Revised National Tuberculosis Control Programme

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

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Foreword

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

The term “Programmatic Management of Drug Resistant TB” (PMDT), refers to programme based DR-TB diagnosis, management and treatment. These guidelines promote full integration of basic TB control and PMDT activities under the RNTCP, so that patients with TB are evaluated for drug-resistance and placed on the appropriate treatment regimen and properly managed from the outset of treatment, or as early as possible. These guidelines are 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. These guidelines are updated to align with the World Health Organization (WHO) End TB Strategy, Sustainable Development Goals and WHO PMDT Guidelines - 2016 to cover advancing the country to scaling up universal access to drug susceptibility testing for all diagnosed and notified TB patients as part of national strategic plan (NSP) 2018-25, the recently endorsed WHO recommended second line – line probe assay (SL-LPA) – a 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.
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<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<tr>
<td>Am</td>
<td>amikacin</td>
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<td>Amx/Clv</td>
<td>amoxicillin/clavulanate</td>
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<td>ARV</td>
<td>antiretroviral</td>
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<td>AST</td>
<td>aspartate aminotransferase</td>
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<tr>
<td>Bdq</td>
<td>bedaquiline</td>
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<td>CAP</td>
<td>Conditional Access Program</td>
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<td>CBNAAT</td>
<td>Cartridge Based Nucleic Acid Amplification Test</td>
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<td>Cfx</td>
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<td>capreomycin</td>
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<td>CP</td>
<td>continuation phase</td>
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<td>Central TB Division</td>
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<td>Compassionate Use Program</td>
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<td>Division of AIDS</td>
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<td>DCGi</td>
<td>Drugs Controller General of India</td>
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<tr>
<td>DDG</td>
<td>Deputy Director General</td>
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<td>DDR-TBC</td>
<td>District DR-TB Center</td>
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<td>DG</td>
<td>Director General</td>
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<td>DGHS</td>
<td>Directorate General of Health Services</td>
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<td>DOTS</td>
<td>Directly Observed Treatment Short-course</td>
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<td>DR-TB</td>
<td>drug-resistant tuberculosis</td>
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<td>DSMC</td>
<td>data safety monitoring committee</td>
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<td>drug susceptibility testing</td>
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<td>E</td>
<td>ethambutol</td>
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<td>Eto</td>
<td>ethionamide</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FQ</td>
<td>fluoroquinolone</td>
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<td>GLC</td>
<td>Green Light Committee</td>
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<td>GFATM</td>
<td>Global Fund for AIDS, Tuberculosis &amp; Malaria</td>
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<tr>
<td>Gfx</td>
<td>gatifloxacin</td>
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<tr>
<td>Gol</td>
<td>Government of India</td>
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<tr>
<td>H</td>
<td>isoniazid</td>
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<tr>
<td>H^h</td>
<td>high dose isoniazid</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>ICT</td>
<td>Information Communication Technology</td>
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<tr>
<td>IP</td>
<td>intensive phase</td>
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<tr>
<td>IpM</td>
<td>imipenem</td>
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<td>IRL</td>
<td>intermediate reference laboratory</td>
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<tr>
<td>Km</td>
<td>kanamycin</td>
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<tr>
<td>LFT</td>
<td>liver function test</td>
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<td>LFX</td>
<td>levofloxacin</td>
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<td>LPA</td>
<td>line probe assay</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>Lzd</td>
<td>linezolid</td>
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<tr>
<td>MDR-TB</td>
<td>multi-drug resistant TB</td>
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<tr>
<td>Mfx</td>
<td>moxifloxacin</td>
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<tr>
<td>Mfx&lt;sub&gt;h&lt;/sub&gt;</td>
<td>high dose moxifloxacin</td>
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<td>MGIT</td>
<td>mycobacteria growth indicator tube</td>
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<td>MoHFW</td>
<td>Ministry of Health and Family Welfare</td>
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<td>NDRS</td>
<td>National Drug Resistance Survey</td>
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<td>NDR-TBC</td>
<td>Nodal DR-TB Center</td>
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<td>NIRT</td>
<td>National Institute for Research in Tuberculosis</td>
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<td>NRL</td>
<td>National reference laboratory</td>
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<td>OBR</td>
<td>Optimized Background Regimen</td>
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<tr>
<td>Ofx</td>
<td>ofloxacin</td>
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<tr>
<td>PAS</td>
<td>p-aminosalicylic acid</td>
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<tr>
<td>PK/PD</td>
<td>pharmacokinetic/pharmacodynamic</td>
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<tr>
<td>PMDT</td>
<td>programmatic management of drug-resistant tuberculosis</td>
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<tr>
<td>PQC</td>
<td>product quality compliance</td>
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<tr>
<td>PSM</td>
<td>procurement and supply management</td>
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<tr>
<td>Pto</td>
<td>protionamide</td>
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<tr>
<td>R</td>
<td>rifampicin</td>
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<tr>
<td>RNTCP</td>
<td>Revised National Tuberculosis Control Programme</td>
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<tr>
<td>RR-TB</td>
<td>rifampicin-resistant tuberculosis</td>
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<tr>
<td>SAE</td>
<td>serious adverse event</td>
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<td>SLDST</td>
<td>second-line drug susceptibility testing</td>
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<td>SLI</td>
<td>second-line injectables</td>
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<td>SL-LPA</td>
<td>second-line line probe assay</td>
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<td>STR</td>
<td>standardized treatment regimen</td>
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<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>Thz</td>
<td>thioacetazone</td>
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<tr>
<td>Trd</td>
<td>terizidone</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>WCO</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>
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<tr>
<td>Z</td>
<td>pyrazinamide</td>
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Chapter 1: Background & Framework for Effective Control of Drug Resistant Tuberculosis

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

1.1 History of PMDT in India

After successfully establishing the RNTCP services across the country in 2006, the PMDT services were introduced in 2007 and complete geographic coverage was achieved by 2013. 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. A horizontal and vertical scale up followed. Definite criteria were set to assess the risk and eligibility for drug susceptibility test (DST). Thus TB patients remaining smear positive during follow up, previously treated patients, HIV positives and contact with a known MDR-TB case were offered DST. This will eventually lead to universal DST, i.e., DST to all diagnosed and notified TB patients. This required a huge laboratory capacity in terms of geographic coverage, DST technology, trained laboratory personnel, quality assurance and certification. From a few national reference laboratories (NRL) with solid or liquid culture and DST facilities, the country has 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).

Equally important is the treatment to the diagnosed DR-TB patients. To begin with only MDR-TB patients were offered treatment with a standard second-line regimen. Later extensively drug resistant (XDR) TB patients and MDR-TB with additional resistance to quinolones or second-line injectables also were treated with standard regimens. Procurement and supply chain management of second-line drugs is complex, since no standardized patient-wise boxes are manufactured and drugs needed temperature regulated storage and repacking.

Offering treatment to DR-TB patient too was complex. It required multidisciplinary DR-TB centres for pre-treatment evaluation, observation and management of adverse drug reactions (ADR), where trained specialists, supporting HR, management information system and airborne infection control facilities were assured.
During 2011 and 12, there was a massive scale up of all these facilities on war footing with concerted efforts of multiple stakeholders resulting in countrywide coverage by 2013.

Later in 2014, base-line second-line DST facilities were established in a few intermediate reference laboratories, which also got scaled up to the entire country in 2015. In 2016, new drugs like Bedaquiline were made accessible to DR-TB patients through a conditional access program (CAP) under RNTCP. 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.

1.2 Magnitude of the DR-TB problem in India

Drug resistant tuberculosis has been known from the time anti-tuberculosis drugs were first introduced for the treatment of TB. Currently the prevalence of Rifampicin (R) and MDR-TB in India is estimated to be around 1,30,000. This translates to around 9.9 patients per lakh population annually (Global TB Report - 2016). Newer and higher quality information from various sources has also allowed us to update our 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 that the problem of drug
resistance has been increasing. The first national anti-tuberculosis drug resistance survey (NDRS) has been recently concluded. As soon as the results are available, more accurate estimates are expected. This will include information on resistance to a single or multiple drugs among the first and second line drugs.

Drug resistance can be to any one or more drugs. 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 have increasingly been available, making available regimens for their treatment also is becoming a programmatic priority.

The detection of DR-TB through the RNTCP has been progressively rising with increased access to various forms of DST. RNTCP detected and initiated treatment in about 27104 patients of MDR-TB and 2127 patients of XDR-TB in 2015.

While prevention of development of drug resistance is of paramount importance for TB control, detection and successful completion of treatment is important to interrupt ongoing transmission and to prevent death. The program has been so far able to successfully treat 46% of the cohorts of patients initiated on treatment 30-33 months ago. The treatment outcomes vary from state to state. A few states were able to treat more than 70% of the diagnosed RR/MDR-TB patients successfully while a few others could successfully treat less than 40%. Death and loss to follow up during treatment were the major reasons for the attrition.

1.3 Causes of drug-resistant tuberculosis

Drug-resistant TB has microbial, clinical, and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. 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 control efforts lead to delay in detection and effective treatment of drug resistance, and are unequipped to 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 in general, are required to prevent of emergence of resistance. Thus, basic TB diagnostic and treatment
services should receive priority. Systems for early detection and treatment of drug-resistant forms of TB, should be integrated into existing TB control services.

Improperly treated patients with resistant strains of TB will constitute a source of ongoing transmission of resistant strains. Thus interruption of transmission is necessary to prevent new patients of DR-TB. 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 sensitive patients as a continuum of care.

1.5 Move to Patient Centric Care

Successful treatment can only result when patient preferences, values and needs are addressed along with PMDT services. This includes ensuring that the diagnosis of DR-TB is early and accurate; the most effective treatment is delivered early, provided in a manner that is easily accessible to the patient. At the same time, confidentiality and dignity of the patient should be protected. It is the responsibility of the health system to ensure that the patient is treated successfully within the society he belongs to, enjoying all supports the society would otherwise provide to its members so that the a new chain of infection to the society is arrested at source and the cured member enriches its material, social and cultural assets.

