief from moderate pain. If possible, stronger analgesics, including morphine, should be
used when appropriate to keep the patient adequately comfortable. The WHO has developed analgesic guides, pain scales and a three step “ladder” for pain relief.

**Infection control measures:** The patient who is taken off anti-TB treatment because of failure often remains infectious. Infection control measures should be continued with reinforcement of administrative, environmental and personal measures, including N-95 mask use for caregivers.

**Nutritional support:** Small meals as needed are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient’s condition deteriorates and during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support, should be treated. Bowel functions should be monitored for regularity.

**Regular medical visits:** When DR-TB treatment stops, regular visits by healthcare providers and the support team should be continued to address medical needs and ensure that infection control practices are being followed. Early identification, periodic assessment and management of post treatment sequelae could be beneficial for the patient.

**Vocational rehabilitation:** Wherever possible, based on the interest of the patient, an appropriate linkage for vocational rehabilitation and new skill learning opportunities through various NGOs may be explored to help the patient regain his/her source of livelihood and move towards socio-economic sufficiency. This would also have an indirect impact on improving the patient’s nutritional, psychological and mental wellbeing.

**Continuation of ancillary medicines:** All necessary ancillary medications should be continued as needed. Opioids help control cough, as well as pain. Other cough suppressants can be added. Bronchospasms can be controlled with a metered dosed inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed. Antiemetic may still be needed and fever treated if the patient is uncomfortable. Appropriate use of alternative medicine may be considered through expert consultation.

**Preventive measures:** Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important. Additionally, patients must be encouraged to move their bodies in bed if able. Keeping beds dry and clean are also important.

**Provide psychosocial support:** Psychological counselling to the patient and family caregivers is critical at this stage, especially to assist patients in the planning of decisions related with the end-of-life stage. Also, emotional support, especially in settings in which strong stigma is attached to the disease would be necessary.

**Respect for patient’s beliefs and values at the end-of-life:** It is common for the patient and family caregivers to develop or increase their interest in spiritual and religious matters once they perceive that the end-of-life is approaching. Healthcare providers should respect those
beliefs and should not impose personal values and practices that prevent the patient to seek and find comfort in services delivered by faith-based organizations.

It incorporates management of side-effects such as breathlessness, fatigue, cachexia and end-of-life crises such as haemoptysis and acute respiratory failure besides anxiety of patients and their families, which typically accompanies these symptoms.

When patient isolation is done, strong measures to prevent loneliness, boredom and sense of abandonment are needed to be in place. These comprise of daily access to family and friends under proper infection control conditions, interaction with staff and access to activities according to the patient’s condition (radio, television, hobbies, etc.).

**Approach: Need for human resources and infrastructure**

Palliative care is provided by a team of physicians, nurses and other health professionals who work together with the primary care physician and referred specialists (or for patients who don't have those, hospital or hospice staff) to provide an extra layer of support. Hence, palliative care is to be initiated by those NDR-TBCs in various states. Further, NDR-TBC staff can counsel and train family members or caretakers of the patient, so that these services are extended as home-based palliative care to patients by family members or caretakers.

In rare circumstances, institution-based palliative care may be initiated with longer duration of admission at selected NDR-TBCs developed in old TB sanatoria. Alternately, states may identify interested NGO’s or faith-based organizations with indoor facilities that could be engaged through an MoU and guided by NDR-TBCs. In all such facilities, airborne infection control measures as per national AIC guidelines must be strictly implemented. Further, as soon as the patient’s condition improves, s/he must be discharged with adequate counselling to the family member or caretaker for home-based palliative care and regular consultative visits to NDR-TBC as and when medically required.

All health workers must receive training in palliative care to enable them extend support to family members or caretakers providing home-based palliative care and to undertake regular contact tracing and extend support to address their problems. Existing expertise from palliative care, HIV and respiratory medicine can, therefore, translate directly to TB. Delivery of palliative care from within respiratory clinical services by existing staff with additional training, with clear criteria for referral to palliative care specialists for complex patients, is to be established. NDR-TBCs should link up with local palliative care and hospice teams from the network of Pallium India and Indian Association of Palliative Care. However, it is of paramount importance from the infection control perspective to avoid sending infectious patients to these palliative care centres where immunocompromised cancer or stroke patients could potentially be infected.
Effective control of the various problems faced by patients and their families is possible across many settings (hospital, hospice, primary care and home-based care) and flexibility in place of delivery need to be established. Palliative and end-of-life care should be delivered to the patient and their family in the setting where they are receiving care, whether an inpatient, an outpatient, or at home. Community-based workers could be trained in palliative care to scale-up existing health care delivery to include pain and symptom control. Having a patient die at home can be difficult for the family and the other way around. Home-based care should be offered to patients and families who want to keep the patient at home, whenever appropriate infection control practices can be followed. Institution-based end-of-life care should be available to those for whom home care is not feasible or desirable.

As far as possible, institution-based palliative care should be minimized to a duration that is absolutely essential as per decision of the concerned NDR-TBC committee. Most palliative care must be home-based through a trained and counselled family member or caretaker with regular visits by health care workers and psychosocial/spiritual support through local community based self-help groups, NGOs or panchayati raj institutions.
Chapter 8: Monitoring and outcome definitions

This chapter provides information on the clinical and laboratory monitoring for patients on treatment for M/XDR-TB. It provides the treatment outcome definitions to be used. [4] [5] [10] [19]

8.1 Clinical monitoring

DR-TB patients should be seen by a medical officer trained in RNTCP PMDT guidelines for clinical evaluation after discharge back to the N/DDR-TBC, at monthly intervals during the IP and at 3-monthly intervals during CP until the end of treatment. The responsible medical officer at N/DDR-TBC should assess clinical, microbiologic and radiologic response to treatment, measure weight, assess possible adverse reactions and encourage the patient to continue treatment. The follow-up visit should result in updating of treatment cards. Close monitoring of patients is necessary to ensure that adverse effects are recognized early by the treatment supporter. Patients should be encouraged to volunteer if they experience any adverse effects, though patients should not be asked any leading question to elicit any adverse reaction. However, if the patient makes any complaint, s/he should be interrogated in detail and necessary action taken.

The treatment supporter should be trained to recognize adverse reactions like nausea, vomiting, diarrhoea, skin rash, loss of hearing, reduced sensation, psychiatric symptoms and jaundice. Training should also be provided on the management of minor reactions and when the patients should be referred to the medical officer. Severe adverse reactions should be referred to an appropriate clinical facility, which may include D/NDR-TBC coordinating care for the patient. Other relevant investigations may be done as and when clinically indicated. These investigations can be done at D/NDR-TBC or any institute as per local arrangement, however patients should not be charged for these investigations. Some patients may need to be hospitalized during treatment for medical or psychosocial reasons.

8.2 Follow-up evaluations during treatment

The follow-up evaluation schedule during treatment for DR-TB patients managed with various regimen classes are summarized in the table 8.1 below:
### Table 8.1 Follow-up evaluation schedule of DR-TB patients during treatment on various regimen classes

<table>
<thead>
<tr>
<th>Regimen class</th>
<th>Regimen for H Mono /Poly DRTB &amp;with FQ/SLI/Lzd resistance</th>
<th>Shorter MDR-TB regimen</th>
<th>Conventional MDR-TB regimen</th>
<th>Regimen for RR-TB with resistance to FQ/SLI ± Lzd (without newer drugs)</th>
<th>Newer drugs containing regimen for RR-TB with resistance to FQ/SLI ± Lzd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>9 – 12 months (3-6m IP, 6m CP)</td>
<td>9 – 11 months (4-6m IP, 5m CP)</td>
<td>24-27 months (6-9m IP, 18m CP)</td>
<td>24-27 months (6-9m IP, 18m CP)</td>
<td>24-30 months in XDR &amp; MPR (6-12m IP, 18m CP)</td>
</tr>
<tr>
<td>Clinical + Wt.</td>
<td>As suggested by treating clinician, at least monthly in IP and quarterly in CP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear mMicroscopy</td>
<td>Monthly till end of IP, monthly in extended IP only if previous month S+ve</td>
<td>With culture at C-DST labs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>End of IP, end of extended IP &amp; end of treatment</td>
<td>Monthly from 3m to end of IP if converted, Monthly in extended IP only if previous month culture +ve, quarterly in CP, 2 consecutive monthly if any culture +ve from 12m onwards</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DST</td>
<td>SL-LPA if S+ve/C+ve at end of IP &amp;/or extended IP &amp; expanded DST if any resistance on SL-LPA</td>
<td>SL-LPA if C+ve at end of IP &amp;/or extended IP or any time in CP &amp; expanded DST if any resistance on SL-LPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. Creatinine</td>
<td>Monthly till 3m, then every 3m till SLI course is completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audiometry</td>
<td>As and when clinically indicated</td>
<td>As and when clinically indicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPT</td>
<td>As and when clinically indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/Hb/platelets*</td>
<td>As and when clinically indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR, TSH &amp; LFT*</td>
<td>As and when clinically indicated</td>
<td>As and when clinically indicated</td>
<td></td>
<td>Monthly in IP, quarterly in CP</td>
<td></td>
</tr>
<tr>
<td>ECG§</td>
<td>As and when clinically indicated</td>
<td>As and when clinically indicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. Electrolytes (Na, K, Cl)</td>
<td>As and when clinically indicated</td>
<td>As and when clinically indicated</td>
<td></td>
<td>As and when clinically indicated</td>
<td></td>
</tr>
<tr>
<td>S. Mg, Ca, Amylase, Proteins, Lipase</td>
<td>As and when clinically indicated</td>
<td>As and when clinically indicated</td>
<td></td>
<td>Quarterly in IP, as and when required</td>
<td></td>
</tr>
<tr>
<td>Specialist cons.</td>
<td>As and when clinically indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term follow-up</td>
<td>at 6, 12, 18 and 24 months after completion of treatment and if found symptomatic, clinical evaluation, CXR, smear and culture. DST would be repeated if culture is positive.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CBC/Hb/Platelets done to rule out bone marrow suppression and anemia only if Linezolid is included in the regimen
* HBsAg and other viral markers (Hepatitis A, C & E) to be done on signs of jaundice during treatment
§ In patients with baseline ECG abnormalities, ECGs must be done on daily basis for the first 15 days if patient is managed with regimen containing Mfx, Bdo, Cfx and further frequency as advised by cardiologist. Repeat ECG after an hour if abnormal at any time to reconfirm with long lead II for one minute.
The most important evidence of response to DR-TB treatment is conversion of sputum smear and culture to negative. Good quality sputum specimen is therefore essential to get reliable results that form the basis of monitoring bacteriological response to treatment.

Smear examination would be used on a monthly basis in IP to guide the decision on moving from IP to CP only in regimen with less than one year of duration \(i.e.,\) H mono/poly DR-TB regimen (3-6m IP) and shorter MDR-TB regimen (4-6m IP). It would be continued on monthly basis if IP needs to be extended if the previous month smear is positive up to a maximum of six months in both regimens. Follow-up culture will be done at the end of IP, end of extended IP and end of treatment.

If smear/culture remains positive at the end of IP and/or extended IP, a fresh specimen/culture isolate of that time will be subjected to SL-LPA to check for amplification of resistance to second-line drugs. If the patient is found to be susceptible to both FQ and SLI class at fourth month of treatment, the intensive phase will be extended on monthly basis up to a maximum of six months. At end of extended IP or later, if any resistance is detected by SL-LPA \textbf{OR} if found to be culture positive, the patient will be declared as treatment failure. The patient is then re-evaluated for a newer drug containing \textbf{OR} DST guided regimen at the nodal DR-TB centre. However, the patient will be continued on CP till declared as treatment failure as detailed above.

Extended DST to Mfx (2.0), Km, Cm and Lzd will be set up on liquid culture on the LPA deposits only for patients who are found resistant to FQ or SLI class on SL-LPA if patient remains smear/culture positive at the end of IP \textbf{OR} the extended IP during treatment with any DR-TB regimen. This would be done if any culture is positive any time in CP in regimen of longer duration. Long term follow-up will be done with six monthly cultures among symptomatic patients till two years after completion of any DR-TB regimen.

Smear conversion is less reliable than culture conversion, which reflects viability of tubercle bacilli even in very low bacilli per ml of sputum and is a more accurate reflection of response to treatment. Hence, for all patients put on longer term regimen, culture will be done as per table 8.1 to decide on moving from IP to CP. Patients will be considered smear converted after having two consecutive negative smears taken at least one month apart. Patients will be considered culture converted after having two consecutive negative cultures taken at least one month apart.

Time-to-culture conversion is calculated as the interval between the date of DR-TB treatment initiation and date of the first of these two negative consecutive cultures (date of sputum specimens collected for culture should be used). Arrangements can be made to collect sputum specimens at the respective DMC which will then be transported to the RNTCP-certified culture and DST laboratory, along with intimation of DTC. Necessary
arrangements for supply of conical tubes for follow-up sputum smear and culture examination should be ensured.

Follow-up sputum culture should be done using liquid culture. If liquid culture is not available, it is to be communicated to Central TB Division. In case of extension of IP, the follow-up culture months will shift by every month of extension of IP till maximum limit of IP for all regimen classes. However, it must be noted that the final treatment outcome of all DR-TB patients will be declared on the basis of follow-up culture results only.

8.3 Treatment outcomes

The progress of the patient on treatment would be monitored using interim as well as final treatment outcomes for various DR-TB regimens.

8.3.1 Interim outcomes

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

**Culture reversion**: Patient is considered to have culture reverted when, after an initial culture conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

The term microbiological conversion/reversion can also be used either for smear or culture based follow ups.

8.3.2 Final outcomes

The final treatment outcome definitions would vary with the duration of treatment. The treatment outcomes are defined for patients on longer term and shorter-term regimen in following section.

**Outcomes for regimen for RR-/MDR-TB (except shorter MDR-TB regimen) and/or XDR-TB patients**

**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 during CP are negative including culture at the end of treatment.
**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.

**Treatment failed**: Treatment terminated or need for permanent regimen change of at least two or more anti-TB drugs in CP because of lack of microbiological conversion by the end of the extended intensive phase or microbiological reversion in the continuation phase after conversion to negative or evidence of additional acquired resistance to FQ or SLI drugs or adverse drug reactions (ADR).

**Died**: A patient who dies for any reason during the course of treatment.

**Lost to follow-up**: A patient whose treatment was interrupted for one month or more for any reasons prior to being declared as failed.

**Not evaluated**: A patient for whom no treatment outcome is assigned.

**Regimen changed**: A TB patient’s need for permanent regimen change of at least one or more anti-TB drugs prior to being declared as failed.

**Outcomes for H mono/ poly DR-TB patients and RR-TB patients put on shorter MDR-TB regimen**

**Cure**: Treatment completed as recommended by the national policy without evidence of failure and culture was negative at end of treatment and on at least one previous occasion.

**Treatment completed**: A patient who has completed treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of microbiological results.

**Failure**: Treatment terminated or need for permanent regimen change of at least two or more anti-TB drugs in CP because of lack of microbiological conversion by end of extended intensive phase or microbiological reversion in the continuation phase after conversion to negative or evidence of additional acquired resistance to FQ or SLI drugs or adverse drug reactions (ADR).

**Died**: A patient who dies for any reason during the course of treatment.

**Lost to follow-up**: A patient whose treatment was interrupted for one month or more for any reasons prior to being declared as failed.

**Not evaluated**: A DR-TB patient for whom no treatment outcome is assigned, this includes former “transfer-out”.

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**Regimen changed:** A TB patient’s need for permanent regimen change of at least one or more anti-TB drugs prior to being declared as failed.

Treatment outcome is defined by reviewing patient PMDT treatment card. The treatment outcome and date the patient stopped treatment is written in the appropriate column in the TB treatment card. The date on which the patient stopped treatment is the date of the last dose of drugs taken. Details of treatment outcome should be updated in Nikshay. The MO of the PHI should record the treatment outcome in the treatment card and sign it. The treatment card of the patients whose outcome has been declared should be handed over to the STS during his routine monthly visits. Every patient started on treatment has to be given one and only one treatment outcome.
Chapter 9: Treatment in special situations

Compared to drug sensitive TB, DR-TB is more demanding in terms of cost of treatment, duration of treatment, higher adverse reactions to second line drugs, resources required by treatment providers and prolonged adherence required by patients. To add to these issues, certain associated special situations make the treatment of DR-TB more difficult. [12] [31] This chapter outlines the management of DR-TB in certain special situations and conditions. These include DR-TB in pregnancy and in children; those co-infected with HIV infection; requiring surgery; in patients with renal impairment; in patients with pre-existing liver disease; seizure disorders; psychiatric illnesses; in extra-pulmonary TB patients; and management of contacts of DR-TB.

9.1 DR-TB in pregnancy

Pregnancy is not a contraindication for treatment of active drug-resistant TB, but poses great risk to both the mother and foetus. There is lack of experience in treating pregnant women with DR-TB. Teratogenicity has been demonstrated with only some of the drugs used to treat DR-TB. However, majority of the studies have demonstrated that it is common during the first trimester. It is prudent to solicit the opinion of an experienced gynecologist/obstetrician while treating such patients.

All women of childbearing age who are receiving DR-TB therapy should be advised to use birth control measures because of the potential risk to both mother and foetus. It should be remembered that oral contraceptives might have decreased efficacy due to vomiting and drug interactions with DR-TB drugs. Thus, for prevention of pregnancy, use of barrier methods (condoms/diaphragms), intrauterine devices or IUDs (CuT) or depot-medroxyprogesterone (Depo-provera) are recommended, based on individual preference and eligibility.

All women of childbearing age identified as presumptive DR-TB should be advised to use a reliable and appropriate contraceptive method till results of culture and DST are available.

All female DR-TB patients of childbearing age should be counselled intensively in relation to use of contraceptive methods. All women of childbearing age should be tested for pregnancy as part of the pretreatment evaluation and whilst on treatment. DR-TB patients found to be pregnant prior to treatment initiation or whilst on treatment are evaluated in consultation with a gynecologist or obstetrician, taking into account factors such as risks and benefits of DR-TB treatment; severity of DR-TB; gestational age; and potential risk to foetus. Further management of DR-TB patients who are pregnant prior to initiation of treatment or whilst on treatment are based on duration of pregnancy.
In pregnant women diagnosed with DR-TB, if the duration of pregnancy is <20 weeks, the patient should be advised to opt for a medical termination of pregnancy (MTP) in view of the potential severe risk to both mother and foetus. If the patient is willing, she should be referred to a gynecologist or obstetrician for a medically terminated pregnancy (MTP) following which a shorter MDR-TB regimen can be initiated (if the patient has not started treatment) or continued (if the patient is already on treatment) by the DR-TBC Committee.

For patients who are unwilling for MTP or have pregnancy of >20 weeks (making them ineligible for MTP), the risk to mother and foetus needs to be explained clearly and a modified conventional MDR-TB regimen started or continued as detailed below:

- for patients in the first trimester (≤ 12 weeks), Km and Eto are omitted from the regimen and PAS is added; and
- for patients who have completed the first trimester (>12 weeks), Km is replaced with PAS. Postpartum, PAS may be replaced with Km and continued until the end of the intensive phase.

In women of reproductive age who have been initiated on shorter MDR-TB regimen and who become pregnant in spite of precautions and use of contraceptives, the risk to the mother and foetus needs to be explained clearly. If the pregnancy is ≤ 20 weeks, the decision on continuing shorter MDR-TB regimen would depend upon the willingness of the patient to opt for an MTP. If she is unwilling for MTP or has a pregnancy > 20 weeks duration, she needs to be shifted to a modified conventional MDR-TB regimen. Similarly, Km must be replaced with PAS in pregnant women considered for initiation or continuation of the regimen for H mono/poly DR-TB. The management of DR-TB patients with pregnancy is summarized in the flow chart in Figure 9.1 below:
Pregnant DR-TB patients need to be monitored carefully, both in relation to the treatment and progress of the pregnancy. This approach should lead to good results, since the patient should be smear-negative at the time of parturition and mother and infant do not need to be separated. Breastfeeding should be encouraged as long as the patient is sputum negative.

Avoid aminoglycosides as it is particularly toxic to the developing fetal ear. Moreover, Eto can increase the risk of nausea and vomiting associated with pregnancy, more so since teratogenic effects have been observed in animal studies. If injectable agents, Eto/Pto, or other drugs were withheld because of the pregnancy, they can be added back postpartum to make a more complete regimen.

For patients with mono- and poly-resistant TB but who are susceptible to R, note that the use of R interacts with the contraceptive drugs, resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving R 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.
9.2 DR-TB in children

Principles of treatment of drug-resistant TB in children[30][12]

- always be treated in consultation with an expert;
- include at least 4-6 bactericidal medications to which the strain is known or likely to be susceptible;
- do not add a single drug to a failing regimen;
- ensure treatment is given for at least 12 months after M. tuberculosis cultures have converted to negative; and
- extend treatment to 24 months in case of HIV infection or cavitatory lesions.