1.6 Universal Drug Susceptibility Testing

The program 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).

Patients are triaged for DST based on their risk of developing drug resistance. Over time the test has been increasingly made available 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 Rifampicin resistance. 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; in these patients Rifampicin resistance information is available as a by-product.

There are several additional DST facilities in the development pipeline. These tests will be made available progressively as they are endorsed for use by the WHO. Recently the WHO endorsed LPA for use for DST of fluoroquinolone (FQ) class and second line injectable (SLI) class; current LPA labs are in preparation for rolling out
this facility. DST on CBNAAT offering more accurate and wider testing of resistance is also in various phases of development.

1.7 DST Guided Treatment

The 2012 PMDT Guidelines were largely prioritised 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 (Rifampicin 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 in-patient and out-patient based treatment initiation for providing increased access to PMDT services. Inpatient-care for those who require it and drug supply chain management have also been decentralised 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 patient centric approach would mean giving more priority for patient’s needs and preferences in view of better adherence. In some patients a family member might be able to better ensure treatment supervision and adherence compared to external individual visiting the home. With the development of information communication technology (ICT) there are also options by which patients can reliably self-report drug consumption and can be monitored by various levels simultaneously. The newer guidelines favour the principle of adherence monitoring to be logically and judicially and thus provide options whereby the most appropriate modality of treatment supervision may be used as a collective decision of the patient, treatment supporter and the concerned medical officer (MO).

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

1.10 Newer Drugs and Regimen

Over the past decade, treatment regimens for drug resistant TB were based on combination regimens of six or more second line oral and injectable drugs administered over a period of 24 to 30 months. There are newer drugs like Bedaquiline and Delamanid currently approved for conditional use under programmatic settings that are expected to improve treatment outcomes. Similarly,
some of the earlier drugs like Imipenem 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 evidences evolve, WHO has recommended a shorter MDR-TB regimen for use for select drug resistance patients based on available evidences to date. This version of the guidelines integrates use of the shorter MDR-TB regimen and newer drug containing regimen under RNTCP with a DST guided optimised background 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.

2.1 Service Cascade of DR-TB

Diagnosis of DR-TB starts with identification of presumptive DR-TB patients. "Presumptive DR-TB" is not an absolute term like "Presumptive TB". It is quite relative, the meaning of which will keep on changing with availability of new drugs, 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 case in a population with high background prevalence to the most potent anti-TB drugs. WHO End TB Strategy recommends every country to advance towards knowing the RR-TB status of all TB patients at the time of diagnosis to guide appropriate treatment decision. 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.

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 multi-drug resistant TB patients. Later, patients remaining smear positive during any follow up, patients with history of previous TB treatment, PLHIV with TB and TB patients who are close contacts of MDR-TB were added to the presumptive list (erstwhile Criteria C). These vertical expansions were aligned with the horizontal geographic expansion since 2010. By 2013, the entire population had access to rapid molecular DST (CBNAAT/LPA) at least against Rifampicin 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 the 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 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. It 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 occurs, reporting of results, referral of confirmed patient for treatment and patients reaching DR-TB appropriate service delivery sites for initiating treatment. At each point, a proportion of patients are lost.
2.2 State-level structure and responsibilities

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

Figure 2.1 Overall PMDT Structures and Roles

![Summary of PMDT Structures and Roles](image)

2.3 DR-TB Centre

Programmatic & clinical management of DR-TB is complex. Treatment of drug resistant TB is not completely based on centralized and institutional care for the entire duration, but the complicated clinical care needs the presence of a clinical expert resource centre. This is the DR-TB Centre. It is a 20-30 bedded tertiary care facility established to serve a population of approximately 10 million, with airborne
infection control complaint ward, facilities for pre-treatment evaluations, treatment initiations, follow-up monitoring and management of adverse drug reactions, complications and co-morbidities. All these activities are supported by programme staff in addition to counselling for patients and data management.

Currently 143 DR-TB centres are established across India, one for approximately every 10 million population. About 5 to 10 districts are attached to each centre. DR-TB patients are admitted for a short period and once stabilized on treatment; they are 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 the DR-TB centres for change of regimens and management of ADRs.

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

Further, since March 2016, 500 Cartridge Based Nucleic Acid Amplification Test (CBNAAT) machines have been made functional in addition to 128 existing machines to cover access to most of the districts in India. These machines are currently utilised 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 the MDR/ RR-TB patients notified was observed in 2nd quarter 2016 which is expected to further increase in future. This is likely to enormously increase the demand for treatment. Treatment capacity needs to be enhanced to balance with this diagnostic capacity at every district in India. This will empower the districts to enable “test and treat approach” to eliminate the delays in diagnostic and treatment initiation pathway for all MDR/RR-TB patients within the district. Decentralization is also necessary to ensure prompt treatment initiations with scale-up to universal DST, shorter MDR-TB regimen and DST guided regimen with or without newer drugs.

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-TB centres will be established accordingly. 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 OPD basis also 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 a RNTCP designated DDR-TBC and NDR-TBC are detailed below.
2.3.1 District DR-TB Centre

The District DR-TB Center (DDR-TBC) will be 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 District DR-TB Centres

The advantages of decentralized “test and treat approach” are as below-

1. Early and faster initiation of treatment of all diagnosed DR-TB patients
2. Bringing care closer to the residence of majority of the DR-TB patients
3. Significant reduction in catastrophic expenditure including loss of work hours and family income
4. Rationally minimize the need and duration for hospitalization
5. Minimizing travel of patients thereby transmission risks during travels
6. Accountability on the district programme management units
7. Rationalise the utilization of existing DR-TB centres to enable them to concentrate in more complex clinical decisions, quality assurance of treatment and research.

The existing 143 DR-TB centres would be designated as NDR-TBCs and would serve as a referral centres for the 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.

Establishing DDR-TBC:

The DDR-TBC can be established at institutes in the given order of preference at i) Medical colleges ii) District Hospitals iii) TB Hospitals iv) NGO/Private/ Corporate institutes/ other sector hospitals with the availability of required clinical expertise. It should preferably be within close proximity of the CBNAAT site/ LPA lab in the district. There should be at-least one DDR-TBC available in the district which should be identified by the STO in consultation with the DTO and the CMO of the district. However, more than one DDR-TBC can be established wherever needed to improve access. The district authorities may take decision to establish more than one centre based on the work load of the first centre and distance to travel by patients in consultation with CTD. The composition and terms of reference of the DDR-TBC Committee is detailed (Annexure 1).

Each DDR-TBC should preferably have an AIC compliant indoor facility to accommodate 2-4 DR-TB patients with male and female separation, outdoor facilities and specialists trained in clinical management of DR-TB patients. The patients who are ambulatory could be managed on OPD basis. DDR-TBCs could operate in public
sector institution or private sector institutions linked with appropriate schemes for private sector engagement (refer to National Partnership Guidelines)

The GoI has issued **National Guidelines for Partnership (2014)**, with three different models of engaging private sector institutions/specialists in the management of DR-TB patients viz, as:-

a. DR-TB centres with wards or
b. On outpatient basis or
c. Private specialist to be provided honorarium for supporting public sector DR-TB patients in clinical management.

The DDR-TBC should be established preferably under the auspices of Department of Respiratory Medicine/ General Medicine in which members are from all clinical departments wherever available. A DDR-TBC 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. DDR-TBCs will continue to be attached to NDR-TBCs for referral and expert consultations.

**Requirements from Institute and Provision from RNTCP for establishment of District DR-TB Centres (DDR-TBCs)**

A. Requirements from the Institute:

1. It should be preferably a Tertiary/Secondary Care Institute
2. At least 2 beds each, for Male & Female separated structurally or temporally within the existing wards / separate isolation areas if available or necessary.
3. An outpatient clinic and a separated well ventilated waiting area preferably an open air shaded area to be made available.
4. Administrative, environmental and personal protective measures for airborne infection control should be in place in all indoor as well as outdoor facilities.
5. All the PMDT services (beds, consultations, diet, investigations, ECG and ancillary drugs for management of adverse drug reactions) to be provided free of cost to the patient
6. DDR-TBC committee need to be formally established with a minimum set of experts available at the district level as per Annexure 1
7. Relevant specialties like Physician, Psychiatrist, Dermatologist, ENT specialist, Cardiologist & Gynaecologist etc. should be available directly or through honorary visits for providing specialists consultations.
8. State level training of DDR-TBC committee doctors (including Chairperson), where level trainers including those from NDR-TBC committee members would serve as facilitators.
9. Routine clinical, radiological, biochemical investigation and ECG facility to be made available for pre-treatment evaluation and follow up monitoring at no cost
to the patients.
10. Ancillary drugs to be provided as per DDR-TBC Committee`s advice at no cost to the patients
11. Doctors, nursing and support staff should be available from the institute.
12. Records and Reports to be maintained for PMDT
13. NIKSHAY entries to be done on a real time basis with regular updates electronically.
14. Financial requirements if any may be availed through institute/state budgets or NHM

B. Provision under RNTCP:
1. The DTO/ MO DTC/ 2nd MO of DTC will provide the support to the District DR-TB Centre
2. A DR-TB Counsellor for counselling patients as per RNTCP Guidelines
3. District DR-TB TB-HIV Supervisor to maintain all records and reports including NIKSHAY entry and coordination with all PHI and TB Unit staff.
4. Training, formats and registers for PMDT
5. Ensuring availability of Second Line Anti TB Drug
6. Computer, Internet Facility and NIKSHAY ID for the institute.

Functions of the District DR-TB Centres (DDR-TB Centres)
The package of services at these DDR-TBCs would include:

1. Pre-treatment evaluation: All the investigations as detailed in the relevant section later 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 need to be established with the private laboratories with proper MoU mechanism as per the schemes available under National Partnership Guidelines. Since the drugs used for the treatment of DR-TB patients are known to produce adverse effects, a proper pre-treatment evaluation is essential to identify patients who are at increased risk of developing such adverse effects.
2. 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. The treatment of the patient can be initiated by the nodal person of DDR-TBC with post facto approval of the other committee members after pre-treatment evaluation of the patient is completed. PMDT treatment card & patient treatment booklet are opened; the first dose is given under supervision and registration of the patients at the DDR-TBC using the revised PMDT treatment register. Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by
the prescribed drug regimen, and if and when they occur, to notify the treatment supporter or health-care provider.

3. Providing Counselling to Patient and Family Members: Counsellor at the DDR-TBC will provide counselling and health education to the DR-TB patient and their family members about the disease, necessity of taking regular and adequate treatment, possible adverse events and steps to be taken, nutritional counselling and assistance to avail 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 Centre facility. It is started at the initial point of contact and carried on a continuous basis at all visits by the patient to a health facility. The continuous counselling and motivation is essential not only for the patient but also of the family members to ensure treatment adherence.

4. NIKSHAY entries and periodic updating from each DDR-TBC.

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

6. Travel enablers will be provide to the patient and one attendant during PTE, initiation of treatment and follow up visits as per RNTCP guidelines

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

8. Management and monitoring of adverse drug reactions: The DDR-TBC committee doctors, nurses, treatment supporters and supervisory staff, will monitor, manage and document all the adverse events routinely. 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 periodic ECGs will be done on a routine basis as per the follow up schedule. These are invaluable for detecting certain adverse effects that are more occult and before serious harm are done. Most of the ADRs can be 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.

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

10. Airborne Infection Control measures would be implemented as per the National infection control guidelines
2.3.2 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-tuberculous mycobacterium (NTMs) and those needing palliative care would be managed at the NDR-TBC.

Establishment of NDR-TBC:

The NDR-TBC must be established under the auspices of Department of Respiratory Medicine or Department of Medicine (if the former department does not exist). NDR-TBC Committee is a clinical committee where 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 the members. Clinical function of these committees should be adequately supported by the administrative or management committees of the institution in which the state TB officer must be an ex officio member. The composition and terms of reference of the NDR-TBC Committee is detailed (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 complaint isolation area in the paediatric ward in the institute of NDR-TBC. However, the government medical colleges / institutes will be eligible for all the provisions from RNTCP listed above along with one-time provision of up to Rs.15 lacs for upgradation of the ward to incorporate airborne infection control measures.

Private Hospitals and NGO Hospitals were considered to serve as NDR-TBC at places where a government medical college is not available. A scheme is available for such engagement under NGO PP guidelines of RNTCP.

Requirements from Institute and Provision from RNTCP for establishment of Nodal DR-TB Centres (NDR-TBCs)

Requirements from the Institute:

1. It should be preferably a Tertiary Care institute
2. Separate ward for male & female patients should be available with at least 10 beds in each
3. All the PMDT services (beds, investigations, ECG and ancillary drugs for management of adverse drug reactions) to be provided free of cost to the patient
4. Relevant specialties including Respiratory Medicine, General Medicine, Psychiatry, Dermatology, ENT, Ophthalmology, Gynaecology, Paediatrician and Cardiologist should be available directly or through linkages.
5. NDR-TBC Committee to be formed
6. National Training of NDR-TBC committee members (including Chairperson)
7. National Air Borne Infection Control Guidelines to be implemented in DR-TB wards and out-patients setting. (Annexure 2)
8. Routine clinical laboratory investigation facility to be made available for pre-treatment evaluation and monitoring
9. Ancillary drugs should be available
10. Management of adverse drug reactions (ADRs) as per PMDT Guidelines
11. Doctors, Nursing and support staff should be available from the institute
12. Records and Reports to be maintained for PMDT
13. Quarterly reports to be submitted electronically

Provision under RNTCP:
1. Remuneration of Sr. Medical Officer & Statistical Assistant and Counsellor
2. Training, formats and registers for PMDT
3. Second Line Anti TB Drugs
4. Computer, Internet Facility and NIKSHAY ID for the facility

Functions and responsibilities of Nodal DR-TB Centres

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

1. Pre-treatment evaluation: Patients should be examined by the specialist members. The pre-treatment 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 the schemes available under National Partnership Guidelines. Pre-treatment evaluation should include a thorough clinical evaluation by a physician, chest radiograph, haematological and bio-chemical tests detailed below. Since the drugs used for the treatment of DR-TB are known to produce adverse effects, a proper pre-treatment evaluation is essential to identify patients who are at increased risk of developing such adverse effects. A thorough clinical examination should be done during the pre-treatment evaluation. Details of pretreatment evaluation are given in relevant sections.
2. Treatment initiation of DR-TB/NTM patients: PMDT treatment card & patient treatment booklet are opened; the first dose is given under supervision and registration of the patients at the NDR-TBC using the revised PMDT treatment register
3. Providing counselling to patient and family members
4. Nikshay entries and periodic updating.
5. Travel enablers - Will be provided to the patient and one attendant during PTE, initiation of treatment and follow-up visits as per RNTCP guidelines
6. Follow up monitoring
8. Providing clinical decision, referral, management support and training to districts

2.4 Coordination

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

- Central TB Division (CTD), Ministry of Health and Family Welfare, Government of India: The CTD is the central coordinating body for the activities described in the framework. Commitment of the necessary resources, particularly towards a strong central management team, ensures that all aspects are in place from the procurement of second line anti-TB drugs to the appropriate implementation and monitoring of the PMDT service. As needed, partnerships with all relevant health care providers can be built. The CTD is supported by a National PMDT Committee, comprised of members from CTD, the three central TB institutes (NTI, NIRT and LRS), medical colleges and WHO.

- Local Health System: RNTCP PMDT activities will be tailored to fit into the respective state and district levels infrastructure. The exact organizational structure of the RNTCP PMDT services may vary between the different settings depending on how the local health care is provided. Transfer between hospitals to outpatient settings or between Treatment centres requires great care, advance planning, 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 the community leaders can greatly facilitate implementation of PMDT, and may respond to needs that cannot be met by the medical services alone. Community education, involvement, and organization around TB issues can encourage a feeling of community ownership of TB programmes and reduce stigma. In some circumstances, communities can also help address the patient’s interim needs including the provision of treatment support, food and/or housing, vocational support etc.

2.5 Overview of model of care

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

Figure 2: Overview of model of care in RNTCP PMDT
Chapter 3: National Plan for Universal Access to Quality Diagnosis and Treatment of DR-TB

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

3.1 RNTCP PMDT Vision

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

Specific objectives are to:

- By end 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 2017-25
  - Universal access to rapid molecular DST for all diagnosed TB patients
  - Universal access to DST guided treatment

RNTCP expects to treat about 100000 MDR-TB, 10000 XDR-TB and 500,000 mono and poly resistant patients per year.

3.2 RNTCP Strategy for Prevention and Control of DR-TB

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
- Implement infection control measures

Stopping transmission of DR-TB

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

**Improving laboratory capacity for rapid diagnosis of DR-TB**

RNTCP has updated its National Laboratory Scale up Plan, integrating contributions from national resources with donor resources under World Bank and Global Fund New Funding Model, with the following set of activities:

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

According to the plan, the annual DST capacity is expected to scale-up to examine >1,44,000 Presumptive DR-TB for diagnosis annually. Including other sectors, there exists now a consolidated list of > 60 labs that can contribute to PMDT scale-up (including the 43 labs identified the national lab scale up plan). In addition, RNTCP is planning to develop and scale-up the availability of some second-line anti-TB drug DST, necessary for diagnosis of XDR-TB among those identified as MDR-TB.

**Initiation and rapid-scale-up of effective treatment services for DR-TB:**

The scaling up of PMDT services is also based on effective service delivery without compromising the quality of basic RNTCP services and achieve universal access. For that 143 NDR-TBCs have already been established, approximately 750 district DR-TB Centres have to be established. Programme treatment infrastructures are provided additional human resource capacity for management and supervision including:

- Pharmacist and Store Assistant at State Drug Store
- Sr. Medical Officer and SA at NDR-TBCs
- DR-TB Counsellors in nodal and district DR-TB centres
- Sr. DR-TB and TB HIV Coordinator in every district
Moreover, the following interventions are also being undertaken to enable system strengthening to effectively scale up treatment services of MDR-TB:

- Advocate with Indian Drug Manufacturers with Global Drug Facility (GDF) support
  - Adhere to WHO Prequalification and GDF Quality Assurance systems,
  - Develop second-line drug production plans to meet national drug demand,
- Integrated national on-line electronic recording and reporting system,
- Advocate rational use of anti-TB drugs (FQ in respiratory patients) with all professional associations and practitioners,
- Procurement of rapid automated Cartridge-based Nucleic Acid Amplification Testing (CB-NAAT) for decentralized DST in districts, starting with difficult/inaccessible locations without sufficient laboratory capacity,
- Establishment of second line LPA with access to all MDR-TB patients
- Procurement of second line anti-TB drugs for management of MDR-TB patients scaled up to 100000 MDR-TB, 10000 XDR-TB and 500,000 mono and poly resistant patients per year by 2020

3.3 National Strategic Plan (2017-25)

RNTCP has 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 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 must strive to consolidate the current policy of offering DST to presumptive MDR-TB Criteria C and CBNAAT to presumptive TB among PLHIV, Children and EPTB 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). The national PMDT and lab scale up plans have been accordingly updated for next five years (2015-20) to align it with this goal and part of its funding is secured through the Global Fund NFM. The revised RNTCP Technical and Operational Guidelines 2016 (updated in accordance to WHO End TB Strategy) and guidelines for use of Bedaquiline under conditional access in RNTCP PMDT on March, 21st 2016 recently released and expansion of 500 CBNAAT machines was launched by the Hon’ble Health Minister of India.