Building a treatment regimen

The principles of designing a WHO recommended regimen detailed in the previous chapter also applies to children. However, newer drugs like Bdq are not yet recommended in children as the evidence is yet to evolve. However, they can be offered the shorter MDR-TB regimen. Thus, children would be managed with regimen designs without newer drugs as in Table 7.3 and 7.4, depending on the DST pattern and other parameters for mixed pattern DR-TB.

WHO recommends that in children with less severe forms of DR-TB, a regimen free of SLI may be designed keeping in view the aforementioned principles. [12] Thus, in such patients, the regimen design suggested in Table 7.3 and 7.4 could be applied if the child is detected as RR-TB or H mono/poly DR-TB by replacing Km with a suitable second-line drug.

The dosages for drugs used in various DR-TB regimens by weight bands for paediatric DR-TB patients are enumerated in Annexure 10. [31] The monitoring of DR-TB treatment in children would be as per the suggested schedule by regimen type in Table 8.1. However, the paediatrician of the N/DDR-TBC must regularly evaluate the progress of the child on treatment and initiate any other investigations as suggested.

9.3 DR-TB with HIV co-infection

The presentation of DR-TB in the HIV-infected patient does not differ from that of drug sensitive tuberculosis in the HIV-infected patient. However, the diagnosis of TB in HIV positive persons can be more difficult and may be confused with other pulmonary or systemic infections. As the HIV disease progresses and the individual becomes more immune compromised, the clinical presentation is proportionately more likely to be EP or smear-negative than in HIV-uninfected TB patients. This can result in misdiagnosis or delays in diagnosis and in turn, higher morbidity and mortality.
With the nationwide scale-up of intensified TB-HIV package, it is expected that more and more numbers of TB patients know their HIV status and if found HIV positive, must be linked to ART centres and provided co-trimoxazole preventive therapy (CPT). Early diagnosis of drug-resistant TB and HIV, prompt initiation of appropriate second-line anti-TB drugs and ART, sound patient support and infection control measures are essential components in the management of drug-resistant TB in PLHIV.

**Diagnosis of DR-TB among PLHIV**

Four symptom (4S) screening is carried out regularly during each visit among PLHIV persons approaching ART centres. The RNTCP guidelines are offering CBNAAT testing for all presumptive TB among PLHIV patients for early diagnosis of TB and DR-TB. The other possibility of identifying DR-TB PLHIV patient is HIV reactive patient found amongst the established DR-TB patient. Assessment of HIV status is one of the important TB/HIV collaborative activities, thus, majority of DR-TB patients know their HIV status and many would have been diagnosed with the help of a molecular test.

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

**Initiating ART in patients with DR- TB**

The use of ART in HIV infected patients with TB improves survival for both drug-resistant and susceptible disease. However, HIV infected DR-TB patients without the benefit of ART may experience mortality rates exceeding 90%. The likelihood of adverse effects could compromise the treatment of HIV or DR-TB if both treatments are started simultaneously. Second-line anti-TB drugs should be initiated first, followed by ART as soon as second-line anti-TB drugs are tolerated. Generally this should be within the first two weeks of initiating DR-TB treatment. On the other hand, undue delay in starting ART could result in significant risk of HIV related death amongst DR-TB patients. Co-trimoxazole can be provided to all patients with HIV as per WHO recommendation.

Based on the WHO Guidelines on ART for HIV infection in adults and adolescents; irrespective of CD4 cell counts, patients co-infected with HIV and TB should be started on ART as soon as possible after initiating TB treatment. The ART should be initiated as soon as possible in all HIV/TB co-infected patients with active TB (within 8 weeks after the start of TB treatment). However, if the CD4 cell count is below 50 cell/cmm, start ART
simultaneously with ATT, with strict clinical and laboratory monitoring. All new co-infected patients should be initiated on FDC of Tenofovir, Lamivudine and Efavirenz (TLE) single pill-based first-line regimen to be taken at bedtime irrespective of Hb level/ CD4 count as per ART guidelines laid down by the National AIDS Control Organization (NACO).

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

If the patient is already on a sensitive TB drug regimen, s/he should be switched over to an appropriate DR-TB regimen by closing the previous treatment with a ‘regimen change’ outcome. Assessments of therapeutic response to both infections should be carried out regularly including close monitoring of potential adverse effects including psychiatric assessments and nutritional status. Patients with drug-resistant TB and HIV may suffer from severe wasting, diarrheal diseases and malabsorption syndromes. Wherever possible, patients with drug-resistant TB living with HIV should be offered socioeconomic and nutritional support. The programme also monitors treatment outcomes separately for HIV TB patients. Considering the risk of developing primary DR-TB among susceptible close contacts, effective TB infection control measures are mandatory. If the patient shows signs of TB treatment failure, further evaluation is warranted. In addition, the ART regimen should be evaluated for possible treatment failure as described in other WHO guidelines.

**Concomitant therapy with ART or other medicines**: Rifampicin (R) is not used in DR-TB treatment; they are used in the treatment of R-sensitive poly- and mono-resistant TB, which has drug interaction with Protease Inhibitor (PI). Newer drug like Bdq are metabolized by the CYP3A4 having multiple drug interactions with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors (NNRTI). This has been detailed in section 7.6.

**9.4 Role of surgery in management of DR-TB**

In DR-TB patients with localized disease, surgery, as an adjunct to chemotherapy, can improve outcomes provided skilled thoracic surgeons and excellent postoperative care is available. When unilateral resectable disease is present, surgery should be considered in the following cases:
- absence of clinical or bacteriological response to chemotherapy despite six to nine months of treatment with effective anti-TB drugs;
- high risk of failure or relapse due to high degree of resistance or extensive parenchymal involvement;
- morbid complications of parenchymal disease e.g. haemoptysis, bronchiectasis, broncho-pleural fistula, or empyema;
- recurrence of positive culture status during course of treatment; and
- relapse after completion of anti-TB treatment.

WHO has recommended surgical procedures like wedge resections or lobectomy in patients with localized lesions. If surgical option is under consideration, at least six to nine months of chemotherapy is recommended prior to surgery to ensure culture conversion. [12] Linkages may be established with existing institutions of excellence where patients can be referred for expert opinion and decisions taken to provide surgical options after a detailed review of the patient. States need to identify institutes with capacity to conduct thoracic surgery and link up DR-TBCs to such institutes with support to the patient to cover costs involved for surgery through innovative mechanisms.

9.5 DR-TB in patients with renal impairment

Renal insufficiency due to longstanding TB disease itself, previous use of aminoglycosides or concurrent renal disease is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal impairment. Care has to be taken to see if DR-TB patients require aminoglycosides for 6 months or more. Other drugs, which might require a dose or interval adjustment in the presence of mild to moderate renal impairment, are E, FQ, Cs and PAS. In the presence of severe renal impairment, many other drugs may require adjustments (Table 9.3).

In DR-TB patients, blood urea and serum creatinine should be monitored prior to treatment initiation, monthly for 3 months after treatment initiation and then every three months whilst injection Km is being administered. In patients with mild renal impairment, the dose of aminoglycosides may be reduced. In the presence of severe renal failure, the aminoglycoside therapy should be discontinued and replaced with other potent non-nephrotoxic anti-TB drugs.
Table 9.3 Dose adjustment of anti-TB drugs in presence of renal impairment

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

*aCompanion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis 2014. [30]

Estimated creatinine clearance calculations:
Men: Ideal Body Weight (kg) X (140 – age) / 72 x serum creatinine (mg/dl)
Women: 0.85 X Ideal Body Weight (kg) X (140 – age) / 72 x serum creatinine (mg/dl))
9.6 DR-TB in patients with pre-existing liver disease

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

Once a patient on second-line drugs develops hepatitis, other etiologies should be excluded such as viral hepatitis, alcoholic hepatitis, drug induced hepatitis by non-TB drugs etc., Further management should be on the same line as in non-DR-TB patients.

DR-TB patients having deranged liver function test (LFT) during pretreatment evaluation should be strictly monitored through monthly LFTs while on treatment. However, routine LFT is not recommended in all patients.

9.7 DR-TB in patients with seizure disorders

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

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

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

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

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

FQ and Eto have been associated with psychosis. Pyridoxine prophylaxis may minimize the risk of neurologic and psychiatric adverse reactions. Cs may cause severe psychosis and depression leading to suicidal tendencies. However, the use of Cs is not absolutely contraindicated for the psychiatric patient. Adverse effects of Cs may be more prevalent in the psychiatric patient but the benefits of using this drug often outweigh the potential higher risk of adverse effects. Close monitoring is recommended if Cs is used in patients with psychiatric disorders. If patient on Cs therapy develops psychosis, anti-psychotic treatment should be started and Cs therapy should be temporarily suspended. Once symptoms resolve and patient is stabilized, Cs therapy may be resumed. Such patients may require antipsychotic treatment till anti-TB treatment is completed. When any patient on DR-TB treatment develops psychosis, other etiologies such as psychosocial stresses, depression, hypothyroidism, illicit drug and alcohol use, should also be looked for.

All health care workers treating drug-resistant TB should closely work with a psychiatrist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patients being a danger to him/herself or others. Mechanisms to deal with psychiatric emergencies (often inpatient psychiatric hospital admissions) should be available 24X7. Proper infection control measures must be taken for the smear-positive patient who requires hospitalization.
9.9 Management of DR-TB in extra pulmonary TB patients

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

Investigations and pretreatment evaluation

Patients would be sent to the DR-TBC for pretreatment evaluation and treatment initiation. EP DR-TB patients will undergo all those pretreatment investigations as done for pulmonary DR-TB patients as part of pretreatment evaluation prior to initiating regimen for DR-TB.

In addition, ultrasound of abdomen of the patient will also be done, if necessary, to rule out involvement of other organs and abdominal nodes. If required, additional imaging investigation will be done to rule out any other conditions.

Initiation of treatment

After pretreatment evaluation, treatment for EPDR-TB should be initiated based on weight of the patient. Treatment regimen, weight band and schedule for EP DR-TB patients will remain the same as for pulmonary DR-TB.

Monitoring progress during treatment and follow-up

Clinical monitoring is the most important criteria for the follow-up of patients with EP DR-TB. Regular patient monitoring and periodic follow-up of nodes and other EP symptoms with culture from the discharging node/sinus is the key in monitoring of treatment in EP lymph nodal DR-TB.

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

**Clinical monitoring:** This is important in case of EPDR-TB. Monitoring and follow-up can be done clinically based on the following:

- weight gain;
- decrease or increase in symptoms (healing of ulcer/scrofuloderma);
- increase or regression in size of nodes (possibility of Immune Reconstitution Inflammatory Syndrome (IRIS) to be considered and differentiated from disease progression);
- appearance of new nodes;
- if chest symptomatic, monthly sputum for AFB and chest X-ray (to rule out pulmonary involvement);
- other EP sites to be monitored (USG abdomen, if necessary);
- serum creatinine-monthly for first three months of treatment and then quarterly till the patient receives Km and further when clinically indicated;
- liver function test, as clinically indicated;
- USG-abdomen, if necessary; and
- monitoring for drug adverse reactions.

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

9.10 Management of contacts of DR-TB

‘Close contacts’ of drug-resistant TB (DR-TB) patients are defined as 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. Contact tracing is an underutilized strategy that can stop the transmission of multidrug-resistant strains. Studies have shown that contact investigation is a high-yield strategy that, in many high-burden TB countries, probably merits more resources even for regular, drug-susceptible TB patients. [34]

All close contacts of DR-TB patients should be identified through contact tracing and evaluated for active TB disease as per RNTCP guidelines.

If the contact is found to be suffering from pulmonary TB disease irrespective of the smear based microbiological confirmation, s/he will be identified as a “Presumptive DR-TB”. The patient will be initiated on regimen for new or previously treated patient based on their history of previous anti-TB treatment. Simultaneously, two sputum specimens will be transported for culture and DST to an RNTCP-certified C&DST laboratory where s/he will be evaluated as per DR TB diagnostic algorithm (Figure 5.2).

If the patient is confirmed as having DR-TB, appropriate DR-TB treatment must be initiated. Further, the patient will be sent to the DDR-TBC ward for pre-treatment assessment and initiation of appropriate regimen. Among asymptomatic contacts of patients with DR-TB, it would be important to rule out active TB by appropriate clinical examination and investigation. Although alternative prophylaxis treatments have been suggested, there is no consensus regarding the choice of drug(s) and the duration of treatment. Prompt treatment
of DR-TB in index case is the most effective way of preventing the spread of infection to others. There are multiple opportunities to investigate contacts of DR-TB patients, namely:

**Patient:** Contact investigation starts with education of the DR-TB patient. Patients should be educated about the infectiousness of their disease and the high risk of transmission to contacts who share the same living space. While they should not be unduly alarmed, they should be informed that their family members are likely already infected with DR-TB, so the most important intervention is to monitor them closely for symptoms of active TB.

**Family:** One of the most important reasons to do a home visit for every DR-TB patient at the initiation of DR-TB treatment is to do contact investigation. A community nurse or health care provider should educate the family that they are all likely already infected with DR-TB, and explain the importance of notifying the community or clinical team quickly about family members who develop symptoms of active TB.

**Clinical team.** The clinical team has multiple opportunities to inquire about the health of the DR-TB patient’s family contacts. At every clinical evaluation, doctors and nurses should ask the patient whether any family member has developed TB symptoms.

**Community nurses or health care providers educated on DR-TB:** During home visits to check adherence or assess the social situation, the community nurse should inquire if there are any family members who have developed symptoms of active TB. The community nurse may directly interview family members at their home as they are best suited to address fears or doubts about the health system or other social barriers to treatment for DR-TB contacts.

**Community health workers:** In community-based programmes that incorporate home-based treatment support, community health workers are the closest to the family and are most likely to identify family members with TB symptoms. This is particularly true for members of the extended family who visit periodically. The following measures should be taken to prevent spread of DR-TB infection:

- early diagnosis and appropriate treatment of DR-TB patients;
- counselling patient and family on infection control measures like cough etiquette and sputum disposal;
- screening of contacts as per RNTCP guidelines; and
- further research into effective and non-toxic chemoprophylaxis in areas of high DR-TB prevalence.
Chapter 10: Managing adverse reactions

DR-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 drug-resistant TB, relieving unnecessary suffering. This section also includes ADR recording and reporting mechanism with Pharmacovigilance Programme of India (PvPI):

- monitoring for early detection of ADR;
- commonly encountered ADRs with the regimen used;
- strategies for managing and reporting ADRs; and
- documentation and reporting of ADR (pharmacovigilance).

The timely and intensive monitoring for and management of, adverse effects caused by second-line drugs are essential components of DR-TB programmes.

Poor management of adverse effects increases the risk of default or irregular adherence to treatment and may result in death or permanent morbidity. The ability to monitor patients for adverse effects daily is one of the major advantages of having a treatment supporter over self-administration of drug-resistant TB treatment.

Table 10.1 Notable adverse reactions to drugs used for DR-TB patients [31]

<table>
<thead>
<tr>
<th>Common or relevant adverse effects of drug-resistant TB therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>Abdominal pain</td>
<td>Visual disturbances</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Anorexia</td>
<td>Seizures</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Gastritis</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>Peripheral neuropathy</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Hearing disturbances</td>
<td>Depression</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Headache</td>
<td>Tinnitus</td>
<td>Hepatitis (hepatotoxicity)</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Allergic reaction</td>
<td>Renal failure (nephrotoxicity)</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>Rash</td>
<td>QT prolongation</td>
</tr>
</tbody>
</table>

Adverse effects are easy to recognize and are usually reported by patients when they experience it. However, few effects may not be reported by patients in the presence of other major adverse effect/s. All treatment supporters, including hospital, clinic or community health workers should be trained to screen patients regularly for symptoms of common adverse effects. They should be trained in simple adverse effect management and on when to refer patients to a nurse or physician. Certain laboratory investigations are required on routine basis during the course of treatment to monitor the ADR.
Table 10.2 Additional monitoring for patients on DR-TB regimens [31]

<table>
<thead>
<tr>
<th>Monitoring Evaluation</th>
<th>Recommended action in specific situations beyond routine follow up evaluation schedule (refer Table 8.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>Every one to three weeks in HIV infected patients, diabetics and other high-risk patients.</td>
</tr>
<tr>
<td>Serum electrolytes (Na, K, Cl)</td>
<td>Every one to three weeks in HIV infected patients, diabetics and other high-risk patients.</td>
</tr>
<tr>
<td>Serum magnesium and calcium</td>
<td>Check magnesium and calcium blood levels whenever hypokalaemia is diagnosed. Repeat if any electrocardiogram (ECG) abnormalities develop (prolonged QT interval).</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td>Every three months if receiving Eto/Pto and p-aminosalicylic acid (PAS). Every six months if receiving Eto/Pto or PAS, but not both together. TSH is sufficient for screening for hypothyroidism and it is not necessary to measure hormone thyroid levels. Monthly monitoring for clinical signs/symptoms of hypothyroidism is also necessary.</td>
</tr>
<tr>
<td>Liver serum enzymes (SGOT, SGPT)</td>
<td>Periodic monitoring every six months if receiving Eto/Pto for extended periods or for patients at risk for or with symptoms of hepatitis. For HIV-infected patients monthly monitoring/or patients on Bdq, monthly monitoring/or patients with viral hepatitis, monitoring every one to two weeks for the first month and then every one to four weeks is recommended.</td>
</tr>
<tr>
<td>HIV testing</td>
<td>Repeat if clinically indicated.</td>
</tr>
<tr>
<td>Haemoglobin and white blood cell count, Platelets</td>
<td>If on Lzd, monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use of Lzd. For HIV-infected patients on Zidovudine, monitor monthly initially and then as needed based on symptoms.</td>
</tr>
<tr>
<td>Amylase, Lipase and S. protein (Albumin:Globulin)</td>
<td>Indicated for work-up of abdominal pain to rule out pancreatitis in patients on Lzd, Bdq, Dlm, D4T, ddI or ddc.</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>Indicated for work up of lactic acidosis in patients on Lzd or antiretroviral treatment (ART).</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>If receiving Gfx, monitor fasting blood glucose at baseline and monitor monthly. Educate/remind patients on signs and symptoms of hypoglycaemia and hyperglycaemia monthly.</td>
</tr>
<tr>
<td>Audiometry (hearing test)</td>
<td>Ask patients about changes in hearing at every clinic visit and evaluate their ability to participate in normal conversation.</td>
</tr>
<tr>
<td>Vision tests</td>
<td>For patients on long-term E or Lzd perform at least a visual acuity test with Snellen charts and colour vision test at baseline (as a small percentage of the population has colour blindness). Repeat the test for any suspicion of change in acuity or colour vision.</td>
</tr>
<tr>
<td>Educational, mental health and social consultation</td>
<td>At baseline by personnel trained in health education, mental health and social issues relevant to TB management; during treatment and repeat as indicated. Refer to social worker, psychologist or psychiatrist when indicated.</td>
</tr>
</tbody>
</table>
10.1 Management of adverse drug reactions

The treatment supporter will monitor and record all adverse events routinely. Laboratory screening tests will be done on a routine basis as per national guidelines. The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects or poor outcomes. Laboratory screening is invaluable for detecting certain adverse effects that are more occult and before serious harm is done. [31]

Training of all the health staff will be done to identify and manage ADRs.[34] Close monitoring of patients is necessary to ensure that adverse effects of drugs are recognized quickly by healthcare personnel. The ability to monitor patients on a daily basis for adverse effects is one of the major advantages of having a treatment supporter as opposed to self-administration of treatment. It is important for the treatment supporter to be trained to screen patients regularly for symptoms of common adverse effects such as rashes, toxic epidermal necrolysis, gastrointestinal symptoms (nausea, vomiting, diarrhoea), psychiatric symptoms (psychosis, depression, anxiety) jaundice, ototoxicity, peripheral neuropathy, symptoms of electrolyte wasting (muscle cramping, palpitations) and convulsions. Treatment workers should also be trained to identify ADRs and must refer the patient to the MO PHI for minor ADRs and to the DTO for major ADRs. Most ADRs can be managed by the DTO/chest physician of the district hospital. If required, hospitalization can be done at the districts where inpatient facility is available or referred to a referral hospital for admission. A symptom-based approach should be followed to manage minor ADR where the patient is usually able to tolerate ATT drugs and continue medication with symptomatic treatment. Patients with major adverse effects should be managed at the hospital level (they may require admission).

The N/DDR-TBC Committee would be consulted to take decisions regarding reduction/termination of any drug. If any drug is withheld/terminated due to ADR, it would be replaced with an appropriate substitute drug as per DR-TBC committee. Before starting treatment, the patient should be instructed in detail about potential adverse effects that could be produced by the prescribed drug regimen and if and when they occur, to notify a healthcare provider. Proper management of adverse effects begins with pretreatment patient education. Depending on the severity of ADRs, following actions may be indicated:

- if adverse effect is mild and not serious, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option;
- most adverse effects of a number of second-line drugs are dose-dependent. Reducing the dosage of the offending drug or terminating it is another method of managing adverse effects; and
- psychosocial support is an important component of the management of adverse effects. This may be provided through patient education and motivation by treatment supporter, patient support groups like patients association/organization or through group discussions while in the hospital.

The recommended strategies for ADR management are detailed below. [31]

10.1.1 Rash, allergic reaction and anaphylaxis

**Suspected agent (s):** Any drug

**Suggested management strategies**

- hypersensitivity reactions such as pruritus or rash, can occur with any of the drugs used and are commonly managed with antihistamines;
- at the PHC/ field level, if the case is of a mild reaction, the patient will be assured and managed symptomatically by the PHC MO;
- for serious allergic reactions, it will be important to stop all therapies pending resolution of reaction and refer the patient to Nodal DR-TB centre/ tertiary centre for further management. In case of anaphylaxis, the condition will have to be managed with standard emergency protocols;
- other potential causes of allergic skin reactions (like scabies or other environmental agents) will need to be eliminated;
- for minor dermatologic reactions, various agents can be helpful. In this case medication must be continued. This could include antihistamines, Hydrocortisone cream for localized rash, Prednisone in a low dose of 10 to 20 mg per day for several weeks if other measures are not helpful and phototoxicity (may respond to sunscreens, but can also cause rash). Dry skin may cause itching (especially in diabetics). In which case, a liberal use of moisturizing lotion is recommended, since dry skin is a common and significant problem with Cfx;
- once rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. The order of reintroduction will be H, R, Z, Eto, Cs, E, PAS, FQ and Km;
- consider not reintroducing even as a challenge any drug that is highly likely to be the cause; and
- suspend permanently any drug identified to be the cause of a serious reaction.
10.1.2 Gastrointestinal symptoms (nausea and vomiting)

Gastrointestinal symptoms may be due to the bulk of drugs. Patients who complain of nausea or vomiting can be advised to take drugs embedded in a banana.

**Suspected agent(s):** Eto, Pto, PAS, Z, E, Bdq

**Suggested management strategies**

- if vomiting persists, drugs will be administered one hour after one tablet of Domperidone and/or a course of proton pump inhibitor (Omeprazole) or H2 receptor inhibitor (Famotidine, Ranitidine);
- other antacids are usually not given, since they interfere with absorption of FQ;
- in case of severe vomiting, the hydration status of the patient should be monitored and rehydration therapy initiated if required;
- if the offending drug is Eto, the drug is more acceptable if administered with milk, or after milk, or at bedtime to avoid nausea;
- if vomiting is severe, drugs can be withheld temporarily and tests can be conducted to rule out other causes of vomiting like hepatitis;
- assess for danger signs including dehydration, electrolyte disturbance and hepatitis. Initiate rehydration therapy if indicated and correct any electrolyte disturbance. If there is blood in the vomit, check haemoglobin and treat for possible bleeding ulcers; and
- with Bdq, ancillary drugs need to be chosen as mentioned in Section 10.2.

Initiate the following 3-step approach to manage nausea and vomiting:

- history of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card;
- flushing reaction to R or Z is usually mild and resolves with time. Antihistamines can be used. Hot flushes, itching, palpitations can be caused with H and tyramine containing foods (cheese, red wine). If this occurs, advise patients to avoid foods that precipitate reaction;
- any of the drugs can cause hives (urticaria). To identify the drug, introduce drugs one at a time; and
- in case of hives, a desensitization attempt can be made. Any drug that results in anaphylaxis or Stevens–Johnson syndrome should never be reintroduced (not even as a challenge).
**Step 1:** Adjust medication and conditions without lowering overall dose. Give Eto/Pto at night; Eto or PAS twice or thrice daily; light snack (biscuits, bread, rice, tea) before medication; and PAS two hours after other anti-TB drugs.

**Step 2:** Start antiemetic(s) like Metoclopramide 10 mg, 30 minutes before anti-TB medication; Ondansetron 8 mg, 30 minutes before 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.

**Step 3:** Decrease dose of suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.

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**Points to note**

- nausea and vomiting are universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at least in the initial period;
- creatinine and electrolytes should be checked if vomiting is severe. Give intravenous fluids and replace electrolytes as needed;
- another strategy is to stop the responsible medicine for 2-3 days and then add it back, gradually increasing the dose (advice the patient that the medicine will be increased back to a therapeutic dose in a way that is better tolerated);
- odansetron prolongs QT interval; avoid use of odansetron with Bdq or Dlm; and
- for patients particularly anxious about nausea, (and with “anticipatory nausea and vomiting”) a small dose of an anti-anxiety medicine (5 mg of diazepam) can help when given 30 minutes prior to intake of anti-TB drugs.

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**10.1.3 Gastrointestinal symptoms (gastritis & abdominal pain)**

Abdominal pain is often associated with serious adverse effects, such as pancreatitis (Lzd, Bdq), lactic acidosis and hepatitis. If any of these are suspected, it is important to obtain appropriate laboratory tests to confirm and suspend the suspected agent.

**Suspected agent(s):** PAS, Eto, Pto, Cfz, FQs, H, E, and Z

**Suggested management strategies**

- if symptoms are associated and consistent with gastritis (epigastric burning or discomfort, sour taste in mouth associated with reflux) initiate medical therapy with the
use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg once daily). Avoid use of antacids as they decrease absorption of FQ;

- for severe abdominal pain, stop suspected agent(s) for short periods of time (1-7 days);
- lower the dose of the suspected agent, if this can be done without compromising the regimen; and
- discontinue suspected agent if this can be done without compromising the regimen.

### Points to note

- severe gastritis, as manifested by blood in the vomit or stool is relatively rare, but should always be treated to facilitate adherence to treatment;
- if antacids must be used, they should be carefully timed so as to not interfere with absorption of FQ (take two hours before or three hours after anti-TB drugs);
- stop any non-steroidal anti-inflammatory drugs the patient may be taking;
- diagnose and treat for *Helicobacter pylori* infections; and
- severe abdominal distress has been reported with use of Cfz. Although these reports are rare, if this occurs, Cfz should be suspended.

#### 10.1.4 Diarrhoea and/ or flatulence

**Suspected agent(s):** PAS, Eto/Pto

**Suggested management strategies**

- motivate patients to tolerate some degree of loose stools and flatulence;
  - 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; and
  - 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
Points to note

- consider other causes of diarrhoea;
- pseudo-membranous colitis related to broad-spectrum antibiotics (such as FQ) is a serious and even life threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are warning signs of possible pseudomembranous colitis;
- parasites and common waterborne pathogens in the area should be evaluated in the patient and treated;
- lactose intolerance, especially if patient has been exposed to new foods in a hospital not normally part of their diet; and
- loperamide can be used in children over two years of age.

10.1.5 Hepatitis

Suspected agent(s): Z, H, R, Pto / Eto, PAS, FQ, Bdq

Suggested management strategies

- in cases where patient is very sick *i.e.*, meningitis, sputum smear grade 3+, give ATT e.g. Streptomycin, FQ and Cs. Where patient is not seriously ill and one can wait, introduction of ATT can be done once enzyme levels are near normal;
  - if enzymes are more than five times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non-hepatotoxic medications (for example, the injectable agent, FQ and Cs). If hepatitis worsens or does not resolve with the three-drug regimen, then stop all drugs;
  - eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis being the two most common causes) and treat any that are identified; and
  - once enzyme level improves, reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring liver function by testing enzymes every three days. If the most likely agent is not essential, consider not reintroducing it.

Points to note

- history of previous drug hepatitis should be carefully analyzed to determine the most likely causative agent(s); these drugs should be avoided in future regimens;
- viral serology should be done to rule out other etiologies of hepatitis if available, especially to hepatitis A, B and C;
- alcohol use should be investigated and alcoholism addressed; and
- generally, hepatitis due to medications resolves upon discontinuation of the suspected drug.
10.1.6 Giddiness

Suspected agent(s)-Aminoglycosides, Eto, FQ and/or Z

Suggested management strategies

- whenever a patient complains of giddiness, over sleepiness or poor concentration, s/he will have to be counselled;
- if severe, the offending drug should be identified by administering drugs individually and observing response;
- the dose of the offending drug identified may be adjusted or the offending drug terminated if required; and
- aminoglycosides, especially in elderly age group must be kept in mind for giddiness as it may be early sign of 8th nerve toxicity.

Point to note

In cases of severe giddiness, the patient may be referred to the neurologist for further management as per standard protocol.

10.1.7 Haematological abnormalities

Suspected agent(s): Lzd

Suggested management strategies

- stop Lzd if myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs;
- consider restarting with a lower dose of Lzd (300 mg instead of 600 mg) if myelosuppression resolves and if Lzd is considered essential to the regimen;
- consider nondrug related causes of haematological abnormality; and
- consider blood transfusion for severe anaemia.

Points to note

- haematological abnormalities (leukopenia, thrombocytopenia, anaemia, red cell aplasia, coagulation abnormalities and eosinophilia) can rarely occur with a number of other anti-TB drugs; (see individual drug sheets, Part 3)
- there is little experience with prolonged use of Lzd.
10.1.8 Hypothyroidism

Suspected agent(s): Eto/Pto, PAS

Suggested management strategies

In cases of hypothyroidism, opinion of general physician/endocrinologist may be taken.

Points to note

- symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair and constipation, as well as occasional depression and inability to concentrate;
- in cases with abnormal weight gain, hypothyroidism may be ruled out;
- it is completely reversible upon discontinuation of PAS and/or Eto/Pto; and
- combination of Eto/Pto with PAS is more frequently associated with hypothyroidism than when each individual drug is used.

10.1.9 Arthralgia

Suspected agent(s): Z, FQ, Bdq

Suggested management strategies

- initiate with paracetamol in the beginning;
- 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 Z) if this can be done without compromising the regimen; and
- discontinue the suspected agent if this can be done without compromising the regimen.

Points to note

- symptoms of arthralgia generally diminish over time, even without intervention;
- uric acid levels may be elevated in patients on Z. There is little evidence to support the addition of allopurinol for arthralgia. However, if gout is present it should be used; and
- if acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc.
10.1.10 Peripheral neuropathy

Suspected agent(s): Cs, Lzd, H, S, Km, Amk, Cm, FQ, rarely Pto/Eto, E

Suggested management strategies

• to prevent occurrence of such adverse reaction, all patients on an RNTCP regimen for MDR-TB should receive daily Pyridoxine. If peripheral neuropathy develops, an additional 100mg Pyridoxine will be given;
• the commonest offending agent is Lzd, almost 60-70% of the patients on Lzd 600 mg/day may develop neuropathy and pyridoxine does not help in preventing Lzd induced neuropathy. Early recognition of neuropathy symptoms and early dose reduction of Lzd helps to prevent the progression. If there is no improvement or symptoms worsen, Amitriptylline 25mg will be added and if still there is no improvement, patient should be referred to a neurologist;
• correct any vitamin or nutritional deficiencies and increase pyridoxine to the maximum daily dose (200 mg per day);
• consider whether the dose of Cs can be reduced without compromising the regimen. If H is being used (especially H$^{\text{H}}$), consider stopping it and if possible, switching the aminoglycoside to Cm may also be helpful;
• initiate medical therapy:
  - non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms;
  - therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime, the dose may be increased to a maximum of 150 mg) can be tried. Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors and antidepressant drugs;
  - in such a case, refer to specialist for further management; and
  - rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.

Points to note

• patients with comorbid disease (diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of agents listed here; and
• neuropathy associated with Lzd is common after prolonged use and often permanent though it may be irreversible. Thus, suspension of this drug should be strongly considered when neuropathy persists despite above measure.
10.1.11  Headache

**Suspected agent(s):** Bdq, Cs

**Suggested management strategies**

- Rule out more serious causes of headache, including meningitis and other infections of the central nervous system (HIV co-infected patients should receive a head computed tomography scan and cerebrospinal fluid analysis).
- Start analgesics like ibuprofen or paracetamol. Also, encourage good hydration and consider low dose tricyclic antidepressants for refractory headaches.

**Points to note**

- headaches are common during the initial months of DR-TB therapy and can present as migraine or cluster headaches;
- to minimize headaches at the start of therapy, Cs can be started at lower doses of 250–500 mg and gradually increased over 1-2 weeks to achieve the target dose;
- headaches due to Cs and Bdq are usually self-limited; and
- Pyridoxine (Vitamin B6) should be given to all patients receiving Cs to help prevent neurotoxicity.

10.1.12  Depression

**Suspected agent(s):** Psychological and socioeconomic circumstances, chronic disease, Cs, FQ H, Eto/Pto

**Suggested management strategies**

- assess and address underlying emotional and socioeconomic issues (see Chapter 12 on social support);
- assess patients for coexisting substance abuse and refer to treatment if appropriate;
- initiate individual counselling (or group counselling if the patient is sputum smear and culture negative);
- when depression is more significant, initiate antidepressant therapy (amitriptyline, fluoxetine or similar);
- tricyclic antidepressants and selective serotonin reuptake inhibitors should be given together and not given to patients on Lzd;
- lower the dose of the suspected agent if this can be done without compromising the regimen (reducing dose of Cs and Eto to 500 mg daily to see if depression is lessened is a common strategy); and
- discontinue suspected agent if this can be done without compromising the regimen.
Points to note

- socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression;
- depressive symptoms may fluctuate during therapy and improve as illness is successfully treated;
- history of previous depression is not a contraindication to use of agents listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with Cs, if possible; and question the patient regarding suicidal ideation any time the depression is judged to be more than mild.

10.1.13 Psychotic symptoms

Suspected agent(s): Cs, H, FQ,

Suggested management strategies

- stop the suspected agent for a short period (1–4 weeks) while psychotic symptoms are brought under control;
- the most likely drug is Cs followed by H;
- 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 Cs to 500 mg a day) if this can be done without compromising the regimen;
- discontinue suspected agent if this can be done without compromising the regimen; and
- once all symptoms resolve and patient is off Cs, antipsychotic therapy can be tapered off. If Cs 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.

Points to note

- some patients will need to continue antipsychotic treatment;
- previous history of psychiatric disease is not a contraindication to Cs, but its use may increase the likelihood of psychotic symptoms developing during treatment;
- some patients will tolerate Cs with an antipsychotic drug but this should be done in consultation with a psychiatrist, as these patients will need to be under special observation; this should be done only when there is no other alternative;
- psychotic symptoms are generally reversible upon completion of DR-TB treatment or cessation of the offending agent; and
- always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of Cs, which can cause psychosis.
10.1.14 Suicidal ideation

Suspected agent(s): CS, H, Eto/Pto

Suggested management strategies

- hospitalize the patient and put under 24-hour surveillance;
- discontinue Cs;
- request psychiatric consultation;
- initiate antidepressant therapy; and
- lower the dose of Eto/Pto to 500 mg daily until the patient is stable.

Points to note

- keep the patient in the hospital until risk of suicide has passed; and
- if no improvement occurs after holding Cs, hold H and/or Eto/Pto.

10.1.15 Seizures

Suspected agent(s): Cs, H, FQ

Suggested management strategies

- hold Cs, FQ and H pending resolution of seizures;
- initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used);
- increase pyridoxine to maximum daily dose (200 mg per day);
- check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride; and
- when seizures have resolved, restart medication, one at a time. Cs should not be restarted unless it is absolutely essential to the regimen. If Cs is reinitiated, start a dose one weight band lower.

Points to note

- an anticonvulsant is generally continued until DR-TB treatment is completed;
- history of previous seizure disorder is not a contraindication if a patient’s seizures are well controlled and/or the patient is receiving anticonvulsant therapy;
- do not include Cs if an alternative drug is available;
- patients with history of previous seizures may be at increased risk for developing seizures during DR-TB therapy; and
- always check creatinine in patients with new onset seizures. A decrease in renal function can result in high blood levels of Cs, which can cause seizures. Adjusting the dose of Cs in the presence of low creatinine may be all that is needed to control the seizures.
10.1.16  Tendonitis and tendon rupture

**Suspected agent(s):** FQ

**Suggested management strategies**

- if significant inflammation of tendons or tendon sheaths occur, consider stopping FQ;
- give a non-steroidal anti-inflammatory drug (ibuprofen 400 mg four times daily);
- rest the joint;
- if treatment failure is likely without FQ:
  - reduce dose if possible;
  - ensure joint is strictly rested; and
  - inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of FQ.

**Points to note**

- tendon rupture with FQ use is more likely in patients doing new physical activities and more common among older patients and diabetics; and
- tendon rupture is relatively rare in patients on DR-TB regimens with FQ.

10.1.17  Nephrotoxicity (renal toxicity)

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

**Suspected agent(s):** S, Km, Am, Cm

**Suggested management strategies**

- discontinue the suspected agent;
- consider using Cm if an aminoglycoside had been the prior injectable drug in the regimen;
- consider other contributing etiologies (non-steroidal anti-inflammatory drugs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.,) and address as indicated;
- follow creatinine (and electrolyte) levels closely, every 1-2 weeks;
- consider dosing the injectable agent 2-3 times a week if the drug is essential to the regimen and the patient can tolerate (close monitoring of creatinine). If creatinine continues to rise despite twice/thrice a week dosing, suspend the injectable agent; and
• adjust all TB medication according to creatinine clearance in consultation with nephrologist. Also, note that renal impairment may be permanent.

Points to note

• during treatment, blood urea and serum creatinine should be done every month for the first three months after treatment initiation and then every three months thereafter whilst injection Km is being administered;
• silent renal toxicity may be picked up by these routine follow-up biochemical examinations;
• if at any time, the blood urea or serum creatinine becomes abnormal, treatment should be withheld and further management decided upon in consultation with the DR-TBC committee;
• an example of how to calculate a creatinine clearance based on the serum creatinine is provided in Chapter 7, Box 7.2; and
• history of diabetes or renal disease is not a contraindication to the use of agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure.

10.1.18 Vestibular toxicity (tinnitus and dizziness)

Suspected agent (s): S, Km, Am, Cm, Cs, FQs, H, Eto, Lzd

Suggested management strategies

• if early symptoms of vestibular toxicity appear, there may be a need to change dosing of the injectable agent to twice/thrice a week. Also, consider using Cm if an aminoglycoside had been the prior injectable in the regimen; and
• if tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. This is one of the few adverse reactions that may cause permanent intolerable toxicity and can necessitate discontinuation of a class of agents.

Points to note

• ask the patient about tinnitus and unsteadiness every week especially in elderly patients;
• fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity; and
• a degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, H or Lzd. Some clinicians will stop all drugs for several days to see if symptoms are attributed to these drugs. Symptoms of vestibular toxicity generally do not improve on withholding medications.
10.1.19 Hearing loss

**Suspected agent(s):** S, Km, Am, Cm

**Suggested management strategies**

- document hearing loss and compare with baseline audiogram if available (some degree of hearing loss occurs with most patients starting with high frequency loss);
- if early symptoms of hearing loss are documented, change closing of the injectable agent to twice/thrice a week. Also, consider using Cm if an aminoglycoside had been the prior injectable in the regimen; and
- discontinue injectable agent if hearing loss continues despite dose adjustment and add additional drugs to reinforce the regimen. Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient’s desire to maintain hearing.

**Points to note**

- patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of DR-TB therapy;
- hearing loss is almost always permanent. Continuing the injectable agent despite hearing loss almost always results in irreversible deafness;
- while benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from its use; and
- cochlear transplant can also be considered.

10.1.20 Optic neuritis

**Suspected agent(s):** E, Lzd, Eto/Pto, Cfz, Rifabutin, H, S

**Suggested management strategies**

- stop E and Lzd. Do not restart; and
- refer patient to an ophthalmologist.

**Points to note**

- the most common drugs are E and Lzd; the condition usually reverses with cessation of the drug; and
- improve diabetes control in diabetic patients.
10.1.21 Metallic taste

**Suspected agent(s):** Eto/Pto, FQs

**Suggested management strategies:** Encourage the patient to tolerate this side effect.

**Point to note:** Normal taste returns when treatment is stopped.

10.1.22 Electrolyte disturbances (hypokalaemia and hypomagnesaemia)

**Suspected agent(s):** Cm, Km, Am, S

**Suggested management strategies**

- evaluate potassium levels;
- if potassium is low, check for magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all patients of hypokalaemia);
- replace electrolytes as needed. Dose oral electrolytes apart from FQ as they can interfere with FQ absorption; and
- manage electrolyte disturbances

**Points to note**

- if severe hypokalaemia is present, consider hospitalization;
- amiloride, 5–10 mg daily, or spironolactone, 25 mg daily, may decrease potassium and magnesium wasting and thus useful in refractory patients; and
- oral potassium replacements can cause significant nausea and vomiting and oral magnesium may cause diarrhoea.