The National PMDT Scale up Plan for 2017-2020, an operational plan, was developed by consolidating the 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 north east zone from 2015-2016. The plan was developed with
the objective to align the RNTCP vision for PMDT scale up plan with state plans, second line drugs and laboratory capacity. Outputs include 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, Delamanid, Shorter MDR-TB Regimen and DST guided treatment.

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

Stages for PMDT scale up (2017-18) are as follows:

Stage 1: Consolidate Criteria C + CBNAAT to Key Populations + baseline SLDST (FQ+SLI)
Stage 2: Stage 1 + Universal DST to all notified TB patients
Stage 3: Stage 1 + Bedaquiline & DST Guided Treatment
Stage 4: Stage 3 + Stage 2

With the upcoming NSP (2017-2025), under the RNTCP, the following estimations would be applicable:

Table 3.1 Estimates for NSP (2017-25)

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<td>NTMs initiated</td>
<td>2003</td>
<td>4860</td>
<td>8141</td>
<td>48600</td>
<td>36450</td>
<td>27000</td>
</tr>
<tr>
<td>XDR notified</td>
<td>2503</td>
<td>2970</td>
<td>3554</td>
<td>4140</td>
<td>3105</td>
<td>2475</td>
</tr>
<tr>
<td>XDR initiated</td>
<td>2253</td>
<td>2673</td>
<td>3198</td>
<td>3726</td>
<td>2795</td>
<td>2228</td>
</tr>
</tbody>
</table>
Chapter 4: Laboratory Services for Programmatic Management of Drug Resistant TB

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 Drug Resistant TB described in this chapter will ensure comprehensive diagnostic and drug susceptibility testing of patients to enable timely treatment decision for appropriate regimen. To this affect a staggered testing algorithm utilizing newer rapid diagnostic technologies such as CBNAAT, first & second Line LPA in line with WHO guidelines and expert committee meetings is detailed.

Overall, the programme need to strive to provide every TB patient with Rifampicin susceptibility status (resistant/sensitive) by providing universal access to at least Rifampicin susceptibility testing through UDST.

This chapter describes 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, job responsibilities of the State TB Officer, STDC Director, Microbiologist and LTs of IRL and other C-DST laboratories, LTs of CBNAAT laboratories. 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.

4.2 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 rifampicin by RNTCP approved genotypic or phenotypic methods
- confirmation of the species as M. tuberculosis by Immuno-chromatographic assay

Clinical laboratory services are required for the proper evaluation and monitoring of patients, including basic haematology, biochemistry, serology, and urine analysis. These would also be available at the DR-TB Centres identified by the state through public or private facility. Refer to pre-treatment evaluation for details.
4.3 Definition of accreditation and certification:

Laboratory Accreditation means third-party certification by an authorized agency using internationally approved standards for evaluating the competence of laboratories to perform specific type(s) of testing and is a formal recognition of competent laboratories. It includes all aspects of the laboratory 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 fulfil 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. RNTCP is in the process of getting TB C-DST laboratories accredited under the NABL mechanism.

4.4 Definitions

RNTCP has scaled up laboratory services for drug-susceptibility testing nationwide. Presumptive DR-TB: It refers to those TB patients who have failed treatment with first line drugs, paediatric TB non responders, TB patients who are contacts of DR-TB (or Rif resistance), TB patients who are found positive on any follow-up sputum smear examination during treatment with first line drugs, previously treated TB patients, TB patients with HIV co-infection.

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 (MR): A TB patient, whose biological specimen is resistant to one first-line anti-TB drug only.
- Poly-Drug Resistance (PDR): A TB patient, whose biological specimen is resistant to more than one first-line anti-TB drug, other than both Isoniazid and Rifampicin.
- Multi Drug Resistance (MDR): A TB patient, whose biological specimen is resistant to both isoniazid and rifampicin with or without resistance to other first line drugs, based on the results from a quality assured laboratory.
• Rifampicin Resistance (RR): A TB patient, with resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs excluding Isoniazid. Patients, who have any Rifampicin resistance, should also be managed as if they are an MDR-TB case.

• Extensive Drug Resistance (XDR): A MDR-TB patient, whose biological specimen is additionally resistant to a fluoroquinolone (Ofloxacin, Levofloxacin, or Moxifloxacin) and a second-line injectable anti TB drug (Kanamycin, Amikacin, or Capreomycin) from a quality assured laboratory.

It is to be noted that rifampicin resistance is quite rare without isoniazid resistance. The great majority of DST results with rifampicin resistance will also be isoniazid resistance, i.e. MDR-TB. This has also been substantiated by National Drug Resistance Survey (NDRS). Therefore RNTCP has taken the programmatic decision that patients, who have any rifampicin resistance, should also be managed as if they are an MDR-TB case and this is in line with the 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 Rapid molecular diagnostic testing:

• Line Probe Assay (LPA) for detection MTB complex and resistance to first line drugs R, H and second line drugs FQs and SLIDs
• Cartridge Based - Nucleic Acid Amplification Test (CBNAAT) Xpert MTB/Rif testing using the Gene-Xpert platform for now

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 follow up of patients on drug resistant TB treatment and help detect early recurrence. Thus, it will act as an indicator of relapse free cure for drug sensitive and drug resistant TB. Line Probe Assay (LPA) provides rapid diagnosis of R and H resistance as well as resistance to FQs and SLIDs. LPA can yield results in 72 hours. Nucleic Acid Amplification Test (NAAT) provides accurate and rapid diagnosis of TB by detecting Mycobacterium tuberculosis (M. tuberculosis) and Rifampicin (R) resistance conferring mutations. The test can be performed in 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, Extra-pulmonary TB and in key population such as PLHIV, socially and clinically vulnerable groups and in active case finding efforts. Culture:

• Automated Liquid culture systems e.g. BACTEC MGIT 960, BactiAlert or Versatrek etc.
• Solid (Lowenstein Jensen) media
Drug Susceptibility Testing:

- Modified Proportion sensitivity testing using the MGIT 960 system (for both first and second line drugs)
- Economic variant of Proportion sensitivity testing (1%) using LJ medium (as a back-up when indicated)
- Following drugs will be tested for susceptibility by LC:
  - First line drugs - Rifampicin, Isoniazid, PZA*  
  - Second line drugs - Levofloxacin, Moxifloxacin, Kanamycin, Capreomycin, Amikacin  
  - Other drugs - Linezolid, Clofazimine*, Bedaquiline*, Delamanid* 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 have 3 main functions (1) Imparting trainings (2) quality assurance [QA]. (3) Provision of Culture and DST for M. tuberculosis. The third-tier is the National Reference Laboratories (NRL). The overall quality assurance of the IRL and any other culture and DST laboratories (Medical colleges, NGO, Private etc.) is the responsibility of the designated NRL to which the State is linked. NRLs are also responsible for all training activities and EQA for culture and DST and molecular diagnostics (LPA & CB-NAAT) for state level staff.

4.7 Choice of Diagnostic Technology:

Programme has substantially scaled up the laboratory capacity of various Culture and 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 as follows

<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>

Similarly for follow up cultures, wherever available, liquid culture will be preferred over solid culture. However, there will be liquid cultures for at least the crucial
months of follow-up and over and beyond this, it will be determined by the workload of individual laboratories.

4.8 Specimen Collection & Transportation to Culture-DST Laboratories

Obtaining good quality specimens of adequate volume is critical to ensure correct diagnosis. The Laboratory technician needs to explain the process of collecting “a good quality sputum specimen” while adhering to airborne infection control measures. Programme recommends collection of sputa one spot and one morning, or 2 spot specimens collected with a gap of at least one hour (60 minutes) if the patient is coming from a long distance or there is a likelihood that the patient is unlikely to return to give second specimen. Ideally, a sputum specimen should have a volume of 2-5ml and preferably be mucopurulent. Care should be taken to ensure that specimens sent for molecular testing are not heavily blood stained or contaminated. 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 centers (DMC or PHI level) by trained LT and transported in cool chain on the same day to the nearest CBNAAT lab for all eligible patients. At the CBNAAT sites, based on results of RR-TB or RS-TB, the second specimen need to be re-packed by the LT at CBNAAT site and transported to the RNTCP C-DST laboratory in cool chain on same day for second line LPA (SL-LPA) or First line LPA (FL-LPA) respectively along with the updated RNTCP request form for examination of biological specimen for TB. All specimen 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, human carriers 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 below.

The following points are critical for the collection of fresh sputum specimens at designated collection points:

- The 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 for testing biological specimen form, polythene bags, tissue paper roll as absorbent, parafilm tapes, brown tape for packaging box, permanent
marker pen, labels, bio-hazard sticker, scissors, spirit swab etc. should be supplied to the DMCs for collection of sputum through the DTO.

- The 50-ml conical tubes should carry a label indicating the date of collection of the specimens and the patient’s details like name, date of specimen collection, name of DMC/DTC, Lab. No: XYZ, specimen A or B
- The Lab technicians at DMCs should be trained to carefully pack the sputum specimens in the cold box to avoid spillage of the specimens.
- The LT of DMC issuing the conical tubes to the patients should also give clear instructions to the patients on correct technique of collection of the sputum. Also the date of issue of the conical tubes to the patient should be recorded.
- The LT of the DMC should ensure that the request for testing biological specimens form is packed in a separate plastic zip pouch and placed in the cold box before sealing the lid of the box. Also, the bio-hazard symbol should be pasted on the external side of the cold box along with the label indicating the postal address of the C-DST Lab assigned.
- The LT of the DMC should promptly inform the specimen transport agency like a courier / speed post service, speed post or a human carrier to collect and transport the specimens
- As per the national guidelines for Biomedical waste management (Annexure 3) the containers used for transporting sputum specimens to the C-DST laboratory should be labelled with a “BIO-HAZARD” sticker.
- For every DR-TB suspect referred by the MO-DMC, the date of referral and transport of sputa specimens to the Culture & DST laboratory should be entered in the “Remarks” column of the respective DMC Lab register and the TB notification Register and in the Referral for Culture and DST Register held at the DTC (See Annexure 12). Alternatively the DR-TB suspect referred to nearby DMC selected for specimen collection and transport for C-DST may be 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 for C-DST from where these will be packed in cold boxes and transported to the C-DST laboratory for culture and DST.
- 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.
Figure 4.1 Technical Specifications of Transport Box for Sputum Specimen transportation in Cool Chain

- **A: Gujarat Model**: Total capacity up to 4 Falcon Tubes (from peripheral DMCs)
- **Thermocol Box**: Outer dimension (Cm): 18.5 X 12.5 X 13 Inner dimension (Cm): 14.25 X 8.25 X 10.25
- **No. of gel packs required**: 2
- **Weight of fully packed consignment box**: 400 grams.
- **Approximate cost of courier charge**: 60-70 Rupee per box

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

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

(This is a onetime use box. Thermocol boxes and gel packs are not reused.)