10.1.23 QT prolongation

**Suspected agent(s):** Bdq, Dlm, FQ, clarithromycin, Cfz

**Suggested management strategies**

- any patient found to have a QTc value greater than 500ms, stop all suspected QT prolonging drugs;
- repeat ECG and confirm the prolongation;
- check potassium, calcium and magnesium levels;
- electrolyte levels should be maintained in the normal range in any patient with an elevated QT interval;
• avoid other drugs that increase the QT interval. Monitor the patient’s renal and hepatic function and adjust the dose of FQ if impairment is present;
• consider suspension of FQ if risk of torsades de pointes outweighs benefits of the drug; and
• also see relevant section for more information on QT interval monitoring with Bdq and Dlm.

**Points to note**

• QT interval is measured from the end of the QRS complex to the beginning of the T wave on a standard ECG. The QT is corrected for heart rate, which is referred to as the QTc and calculated by most ECG machines;
• values above QTc 450 ms are referred to as prolonged. Patients with prolonged QTc are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life threatening;
• FQ may cause prolongation of the QTc. Mfx and Gfx cause the greatest QTc prolongation, while Lfx and Ofx have a lower risk; and
• currently, ECG monitoring prior to initiation and during DR-TB therapy is only required with the use of Bdq, Dlm, or when two drugs known to prolong QT (e.g. Mfx, Cfz) are combined in the same regimen.

10.1.24 Gynaecomastia

**Suspected agent(s):** Eto/Pto

**Suggested management strategies**

• breast enlargement can be a troublesome side effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported; and
• encourage patients to tolerate this side effect.

**Point to note:** Resolution occurs after treatment is stopped.

10.1.25 Alopecia

**Suspected agent(s):** H, Eto/Pto

**Suggested management strategies**

• hair loss can occur or there can be significant thinning of the hair, but this is temporary and not progressive during treatment; and
• encourage patients to tolerate this side effect.

**Point to note:** Significant cosmetic change has not been reported.
10.1.26 Superficial fungal infection and thrush

**Suspected agent(s):** FQ

**Suggested management strategies**

- topical antifungal agents or short course oral antifungal drugs are helpful; and
- Exclude other diseases if response to treatment is not prompt (such as HIV).

**Point to note:** Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.

10.1.27 Lactic acidosis

**Suspected agent(s):** Lzd

**Suggested management strategy:** Stop Lzd if lactic acidosis occurs.

**Point to note:** Lactic acidosis can be managed at the Nodal DRTB centre as per standard protocol and monitored with a blood test that measures lactic acid.

10.1.28 Dysglycaemia and hyperglycaemia

**Suspected agent (s):** Gfx, Eto/Pto

**Suggested management strategies:** Replace the offending drug with a suitable drug.

**Point to note:** Treat diabetes as needed. Good glucose control is important during treatment.

**10.2 Specific toxicities due to Bedaquiline**

Monitoring for specific toxicities is based on target organs defined in preclinical toxicity studies. For monitoring the specific toxicities related to second-line TB drugs, the RNTCP guidelines should be followed. (eye care, audiometry, etc.)

Management of patients with AST and/or ALT elevations, amylase and/or lipase elevations, musculoskeletal system and cardiac muscle abnormalities, cardiac rhythm disturbances, gastrointestinal system disorders or other toxicities is enumerated below. [4] [32] [10]
**AST and/or ALT elevations**

Management will be at the discretion of the physician, according to generally accepted medical practice standards.

In Grade 1 (\(>1.0 \text{ to } <2.0 \times \text{ULN}\)) or Grade 2 (\(>2.0 \text{ to } <3.0 \times \text{ULN}\)) AST or ALT elevation, patients may continue Bdq. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation; and

In Grade 3 (\(>3.0 \text{ to } <8.0 \times \text{ULN}\)) or Grade 4 (\(>8.0 \times \text{ULN}\)) AST or ALT elevation, patients are allowed to temporarily discontinue treatment of the suspected causative agent (usually Eto, Z or PAS). AST, ALT and serum bilirubin should be monitored as frequently as necessary to manage the patient’s condition.

If ALT and AST do not return to baseline, Bdq may be temporarily withheld for up to two weeks. Additional tests should be performed to evaluate the cause of hepatitis (e.g. hepatitis A, B, C). Liver enzymes, including serum bilirubin should be monitored as frequently as necessary to manage the patient’s condition. If LFT improves, then the rest of the dosages of Bdq can be given. For patients who fail to show improvement in the clinical course and to return to baseline values of AST and ALT, it is recommended that the patient discontinue Bdq.

**Amylase and/or lipase elevation**

Management will be at the discretion of the physician, according to generally accepted medical practice standards.

In Grade 1 (\(>1.0 \text{ to } <1.5 \times \text{ULN}\)) or Grade 2 (\(>1.5 \text{ to } <2.0 \times \text{ULN}\)), patients may continue BDQ and should be carefully evaluated and followed closely.

In Grade 3 (\(2.0 \text{ to } <5.0 \times \text{ULN}\)) or Grade 4 (\(>5.0 \times \text{ULN}\)), for asymptomatic grade 3 amylase elevations with no history or concomitant disease of pancreatitis, patients may continue Bdq but should be carefully evaluated and followed closely.

For confirmed grade 4 elevations of amylase and confirmed grade 3 or 4 elevations of lipase, it is recommended that the patient discontinue BDQ.

**Musculoskeletal system and cardiac muscle abnormalities like Myalgia**

In Grade 1 (mild with no limitation of activity), patients may continue Bdq and be carefully evaluated and followed closely.
In Grade 2, there may be muscle tenderness at site other than injection site or with moderate impairment of activity.

In Grade 3, there could be severe muscle tenderness with marked impairment of activity.

In Grade 4 (Frank myonecrosis), it is recommended that the patient discontinue Bdq.

**Cardiac rhythm disturbances**

*QT interval monitoring:* An ECG should be obtained before initiation of treatment and daily for the first two weeks, then every two weeks for three months and then monthly. ECGs should be done at least weekly throughout the Bdq course if other QT prolonging drugs like FQ (Mfx, Gfx), Cfx or macrolide antibacterial drugs (erythromycin, clarithromycin, azithromycin) are included in the regimen. Other drugs with additive or synergistic QT prolongation observed when Bdq is co-administered are those with serotonin 5-HT3 receptor antagonist (ondansteron), prokinetics (Cisapride),azole agents (ketoconazole, itraconazole, fluconazole), common ART drugs, antimalarials (chloroquine and quinine sulfate), some drugs used for psychiatric disorders (chlorpromazine, haloperidol, thioridazine) and drugs known to lower serum electrolytes. If possible, avoid use of QT prolonging drugs with Bdq. If it is absolutely necessary to include a QT prolonging drug and increase ECG monitoring as described earlier.

QT prolongation can result in ventricular arrhythmias (Torsades de Pointes) and sudden death. It is therefore imperative that ECGs be used to monitor the QT interval regularly during Bdq use.

In Grade 1 (asymptomatic) or Grade 2 (asymptomatic, transient rhythm abnormality not requiring any treatment) there could be cardiac rhythm disturbances. Patients may continue BDQ and be carefully evaluated and followed closely.

In Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4 (unstable dysrhythmia requiring hospitalization and treatment) there could be cardiac rhythm disturbances. It is recommended that the patient discontinue Bdq.

A normal value for the corrected QTcF interval is less than 0.44 seconds (440 ms). Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.

- value greater than 440 ms is considered prolonged but does not need action until >450 ms;
- value between 450 – 480 ms: Rule out other causes of prolonged QTc, before deciding to withhold Bdq;
value greater than 480 ms (or an increase of greater than 60 ms from baseline) should trigger the following actions:

- repeat ECG to confirm prolongation;
- check for serum K, Mg and Ca and correct the levels if found to be abnormal. Withhold BDQ until electrolytes have normalized;
- if the QTc interval is between 480 and 500 ms, the patient is stable and electrolytes are within normal values, repeat weekly ECG to confirm that the QTc interval is stable; and
- if the QTc interval is > 500 ms (confirmed by repeat ECG), discontinue Bdq and all other QTc-prolonging drugs in the regimen.

BDQ and all other QTc-prolonging drugs are to be discontinued if the patient develops a clinically significant ventricular arrhythmia. If BDQ is stopped for QTc prolongation, monitor ECG at least weekly to confirm that QTcF interval has returned to baseline. If syncope occurs, obtain an ECG to detect QT prolongation. Because of the long half-life of BDQ, if the ECG has QTc prolongation at week 24, ongoing weekly monitoring should take place until QTc interval normalizes (even though the drug is no longer being given).

If a QTcF of greater than 500 ms is recorded and confirmed by a repeat ECG, it is recommended that BDQ and all other QTc-prolonging drugs be discontinued. Such patients must be closely monitored until the resolution of the prolonged QTcF. The physician should rule out other causes of QTc prolongation such as electrolyte imbalances and steps should be taken to remedy any underlying causes of such prolongation.

**Gastrointestinal system disorders**

Patients with Grade 4 elevation of gastrointestinal parameters should be hospitalized and monitored closely. In case of Grade 4 nausea (hospitalization required) or Grade 4 vomiting (physiologic consequences requiring hospitalization or requiring parenteral nutrition), the patient’s BDQ treatment should be discussed with the DR-TBC Committee.

**Other toxicities**

**Grade 1 or 2**: Patients who develop grade 1 or 2 AE or laboratory toxicity may continue intake of BDQ.

**Grade 3 or 4**: Patients who develop grade 3 or 4 AE or laboratory toxicity should be carefully evaluated by the physician. Patients may discontinue intake of BDQ if, in the opinion of the physician, AE or laboratory toxicity possess significant risk for the patient in case of continued treatment. Patients should be followed as appropriate until resolution of the AE or toxicity. Refer DAIDS criteria for grades [36].
Patients should be monitored for the common side effects of concomitant TB therapy, including decreased hearing, tinnitus, vision changes, dizziness, psychosis, depression, tremors, nausea, vomiting, diarrhoea, joint pain and renal function.

ADR management is crucial to improve treatment compliance of DR-TB patients. Majority of the side effects and ADR management is possible with a simple intervention which can be easily executed even at peripheral level. Following drugs can be used for common side effects or ADR reported by patients.

Table 10.3 Drugs used in management of adverse event[30]

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<tr>
<th>ADRs</th>
<th>Suggested drugs to manage the ADR</th>
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<tr>
<td>Nausea, vomiting, upset stomach</td>
<td>Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate, domperidone</td>
</tr>
<tr>
<td>Heartburn, acid indigestion, sour stomach, ulcer</td>
<td>H2-blockers (ranitidine, cimetidine, famotidine, etc.), Proton pump inhibitors (omeprazole, lansoprazole, etc.) Avoid antacids because they can decrease absorption of fluoroquinolone eg. aluminium hydroxide</td>
</tr>
<tr>
<td>Oral candidiasis (non-AIDS patient)</td>
<td>Fluconazole, clotrimazole lozenges, Nystatin suspension, itroconazole liquid</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Depression</td>
<td>Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)</td>
</tr>
<tr>
<td>Severe anxiety</td>
<td>Lorazepam, diazepam, clonazepam</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Any hypnotic</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal Effects), Buromazine, thioridazine</td>
</tr>
<tr>
<td>Seizures</td>
<td>Phenytoin, carbamazepine, valproic acid, phenobarbital</td>
</tr>
<tr>
<td>Prophylaxis of neurological complications of cycloserine</td>
<td>Pyridoxine (vitamin B6)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Vestibular symptoms</td>
<td>Meclizine, dimenhydrinate, prochlorperazine, Promethazine</td>
</tr>
<tr>
<td>Musculoskeletal pain, arthralgia, headaches</td>
<td>Ibuprofen, paracetamol, codeine, diclofenac</td>
</tr>
<tr>
<td>Cutaneous reactions, itching</td>
<td>Hydrocortisone cream, calamine, caladryl lotions</td>
</tr>
<tr>
<td>Systemic hypersensitivity Reactions</td>
<td>Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids(prednisone), injectable steroids (dexamethasone, methylprednisolone)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Levothyroxine</td>
</tr>
<tr>
<td>Electrolyte wasting</td>
<td>Potassium, magnesium and calcium replacement therapy (oral and intravenous formulations)</td>
</tr>
</tbody>
</table>
10.3 Role of DR-TB centre committee in management of adverse reactions

Whenever a patient has serious adverse reactions to any of the second-line anti-TB drugs, ideally, s/he is admitted at the DR-TB centre and the committee decides on further management of the patient. This may require withholding or discontinuing the offending drug in the treatment regimen. The committee will be responsible for arranging the drugs to be given for managing these reactions. Timely and intensive monitoring for identifying and managing adverse reactions are essential components of the PMDT services. This will help improve the patient’s adherence to treatment, reduce mortality, ensure timely management of ADR and obtain better treatment outcomes. Ancillary drugs for the management of adverse reactions should be made available to the patient free of cost. Proper training of staff and support to the patient are other important activities that are required.

10.4 Pharmacovigilance in TB programme

Pharmacovigilance is defined by the World Health Organization (WHO) as the “science and activities relating to the detection, assessment and prevention of adverse effects or any other drug-related problem”. The overall objective of the pharmacovigilance programme is to improve patient care by assessing both the harm and benefit received from the drug. More than 200 ADR Monitoring Centres (AMCs) are currently collecting ADR related information at various levels (which is usually at the Medical College level). The Pharmacovigilance Programme of India (PvPI) is a national programme for surveillance of ADR related information. DR-TB management is inclusive of newer drugs which require a robust system of monitoring and reporting of ADR related information to build the guideline for safe use of drugs. [37]

Since newer drugs like Bdq, Dlm and not frequently used drug formulation like Mfxⁿ, Hⁿ would be there in various regimen, aDSM is essential. [17] [12] Hence, RNTCP in collaboration with PvPI and support from WHO India developed the comprehensive cohort event monitoring system for aDSM for DR-TB patients. This platform is initially used at DR-TB centers involved in Bdq (newer drugs) containing regimen. Now, this mechanism of CEM is expanded to all DR-TB centres. A drug safety monitoring committee periodically monitors the occurrence of AE/SAE including deaths of patients while on newer drugs containing regimen for necessary signaling and guidance to the programme on their safety and efficacy.

The PvPI recommends reporting of any adverse event (AE) or serious adverse event (SAE) to be done using a suspected ADR reporting format. This has been adopted by RNTCP for drug susceptible TB patients put on first-line treatment using existing mechanisms available under PvPI. In addition, ADR reporting is also possible through the use of mobile app ADR available on android/IOS platforms and toll-free number (18001803024) [36] [37]
However, based on a consensus between RNTCP and PvPI, reporting of SAE is done using cohort event monitoring (CEM) forms for all forms of DR-TB patients initiated on treatment in India. At the time of initiation of any DR-TB treatment regimen, CEM – treatment initiation form (Annexure 12A) is filled in hardcopy and same is entered in Nikshay within 24 hours. During the course of treatment CEM – treatment review form (Annexure 12B) should be filled for any SAE that is reported. Also, any SAE should be managed at the appropriate health facility level and reported in Nikshay within 24 hours by the health facility managing the SAE/parent health facility. For the patients under the conditional access programme, CEM – treatment review form (Annexure 12B) will be filled as per the defined follow-up schedule.

10.5 Adverse event monitoring and reporting

Timely, accurate and complete reporting and analysis of adverse events are required to be reported under the programme. This is crucial for the protection of patients.

Adverse event definitions and classifications[36][37]

**Adverse event:** An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (definition as per the International Conference on Harmonization [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition or abnormal results of diagnostic procedures including laboratory test abnormalities.

**Serious adverse event:** A serious adverse event (SAE) based on ICH is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it more severe.)
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a suspected transmission of any infectious agent via a medicinal product; and
is medically important.¹

**Non-serious adverse drug reaction (ADR)** (associated with use of the drug): Any untoward medical occurrence that does not meet the above criteria to be serious and considered associated with use of the drug.

**Life-threatening**: Any event in which the patient was at risk of death at the time of the event; does not refer to an event, which hypothetically might have caused death if it were more severe.

**Associated with use of the drug**: An AE is considered associated with use of the drug if attribution is possible, probable or very likely.

**Attribution definitions**

Causality assessment will be done by the physician at DR-TBC and are divided in five categories (mentioned below). The drug safety monitoring committee (DSMC) for BDQ conditional access will review and confirm causality of all serious events/reactions in relation to therapy.

**Not related**: An AE that is not related to the use of the drug.

**Doubtful**: An AE for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s) or the relationship in time suggests that a causal relationship is unlikely.

**Possible**: An AE that might be due to the use of the drug. An alternative explanation, e.g. concomitant drug (s) or concomitant disease (s) is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

**Probable**: An AE that might be due to use of the drug. The relationship in time is suggestive, e.g. confirmed by de-challenge. An alternative explanation is less likely, e.g. concomitant drug (s), concomitant disease (s).

**Very likely**: An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug (s), concomitant disease (s). The relationship in time is suggestive, e.g. confirmed by dechallenge and rechallenge.

¹Medical and scientific judgment exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of other outcomes listed in the definition above. These is usually considered serious.
Severity criteria

An assessment of severity grade will be made using the following general categorical descriptors:

**Mild:** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

**Moderate:** Sufficient discomfort is present to cause interference with normal activity.

**Severe:** Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject, e.g. laboratory abnormalities.

Reporting of AE, SAE and pregnancy

All SAEs and AE's (non-serious adverse events which are possibly, probably or very likely related to administration of BDQ) that fit the definition as detailed later relate to detailed formats for AE reporting and pregnancy occurring during the programme. They must be reported by the physician to RNTCP as they occur. If pregnancy occurs during BDQ treatment, BDQ must be stopped and OBR modified as per RNTCP PMDT guidelines. Any death of a patient occurring during treatment in a BDQ-containing regimen, regardless of causality, must be reported as SAE and a verbal autopsy (Annexure 13) should be undertaken. It is recommended that the patient be questioned before commencement of treatment and at each subsequent consultation in order to obtain a detailed description of any sign of toxicity or adverse drug reaction, which they might have experienced. The standard WHO formats for cohort event monitoring in the prescribed formats need to be maintained for every patient. RNTCP will ensure that strict aDSM is implemented by all NDR-TBC and district physicians for ambulatory patients. Figure 10.1 on ADR management and data capturing format related to Pharmacovigilance is shown below.
The treating physician at N/DDR-TBC and medical practitioners at periphery will observe patients for any adverse events (spontaneous reporting by patient and active screening) and manage as per laid down criteria in document. The SAE will be reported to ADR monitoring centre (AMC) and CTD within 24 hours. Cohort Event Monitoring (CEM) will follow the patient pathway from registration to treatment outcome. Patient details will be captured as baseline (before starting treatment) and will get updated at regular monthly intervals till completion of treatment. The primary responsibility of filling up above forms will be with the treating physician. The Nodal officer will be responsible for data entry in Nikshay with help of SA at NDR-TBC and DR-TB supervisor at DDR-TBC centre. Concerned DTO should make necessary arrangements for data entry in absence of abovementioned support staff.

Once relevant forms CEM are filled in Nikshay, information is directly communicated to PvPI through Vigiflow connecting bridge for signal generation. The centers need to ensure reporting of SAE within 24 hours to the Central TB Division using Nikshay followed by email to ddgtb@rntcp.org. Records need to be maintained in hard copies at respective centers.

The ADR data submitted to Vigiflow will be analyzed by PvPI and shared with CTD on regular basis. The data with action required on immediate basis will be shared with CTD by PvPI.

Safety assessment measure is the proportion of patients experiencing a Grade 3 or greater adverse event, as defined by DAIDS (Division of AIDS) criteria during treatment and follow-up. [37]
Chapter 11: Treatment support

Tuberculosis, including the drug-resistant forms are completely curable with early detection and complete treatment. However, even the "short course" chemotherapy for drug sensitive TB might not be perceived as really short by the patient. Treatment of DR-TB, poses a greater challenge due to its longer course. It is observed that approximately 50% of DR-TB patients do not complete treatment, often due to loss to follow-up or death.

Early detection of drug resistance through rapid diagnostics and early initiation of treatment favours good prognosis. Adverse drug reactions, comorbidities, social neglect and catastrophic expenditures are major deterrents to successful treatment completion and relapse-free cure. A patient-centric approach ensuring adequate medical, social, psychological and nutritional support is essential for good quality of life. These supports are to be built into a well-tailored treatment support programme customized for each DR-TB patient. [13] [3]

Treatment support is the compendium of services provided to the patient enabling them to successfully complete the treatment. These services include therapeutic, emotional, social and financial support.

11.1 Principles of treatment support

The principles of treatment support entail minimizing patient travel, delay in treatment initiation and follow-up, catastrophic expenditure and infection in transit. It also includes maximizing patient satisfaction, adherence to treatment and transparency in operations.

Treatment support is not applied to all patients at all times in a uniform fashion. Some patients may not need additional support other than diagnosis and treatment TB including DR-TB. Some may need total support including social, nutritional, financial and residential support and special support for management of substance abuse, comorbidity etc., Even though the patient is in need of support, s/he may not request for it since s/he may not be aware that such support could be availed through the healthcare team. Hence the need for support should be assessed and process of providing support initiated by the health system. However, health system may not be equipped to provide all forms of support with its own resources. In such situations, health system personnel should be able to link the patient to appropriate sources of support. There are successful examples in many states for such coordination that resulted in preventing unfavourable outcomes.
11.2 Patient-friendly approach

All staff in the DR-TB service delivery institutions and field should be considerate and behave humanely to patients suffering from DR-TB. They need to be trained and monitored for the same. Some of them may have concerns about working close to a DR-TB patient and getting infected with DR-TB; these need to be addressed in their training. All patients must be provided with a feedback form with rating scales for staff behaviour, health facility cleanliness and details of costs incurred. This feedback should be collected on a monthly basis and monitored at the district level. Initially these may be done on a paper-based system which will eventually be migrated into an ICT-based system. Once migrated to ICT-based evaluation, it could get linked to the annual performance report of health staff for further assessment.

11.3 Diagnosis and treatment initiation

Presumptive DR-TB patients are identified at the PHI/ private health facility and counselled by the MO-PHI/ treating physician regarding their status as presumptive DR-TB and subsequent course of action. Patients then need to present themselves to a DMC for specimen collection and transport to the relevant laboratory for DST. Some of the patients may need support to travel to the specimen collection centre. The MO/treating physician will ensure they receive the eligible financial support from the programme provision.

The lab technician should communicate the result of DST to the MO-PHI/ treating physician, patient and DR-TBC at the earliest possible time. In case the result indicates drug resistance, the patient will be asked to visit the nearest DR-TBC. In the DR-TBC, the PTE and any inpatient care should be completely free of cost. In case the service is chargeable, the same needs to be reimbursed to the patient. The DR-TB Counsellor/equivalent at the DR-TBC is the nodal person for ensuring that appropriate services are provided to the patients.

If the patient has not reached the DR-TBC within a week of the result being announced, tracking action will have to be initiated by the DR-TB Counsellor in coordination with the District DR-TB Coordinator, STS and MO-PHI. For this purpose, the DR-TB Counsellor should have an electronic directory of field staff, who will assist in tracking. Patients referred for treatment initiation or further management to DR-TBC, should be advised to report to the DR-TB Counsellor. The patient should be provided with contact details of the necessary staff at the DR-TBC. Once the patient reports to the DR-TB Counsellor, s/he should counsel the patient about DR-TB drugs and treatment regimen, adverse drug reactions, follow-up and access to services.

In the DR-TBC, all patients needing in-patient care should be admitted under a committee member designated as nodal clinician responsible for DR-TB management. Patients who do not need in-patient care will be attended to by the nodal clinician who will coordinate
consultations and referral to other members of the committee or other clinical care. In case, services needed are not available under the same institution, the DR-TB counsellor should coordinate the same under the guidance of the nodal clinician. To minimize delays in pretreatment clinical evaluation, individual clinical specialists may evaluate the patient separately and convey their findings or comments in writing in the Treatment book. The nodal clinician, after considering the remarks or recommendations of members, will initiate treatment on the appropriate regimen. In no case, should the patient be kept waiting for beds, consultation with specialists and enablers.

11.4 Domiciliary, ambulatory and inpatient care

Patients on ambulatory care and those stabilized after inpatient care will be referred to the concerned PHI through a filled PMDT-referral for treatment form. The patient will carry his/her copy of the Treatment book. The DR-TB counsellor should counsel the patient on the various drugs that have been initiated and their adverse effects. Patients should be provided with a list of adverse drug reactions along with necessary actions to be taken. The Counsellor should train the patient about the possible adverse event. The DR-TB counsellor should also intimate the referral and relevant details of treatment in advance to the MO-PHI or treating clinician to arrange for drugs and necessary support.

All patients may not need inpatient care. However, patients such as those who are seriously ill, those to be initiated on newer drug regimens, patients who need management of drug reactions and patients from distant geographical locations, will preferably be managed as inpatients. Facilities such as diet and stay for patient and one attendant, ancillary drugs and any other related procedures should be provided free of cost.

11.5 Treatment supervision

In view of the potential adverse reactions of second-line drugs, the MO-PHI should arrange for provision of daily treatment supervision by a trained treatment supporter. Treatment supervision may be provided based on the collective decision of the patient and the MO-PHI through any of the various options available, such as health care worker, community volunteer, private provider, family observation of treatment Electronic Pill Box (Annexure 14), ICT support etc.,

11.6 Follow-up of treatment

The DR-TB Counsellors, DR-TB-HIV Coordinators, DR-TBC SA should track pending follow-up cultures and consultations and the information update at various centres. They should coordinate among themselves to ensure that their records are currently valid. Timely alerts should be provided to health staff and patients for prompting follow-up testing and consultations through ICT when available. ICT should also support real time record updating
at various levels. The need for counselling would be reassessed and done on each visit of the patient to their health facility by the MO-PHI and or DR-TB Counsellor. The patient should be reviewed monthly by the MO-PHI for treatment response, adverse drug reaction and follow-up specimen collection. Also, details of the same should be recorded in the relevant sections of the treatment book.

At no point during the diagnosis, pretreatment, treatment and follow-up, should the patient incur any direct cost to avail any service. The patient may incur some indirect costs such as travel expenses and loss of wages while accessing services. These are expected to be at least partially supported through the financial enablers provided to the patient at various stages post notification. These financial enablers are expected to be provided to the patient by a Direct Beneficiary Transfer (DBT) system.

11.7 Patient support for comorbidities

Many patients undergoing treatment for DR-TB might also be diagnosed with additional ailments such as hypertension, diabetes, COPD. The MO-PHI should ensure that treatment services for these comorbidities are made available.

11.8 Social support at the community level

During ambulatory care the MO/treating physician and staff of the PHI should identify the need for various forms of social support such as travel, nutrition, de-addiction, social security schemes and link the patient to sources that provide these supports. Occasionally this support may have to be locally initiated and financed. Social interventions with stewardship of the community have been found to be effective in promoting treatment adherence.

11.9 Treatment support for detection and management of ADRs

Adverse drug reaction (ADR) is a major cause for fatality and loss to follow-up. Patients should be carefully watched to detect and manage ADRs at its onset. Nodal Clinician and DR-TB Counsellor should educate the patients on potential adverse reactions, their signs and symptoms, necessity of timely reporting and their recording in the ADR section of treatment book. The STS responsible for supervision of the patient at home should actively search for signs and symptoms of ADR on every visit. Additionally, they need to keep in touch with the patient over phone to actively enquire for ADRs. Patient should be encouraged to report even the mildest symptom and record them in the ADR diary. On self-reporting by the patient or on elicitation by health worker, the MO PHI/treating physician should clinically examine and investigate for the cause. Some of the ADRs like a drug induced gastritis or itching might be mild and managed at the PHI level. Moderate or severe forms of ADRs such as toxicities to liver, kidneys or nervous system, psychiatric
abnormalities may warrant stopping of drugs and referral to the DR-TBC immediately. The MO should fill a referral for the treatment form with detailed history of the ADR and refer the patient with advance intimation to the nodal clinician and DR-TB Counsellor. Based on the ADR management guidelines, modifications in the present regimen may be made at the DR-TBC. Once the patient is referred back, the MO PHI should ensure that the patient has understood the modifications and educate the treatment supporter for the same. DTO needs to review ADR management at PHIs during the district review. [35] [36]

11.10 Support for airborne infection control

Principles of good DR-TB management include early detection, appropriate treatment and practice of infection control measures. All TB patients should receive counselling on prevention of airborne infection at home and at work place. Patients should be provided with spittoon, disinfectant and reusable masks and educated on their use. During house visits, the peripheral health workers should observe patient practicing cough hygiene and reinforce AIC messages. [14]

11.11 Patient helpdesk

At all service provision levels there are possibilities where the patient needs may not be adequately addressed. Patients should provide such feedback in the form of a help request or query to the system through a help desk mechanism. These can be submitted to the DTO on paper or email or through a website or ICT when available. Once such feedback is received, the District TB officer should categorize it based on the level at which the feedback is related and whether it needs action or not. Even if it does not require action, the message should be responded to. If it needs further action, the DTO must assign a competent authority to address the request/grievance along with a suitable time to review it. All feedback should be registered to a central state-wide registry. If the request/grievance is not addressed at a particular level it will be escalated to the next higher level. At all critical points, the patient should be informed of the status of his/her submission and have the ability to confirm that the grievance has been addressed. The turnaround time of various types of grievances and successful resolution should be monitored and included as a part of the quality assessment of TB care in the country.
Chapter 12: RNTCP PMDT reporting and recording system

This chapter describes the information system for patients that fall under RNTCP PMDT. It also provides details on both paper-based as well as electronic reporting and recording system.

12.1 Aims of the information system

- to allow managers at different levels in RNTCP to follow overall programme performance through the distribution and trend in DR-TB notification; and the response to treatment in DR-TB patients treated with RNTCP regimen;
- to aid the staff in the treatment units in providing adequate management of the individual patient; and
- to enable real-time monitoring of the patients and real-time generation of reports.

There is the eNIKSHAY platform, which envisages that there will be different e-Health and m-Health solutions, that will ensure that the data is captured at the origin with web and mobile platforms for all levels. Data thus collected would then be analysed and shared with concerned all authorities in real time for actionable course correction.

12.2 Scope of the information system

The information system for RNCTP PMDT is based upon and is an extension of, the basic RNTCP information system. The forms are therefore made as similar as possible to the existing forms in RNTCP. This chapter defines the minimum instruments and variables of the information system, necessary to satisfactorily implement and monitor treatment with various RNTCP regimens for DR-TB. This information system does not include all the detailed information that the treatment units may need to manage the individual patient. This is contained in the clinical record and other special forms used in the wards or clinics and depends on the local requirements and practices.

12.3 Records, reports and flow of information

The following section describes the forms, registers and reports that will be used for RNTCP PMDT to enable proper recording of diagnosis, monitoring and care, in addition to the reporting of outcomes. [5] [32]

The overall flow of information for data management in PMDT with hard copies and NIKSHAY/e-NIKSHAY is depicted in Figure 12.1 below:
12.3.1 RNTCP Request Form for examination of biological specimen for TB (Annexure 15A)

All individuals who are presumptive TB or presumptive DR-TB are required to have a sputum or an appropriate EP specimen examination for diagnosis. The comprehensive Request form for examination of biological specimen for TB is to be used for requesting for microscopy, CBNAAT or culture DST or chest X-ray or TST or any other tests. It is essential to record patient details, reason for testing and type of tests requested. The front page of the form is for recording patient details, reason for testing (diagnosis or follow-up), test requested, result of sputum smear microscopy and NIKSHAY ID (expected in case of notified TB patient subjected for DR-TB screening). This form should be filled by the staff of the health facility that is sending the specimen with a request for examination and expected to be transported along with specimen to the concerned laboratory or health facility for the requested test. Back page is to report the results of CBNAAT, LPA, DST and any other tests requested.

For all specimens sent from peripheral health institutes, test requests should be initiated from the specimen collecting health facility and entered in NIKSHAY/e-NIKSHAY on the spot in real time. This will enable instant online intimation about the upcoming specimen at the
health facility (CBNAAT site or C-DST laboratory) where these tests are requested prior to receipt of the specimen while it is in transit. The result will be updated at the testing health facility in NIKSHAY/e-NIKSHAY on real time to save time required to scan results and send it to the concerned health facility. Final report of the test may be printed out through NIKSHAY at any health facility. Real time data entry helps the programme to disseminate information at all levels like N/DDR-TBC, District, TU and PHI to initiate reflex actions for further patient management on real time basis.

12.3.2 RNTCP laboratory register for culture, CBNAAT and drug susceptibility testing (Annexure 15L)

The RNTCP laboratory register for culture, CBNAAT and DST is used to record CBNAAT, LPA and culture and DST examination results. This will be maintained by the concerned laboratory staff. Results of all specimens tested at these sites are expected to be entered in NIKSHAY/ e-NIKSHAY. For all presumptive DR-TB patients, test results should be updated in existing NIKSHAY ID to maintain continuity while presumptive TB patients tested at these laboratories, NIKSHAY ID may be generated, after ensuring that it is not generated elsewhere. The individual should be notified if diagnosed with TB and NIKSHAY ID should be shared with along with the report. Results of subsequent tests carried out will be entered in the same ID. This gives an opportunity to easily extract the test results of all specimen provided by the patient and thereby track his/her response to the treatment. All the follow-up investigations carried out will be entered periodically using the same NIKSHAY ID.

12.3.3 RNTCP PMDT referral for treatment form (Annexure 15H)

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

Referral module in NIKSHAY facilitates access to patient information through NIKSHAY ID. Provision of shifting of patient from one district to another is possible if the patient has changed his/her residence permanently. In NIKSHAY, the referring health facility must update details under ‘request for transfer’ section to intimate receiving health facility about the transfer even before the patient reaches. In addition to information mentioned in ‘request for transfer’ section, the receiving health facility is able to access all other patient information as well. The accountability of transferred patient is now with the receiving health facility and the treatment initiating facility.
12.3.4 RNTCP PMDT treatment card (Annexure 15 E)

The RNTCP PMDT Treatment card is a key instrument for the treatment supporter administrating drugs daily to the patient. The card will be initiated at D/NDR-TBC when the patient is initiated on treatment either on outpatients or indoor basis. The original treatment card will be maintained at the respective DR-TBC and copy kept by the treatment supporter. The card should be updated daily, documenting the administration of drugs by the treatment supporter. The card is the source to update periodically the PMDT register and adherence details on NIKSHAY. Accountable systems have to be developed locally for updating cards at all levels. When or if the patient moves from DR-TBC to his/her district of residence a copy of the card, must follow the patient. Once the patient has switched to other regimen at NDR-TBC, a new set of treatment cards along with new treatment booklet should be prepared for the patient and the same shared with the field. A copy of this card may be used as a notification form and to inform final outcome of treatment.

Newer ICT solutions (MERM etc.,) to promote information management about the patient’s treatment adherence are being tested at field level for DR-TB patients. This will help in auto updation of treatment adherence details in NIKSHAY/e-NIKSHAY as well as flag patients with frequent treatment interruptions to prompt visits of health care providers and supervisors to intervene and retrieve the patient on treatment. If the patient is under the ICT monitoring system, treatment card in hard copy should be maintained at the treatment supporter level. A treatment supporter will be relieved from the regular updation of treatment card in NIKSHAY during such condition. The card contains the following sections:

**Page 1 of the treatment card:**

**Basic demographic information:** Name, sex, age, address, telephone number, state, DR-TBC, district, TU, PHI and details of the treatment supporter. Some part of this information will be auto populated from available information while other information can be added at district or N/DDR-TBC level which should be supplemented by treating PHI.

**PMDT TB number:** This is a new unique patient identification number given to the patient at the DR-TBC on initiation of treatment. The PMDT TB number should include S.No./Nodal or District/Name of DR-TBC code/year of initiation of treatment. E.g. PMDT TB number of first patient started on treatment at Nagpur DDR-TBC during 2017 will be 1/D-NGP/2017. Every year PMDT TB number will be started at 1. The Nodal DR TB center will maintain its PMDT number separately starting from 1st of every year. E.g. PMDT number of 1st patient initiated at Nodal DR-TB center belong to Nagpur District will be 1/N-NGP/2017. The district where the Nodal DR-TB center is located has to maintain separate District DR-TB PMDT register if center is also functioning as DDR-TBC. This would remain as a transitory system till the time most DR-TB patients are tracked with the help of NIKSHAY. This will be done till it is time to
completely transition from paper-based registers to autogeneration of electronic registers from NIKSHAY PMDT modules directly.

**NIKSHAY ID:** NIKSHAY ID refers to the unique ID which is generated at the time of testing for TB. As per RNTCP TOG, all TB patients are to be notified at the time of diagnosis. This information is recorded in the TB Notification register. Pool of all DR-TB patients (RR/MDR/H Mono/poly etc.,) diagnosed either at CBNAAT lab or C& DST labs or in private lab will be updated digitally. The NIKSHAY ID will capture all subsequent events that are taking place for diagnostic and treatment pathways. This creates a lifecycle approach where multiple events happen for a single patient pertaining to diagnosis and treatment pathways which are captured in a single NIKSHAY ID. All relevant information of a particular patient would be available with the same NIKSHAY ID which can be printed at all accessible users’ levels. Once the patient is initiated on treatment, details are captured in PMDT treatment register that is maintained at D/NDR-TBC and PMDT number is assigned. The NIKSHAY ID has a provision to capture more than one PMDT number generated at different D/NDR-TBC while patient transfer is done. This provides a log of patient information that helps in tracking all updates starting from DR-TB diagnosis to long-term treatment outcomes.

**Reason for testing:** This section lists and describes details of the reason for testing. This includes types of patient that have to be ticked as applicable for new, previously treated, presumptive TB, private referral, presumptive NTM, criteria for presumptive DR-TB, presumptive H mono/poly and criteria for presumptive XDR-TB.

**Drug susceptibility test (DST) results at diagnosis**

Detail DST information for each patient is captured with date of specimen collection. All DST results for CBNAAT, LPA and LC-DST are captured here once the result is received. SL LPA result is available as FQ and/or SLI class resistance. Resistance is captured as R against all drugs that belong to that group. Once LC-DST result is available, it is mentioned in lower section of DST preferably.

**HIV testing:** This section lists the date of testing, PID number, date of starting CPT and ART (wherever applicable). As per the national policy, information sharing on HIV status of patients should be restricted within health care facilities based on the concept of “shared confidentiality”. Hence, this information must not be written on the copy of the card held by the treatment supporter and patient booklet.

**Contact tracing:** This section details number of household contacts screened, number of presumptive TB patients identified, number of presumptive TB patients evaluated, number diagnosed with TB and number of DR-TB diagnosed. First contact screening should be carried out at the time of treatment initiation, however, this should be a continuous process during the course of treatment as any close contact may present with TB symptoms at any
point of time during the course of treatment for index patients. In pediatric DR-TB patients, reverse contact tracing to search for an adult index patient in the household must be considered by health care workers.

Page 2 of the treatment card:

_Treatment regimen_: The RNTCP regimen for MDR/RR-TB, XDR-TB, H mono/poly resistant TB, modified regimen for MDR/RR + FQ/SLI resistant, modified regimen for mixed pattern resistant and regimen containing newer drugs are recorded in this section.

_Drugs and dosages_: This section details drugs and dosages used including status of eligibility and consent for regimen containing newer drug. In NIKSHAY/e-NIKSHAY, default value of drugs and doses based on treatment regimen and weight will be auto populated. However, modification in doses and drug included in regimen may be possible if required.

_DR-TB centre Committee meetings_: There should be periodic meetings of the DR-TBC committee, with caregivers involved with DR-TB patients, in which the progress of the individual patient is reviewed. This section provides space to record major changes by the committee, like extension of IP; change of IP to CP; completion of treatment; severe adverse reactions; change of treatment, declaring treatment outcome etc., Date of decision taken is an important parameter which needs to be captured in this section. Some decisions may be taken at peripheral level in consultation with DR-TBC like discontinuation of medicine due to serious ADR.

Page 3 of the treatment card:

_Monitoring of culture/other investigations_: Record the date, specimen number and result of the monitoring culture examinations and other investigations like Serum Creatinine, LFT, ECG/QTC interval, Electrolyte (K, Mg, Ca) and UPT. The culture date is the date on which the sputum was collected from the patient for these tests. Follow-up investigation carried are also captured in the relevant month of follow-up.

_Blood sugar_: This section details date of testing of Random Blood Sugar (RBS), Fasting Blood Sugar (FBS) and Date of starting treatment of diabetes (wherever applicable).

_Thyroid function test_: This section details date and level of testing of T3, T4 and TSH.

_CXR_: Details of the report of Chest X rays performed should be entered in relevant section.

Page 4 of the treatment card:

_Patient detail_: This details name of patient, initial weight and height, date of starting intensive phase, date of stopping Bdq and date of starting continuation phase.
**Detail of change**: This portion details date of change of regimen and reason for change.

**DST**: Record the date, type of culture test used and results of all DST performed on the treatment card. Enter ‘R’ for resistant and ‘S’ for sensitive under drugs for which DST has been performed at the RNTCP-certified laboratory. Drugs which have not been tested will remain blank.

**Page 5 and 6 of the treatment card**:

**Record of administration of drugs**: One line per month which makes it easy to assess adherence. One box is checked for each day the treatment is administered. Regimen is going to modify based on SL-LPA and LC-DST results. A down arrow is placed in the cell of regimen modification date to indicate day when regimen modification was done. Details information regarding drug modification is written in the place where DR-TB committee decision is captured. Any modification made should be indicated in patient adherence record as well. The CP should be documented on new line.

**Page 7 of the treatment card**:

**Date and details of retrieval action**: These should be taken and recorded in relevant section.

**Date and details of adverse drug reactions**: These actions should be taken and recorded in the relevant section.

**Patient follow up visit details**: All DR-TB patients need to be counselled about monthly clinical follow up with doctor and finding of this visit along with date should be documented in this

**Outcome of treatment**: At the end of treatment, the outcome should be recorded on the treatment card. The outcome definitions are given in Chapter 10.