The specimen collection and transportation from extra-pulmonary TB (EP-TB) sites and children need to be done as per the SOP under RNTCP (Annexure 4)
4.9 Certification & Quality Assurance for Culture - DST Laboratories:

The components of Quality assurance for C-DST include Internal Quality Control (IQC) and External Quality Assessment (EQA) mechanisms.

Internal Quality control 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. External quality assessment is not performed for culture. Internal quality control 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.

Figure 4.2: External Quality Control for TB Culture and DST laboratories

External quality control for both LJ as well as MGIT is performed in two stages, initial retesting as one time activity where the NRL retests ten strains out of hundred 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 thirty 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 twenty strains out of 50 performed in duplicates at the participating laboratory. This is followed by annual proficiency testing with panel strains. PT Benchmark:

- Invalid LPA results – Less than 10%
- Contamination of negative control – Clean in all runs
- Internal Concordance – Greater than 95%
- External Concordance – Greater than 95%

Quality assurance for CBNAAT: Each CBNAAT cartridge contains internal controls: Specimen Processing Control (SPC) and Probe Check Control. If 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. SPC must be:

- positive when the result is MTB Not Detected
- SPC can be negative or positive when the result is MTB Detected
- The test result is invalid if the SPC is negative when the test result is 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 be visited by IRL/NRL during their EQA visits. Poorly performing sites should be prioritized for onsite visits. All newly inducted laboratory staffs must undergo an induction training and periodic refresher training, as prescribed under RNTCP

4.10 Non Tuberculous Mycobacteria (NTM)

There are a large number of mycobacteria other than Mycobacterium tuberculosis, which are now being increasingly recognized as a cause of human disease. Commonly referred to as Non-tuberculous 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 and they are distinct from Mycobacterium tuberculosis in their characteristics that they can survive outside the human or animal host. They are generally non-pathogenic or opportunistic pathogens and most commonly cause disease when there is immunosuppression or injury except for few species which infect immune-competent humans.

Often these bacteria Habit the respiratory passages in the form of commensal organisms. Pulmonary infection from NTM though rare, can cause disease similar to tuberculosis. 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. kansasii generally occurs in elderly persons especially males who are smokers or having pre-existing 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. chelonae 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 all are helpful in determining whether the isolated mycobacteria are to be considered the 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.

**Table 4.1: Ten Most Frequently Isolated Non-Tuberculous 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>M. avium complex (M. avium, M. intracellulare, minor species)</td>
<td>Pulmonary, Lymph nodes, Disseminated disease</td>
<td>Slow</td>
</tr>
<tr>
<td>M. kansasii</td>
<td>Pulmonary, Disseminated disease</td>
<td>Slow</td>
</tr>
<tr>
<td>M. xenopi</td>
<td>Pulmonary</td>
<td>Slow</td>
</tr>
<tr>
<td>M. malmoense (NW Europe)</td>
<td>Pulmonary</td>
<td>Slow</td>
</tr>
<tr>
<td>M. ulcerans</td>
<td>Skin</td>
<td>Slow</td>
</tr>
<tr>
<td>M. marinum</td>
<td>Skin</td>
<td>Intermediate</td>
</tr>
<tr>
<td>M. abscessus</td>
<td>Pulmonary, Skin</td>
<td>Rapid</td>
</tr>
<tr>
<td>M. cheloneae</td>
<td>Skin, Soft tissues, Disseminated disease</td>
<td>Rapid</td>
</tr>
<tr>
<td>M. fortuitum</td>
<td>Skin, soft tissues, Pulmonary</td>
<td>Rapid</td>
</tr>
<tr>
<td>M. scrofulaceum</td>
<td>Lymph nodes</td>
<td>Rapid</td>
</tr>
<tr>
<td>M. haemophilum</td>
<td>Disseminated disease</td>
<td></td>
</tr>
</tbody>
</table>

The minimum evaluation of a patient presenting with features suggestive of nontuberculous mycobacterial (NTM) lung disease should include the following:

1. chest radiograph or, in the absence of cavitation, chest high-resolution computed tomography (HRCT) scan;
2. three or more sputum specimens for acid-fast bacilli (AFB) analysis; &
3. exclusion of other disorders, such as tuberculosis (TB).
4. expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination. Patients who are 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.

v. 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 fit best with Mycobacterium avium complex (MAC), M. kansasii, and M. abscessus.

A- Clinical
1. Pulmonary symptoms: Cough, hemoptysis, fever, weight loss or organ specific signs and symptoms etc.
2. Exclusion of any other etiologies

B- Radiological
1. Radiological findings: nodular or cavitary opacities on chest radiograph
2. Or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules AND

C: 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 sputum results available with:</td>
<td>Two positive cultures regardless of the results of AFB smear</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Single available bronchial wash or lavage with:</td>
<td>One positive culture regardless of the results of AFB smear</td>
</tr>
<tr>
<td>OR</td>
<td></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>Compatible histopathology- (granulomatous inflammation) and a positive sputum or bronchial wash culture for NTM</td>
</tr>
</tbody>
</table>

Guidelines for making the diagnosis of NTM-pulmonary disease

i. Clinical features of an indolent, respiratory disease – cough, expectoration, fever and other constitutional symptoms.
ii. 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.

iii. Histopathological features of mycobacterial/granulomatous disease or culture of NTM from biopsy specimens.

iv. Radiological features of nodular infiltrates with or without cavitation and/or bronchiectatic lesions.

v. Underlying host conditions: Immunosuppression, AIDS, alcoholism, COPD, cystic fibrosis, diabetes, malignancies, prior TB, oesophageal motility disorders etc.

vi. Absence of other causes of pulmonary lesions, such as tuberculosis, aspergillosis, etc.

vii. Persistence of AFB after anti-tuberculosis treatment for two weeks or more with CBNAAT or LPA report not detecting Mycobacterium tuberculosis.

viii. Smear positive, CBNAAT negative, LPA TUB band negative with or without rifampicin resistance in patients of presumed MDR at diagnosis also need to be evaluated.

The diagnostic processes for NTM to be followed at C-DST laboratories are detailed in (Annexure 5). The laboratory staff would be separately trained in these standard operating procedures for laboratory confirmation of NTM.
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 prevent the patient from spreading the disease to others, developing a resistant strain to more drugs, and progressing to chronic state of permanent lung damage.

5.1 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:

**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>• Co-morbidities 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 clinics/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 patients 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 (or R resistance), TB patients who are found positive on any follow-up sputum smear examination during treatment with first line drugs, previously treated TB patients, 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 rapid molecular method. CBNAAT is the preferred rapid molecular diagnostic test under RNTCP. At the CBNAAT site, two specimens will be collected as detailed in the diagnostics section. 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. Please refer to RNTCP Laboratory manuals on Standard Operating Procedures for C-DST, LPA and CBNAAT testing.

**Turnaround time:** Genotypic testing is much faster than phenotypic methods, as these are not growth based tests allowing for timely diagnosis and prompt treatment initiation. DST results by 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.

**Figure 5.1 Operational process of specimen referral**

Once the MO PHI confirms that the patient is a presumptive DR-TB patient, he/she 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 for testing biological specimen for TB form. 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 on the next day early morning and go with the early morning specimen and records to the nearest DMC identified for
 specimen collection for C-DST by the DTO. The spot specimen can be collected in such cases when the patient arrives to submit the early morning specimen. Alternatively, specimens can be collected at such DMCs and PHIs and transported in vaccine carriers by the staff on the same day to the nearest DMC identified as specimen collection centre for C-DST for packing in cool boxes and further transport to through courier or speed post. If there is likely to be a delay in transporting the specimens, the specimens should be stored in a refrigerator at the peripheral DMC / PHI with bio-safety 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 rifampicin 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:

1) **Bacteriologically positive after intensive phase** of a course of TB/DR-TB treatment
2) **Failure to respond to treatment** as per RNTCP definitions
3) **Recurrence of TB** diagnosed after a course of TB treatment
4) For patients who are retrieved **after loss to follow-up**
5) 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 patient not returning for the second collection or travelling from long distances 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 disease. Those presumed to have TB belonging to the paediatric age group, people living with HIV, extra-pulmonary group, smear negative chest X-ray suggestive of TB will be offered CBNAAT test. By virtue of using CBNAAT as the TB diagnostic test, the rifampicin status is also available simultaneously along with TB detection.
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 simultaneously done. Culture Isolates would be preserved for future DST to Cfx & BDQ when available & 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
The non 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 (universal DST) which is knowing the DR status of the patient at least to the key first line drug rifampicin to guide decision of the appropriate treatment. Based on the result obtained on the CBNAAT, the patient would be classified as rifampicin resistant (RR TB) or rifampicin susceptible (RS TB).