**Post treatment follow-up clinical & sputum**: This section detail 6, 12, 18 and 24 post treatment follow up months of clinical, sputum and chest X-ray follow-up of the patients.

12.3.5 TB Notification register (Annexure 15I)

A TB notification register is maintained at each peripheral health facility. This register contains records of all patients diagnosed with TB and eligible for TB treatment, regardless of initiation of treatment. Registration data is based on date on which a TB patient is diagnosed. All newly diagnosed TB patients and newly diagnosed DR-TB patients need to be notified in TB notification register at all diagnosing health facilities. All newly diagnosed DR-TB patients should be considered as new episode and patient details should be entered in
new row in TB notification register with the same NIKSHAY ID. Majority of DR-TB diagnostic labs (CBNAAT and C& DST) are located at health facility (PHI) where TB notification register is already maintained. Same TB notification register needs to be used to notify diagnosed DR-TB patients unless there is need of separate TB notification register at DR-TB diagnosing health facility. If NIKSHAY ID is available, where the patient is already notified to the programme at the time of TB diagnosis, same ID will be used to notify it for DR-TB diagnosis. If presumptive TB patient diagnosed as DR-TB patient and NIKSHAY ID was not generated any time in the past, a diagnostic health facility will notify this patient and generate NIKSHAY ID.

Once the patient is notified in TB notification register (hard copy) for DR-TB episode, status of treatment must be updated against that episode. Treatment outcome of previous episode should be updated in TB notification register and in NIKSHAY at the concerned health facility. For every patient, the status of treatment should be recorded and this could be any one of the following:

- initiated on first-line treatment in the same health facility;
- initiated on treatment outside the health facility;
- initiated on second-line treatment;
- treatment initiated outside RNTCP;
- incomplete/ incorrect address;
- died;
- migrated & untraceable;
- refusal for treatment;
- repeat diagnosis;
- patient already on treatment/ follow-up patient;
- wrong diagnosis;
- referred for treatment with pending feedback; and
- other

In each health facility, TB notification register is maintained by its staff. STS of the respective TB units will support updating and coordination for completing the information.

Once, the patient is initiated on DR-TB treatment, the patient will be entered in RNTCP-PMDT treatment register maintained at the DDR-TBC. TB notification register kept at the peripheral health facility where DR-TB patient is residing does not need to be updated as treatment and follow-up schedule for DR-TB patient is not the purview of TB notification register. However, if needed, PHI may keep a separate RNTCP- PMDT register for the same purpose. Information about DR-TB patients notified from private sector and RNTCP diagnostic labs can be extracted from NIKSHAY.
12.3.6 RNTCP PMDT treatment register (Annexure 15J)

This register is maintained at NDR-TBC and DDR-TBC. Districts where DDR-TBC is away from DTC or have more than one DDR-TBCs, additional register should be maintained at DTC. While TB notification register captures the details about the notified TB patients, the RNTCP PMDT TB register is restricted to patients who have actually started on a second-line TB treatment regimen. Patients should be entered consecutively by their date of treatment initiation. The following is recorded in the PMDT treatment register:

**LEFT side of page:**

**PMDT TB No:** This is a unique identification number for patients initiated on DR-TB treatment and has been described earlier. Every year the PMDT TB number will be started from 1. DR-TB patients transferred in from the other DR-TBC will also find the place in this register with new PMDT number of receiving district.

**Other personal details:** Name, sex, age, address, RNTCP district and TU of residence and name of PHI providing treatment support.

**Reason for testing:** This includes various types of patients that are coded as applicable for various reasons for testing the patient. Only codes to be used as mentioned below the page.

**Site of disease:** Whether pulmonary or EP is mentioned in this column.

**Type:** Type of TB patient whether new, recurrent, Treatment after Lost to Follow-up (TALFU), Failure or Others is mentioned in this column.

**DST details:** Type of test (L J / LC / LPA/ CBNAAT), date of DST and results of DST for various drugs are mentioned in this section. The drug whose DST is not done is kept blank. Extra column is added here for recording name of drug for which DST result might be available in the future within the programme.

**RIGHT PAGE**

**Type of DR-TB patient:** Type of patient, whether H mono-/poly DR-TB,RR-TB, MDR-TB or XDR-TB is mentioned here

**Type of DR-TB regimen:** Type of regimen prescribed for patients as per code mentioned below the page is recorded in this column.

**Microscopy examination, culture & DST results during follow-ups:** Culture result with date during initiation (0 month) and subsequent follow-up culture results are mentioned in this
section without any delay under the specific month of follow-up until the end of treatment. ‘Pos’ for positive and ‘Neg’ for negative result is mentioned.

**TB-HIV collaborative activities:** Date of testing the DR-TB patient, PID no, HIV status (‘Pos’ for positive and ‘Neg’ for negative result) and date of initiation of CPT and ART (wherever applicable) is recorded in this section.

**Final treatment outcome:** The final treatment outcome as described earlier is mentioned in this column. There will be only one outcome for each patient.

**Remarks:** This column is reserved for any additional information that may be need to be given in the register.

### 12.3.7 TB Laboratory Register (Annexure 15K)

This register need to be maintained at microscopy center. All the specimens examined for diagnosis or follow up on microscopy should be entered in the register. It is essential to capture patient information such as contact details and reason for testing, which will aid in approaching the patient subsequently. If any TB patient is eligible for the further DRT/DST, detail of specimen collection and result needs to be updated in respective column of this register. These details are to be captured in TB notification register as well. In case the specimen is send for DST from the other health facility, date of specimen sent and name of health facility sending the specimen is be updated here.

### 12.3.8 RNTCP Laboratory Register for culture, CBNAAT and drug susceptibility testing (Annexure 15L)

All the labs doing DST/DRT/Culture either by genotypic (CBNAAT/ FL-LPA/ SL-LPA) or phenotypic (Solid/ liquid Culture) technology need to maintain this register. All specimens tested by any method need to be entered in this register. This register is used to capture details of specimen tested for diagnosis as well as follow up.

### 12.3.9 RNTCP PMDT treatment book (Annexure 15M)

RNTCP PMDT Treatment Book is the document that must be always available with the patient. When a patient is diagnosed as having DR-TB and is placed on a regimen for DR-TB, RNTCP PMDT patient Treatment book should be filled out by the health care provider at the same time when the PMDT treatment card is filled out at the time of initiation of treatment. This Treatment book will be kept by the patient and should be brought whenever s/he comes to DR-TBC or DTC or PHI for clinical follow-up or for ADR management. The Treatment book contains the following section:
- name, sex, age, complete address, marital status, contact number and Aadhar ID of the patient;
- name & designation and contact number of Treatment supporter;
- name of TB Unit, PHI, DR-TBC, District and State;
- information about Initial home visit, by whom it has been done and on what date;
- information about NIKSHAY ID and PMDT TB numbers;
- essential information about Reason for Testing, which are as follows:
  - whether new or previously treated patient;
  - whether presumptive TB, private referral or presumptive NTM;
  - whether presumptive DR-TB at diagnosis or due to contact of DR-TB patients or follow-up smear positive at end of IP or it is a private referral;
  - whether presumptive H mono/poly resistant TB; and
  - whether presumptive XDR-TB patient due to MDR/RR-TB at diagnosis or four months culture positive or culture reversion or failure of MDR/RR-TB regimen or recurrent patient of second-line treatment.
- information about DST results for different anti-TB drugs;
- information about contact investigation (number of members screened, out of it number of presumptive TB identified, out of which number of presumptive TB patients evaluated, and out of which number of TB patients & DR-TB patient diagnosed);
- information about DR-TB Committee meetings with dates and decisions;
- information about TB site (whether pulmonary or extra-pulmonary) and the different types of treatment regimen under which patient has been provided the treatment, with date of initiation of treatment and date of registration;
- information about weight (in kg) and height (in cms) of the patient;
- information about different weight-bands for DR-TB regimen;
- information about different types of anti-TB drugs prescribed to patients and its dosages;
- information about eligibility and consent of patient if a new drug has been prescribed;
- information about culture results and other investigations (serum creatinine, liver function tests, ECG, complete blood count, serum electrolytes, urine test for pregnancy) done at different interval of continuation of treatment till the end of treatment;
- information about DST results for different first and second-line anti-TB drugs done in different months [with date of specimen collection & type of DST (LJ/LC/LPA/CBNAAT);]
- information about blood sugar testing (random blood sugar and fasting blood sugar) with date and initiation of anti-diabetic treatment;
- information about thyroid function test done at initiation of treatment and at end of six months of treatment;
- information about X-ray test done at different interval;
- information about dates of starting intensive and continuation phase;
• information about change of regimen and reason for the same;
• information about monthly administration of drugs with weight of patient for full duration of treatment;
• information about retrieval action taken for a patient who has missed his doses;
• information in detail about any adverse drug reaction taken place and action taken for its remedy;
• clinical notes made by physicians during visit by DR-TB patient for any complaint, which includes the following:
  - date of visit;
  - chief complaints made by the patient;
  - major findings of clinical examination;
  - different types of investigations done;
  - what treatment provided; and
  - counselling notes.
• Information about treatment outcome of the patient with date; and
• Information about post-treatment follow-up clinical & sputum examination (result with date) done at interval of 6, 12, 18 and 24 months after end of treatment.

12.3.10 Patient counselling register (Annexure 15N)

DR-TB counsellor is supposed to update and maintain this register on a regular basis. Counselling session carried out with the patient and family members at the time of pretreatment evaluation to long-term follow-up are expected to be captured in this register. Priority should be given for counselling of the DR-TB patient, however, counselling services utilized for the DS-TB patient also needs to be captured in the same register.

12.3.11 Additional records and reports for Bedaquiline

In addition to the above, the following two new forms would be introduced for patients treated with BDQ containing regimen:

**Patient education booklet for BDQ-containing regimen**

A detailed patient education booklet has been developed for educating the patient on the use of BDQ (Annexure 9). The patient education booklet must be provided to the patient that contains the list of drugs contraindicated or to be used with caution with BDQ along with the PMDT treatment book. The patient must be motivated to carry these documents at every visit to any health care provider throughout the treatment course.
Cohort event monitoring form

The standard formats for cohort event monitoring (Annexure 12A, 12B) would be used at all the sites for aDSM. Patient initiated on any DR-TB regimen must be covered under cohort event monitoring mechanism from the time of initiation of treatment. Treatment initiation form should be filled at the time of initiation of treatment for any SAE reported during the course of treatment. The review form of CEM is filled by health facility managing SAE. Any SAE needs to be promptly reported by the concerned health facility to RNTCP using the standard form on a real-time case-to-case basis in NIKSHAY.

Hard copies of the CEM forms need to be maintained at the respective health facility. If the patient’s treatment regimen is changed due to any reason, irrespective of duration of treatment, a new CEM - treatment initiation form is filled by the treatment initiating health facility for the new class of regimen the patient is initiated on. The process of data entry and analysis for aDSM and event-based ADR reporting using NIKHSAY and Vigiflow has been described in detail in the Chapter on Adverse Drug Reaction & Monitoring.

12.4 Periodic reporting

There would be no periodic reporting based on paper or excel. This can be prepared as an output of the NIKSHAY/e-NIKSHAY module of PMDT, i.e., laboratory form, treatment card and patient booklet. This can only be possible, if real time entries are made by all labs, DDR-TBC/ NDR-TBC as well as field staff. The dash board will give the process and output indicators as required. However, if states do not ensure real time data entry on NIKSHAY Lab and PMDT module, there remains a threat that incomplete and incorrect data entries may not reflect the real performance of the districts and states in PMDT. For the patient diagnosed from 01 January 2017, all laboratories and DR-TBC are expected to enter the updated RNTCP form for examination of biological specimen for TB and PMDT treatment on real time basis in NIKSHAY for all level of monitoring. However, for historical cohorts, this would be for only six months/12 months. Treatment outcome reports would be prepared for those quarters for which case finding was given till Q4, 2016.

12.5 Computerized systems

All information will be available in both paper and electronic versions. To facilitate better quality of information as well as data analysis, NIKSHAY for real time monitoring of DR-TB patients through Dashboards and monitoring indicators will be used. States are expected to monitor all relevant indicators of diagnosis and treatment initiation cohort. All relevant users will be able to monitor auto calculated monitoring indicator from Nikshay and gradually the whole MIS system will migrate to e-NIKSHAY over a period of time.
12.6 Training in data management

The information system requires knowledge of the RNTCP basic information system, with additional training on the specifics of the RNTCP PMDT MIS. Regular supervisory visits by the central team to the PMDT treatment centres using the information system, are fundamental to maintaining good quality of information. The digital DR-TB register generated by NIKSHAY consists of all DR-TB patients diagnosed by any laboratory including the private sector laboratory available within the district. The status of DR-TB treatment initiation similar to the TB notification register is updated by the district for each DR-TB patient diagnosed within the district. Once the patient is initiated on treatment, all follow-up investigation details must be uploaded by C-DST laboratory while treatment adherence details must be updated by PHI, TU or district in coordination with the respective DR-TBC and C-DST lab.

12.7 Cohort analysis

Patient diagnosed with any type of drug-resistance irrespective of diagnostic technology in specified period is considered in the DR-TB diagnostic cohort for that period. This pool of patients includes DR-TB patients diagnosed and notified from the private sector located in the catering area of the health facility. Reasons for not initiating patients on any treatment regimen need to be updated in NIKSHAY by the concerned health facility where the patient is residing.

Similarly, all patients identified with DR-TB and to be treated with a regimen for DR-TB, should be entered into the RNTCP PMDT register maintained at the DDR-TBC / NDR-TBC. A DR-TB treatment cohort is defined as a group of patients registered for treatment during a specified time period (e.g., one quarter of the year). The date of registration for regimen for DR-TB determines what case finding cohort the patient belongs to. However, since it would take around 2-3 months for most DR-TB patients to be either continued on standard regimen or reclassified to a DST guided regimen with/without newer drugs based on SL-LPA and LC-DST detailed earlier, for analytical purposes, the cohort definition would be done three months after the last day of the quarter for the case finding report. For example, for Q1 (Jan – March), the cohort definition will be done in the 1st week of July to enable accounting of patients in the respective standard or DST guided regimen with/without newer drugs only once and avoid double counting of DR-TB patients in the same quarter due to change in regimen. This will enable monitoring of interim and final outcomes of patients stratified by the specific regimen that the patient was eventually put on.

The cohort analysis would be done electronically as outputs from NIKSHAY which has a feature to maintain a log of all changes made in treatment. For example, based on the CBNAAT result, if the patient is initiated on a shorter regimen and is found to be FQ resistant on SL-LPA, s/he switches over to newer drugs containing regimen and is accounted in a system as a patient on newer drug containing regimen along with cohort. However, the
shorter regimen treatment related detail is still available in NIKSHAY for future reference. Reports for specific periods or cohorts could be generated online through NIKSHAY. Further, auto-generated indicators and interactive maps would be made available to facilitate supervision, monitoring and evaluation at all levels.

Cohort analysis should be performed on all registered DR-TB patients, using the date of DR-TB registration to define the cohort. Cohort analysis of treatment outcomes should also be performed on all patients who receive DR-TB treatment, regardless of treatment duration. The recommended time-frame for DR-TB treatment cohort analyses reflects the long duration of DR-TB treatment regimens. Final analysis should be performed 36 months after the last patient enrolment date in the cohort.

Patients still on treatment at the end of a designated cohort treatment period must be explicitly identified as such irrespective of whether they were culture-positive or negative at the time of cohort analysis. This is an interim status until a final outcome is available. The interim status must be assessed at six months and 12 months of treatment to monitor patient progress.
Chapter 13: Supervision, monitoring and evaluation on PMDT

In this chapter, participants will learn about guidelines for supervision, monitoring and evaluation systems that need to be rationalized in all states and districts to ensure quality of care of DR-TB patients enrolled under the programme. An effort has been made by the programme to standardize these mechanisms along with requisite tools to do so which have been shared in this section.

RNTCP has a robust recording and reporting system in place along with multiple internal/external checks to ensure good quality data generation which forms the basis for existing RNTCP supervision and monitoring strategy.

However, in view of the expansion in programe activities the strategy needs to be more comprehensive with transition from target-focused monitoring of performance to analysis of key process and outcome indicators. Establishing a reliable monitoring and evaluation system with regular communication between the central and peripheral levels of the health system is vital. This requires standardized recording of individual patient data, including information on treatment outcomes, which are then used to monitor indicators.

The strong supervision, monitoring and evaluation ensure that activities are implemented as planned and that the data recorded and reported is accurate and valid; incorporating a system which leads to remedial action to improve performance; serving as a tool to facilitate commitment of higher authorities at different levels, ensuring equitable provision of services to all sections of the community, including vulnerable areas and populations such as urban slums, scheduled caste/tribal/minority pockets etc.; and above all, bringing transparency and accountability.

13.1 Organization of SME for PMDT

The SME will be driven by NIKSHAY/e-NIKSHAY with user-based/institute-based logins, user-based task lists and reminders, escalation matrix enabling prioritization, ICT-based adherence support, including ICT-based adherence monitoring systems like MERM boxes and other modalities. A more comprehensive SME plan is required for use at the state, district, sub-district and field levels. Various registers and reports on PMDT related services will be extracted from NIKSHAY/ e-NIKSHAY. Adherence score of individual patients based on an automated ICT enabled system like the pill box (MERM) or that which is manually updated, will be auto calculated and various relevant escalations generated for different users like NDR-TBC, DDR-TBC, C-DST Labs, CBNAAT labs, District and TU level. The organization of SME activities and the requisite tools are classified in the table below:
Table 13.1: Organization of SME in PMDT

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervision</td>
<td>• Supervisory checklists for various levels (CBNAAT, C&amp;DST labs, N/DDR-TBC, District, TU, DMC, and patient)</td>
</tr>
<tr>
<td>Monitoring</td>
<td>• PMDT outputs and dashboards from NIKSHAY / e-NIKSHAY</td>
</tr>
<tr>
<td></td>
<td>• Monitoring indicators on lab services &amp; PMDT implementation</td>
</tr>
<tr>
<td>Evaluation</td>
<td>• IE formats to include section for implementing states/ districts with access *</td>
</tr>
<tr>
<td></td>
<td>Progress on scale-up plan, visits to D/NDR-TBC, CBNAAT Lab, C-DST Lab, DDS, SDS, patients’ interview etc.,</td>
</tr>
</tbody>
</table>

13.2 Supervision of PMDT services

RNTCP has a robust built in system for supervision. PMDT supervision will be an extension of this system. Similarly, the built in M&E system of RNTCP will be customized according to the levels of implementation and scale-up plans. Further, to guide field level staff to prioritize their activities, there are supportive systems developed under NIKSHAY/ e-NIKSHAY. Use of this supportive mechanism could improve their capacity and quality of services. It is very important to remember that supervision promotes successful implementation of programme policies and processes and M&E ensures that implementation progresses in the right direction to achieve desired targets, objectives and goals.

Objectives of supervision

- build capacity of health staff to implement PMDT procedures correctly;
- ensure that the data recorded and reported is accurate and valid;
- incorporate a system of analysis and review aimed at improving quality of programme implementation;
- increase involvement and commitment of staff at different levels;
- ensure field staff respond to NIKSHAY/ e-NIKSHAY tasks, lists activities and updates missing information promptly;
- provide actionable and timely feedback;
- evaluate impact of training on performance of health staff;
- assess retraining needs; and
- assess stocks and replenishment of supplies.

Preparation for supervisory visit

Since PMDT is not a standalone activity within RNTCP, all functionaries responsible for implementation of RNTCP are bound to supervise and in turn, be supervised in PMDT. A
checklist of activities to be supervised in a centre proposed to be visited is to be prepared in advance. Priority actionable points should be identified from NIKSHAY/ e-NIKSHAY (refer to PMDT supervisory checklists for various levels). Actions taken and pending from the previous supervisory visit must be reviewed during every visit. Review of previous reports is useful for identifying priority areas to be focused during supervision. Existing documents like RNTCP Supervisory registers placed at all health institutions may be used for recording observations on DS-TB as well as DR-TB.

During field visits by State-level supervisors to districts implementing PMDT, a selection of patients on various regimen for DR-TB and their Treatment supporters are to be interviewed. In addition, processes involved in the recording and reporting; drugs and logistics and supply chain management, tracking of transportation of sputum specimens to CBNAAT and C-DST laboratory, status of data update on NIKSHAY/ e-NIKSHAY, referral of diagnosed DR-TB patients to D/NDR-TBC etc., have to be examined in detail.

Modalities of supervision

Though supervision of PMDT must, ideally, be linked to supervision of DS-TB, additional supervisory checkpoints pertaining to PMDT are discussed below. Recommended modalities for supervision by different levels of supervisory staff are presented in Table 13.2. All other RNTCP staff are to follow their terms of reference (ToR) ensuring that diagnosis and care of presumptive DR-TB and patients is taken care of on priority basis. Extensive checklists and monitoring tools have been developed for use by all supervisory staffs and must be put to use. Moreover, all visits to the district and subdistrict levels by district and State level officials have to, mandatorily include supervision of PMDT activity. All Central and State level appraisals have to review PMDT activities using standard PMDT supervisory checklists.