For patients with RR-TB results, the second specimen will be reflexly transported in cool chain from the CBNAAT lab to the nearest C-DST lab for baseline second line DST (SLDST). The specimen is tested for further drug resistance to second line drugs using SL-LPA which will be used to design the treatment regimen, while a LC-DST will be simultaneously set up for second line drugs like Moxifloxacin (Mfx 2.0), Kanamycin (Km), Capreomycin (Cm) and Linezolid (Lzd). The culture isolate will be preserved for future DST to Clofazimine (Cfx) and Bedaquiline (Bdq) whenever available, standardized and WHO endorsed. The results of the LC-DST for individual fluoroquinolones (FQ) and second line injectables (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 fluoroquinolones the cross resistance between Ofloxacin (2.0), Levofloxacin (1.5) and low level Moxifloxacin (0.5) is almost complete (Indian evidence) and thus not useful for clinical management except for higher concentration of Moxifloxacin (2.0) DST which then guides to take a decision to use it at a higher dose if sensitive or to move to a fluoroquinolone free regimen if resistant.

For patients with RS-TB results, the second specimen will be reflexly transported in cool chain from the CBNAAT lab to the nearest C-DST lab for FL-LPA. If during this LPA testing, rifampicin is reported resistant, the deposit is subjected to repeat CBNAAT for confirmation of rifampicin resistance. The final result will be on consensus of the 3 tests (2 CBNAAT and 1 LPA). If 2 of 3 are rifampicin resistant then the final result will be rifampicin resistant; if 2 of 3 are sensitive, then the final result will be sensitive to rifampicin. If the result is H resistant, the SL-LPA and LC-DST will be reflexly offered to the available specimen.

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.
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 to be communicated to the concerned DTO, DR-TB centre/ 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 to be utilised. If the culture result shows early contamination (within 4 days), the same is informed to the DTO within 24 hours and s/he should arrange to send 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 / R resistance.

5.4 Management of patient while DST results are awaited

Any diagnosed TB patient whose RR-TB result is awaited, would be initiated on first line anti-TB treatment using daily FDC and continued on the same if found to be RS-TB.

If RR-TB is detected, the patient is immediately referred for pre-treatment evaluation, and treatment initiation for DR-TB. The first line treatment should be stopped as applicable.

All presumptive TB among key/vulnerable population would be initiated on RR-TB or RS-TB regimen based on the results of CBNAAT.

5.5 Diagnosis in Paediatric Patients

Very limited data is available for MDR-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 MDR-TB in adults, so MDR-TB is common in children in settings where MDR-TB is common in adults with higher morbidity and mortality compared to drug-sensitive disease.

Children who are treatment after lost to follow up, recurrent TB and treatment after failure are presumed patients of MDR-TB. Children usually have pauci-bacillary disease and are sputum negative. So, these definitions are to be used in conjunction with clinico-radiological picture. In addition to it, some other children who are at high
risk of DR-TB viz. contacts of MDR patients and Children living with HIV (CLHIV) and paediatric non responders.

**Approach to diagnose MDR-TB in children**

Careful history of patients in particular, history of contact with MDR-TB case is critical information, also consider child failing first-line TB treatment despite adherence. Clinical examination, investigations relevant for presumptive TB or EP-TB patients need to be carried out. It is important to try to get specimens for culture and DST. 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 MDR-TB for LPA or CBNAAT (e.g. Xpert MTB/RIF) or culture and drug sensitivity testing. Microbiological confirmation should always be done and to ensure correct diagnosis, all efforts must be made to get clinical specimens from the affected site. Sputum, gastric lavage, BAL, lung tap, lymph-node aspiration, excision, CSF, laparoscopic tissue biopsy can be considered. Diagnosis of drug resistant tuberculosis in the absence of Microbiological confirmation must be thoroughly reviewed as it may often be untenable. In presumptive DR-TB, if there is no microbiological confirmation, bacteriologically negative clinically diagnosed MDR-TB can be considered after ruling out alternative diagnosis.

**Table 5.2: Case definitions of DR-TB among children**

<table>
<thead>
<tr>
<th>Terms</th>
<th>New Definition under RNTCP</th>
</tr>
</thead>
</table>
| Presumptive DR-TB patient | - Those who have failed treatment with 1st line drugs  
- Paediatric TB non-responders  
- TB patients who are contacts of MDR-TB (R-resistance) patients  
- TB patients who are found positive on any follow up smear during treatment on 1st line drugs  
- Previously treated TB patients  
- TB patients with HIV co-infection  |
| MDR-TB patient     | A presumptive DR-TB patient whose  
- Biological specimen is resistant to both H and R  
- With or without resistance to other 1st line drugs  
- Based on the results from a quality assured lab  |
| XDR-TB patient     | An MDR-TB patient whose recovered M.Tb isolate is  
- resistant to at least H, R, a fluoroquinolone (Ofx, Lfx, Mfx)  
- AND a 2nd line injectable anti TB drug (Km/Am/Cm)  
- Based on results from a quality assured lab  |
<p>| Mono Resistance    | Resistance to any one of the first line anti TB drugs (HRZES)  |</p>
<table>
<thead>
<tr>
<th>Poly Resistance</th>
<th>Resistance to any two first line drugs but not both H &amp; R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable MDR-TB among Children:</td>
<td>Children wherein bacteriologic confirmation is not available and the decision regarding diagnosis and initiation of treatment be with the NDR-TBC Committee.</td>
</tr>
<tr>
<td>Criteria for diagnosis of “probable MDR-TB” include:</td>
<td></td>
</tr>
<tr>
<td>(a) Contact with known MDR-TB patient or adult who failed/died while on TB treatment</td>
<td></td>
</tr>
<tr>
<td>(b) Clinical and/or radiological deterioration despite regular treatment with new or re-treatment regimen for 3 months.</td>
<td></td>
</tr>
</tbody>
</table>

Perform LPA/CBNAAT for every presumptive DR-TB child for rapid detection of Rifampicin resistance to decide the treatment regimen and further subject specimens to SL-LPA and Liquid Culture DST to diagnose additional resistance to second line drugs as per the integrated diagnostic algorithm.

**Figure 5.3 Diagnostic algorithm approach to presumptive or confirmed DR-TB in children**
Specimen for AFB, CBA-ELISA TB Send MGIT cultures

Specimen AFB positive CBA-ELISA TB Rif sensitive

Start Category II

Await MGIT and DST or LPA

MGIT negative

Continue Category II

MGIT - Mtb sensitive to FLD

Modify regimen

MGIT - Poly drug resistance

Modify regimen, if needed

Specimen AFB positive CBA-ELISA TB Rif resistance

Start MDR regimen

Await MGIT DST to FLD and also perform DST SLD / LPA

Specimen AFB and CBA-ELISA TB Mtb negative

Plan further investigations for alternative diagnosis in association with pediatric pulmonologist Might need a CT Chest and flexible bronchoscopy Remember: still can be DR TB
Chapter 6: Pre-Treatment Evaluation

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

6.1 Referral for pre-treatment 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 the Medical Officers – TB control (MO-TC) & PHI, District DR-TB TB-HIV Supervisor and Senior Treatment Supervisor (STS) and bring the patient to the DDR-TBC where he/she will be counselled by the counsellor. Counselling should include (1) information on the lab results, and the reliability of lab results from CBNAAAT/RNTCP certified C-DST laboratories, (2) the need for additional treatment, (3) the importance of rapid initiation of treatment and adherence to prescribed treatment, (4) the services RNTCP offers for PMDT (5) what the patient should do next, and (6) necessary infection control precautions, and re-assurance to the family against panic or unnecessary stigmatization of the patient.

After counselling, the patient is referred to the DDR-TBC with their DST result and PMDT referral for treatment form as annexed, for pre-treatment evaluation and initiation of standard regimen for DR-TB as appropriate. In addition to those patients diagnosed as Rifampicin-Resistant (RR) or Multi-Drug Resistant (MDR) TB, patients with H mono/poly DR-TB, will also be referred to the DDR-TBC for pre-treatment assessment. Those patients, who have RR-TB, will also be treated with Regimen for MDR-TB.

While the RR/MDR-TB/H mono/poly DR-TB patient is undergoing pre-treatment evaluation, the District 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, a community worker or a community volunteer, or a 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 the medications under supervision at the residence under close monitoring by TBHV/STS. The Treatment Supporter should be given training for drug administration, identification of adverse effects during treatment, the frequency of follow up and record keeping. During IP appropriate arrangement for Injection should be done by the DTO.

6.2 Pre-treatment Evaluation for DR-TB Patients

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

Patients will be referred to the DDR-TBC/NDR-TBC with pre-treatment evaluation results for initiation of treatment. Physician may decide for admission to DDR-TBC/NDR-TBC for pre-treatment evaluation and initiation of treatment or get it done on outpatient basis. Pre-treatment evaluation should include a thorough clinical evaluation by a physician, chest radiograph, and relevant haematological and biochemical tests noted below. Since the drugs used for the treatment of DR-TB have significant adverse effects, pre-treatment evaluation is essential to identify patients at increased risk of developing such adverse effects. The pre-treatment evaluation will vary as per the regimen class and is detailed in the table 6.1 below.

Each of the DR-TB centres (DDR-TBC/NDR-TBC) must ensure that laboratory capacity and consultancy services from various specialists are available, either in-house or through an outsourced mechanism supported under institutional/state govt. mechanisms. Tie up with private facility under New Partnership Guidelines (innovation clause) to be undertaken for investigations not available for avoiding delays in pre-treatment evaluation.

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

Pre-treatment evaluation and treatment initiation must be done at the DDR-TBC. MDR/RR-TB patients (without additional resistance) and H mono/poly DR-TB patients can be initiated on standard treatment regimen at DDR-TBC. DDR-TBC can refer 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 experts 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 Pre-treatment evaluation of DR-TB patients by regimen class:

<table>
<thead>
<tr>
<th>SN</th>
<th>Pre-treatment 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>A thorough clinical examination</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5</td>
<td>Complete Blood Count with 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 (if possible)</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>Psychiatric 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 in 12 leads with long lead (if Mfx\textsuperscript{h}, Bdq, Cfx used)</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 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 cases will be offered referral for HIV counselling and testing at the nearest centre if the HIV status is not known or the HIV test 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 Counselling to Patient and Family Members

Providing counselling and health education to the MDR/RR-TB patient and their family members about the disease and about the necessity of taking regular and adequate treatment is of utmost importance. Health education and counselling is provided to all patients and family members at different levels of health care, from the periphery to the DDR-TBC facility. It is started at the initial point of contact and is continued during all visits by the patient to a health facility.