Table 13.2: Recommended modalities for supervision by different level of supervisors

<table>
<thead>
<tr>
<th>Supervisor</th>
<th>Methodology</th>
<th>Frequency</th>
</tr>
</thead>
</table>
| DTO        | • Conduct interview with health staff and RNTCP key staff involved in PMDT;  
            • Interact with community and local opinion leaders and mobilize their support to help DR-TB patients with diagnosis/treatment;  
            • Randomly interview patients on treatment, their Treatment supporter, family members and community leaders;  
            • Inspect records of DTC, TU, DMCs, PHI and Treatment centre, NIKSHAY entries and stock of drugs;  
            • Check status of card updating and ensure original card at DR-TBC is updated at least once a month with digitalization of adherence data in NIKSHAY manually or by ICT supported mechanism;  | • Visit all TUs every month and all DMCs every quarter;  
            • Visit all CHCs and Block PHCs in the district every quarter, one sub-centre from each Block PHC and proportion of treatment observation centres every quarter;  
            • Conduct supervisory visit at least 3-5 days a week; and |
- Ensure prompt identification of presumptive DR-TB and transport of sputum specimens to lab as per guidelines maintaining cool chain;
- Physically verify stock of PWBs at District, TU and PHI stores;
- Ensure uninterrupted supply of medicines; and
- Liaise with State TB Cell, DR-TBC and designated C-DSTlab

<table>
<thead>
<tr>
<th>MO –DTC</th>
<th>MO–TC</th>
<th>Senior DR-TB TB-HIV Supervisor (this section deals only with PMDT responsibilities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Conduct interview with health staff and RNTCP key staff involved in PMDT;</td>
<td>• Interview MO I/C Block PHC/CHC/PHC/private/NGO hospitals regarding implementation of PMDT activities;</td>
<td>• Assist DTO in organizing direct observation of treatment for DR-TB patients and DR-TB drug logistics management;</td>
</tr>
<tr>
<td>• Interact with community and local opinion leaders and mobilize their support to help DR-TB patients with diagnosis/treatment;</td>
<td>• Randomly interview patients, their Treatment supporter, family members and community leaders;</td>
<td>• Facilitate MOs, STSs, STLss, LTs and other health system staff to subject all Presumptive DR-TB to appropriate diagnostic tests for diagnosis of DR-TB at an RNTCP-certified laboratory;</td>
</tr>
<tr>
<td>• Randomly interview patients on treatment, their Treatment supporter, family members and community leaders;</td>
<td>• Interact with community and local opinion leaders and mobilize their support to help DR-TB patients with diagnosis/treatment;</td>
<td>• Identification and training of Treatment supporters for DR-TB patients and maintenance of a directory of such Treatment supporters at TU and district levels;</td>
</tr>
<tr>
<td>• Inspect records of DTC, TU, DMCs, PHI and Treatment centre, NIKSHAY entries and stock of drugs; and</td>
<td>• Inspect records of TU, DMCs, PHI and Treatment centre, NIKSHAY entries and stock of drugs;</td>
<td>• Maintain district level PMDT records and reports;</td>
</tr>
<tr>
<td>• Check status of card updating at District, TU, PHI and Treatment supporter.</td>
<td>• Check status of updating treatment card, booklet and NIKSHAY / e-NIKSHAY entries; and</td>
<td>• Ensure that records and NIKSHAY entries of all DR-TB patients in the district are updated regularly;</td>
</tr>
<tr>
<td>• Visit at least three patients at their homes per visit including one DR-TB patient on treatment.</td>
<td>• Ensure drug availability for all DR-TB patients during treatment course.</td>
<td>• Visit at least three patients at their homes per visit including one DR-TB patient on treatment.</td>
</tr>
<tr>
<td>• Visit all TUs every month and all DMCs every quarter;</td>
<td>• Visit all DMCs every month;</td>
<td>• Visit all TUs every month and all DMCs every quarter.</td>
</tr>
<tr>
<td>• Visit all CHCs and Block PHCs in the district every quarter, one sub-centre from each Block PHC area and proportion of treatment observation centres every quarter;</td>
<td>• Visit all CHCs/ BPHCs/ PHCs and a proportion of treatment observation centres at least once every quarter;</td>
<td>• Visit all treatment observation centres in the district once in every quarter;</td>
</tr>
<tr>
<td>• Conduct supervisory visit at least 3-5 days a week; and</td>
<td>• Conduct supervisory visits 7 days a month; and</td>
<td>• Visit all treatment observation centres in the district once in every quarter;</td>
</tr>
<tr>
<td>• Visit at least 3 patients at their homes per visit, including one DR-TB patient on treatment.</td>
<td>• Visit at least 3 patients at their homes per visit, including one DR-TB patient on treatment.</td>
<td>• Ensure prompt identification of presumptive DR-TB and transport of sputum specimens to lab as per guidelines maintaining cool chain;</td>
</tr>
</tbody>
</table>
- Supervise all PMDT treatment observation centres once a quarter;
- Coordinate with field staff to ensure drug availability for all DR-TB patients receiving various regimen;
- Update treatment cards and NIKSHAY entries at DDR-TBC;
- Assist DTO in providing training to staff of health facilities under his/ her jurisdiction to carry out PMDT related activities; and
- Establish liaison with private practitioners, NGOs and other sector dispensaries/ hospitals to provide PMDT services as per programme guidelines.

### STS

- Interview MPHS/ MPWs at PHC sub-centre regarding implementation of PMDT activities;
- Interview Treatment supporter of patients on DR-TB treatment;
- Help DTO in identifying/training suitable Treatment supporters for diagnosed DR-TB patients to be initiated on DR-TB treatment;
- Verify records, cards and TB lab register; ensure treatment cards at DTC, TU and PHI as well as NIKSHAY entries are updated at least once monthly;
- Visit and interview all patients eligible for DST who haven’t been tested so far and who are on treatment; ensure they are diagnosed at the earliest and complete treatment as per guidelines; facilitate for follow-up sample collection of all DR-TB patients;
- Ensure drugs and logistics management for patients on treatment;
- Interview health staff of identified private/NGO/other sector health care centres; and
- Impart hands-on training and guidance to Treatment supporters on proper administration of treatment, recording in treatment card and prompt identification of adverse drug reactions.

### STLS

- In consultation with DTO and MO-TC, put systems in place to ensure all presumptive DR-TB are diagnosed at the earliest; facilitate transport of sputum specimens of these presumptive DR-TB to the designated RNTCP-certified lab for C-DST;
- Visit all microscopy centres in the jurisdiction of the TU at least once a month; and
- Visit all microscopy centres, review lab records, check stocks of conical tubes, packing materials, lab form and specimen transport boxes and ensure that cool chain is maintained; ensure NIKSHAY entries from all labs; and
- Impart hands-on training and guidance to LTs on identification of presumptive DR-TB and transport of their sputum specimens to the lab as per guidelines with proper documentation.

- Visit all PHIs at least once a month and all Treatment Centres once a quarter;
- Visit all diagnosed DR-TB patients at their home within a month of treatment initiation; and
- Conduct supervisory visits at least 5 days a week.

- Visit all microscopy centres in the jurisdiction of the TU at least once a month; and
- Visit all sputum collection centres at least once a month.
**13.3 Surveillance**

Well-performed surveillance is an instrument for informing healthcare workers, public health experts and decision makers in order to guide and prioritize their action. It is a basic component in the control and elimination of TB and provides information on the epidemiology of disease, evolution of trends and description of groups in the population at increased risk of TB and unfavourable prognosis. It is an essential element in monitoring effectiveness of interventions aimed at control and elimination of the disease.

A good TB surveillance system would require timely notification of all TB patients in the population and should be able to capture necessary variables for demographic, clinical, socioeconomic, geographic and spatial characteristics to enable better understanding of local epidemiology and trend of TB.

TB surveillance should include data from laboratories as they play a pivotal role in TB diagnostics and patient ascertainment. This will help ensure completeness of reporting. Surveillance of TB should address current challenges of the disease. In that sense, surveillance of drug resistance and treatment outcome monitoring are essential tools for evaluation of TB programme. Reliable case-based notification systems are vital for a good surveillance system and surveillance should be enhanced for vulnerable groups.

NIKSHAY/ e-NIKSHAY will play a pivotal role in surveillance of DR TB patients by capturing important information at source and disseminating it at various levels and thereby acquire patient-wise information.

**Objectives**

- evaluate epidemiological characteristics of TB in the population over time and geography, within states, regions and across the country as a whole;
- monitor performance of TB management activities and feed this information into the decision making cycle to allow for appropriate interventions to upgrade districts, state and national TB plans; and
- identify and describe vulnerable populations at increased risk of TB and unfavourable prognosis to which targeted public health activities should be addressed.

**Strategies/actions**

*Evaluating epidemiological characteristics of TB:* Doing this by strengthening nationwide surveillance systems and other sources of data collection; and reinforcing use of standard reporting and definitions including DR-TB patients to gather reliable data that is comparable within and between states, and internationally over time;
Developing use of enhanced lab techniques: This could include DNA fingerprinting and molecular typing to evaluate spread of DR-TB patients and identifying outbreaks; integrating lab, clinical and epidemiological data on TB patients, at district, state and national levels; creating algorithms for detection of local outbreaks and clusters.

Monitoring TB elimination activities: This can be achieved by expanding drug-resistance surveillance activities to monitor and improve patient management; expanding drug-resistance surveillance activities to monitor and improve patient management; collecting TB patients with lab information on comorbidity status to improve care such as joint management of TB/HIV coinfected patients, TB/DM management etc.; and enhancing collection of information on case notification, monitoring treatment adherence, social support and treatment outcomes at all levels in order to monitor and improve patient management

Identifying and describing vulnerable populations for TB: Analyzing routine surveillance data and performing ad-hoc surveys to identify vulnerable populations; and enhancing or implementing TB surveillance in migrants, prisoners and other vulnerable populations according to the particular situation in the district/state.

Establishing TB surveillance system from district to national levels: Doing this by setting up TB surveillance units at district level in DTC, at state level in STDC and national level at NTI; - setting up sentinel surveillance units at medical colleges and lab surveillance units at all IRLs and NRLs; and using e-NIKSHAY as the major data source with analytical outputs readily available at all levels.

13.4 NIKSHAY

NIKSHAY is the platform for the National Tuberculosis Programme Surveillance System. It envisages establishing ICT enabled state-of-art surveillance system with system utilization by 100% stakeholders, ensuring 100% notification of TB patients at diagnosis (microbiologically confirmed and clinically diagnosed). The programme envisions continuous monitoring and treatment adherence for all TB patients registered with e-NIKSHAY, enabling tracking of all registered TB patients across TB elimination lifecycle, geographies, transfers and referrals.

The first step is to ensure complete a entry in all formats of R&R. Dashboard functions to track activities and online monitoring indicators with graphical and geomapping displays in NIKSHAY/e-NIKSHAY is helpful in programme monitoring provided completeness of data entered is ascertained. Primarily, the source of information for all monitoring indicators will be NIKSHAY. Thus validation of actual report and the entered report should be done at each level to sustain quality of information available digitally. Patient-wise details and aggregated monitoring indicators for specified period is available within NIKSHAY.
13.5 e-NIKSHAY

In an attempt to reduce the TB burden in the country, it is envisaged that an ICT system such as e-NIKSHAY could help with coordinated planning and action that is required at various levels. This would be from improving patient awareness and ease of access to TB care to time bound and effective diagnosis and treatment by the service providers. The goal would be to develop a common integrated platform as an open system to engage ecosystem stakeholders towards effective, timely and quality assured diagnosis and effective treatment of TB. It would essentially use a case-based approach to the TB lifecycle, enabling patient-based tracking and monitoring allowing for stakeholder integration, as well as timely and accurate reporting and real time decision support.

RNTCP shall roll-out e-NIKSHAY with support to states on logistics and trainings. This platform will serve as a web-based, case-based recording and reporting system which will also feed into routine surveillance of drug-resistant TB in the country. e-NIKSHAY will be rolled-out initially in the states of Gujarat and Maharashtra and gradually scaled-up nationally by end of 2018.

Role of e-NIKSHAY in recording, reporting and SME

- e-NIKSHAY will gradually replace the cumbersome paper-based system of recording and reporting. Options shall be provided to capture the event at origin through provision of mobile/web applications, tablets and call centres on real-time basis. This will change and improve reporting structures for more agility and efficiency by providing relevant reports at relevant levels without delay due to paper-based collection, collation and compilation of reports.
- e-NIKSHAY will generate user specific task lists on real time basis according to their job responsibilities aiding staff to prioritize tasks at various levels. ICT enabled adherence mechanisms (99 DOTS, MERM, etc.,) will feed treatment related information from patients and providers into e-NIKSHAY enriching it as a patient care and support platform to prioritize patients for differential care.
- e-NIKSHAY will aid the referral and feedback mechanism under the programme by providing real time information on referral of patients for treatment initiation and ADR management. This will aid the programme to manage referral and provide feedbacks thereby decreasing lost to follow-up and improved tracking of patients nationally.
- e-NIKSHAY will populate dashboards for all supervisory staff at various levels to aid in their day-to-day work by providing dashboards for different facilities, categories of staff and geographies. This will aid supervisors and programme managers in identifying areas, both thematic and functional for intensive supervision.
- e-NIKSHAY shall generate interactive tables of real time monitoring indicators to aid review at various levels. The platform will generate alerts in the form of SMS, emails and call from call centres for patients, providers and supervisors for actions to promote
favourable outcomes and improve programme management efficiency. The indicators shall be projected as interactive tables/maps to promote information driven monitoring at all levels.

13.6 Programme monitoring

Monitoring is the process of observing whether an activity or service is occurring as planned. It implies systematic and purposeful observation, aiming to identify any diversion from the planned course of action. It is a routine tracking of programme using input, process, output and outcome data collected on a regular and ongoing basis. This helps identify the need for more formal evaluation of activities and find timely solutions to the problems.

Monitoring in TB programmes is of paramount importance for ongoing programme planning and implementation.

A good monitoring strategy moves beyond the widely used case detection and treatment outcome indicators and applies the concept of input, process, output, outcome and impact indicators for measurement of key programme activities.

Monitoring indicators: Various components of programme service delivery are fed in NIKSHAY from where various input, process and outcome indicators are drawn for different levels of health facilities. Analysis of these indicators will help in monitoring improvement in programme performance. List of monitoring indicators is placed at Annexure 16.

13.7 Online clinics (Project ECHO)

Project ECHO (Extension of community health care outcomes) is an innovative continuing education model that uses Zoom video conferencing to link specialist teams (“hubs”) with primary care providers and educators (“spokes”) in rural and underserved areas. The benefits of the ECHO model™ are numerous, including ongoing education, greater access to high quality care and specialists for patients, improved provider networks, and reduced costs from inappropriate and untimely care.

Project ECHO aims to have better integration into health systems across the country. Zoom is the application which provides a platform for linkages either through website or mobile application. Zoom platform is downloaded through https://zoom.us/download and once it is installed in the system, it can be accessed via https://zoom.us/signin for web-link while mobile application is downloadable from play store as ‘ZOOM cloud meetings’.

This platform is intended to be used for clinical and programmatic discussions to improve quality of care for DR-TB patients in India.
Chapter 14: Supply chain management in PMDT

This chapter outlines the guidance regarding procedures for inventory management of second-line drugs used in the treatment of drug-resistant TB.

14.1 Overview of drug distribution flow

All drugs used in the various DR-TB regimens shall be supplied through a centralized procurement system at Central TB Division, MoHFW, GoI. Supplies of the second-line drugs shall be from the respective Government Medical Store Depot (GMSD)/ Central Medical Services Society (CMSS) to the state drug store (SDS). An advance intimation of all drug supplies shall be communicated to the States for SDS to make available requisite space in the drug store. The State/ SDS shall be supplied only loose form of second-line anti-TB drugs (SLD). On receipt of drugs, the SDS shall acknowledge the receipt to CTD.

The SDS shall repack the loose drugs into one-monthly patient-wise boxes of Type A (oral drugs common in IP and CP), Type B (IP Plus boxes) and supplies to districts for treatment. SDS shall be preparing ‘standardized drug boxes’ for standard regimen and supplies to districts, namely for shorter MDR/RR TB regimen, conventional MDR-TB regimen and regimen for H mono/poly DR-TB. SDS shall supply additional loose quantity of SLD to districts for constituting modification. Drug requirement for treatment initiation at DDR-TBC/NDR-TBC, SDS shall supply loose SLD to all DDR-TBC and NDR-TBC based on consumption pattern. However, when the state shall build the capacity of the districts, including having dedicated full-time human resource support at DDS level, entire exercise of preparation of patient-wise boxes shall need to be conducted at DDS under the guidance and supervision of DTO.

Modification/ change in regimen may be required during the course of treatment based on the decision of NDR-TBC. In such patients, the supply of the monthly box would be as per the regimen-class to which the patient is reclassified to. For regimen containing Bdq, on discharge, the patient will carry the bottle containing BDQ and hand it over to the treatment supporter under supervision of the DR-TB/TB-HIV supervisor. This will be included in the first-monthly Type B box for the intensive phase containing SLI and oral drugs in which are issued to the treatment supporter. The bottle will remain under custody of the treatment supporter up to 24 weeks, while the Type B box will be issued on a monthly basis.

For maintaining inventory of BDQ and its accountability, once BDQ bottle is issued to patients from NDR-TBC with written information to concerned DDS, the stock is entered in the stock register at DDS. The bottle provided to the patient must be handed over to the treatment supporter. District DR-TB TB-HIV Supervisor shall be the link for passing
information to DDS keeper regarding BDQ stock supplies to treatment supporter. DDS keeper shall keep a record of the patients’ stock of BDQ in the district drug stock register.

**14.2 Technical specification of patient-wise box**

The technical specification of the monthly patient-wise box for DR-TB patients is detailed in Annexure 17. The patient on intensive phase (IP) shall be put on Type A and Type B boxes in each month. During the continuation phase (CP), the patient will be put on only Type A box for the entire duration.

*For IP*: Type A box + Type B box of same weight band; and
*For CP*: Type A box of same weight band.

These drug boxes will be prepared at the SDS for all standard weight bands. For <16 kg patient, boxes will be prepared from the loose drug provided.
### 14.3 Constitution of patient-wise boxes and role of various drug stores

**At State drug store level**

SDS shall formulate drug boxes (Type A and B) for shorter MDR-TB regimen, conventional MDR-TB regimen and regimen for H mono/poly DR-TB and supplies to linked districts.

**Table 14.1 Drug boxes for standard DR-TB regimen**

<table>
<thead>
<tr>
<th>Type A (Oral drug box)</th>
<th>Type B (IP plus box)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shorter MDR-TB regimen</strong></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin – high dose (Mfx&lt;sup&gt;h&lt;/sup&gt;)</td>
<td>Kanamycin (Km)</td>
</tr>
<tr>
<td>Clofazimine (Cfz)</td>
<td>Isoniazid – high dose (H&lt;sup&gt;h&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>Ethionamide (Eto)</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td></td>
</tr>
<tr>
<td>Pyridoxine (Pdx)</td>
<td></td>
</tr>
<tr>
<td><strong>Conventional MDR-TB regimen</strong></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin (Lfx)</td>
<td>Kanamycin (Km)</td>
</tr>
<tr>
<td>Ethionamide (Eto)</td>
<td>Pyrazinamide (Z)</td>
</tr>
<tr>
<td>Cycloserine (Cs)</td>
<td></td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td></td>
</tr>
<tr>
<td>Pyridoxine (Pdx)</td>
<td></td>
</tr>
<tr>
<td><strong>H mono/poly DR-TB regimen</strong></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin (Lfx)</td>
<td>Kanamycin (Km)</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td></td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td></td>
</tr>
</tbody>
</table>
At District drug store level

When modification in regimen suggested by DR-TBC, DDS keeper shall take a call and prepare modified boxes from loose SLD supplied from SDS. The state shall provide necessary support for capacity building of DDS for carrying out entire exercise of preparing standardized patient-wise drug boxes decentralized at DDS level. Dedicated full time DDS keeper is mandatory to be recruited/ placed for successful decentralized system of preparation of drug boxes at DDS level.

The drug dosage for DR-TB for adults by weight band and for children (less than 30 kg body weight) by mg per kg body weight are detailed earlier in the chapters on treatment and special situation respectively.

Patient initiated on DST guided regimen will receive monthly box as per the regimen decided by NDR-TBC prepared by DDS. If the regimen is modified for the patient or patient is under the DST guided regimen, DDS needs to ensure that the change in regimen should be incorporated in supply of subsequent boxes.