DDR-TBC/NDR-TBC counsellors to provide counselling for all DR-TB Patients - on 1) the nature and duration of treatment, 2) importance of adherence to treatment and need for complete and regular treatment, 3) possible side effects of drugs and 4) the consequences of irregular treatment or pre-mature cessation of treatment. It is advisable to involve close family members during the counselling, since family support is an essential component in the management. Patients should be advised to report any side effects immediately. Female patients should receive special counselling on family planning.
Chapter 7: Treatment of Drug Resistant TB

This chapter provides guidance on the treatment of such DR-TB patients and deals with the following:

1. Classification of patients based on drug resistance pattern
2. Classes of Anti TB drugs recommended for the treatment of DR-TB patients
3. Newer anti-TB drugs
4. Integrated DR-TB algorithm
5. Treatment Initiation
6. Regimen type (including newer drugs)
7. Drug dosages and administration
8. Treatment Duration
9. Patient Flow
10. Management of Treatment Interrupters
11. Transfers of DR-TB Patients
12. Managing patient referrals from other sectors for DR-TB evaluation and treatment
13. Palliative care

7.1 Classification of patients based on drug resistance pattern:

The following is the classification of drug resistant TB patients based on the results from a quality assured laboratory:

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

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

- **Rifampicin Resistance (RR):** A TB patient, whose biological specimen is resistant to rifampicin, detected using phenotypic or genotypic methods, without resistance to other anti-TB drugs.

- **Multi Drug Resistance (MDR):** A TB patient, whose biological specimen is resistant to both isoniazid and rifampicin with or without resistance to other first line 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 (Km, Am, Cm).
7.2 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 are aligned with revised classification as per WHO PMDT Guidelines 2016 as per the table below.

Table 7.1: Grouping of anti-TB drugs

<table>
<thead>
<tr>
<th>New Grouping of Drugs</th>
<th>Levofloxacin</th>
<th>Moxifloxacin</th>
<th>Gatifloxacin</th>
<th>Lfx</th>
<th>Mfx</th>
<th>Gfx</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Second-line injectable agents</td>
<td>Amikacin</td>
<td>Capreomycin</td>
<td>Kanamycin (Streptomycin)</td>
<td>Am</td>
<td>Cm</td>
<td>Km (S)</td>
</tr>
<tr>
<td>C. Other core second-line agents</td>
<td>Ethionamide / Prothionamide</td>
<td>Cycloserine / Terizidone</td>
<td>Linezolid</td>
<td>Clofazimine</td>
<td>Eto/Pto</td>
<td>Cs/Trd</td>
</tr>
<tr>
<td>D. Add-on agents (not part of the core MDR-TB regimen)</td>
<td>Pyrazinamide</td>
<td>Ethambutol</td>
<td>High-dose isoniazid</td>
<td>Z</td>
<td>E</td>
<td>H&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
<td>Delamanid</td>
<td></td>
<td>Bdq</td>
<td>Dlm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-aminosalicylic acid Imipenem-cilastatin4 Meropenem4 Amoxicillin-clavulanate4 (Thioacetazone)</td>
<td></td>
<td>PAS</td>
<td>Ipm / Mpm</td>
<td>Amx-Clv (T)</td>
<td></td>
</tr>
</tbody>
</table>

7.3 Newer Anti TB Drugs

After almost five decades of discovery of Rifampicin, in late 2012 the first new drug named Bedaquiline (BDQ) with anti-TB effect was approved for treatment of multi-drug resistant TB by US FDA. This was followed by approval of another new drug Delamanid stringent regulatory authority of various countries. The drug development pipeline of new and re-purposed drug has gained momentum in the recent past and more new molecules are expected to be approved in 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 tuberculosis*. Strong bactericidal and sterilizing activities against *M. tuberculosis* 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 needs 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. There is emerging evidence that BDQ demonstrates cross-resistance with Clofazimine.

In June 2013, WHO published interim policy guidance for the use of BDQ in conjunction with the 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 pyrazinamide (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 also published the Implementation plan for introduction of BDQ for treatment of MDR-TB at country level to support country efforts towards the implementation of recommended new drugs or treatment regimens with particular emphasis on active drug safety monitoring (aDSM) in absence of Phase III results on safety and efficacy of the drug.

**7.3.1 Regulatory Approvals for Bedaquiline in India:**

After a thorough review of the available evidences from various phased trails up to phase IIb; evidences emerging from various early implementing countries; WHO Interim guidelines for use of Bedaquiline; regulatory processes adopted by 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 Honourable Supreme Court of India approved the use of BDQ (100 mg) in adults aged 18 or over 18 years as part of 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 RNTCP framework for conditional access through the PMDT programme for treatment of MDR-TB patients only”. Soon after this, on 4th January 2015, the Drug Controller General of India (DCGI) granted an import license to Janssen (M/s. Johnson & Johnson Limited, India) dated 04 January
2015, 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 active drug safety monitoring (aDSM). In March 2016, RNTCP introduced BDQ through conditional access programme at six DR-TB centres in the country initially and based on the lessons learnt, preparation for expansion of access to BDQ has been initiated in all states in 2017.

7.3.2 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**
- Females should not be pregnant, or not be using effective non-hormone-based birth control methods. They should be willing to continue practicing birth control methods throughout the treatment period, or have been post-menopausal for the past 2 years.
- Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation.

**Exclusion criteria:**
- Currently having uncontrolled cardiac arrhythmia that requires medication;
- Has any of the following QT/QTc interval (Annexure 22) characteristics at screening:
  - A marked prolongation of QT/QTc interval, e.g. repeated demonstration of QTcF (Fredericia correction) interval > 450 ms;
  - A history of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalaemia, family history of long QT syndrome;
- Has evidence of chorioretinitis, optic neuritis, or uveitis at screening which precludes long term linezolid (Lzd) therapy;
- Has 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 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 (>1.5 times ULN);
  - Lipase grade 2 (with no signs or symptoms of pancreatitis) or greater (>1.5 time ULN).

**Note:** If the results of the serum chemistry panel, haematology or urinalysis are outside the normal reference ranges (including the above listed parameters), the patient may still be considered if the physician judges the 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 the DST results for the key first line and second line drugs and would be managed with DST guided regimens.

BDQ is indicated if such a regimen is not feasible because of:

i. in vitro resistance to fluoroquinolones and/or second-line injectable drugs;
ii. known adverse reaction, poor tolerance or contraindication to any component of the combination regimen; or
iii. unavailability or lack of a guaranteed supply of a drug(s).

Accordingly, the following subgroups of patients will be eligible for BDQ:-

1. MDR/RR-TB with resistance to any/all FQ OR to any/all SLI
2. XDR-TB
3. Mixed pattern resistant TB (XDR-TB + additional FL/SL resistant TB)
4. Treatment failures of MDR-TB + FQ/SLI resistance OR XDR-TB

The regimen design with or without newer drugs, pre-treatment evaluation, treatment initiation, duration, modification and monitoring, active drug safety monitoring, supply chain management is described in details in the relevant sections of the guidelines.

7.4 Integrated Drug Resistant TB Algorithm

The integrated DR-TB algorithm 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 the subsequent sections.

7.5 Treatment Initiation:

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.

If the CBNAAT reveals RS-TB, the second specimen of the patient must be immediately packed and transported from the CBNAAT lab to the nearest LPA laboratory for first line LPA and the patient is initiated on the first line treatment at the PHI level. If LPA reveals H mono resistance, this would serve as a surrogate for poly DR-TB (all first line drugs except rifampicin) and the patient must be counselled by the PHI staff to visit the DDR-TBC with a family member for further management without any further delay.

If the CBNAAT reveals RR-TB, patients must be counselled by the PHI staff to visit the DDR-TBC for further management with a family member without any further delay.
Conventional MDR TB Regimen (24 m) for pregnant women or for EP TB patients
*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 simultaneously done. Culture isolates would be preserved for future DST to Cfx & BDQ when available & 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

Figure 7.1 Integrated Drug Resistant TB Algorithm

Presumptive TB

All diagnosed TB patients

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

CBNAAT

CT

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

RR TB

RS TB

First line treatment

FL-LPA*

SL-LPA**

FQ and SLI Sensitive

FQ and/or SLI Resistance

H Resistant

H Sensitive

Newer Drugs & DST guided treatment

Continue same regimen

H mono/poly resistant TB regimen

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
*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 simultaneously done. Culture isolates would be preserved for future DST to Cfx & BDQ when available & 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
The second specimen of the patient must be immediately packed and transported from the CBNAAT lab to the nearest LPA laboratory for all diagnosed RR-TB to be subjected to SL LPA and LC DST at baseline for Mfx (2.0), Km, Cm and Lzd. The results of second line LPA are expected to be available within a week followed by the result LC DST after 6-8 weeks of specimen submission.

The DDR-TBC committee carries out the pre-treatment evaluation (including clinical, radiological, surgical evaluation) of the patient, provides counselling, initiates active drug safety monitoring (aDSM) activities like assessing the baseline history of known adverse/serious adverse events (AE/SAE), biochemical investigations, ECG etc. and initiates him/her on the appropriate standard treatment regimen.

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.

For all laboratory confirmed RR-TB patients, the DDR-TBC will initiate the standard shorter MDR-TB regimen (9-11 months) after careful assessment and management of pregnancy or if the patient has EPTB through specialist consultation if required. Such patients, if after assessment, are found to be not eligible for shorter MDR-TB regimen, they are initiated on standard conventional MDR-TB regimen (24-27 months). Similarly, a laboratory confirmed H mono resistant TB patient is initiated on a standard regimen for H mono/poly DR-TB.