14.4 Packing instructions

- packaging of loose drugs into Type A & B boxes should be done under guidance of the STO/Medical Officer/Drug logistics In-charge at State level and district level;
- one monthly pouch of Cap. Cs & Tab. E each should be made from plastic bag with ziplock facility in which 1 gm. pouch of silica gel desiccant should be kept. In each Type A box, one pouch of silica gel desiccant of 4 gm. weight should also be kept;
- each Type A & B box should be numbered consecutively at SDS. The record of the serial no. of the box should be maintained at the State, District & Sub-district (TU) Drug Stores. This would be of help while tracking a particular box. Later on, this exercise will be taken care of by Nikshay-Aushadhi software;
- label on the boxes to clearly mention the following:
  - item-wise name of drugs with quantity of each drug in the box;
  - batch no. & DOE of individual drugs;
  - DOE of boxes-expiry date of the drug having shortest expiry;
  - date of issue of the box from SDS;
  - serial number of the box;
  - storage instructions on the box for ensuring adequate precautions in storage of the drugs, especially at Treatment supporter level. Some suggested messages are: “store in a cool and dark place, preferably in a clean cupboard”; “do not expose to direct sunlight”; “keep away from children/unauthorized persons”; and or “box to be closed properly every time after withdrawal of drugs”.

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Prototype of label is suggested in Annexure 18. The Nikshay-aushadhi software helped in preparing boxes by estimating number of boxes of required regimen that can be prepared from available stock. Label for prepared boxes to be printed directly from the system. For each cycle of box preparation, a label which contains expiry-wise drug content of these boxes to be generated through the system. This label should be used to paste over the boxes prepared during that cycle only. Other steps include:

- **Repackaging process for utilizing Medication Event Reminder Monitors (MERM) system.** ICT enabled monitoring systems for DR-TB patients are currently under feasibility testing at various sites. Majority of these are capable of monitoring pill-in-hand status for DR-TB patient. It is one such system where ‘a specialized container’ capturing a set of information is directly sync with the server. Drugs are kept inside this battery operated specialized container and when it’s opened, it records date and time of each medication taking event. Usually it holds drugs for one month which should be replenished with the drugs for the next month. The monthly box prepared for standardized regimen or loose drugs is available at the district and/or TU level and should be used to refill the box.

- **Barcoding and real time tracking system:** First-line drugs provided under the programme are barcoded and programme is in plan to have second-line drugs also made available with barcode. The NIKSHAY-AUSHADHI software has an in-built feature of tracking drug stock with the help of barcode. The barcode may be printed at state or district level as per the programme guideline and pasted over the boxes where it is prepared.

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

The management cycle of second-line anti-TB drugs comprises six elements, namely, drug selection; quantitative assessment of drug requirements; management of procurement; distribution protocol; assurance of drug quality; and ensuring rational drug use. Accurate demand forecasting of second-line anti-TB drugs, (correct quantification of drug needs for a specific period of time) is one of the elements guaranteeing an uninterrupted drug supply.

*Inventory management:* Procedures for ongoing tracking and replenishment of the inventory of second-line anti-TB drugs at SDS and all subordinate stocking points ensures these are maintained at or close to the stocking norms presented below:
Table 14.2 Standard drug box for regimen for H mono/poly DR-TB

<table>
<thead>
<tr>
<th>Level</th>
<th>Stock for utilization</th>
<th>Reserve stock</th>
<th>Drug requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHI</td>
<td>1 month</td>
<td>1 month*</td>
<td><em>(Monthly consumption x 2) – (existing stock in PHI at end of the month)</em></td>
</tr>
<tr>
<td>TU drugstore</td>
<td>0 months</td>
<td>1 months</td>
<td><em>(Quarterly consumption/ 3) x 3 – (existing stock in TU including PHI drug stores at end of the quarter)</em></td>
</tr>
<tr>
<td>DTC drugstore</td>
<td>0 month</td>
<td>2 months</td>
<td><em>(Quarterly consumption/ 3) x 5 – (existing stock in DTC drug store including TU &amp; PHI drug stores at end of the quarter)</em></td>
</tr>
<tr>
<td>SDS</td>
<td>0 months</td>
<td>3 months</td>
<td><em>(Quarterly consumption/ 3) x 8 – (existing stock in SDS including stocks at all districts at end of the quarter)</em></td>
</tr>
</tbody>
</table>

*All PHIs may not have a reserve stock. Only PHIs where patient/s are initiated or on treatment will have reserve stock of second line drugs.

14.6 Monitoring of drug distribution and supply chain management

**Distribution from Centre to SDS:** as mentioned in overview of this chapter, loose SLD shall supply to SDS directly from centre. The SDS pharmacist shall prepare a Monthly Stock Statement (MSS) providing details of receipts, issues and opening/closing balance of drugs as well as details of monthly Type A & B boxes, as at the last day of each calendar month in the prescribed format. The MSS shall be sent to STO by the 7th of every month, by all SDSs, in the state. The statement shall facilitate determination of drug stocks available with SDS(s) within the state. MSS shall thereafter be forwarded to CTD through the STO, by the 10th of every month. In the event of more than one/multiple SDSs within the state, all the MSSs shall be forwarded to CTD within the timelines stated above.

**Distribution from SDS to District:** The SDS will supply drugs to the DTC in the form of monthly patient-wise Type A and Type B drug boxes. It shall review monthly consumption report received from linked districts and issue Type A & B boxes as well as loose medicine to the district. Format for monthly consumption report to be sent by the district is attached as Annexure 19. The DTC shall send the boxes to its implementing TU in a similar manner on monthly basis and then monitor through the TU monthly SLD requirement report. Buffer stocks of both Type A & B boxes of all weight bands shall be held at all levels as per stocking norms. DTO will ensure arrangement for supply of monthly drug boxes of Type A & B from
the respective PHI to the Treatment centre. The STS shall identify the Treatment supporter in consultation with MO-PHI and the patient. Considering roll-out of DST guided treatment, SDS will supply loose core oral SLD to the DDS for modification in regimen.

**Distribution of SLD to DR-TBC:** Issuance of loose drugs to DR-TBC (including DDR-TBC) from SDS shall be based on the monthly stock statement submitted by DR-TBC, to ensure adequate stocks for a month of treatment, plus a buffer of one month. On discharge from DR-TBC, patient shall be given drugs for 7 days to cover the transit period. During this time, it is expected that the patient shall reach home for the ambulatory treatment and commence therapy from monthly IP box which has by then been issued to the respective treatment supporter. For patient put on BDQ treatment, BDQ bottle contains entire course of treatment for one patient which shall be earmarked for each enrolled patient and handed over to treatment supporter in supervision of District DR-TB TB-HIV Supervisor.

**Distribution from DDS to TU drug stores:** Buffer stock equivalent to one month will be kept at the TU. The drug boxes will be supplied from the TU to PHI. It will then be transferred from the TU to respective PHI on instruction of DTO as per monthly consumption report submitted by TU.

**Distribution from TU drug store to PHI:** Buffer stock equivalent to two months will be kept at the PHI at the beginning of each month. The drug boxes will be supplied from PHI to Treatment centre/ Treatment supporter. All PHIs may not have reserve stock. Only PHIs where patient/s are initiated or on treatment will have reserve stock of second-line drugs.

Drug stock register (Annexure- 20) is to be maintained in the drug stores at all levels. Details such as drugs received, distributed and balance stock are to be entered in this register. Drug distribution mechanism is supported by Nikshay-aushadhi where drugs stock, dispatch and return of drug can be reported through tracking of the drug. The system is able to capture information log of boxes allotted to the patients who are provided by each health facility who is using this software for drug management purpose. Hardcopy reporting will be discontinued once all health facilities embark on the Nikshay-aushadhi.

**Scenario 1 - Modification in regimen:** If N/DDR-TBC committee decides on modification of regimen, DDS shall prepare modified Type A or B boxes from available standard boxes using loose SLD available at district level and arrange supply to treatment supporter.

**Scenario 2 - Extension of intensive phase:** If IP of the patient is required to be extended; the respective N/DDR-TBC committee shall inform DTO who will intimate the same to the MO-PHI and the respective TU. The PHI will release 1 Type A and Type B to the respective treatment centre from where the patient is taking treatment. When the patient is switched to CP, the DTO shall intimate the same to the MO-PHI and the respective TU. On instruction of DTO, the PHI will release 1 Type A box only to the respective Treatment centre from
where the patient is taking treatment. During the period between when the DTO has been notified of the decision to change over to CP and the delivery of drug box from the PHI to the Treatment centre, the patient’s IP shall be continued. All patients who are given an extended IP must complete the monthly box of a full month of extension.

**Scenario 3 - Change in regimen:** If DR-TBC Committee decides to change the regimen then DDS shall arrange supply of new treatment regimen box from PWB supplied from the SDS.

### 14.7 Reconstitution: Repackaging and use of partially used IP/CP boxes

- in case of default/death/transfered-out/treatment stopped patients, unconsumed boxes shall be brought back from Treatment centre to PHI to TU to DTC within the shortest possible time. All loose drugs remaining in the boxes received back shall be accounted for in the Stock register and Nikshay-aushadhi at the DDS and issued as per FEFO principles to either DR-TBC or for repackaging into monthly Type A or B boxes;
- partially used BDQ bottle shall be sent back to SDS where repackaging will also be done. Remaining tablets in the bottle received back shall be accounted for in the reconstitution register (Annexure-21) and Nikshay-aushadhi at SDS. Upon reconstitution, the bottle shall be accounted for in the Stock register (loose tablets to be mentioned in remarks column) to be issued as per FEFO principles. When reconstitution is done, tablets of same expiry can be considered using same container to a maximum of 188 tablets. These reconstituted containers shall be used for treatment of subsequent patients found eligible for Bdq. All such drugs that are taken from the new containers shall be collected as a group of 188 tablets of same expiry and put in a light resistant container as per advice from the manufacturer. The actual expiry of tablets should be mentioned over the container;
- in the event of SDS falling short of 188 tablets from an expiry batch, reconstitution can still be done using number of tablets to complete 188 tablets with another expiry batch. In such a case, tablets of the respective expiry should be retained in their same respective containers and issued to patients and providers with counselling to consume the tablets with the nearest expiry first; and
- if expiry of remaining tablets is less than six months, the same shall be consumed at NDR-TBC for admitted patients. It will be adjusted from the new long expiry bottle on discharge.

### 14.8 Guidelines for storage of second-line anti-TB drugs for State and District drug store

**Storage space**

Requirement of space for various levels of drug stores should be based on the estimated number of DR-TB patients likely to be placed on treatment in the concerned state for whom
the maximum quantity of drug stocks are to be maintained at the concerned stocking unit. The recently completed national DRS and the programme surveillance data on PMDT would form the basis for quantification and storage space that will need to be worked out separately for each SDS and DDS.

**Specifications for drug stores**

- should preferably comprise one large room; where multiple rooms already exist, they should be contiguous or proximate to each other;
- preferably separate space for storage, handling and repacking into Type A & B boxes;
- ceiling to have a height of at least 3 metres;
- lockable door and at least one window with grill;
- proper lighting;
- even-level, ‘pukka’ floor;
- plastered walls and ceiling with whitewash without any kind of seepage in the room;
- in a situation where separate room for storing second-line drugs is not possible, an attempt to demarcate and enclose a specified area for storing the drugs should be made within the larger store. This will ensure required temperature control for the drugs;
- architects should be consulted for making suitable modifications in the existing drug store/construction of a new drug store for the same;
- signage board with instructions in local language should be put near the entrance of the store to remind concerned officials regarding good storage practices;
- ideally, vacuum dewatered flooring (VDF) should be used; however depending on the feasibility, such flooring may be done at SDS level;
- in case it is feasible at SDS level, separate areas should be demarcated for receiving and dispatching the drugs;
- contract for pest control should be entered into by the State to ensure drug stores being free from pests, rodents etc.; and
- the SDSs shall have adequate mechanism to continuously monitor temperature and humidity of the stores as detailed below:

**Shelves, racks & storage arrangements**

- if sufficient space is available on the existing storage shelves in the SDS, these shelves made of 40 mm bore medium quality (external diameter - 48.3 mm) mild steel pipes should continue to be used as per existing RNTCP guidelines. New shelves, if required, are to be made from prefabricated slotted angles ensuring sufficient ‘gap’ between cartons from ceiling, floor and walls, facilitating ventilation and free movement of air;
- shelves to be positioned so that there is no possibility of seepage into cartons;
- typically, five rows of shelves to be fabricated, one on top of the other into racks. A single rack to be long enough to accommodate up to a minimum of three cartons on each shelf;
in case of a broad room, there shall be multiple rows of racks, all parallel to one another. There should be sufficient space between parallel blocks of racks and walls, to facilitate free movement of men and trolleys for smooth stacking and removal of cartons. In case of a long and narrow room, racks to be positioned in such a way that there is sufficient space between them and the walls;

- drug cartons to rest on shelves and not on each other, to prevent eventual sagging of the cartons in the bottom row;
- rows and columns, where drugs are stored should be defined and locations to be assigned a unique identification number; and
- in future, if SDS of a particular state has to handle a large volume of drugs and occupy larger space, the walkway space (between racks across the storeroom) can be of 3 metres. In such a situation, material handling equipment will be required.

Stacking arrangement

- name of the drugs along with their expiry dates to be indicated on stickers pasted on the face of cartons/ drug boxes. These should be written again by hand, in large easily visible characters using a coloured, permanent marker pen;
- each drug should be stored in a single location within the store in order of date of expiry;
- additionally, drugs of the same expiry should be stored together at the same location;
- recognizing the above rules, drugs expiring earliest should be so stored that they are issued first. For example, in case IP (> 70 Kgs) boxes are placed on multiple shelves in a single part of the store, boxes expiring earlier should be stored at ground level and fresher boxes (which shall expire later) on elevated shelves. This method of stacking shall ensure that drugs that shall expire first shall automatically be issued first, based on the principle of FEFO (First Expiry First);
- Expired drugs should be segregated, sealed and stored in a separate area (quarantine) of the store eliminating the possibility of their issue to patients. Expiry dates should be highlighted in these boxes; and
- bin cards at SDS level to be displayed, providing details of receipts, issues, closing balance (quantity) and expiry dates of drugs. Only Na-PAS is a slow moving drug and should be stored at higher level shelves. Rest all other second-line drugs are fast moving, hence, should be stored on lower shelves.

Control of humidity and temperature

- monitoring of humidity and temperature is important. Hygro-thermometers are to be installed up to TU drug store levels to monitor humidity and temperature regularly. The record of both these variables should be maintained in charts properly and checked on a daily basis by the concerned store in-charge. This should be reviewed by STO/ Officer in-charge of SDS and necessary corrective measures taken immediately;
control of humidity must be ensured at all times. In order to keep humidity levels below the maximum 60% recommended for storage of drugs, following measures to be taken:

- **Ventilation**: Open windows or air vents of the store to allow air circulation. Ensure all windows have screens/ wire mesh to keep out insects and birds and have metallic grills/ iron bars. Drug boxes/cartons to be placed on shelves ensuring there is sufficient space between shelves and walls of the storeroom;
- **Packaging**: The cartons/drug boxes should not be opened unless necessary;
- **Circulation**: Use fans to circulate fresh air from outside;
- **Protection from sunlight**: To protect drugs from sunlight, following measures may be taken: Shade the windows or use curtains if they are in direct sunlight. Keep products in cartons/drug boxes. Do not store or pack products in sunlight. Maintain trees around the premises of the drug store to help provide shade and cooling. Check their condition regularly to prevent any untoward incident;
- **Control of temperature**: The second-line anti-TB drugs should preferably be stored below 25\(^0\) C. In the area specified for storing second-line drugs, temperature of about 20\(^0\) C should be maintained with help of air conditioners (tonnage would depend on size of the room); and
- **Power supply**: Regular power supply should be available for air conditioning in the SDS. Arrangements for backup power supply should also be made through solar panels/ fuel-based power generators.

The purpose of information provided above is to emphasis that drugs be stored in cool and dark place for proper efficacy. However, after drug boxes are moved outside temperature controlled (AC) environment till it is consumed by the patients. All efforts must be made to store drug boxes in cool and dry place.

### 14.9 Quality assurance of drugs

The quality assurance component of the RNTCP drug supply system ensures that each drug used by a patient is safe, efficacious and has appropriate standards of quality. As per the protocol developed by Central TB Division (CTD), random samples of second-line Anti TB Drugs shall be picked from all stocking points in the field and sent for testing by an independent drug testing laboratory contracted by CTD to ensure quality of drugs is continuously maintained and remains the same throughout the supply chain of the drugs. This should be done based on communication sent by CTD to concerned states and districts.

### 14.10 Waste disposal guidelines

If any drug expires due to reasons beyond control, it should be disposed off after writing off the loss as may be required under the rules and thereafter procedures laid down in the
Rules under Drugs & Cosmetics Act and Biomedical Waste (management and handling) Rules of Government of India.

14.11 Guidelines for recording and reporting of SLD

The recording and reporting system for drug stock management from SDS to the DR-TBC and to Districts, TB Units and PHIs has been recently revised to suit the 1 monthly patient-wise boxes system. Formats for drug logistics management of second-line drugs under PMDT are described in Annexure 19. An ICT based recording and reporting systems up to PHI level for the real time data, inventory management, demand generation, analytical tools, drugs accountability, forecasting & anticipation have been identified and will soon be implemented under RNTCP. Bar code reader, scanner and printer too shall be provided up to the district level.

14.12 Nikshay-aushadhi: Supply chain management software solution

The Nikshay-aushadhi, Centre For Development of Advanced Computing (C-DAC)'s web-based TB drug supply management system is a major step towards adapting technology to improve supply chain management of TB drugs in State level and district stores, TB Unit (TU), peripheral health institutions (PHIs), DR-TBC and treatment supporter centres. These applications deal with demand and distribution of all essential anti-TB drugs and consumables required at State, district, TU, DMC and PHI level.

It also caters to data from Government Medical Stores Depot (GMSD) and the procurement agency, currently CMSS. The advantage of inventory automation is to get the complete detail of stock on hand at various levels, supplies in pipeline and distribution and consumption patterns in the state, up to higher management level. This will help in anticipation of future requirement while ensuring dramatic improvement in performance along with reducing costs. Integration of Nikshay-aushadhi system with current Nikshay-aushadhi enhances its user-friendliness.
Chapter 15: Infection control measures

Evidence indicates that DR-TB is similar in transmissibility to DS-TB. Thus, infection control policies and strategies are not much different for DR-TB. 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. Actions are required at national and subnational level to provide managerial direction and at health facility level to implement airborne infection control measures. [14]

15.1 Activities for national and sub-national airborne infection control (AIC)

- identify and strengthen a coordinating body for TB infection control, ensuring that TB infection control is part of a general infection prevention and control programme;
- develop a comprehensive budgeted plan for implementation of TB infection control at all levels;
- ensure that health facility design, construction, renovation and use are as per prescribed criteria;
- conduct surveillance of TB disease among health workers, and conduct assessment at all levels of the health system and in congregate settings;
- address TB infection control advocacy, communication and social mobilization;
- monitor and evaluate the set of TB infection control measures; and
- enable and conduct operational research.

15.2 Measures for facility-level TB infection control

- identify and strengthen local coordinating bodies for TB infection control as part of the facility wide comprehensive infection prevention and control programme. In addition, develop a facility plan (including human resources and policies and procedures to ensure proper implementation of the controls listed below) for implementation:
  - adequate ventilation (ACH >12 per hrs) should be maintained for high priority health facility like DR-TB wards, ART centre, TB containment laboratory etc.;
  - beds should be arranged with 6 feet distance in between them;
  - staff should be trained for standard precaution, airborne infection control precaution, use of personal protective equipment (PPEs) and importance of educating patient to follow the same;
  - availability of different size of N 95 particulate respirators; and
- renovating existing facilities and constructing new ones to optimize implementation of infection controls. Seating rearrangements within the room or ward, patient flow within health facility premises could have significant impact on airborne infection control.

- conduct on-site surveillance of TB disease among health workers and assess the facility;
- address advocacy, communication and social mobilization for health workers, patients and visitors;
- monitor and evaluate the set of TB infection control measures; and
- participate in research efforts.

National guideline for infection control in all health care settings including DR-TB care settings includes having an integrated implementation plan for administrative, environmental and personal protective equipment.

15.2.1 Administrative controls

- promptly identify people with TB symptoms (triage), separate infectious patients, control spread of pathogens (cough etiquette and respiratory hygiene) and minimize time spent in healthcare facilities;
- Ensure linen and waste management;
- clean and disinfect patient-care equipment;
- provide a package of prevention and care interventions for health workers; and
- Observe standard universal precautions, body substance isolation and airborne precautions.

15.2.2 Environmental controls

- use ventilation systems including mechanical ventilation system; and
- use of ultraviolet germicidal irradiation fixtures, at least when adequate ventilation cannot be achieved.

15.2.3 Personal protective equipment

- use particulate respirators (N95) for staff; and
- use of surgical mask or cloth to cover the cough at the patient level.
References


[34] Morrison J et. al, "Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis.," Lancet Infectious Diseases, 2008.


[36] "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events," Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services, 2014.