The patient is initiated on standard regimen at DDR-TBC on indoor or outpatient basis and subsequently sent for ambulatory treatment to the MO-PHI for continuation of treatment regimen and regular follow-up.

**Ambulatory Treatment Initiation of DR-TB Patients:**

Wherever possible, DR-TB patients can be initiated on treatment on ambulatory basis. The DDR-TBC Committee can decide on case to case basis the need for admission for DR-TB Patients for initiation of treatment.

In both the scenario, DTO refers the patient to the identified treatment supporter with information to MO-PHI, provides drugs and records to the treatment supporter.

The results of SL-LPA are expected to be available within a week of specimen submission. The pre-treatment evaluations, baseline aDSM assessment as applicable would be considered valid for assessment of the patient and regimen change. The LPA lab must report whether the specimen is resistant to all SLIs (i.e. rrs mutation) or only Kanamycin (eis mutation).
Table 7.2: Management differences in ambulatory v/s indoor DDR-TBC

<table>
<thead>
<tr>
<th>Ambulatory Treatment Initiation</th>
<th>Treatment Initiation on Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DDR-TBC committee decides to initiate DR-TB treatment.</td>
<td>• DDR-TBC committee decides to initiate DR-TB treatment.</td>
</tr>
<tr>
<td>• MO-TC / PHI informed as soon as decision taken, so unit level preparations can be ready.</td>
<td>• MO-TC / PHI informed as soon as decision taken, so unit level preparations can be ready.</td>
</tr>
<tr>
<td>• Treatment card/book opened by DDR-TBC and patient registered in RNTCP PMDT Register. NIKSHAY ID of such patients will be provided at DDR-TBC, if not already available.</td>
<td>• Treatment card opened and patient registered in the RNTCP PMDT Register at DDR-TBC. NIKSHAY ID of such patients will be provided at DDR-TBC, if not already available.</td>
</tr>
<tr>
<td>• Treatment initiated by DDR-TBC and the first dose given under supervision at the DDR-TBC</td>
<td>• Patient discharged after at least one week post treatment initiation with maximum 7 days drug supply for the transit.</td>
</tr>
</tbody>
</table>

As soon as available, the results of baseline SL-LPA and LC-DST are communicated from the C-DST lab to DDR-TBC, DTO, MO-PHI and the patient. Based on the results, if no additional resistance is detected, the patient will be continued on the same regimen at the district level.

If additional resistance to FQ and/or SLI is reported the standard regimen of these patients would be stopped. The patient is counselled by the PHI staff and referred to the NDR-TBC for a regimen change where the committee would revisit the regimen of the patient for a decision to re-design the regimen based on the DST pattern with or without newer drugs based on eligibility and patient consent. As the patient is still 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 treatment outcome, the patient would be accounted for the most recent episode of treatment.

Apart from this, while monitoring progress of patients continued on the same regimen (shorter MDR-TB or conventional MDR-TB or H mono/poly DR-TB) at the district level, 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 DDR-TBC with copy of all records for baseline pre-treatment 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. However, for patients who are declared regimen change in CP will be
declared with outcome as “Failure” and re-registered for the next episode of an appropriate treatment.

The patient will be re-classified as per DST pattern and re-registered as a new episode of treatment on the same NIKSHAY ID. The 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 re-classification. 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 23) 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. After this, a written informed consent (Annexure 24) will be obtained from patients before administration of BDQ containing regimen. Cohort Event Monitoring (CEM) treatment initiation form need to be completed and uploaded on NIKSHAY for all patients considered for BDQ containing regimen only at the initial six DR-TB centre involved in BDQ conditional access programme.

All patients eligible for newer drugs containing regimen would be managed in an inpatient 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 inpatient management rests with the NDR-TBC committee and must be well-documented for every patient. After discharge, the treatment will be continued on ambulatory basis with strict adherence to treatment and the follow up schedule. All measures for airborne infection control must be implemented as per the national AIC guidelines while managing all TB patients. In exceptional patients who are not seriously ill, are ambulatory, are residing close to the NDR-TBC and are willing to visit the NDR-TBC for periodic ECG and clinical evaluation, the NDR-TBC committee may decide to manage the patient on ambulatory basis.

7.6 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 pyrazinamide 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 high-dose isoniazid (H\textsuperscript{H}) and/or ethambutol.

It has been observed in the recent national drug resistance survey in India that almost all the H resistance detected among RR-TB patients were based on mutation at KatG. Hence, inclusion of H\textsuperscript{H} in the DR-TB regimen design has been completely ruled out in India. Similarly, there was no correlation observed between Eto resistance with H resistance at INA mutation and hence this has not been considered in the regimen design. The correlations between individual drugs within FQ class and SLI class drugs have been detailed earlier in the section of the integrated diagnostic algorithm.

BDQ containing regimen would contain BDQ + 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, it will be avoided in BDQ containing regimen.

Designing a regimen is the prerogative of the DR-TB Center Committee. The regimen could be with or without inclusion of newer drugs like BDQ and would be classified into the following types:

**At the DDR-TBC:**
1. H Mono/Poly drug resistant TB
2. MDR/RR-TB
   a. Shorter MDR-TB regimen
   b. Conventional MDR-TB regimen

**At the NDR-TBC:**
3. MDR/RR-TB with additional resistance to any/all FQ or SLI
4. XDR-TB
5. Mixed pattern drug resistant TB
   a. with H mono + FQ/SLI/Lzd resistance
   b. with MDR/RR-TB + FQ/SLI + Lzd resistance
6. Non tuberculous mycobacterium (NTM)

**7.6.1 H Mono/Poly drug resistant TB**

On receiving the reports showing H mono resistant on LPA that serves as a surrogate for first line drugs poly resistant TB (excluding R), the patient and their family members should be counselled and referred to the nearest district DR-TB centre. Baseline SL DST will be performed as detailed above.

The DDR-TBC will undertake the pre-treatment evaluation (including clinical and radiological evaluation) and initiates the patient on the standard treatment regimen as in Table 7.3
7.6.2 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 EP’TB patients (see sections later).

a. 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 rifampicin-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 could receive the shorter MDR-TB regimen.

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 rifampicin resistant-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 fluoroquinolone 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, H, E, Eto, Cfx) apart from those mentioned, owing to the unreliable nature of the tests.

**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 9 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
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 pyrazinamide and/or fluoroquinolones on shorter MDR-TB regimens, even if in general it remained high and exceeded that in the patients on individualised, conventional regimens (although the differences were not statistically significant).

**Table 7.3: Treatment success in patients treated with a shorter MDR-TB regimen versus 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 the conventional MDR-TB regimens (24-27 months) with poor treatment outcomes in MDR-TB of about 46% in India (2013 cohort). The shorter MDR-TB regimen is detailed in Table 7.4.

**b. Conventional MDR-TB regimen**

Those patients who are not considered eligible for shorter MDR-TB regimen (particularly after assessment in pregnant women, EPTB) should be initiated on conventional MDR-TB regimen as in Table 7.4.

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 detailed in Table 7.4.
Table 7.4: 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 Cfx Z H(^h) E</td>
<td>(5) Mfx(^h) Cfx 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>

7.6.3 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. This will also be applicable in patients found susceptible to both FQ class and SLI class on baseline SL-LPA, but found resistant to any of the FQ or SLI drugs on LC-DST. Patients who have consented and are found to be eligible would be initiated on newer drugs containing regimen while rest of the patients would be initiated on a DST guided regimen and re-classified. The regimen design is detailed in Table 7.5.

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 re-classified as XDR-TB.

7.6.4 XDR-TB

All XDR-TB patients identified with SL-LPA or LC-DST would also be assessed for eligibility for newer drug containing regimen and re-classified as above. The regimen design is detailed in Table 7.5.
7.6.5 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 re-classified 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 7.5.

Similarly, RR-TB patients with additional resistance to FQ and/or SLI with Lzd resistance detected on LC-DST will also be re-classified as mixed-pattern DR-TB. Apart from this, patients who are failing any DR-TB regimen or have drug intolerance or contraindications or who return after interruption (>1 months) or emergence of any exclusion criteria would be re-evaluated and if these events prevent them to be managed with any of the above regimen classes, the patients would also be re-classified as mixed-pattern DR-TB.

All such patients would also be assessed for eligibility for newer drug containing regimen and re-classified as above. The regimen design is detailed in Table 7.5.

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 7.5.

**Replacement drugs in sequence of preference:**

In case of adverse drug reaction, poor tolerance, documented resistance, 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 as follows if not already used: **Eto, Cs, Lzd, Cfx, E, Bdq** (in RR-TB patients also where a WHO recommended regimen could not be formed), **PAS, Amx-clv**.

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 be continued to be reported on the same regimen. However, if the replacement of drugs affects the regimen class, then these patients would need to be reclassified as mixed pattern DR-TB. This decision would be based on the judgment of the NDR-TBC committee.
Table 7.5: 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 Lzd Cfx + (6) Bdq</td>
<td>(18) Eto Cs Lzd Cfx</td>
<td>0 GpA + 1 GpB + 2 GpC + Z + add on 2 GpC + 1 GpD2</td>
</tr>
<tr>
<td></td>
<td>MDR/RR+ res to SLI class</td>
<td>(6-9) Lfx Cm Eto Cs Z Lzd Cfx + (6) Bdq</td>
<td>(18) Lfx Eto Cs Z Lzd</td>
<td>1 GpA + 1 GpB / 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) Mfx Km Eto Cs Z Lzd Cfx</td>
<td>(18) Mfx Eto Cs Z Lzd Cfx</td>
<td>1 GpA / 2 + 1 GpB + 2 GpC + Z + add on 2 GpC</td>
</tr>
<tr>
<td></td>
<td>MDR/RR+ res to SLI class</td>
<td>(6-9) Lfx Cm Eto Cs Z Lzd Cfx</td>
<td>(18) Lfx Eto Cs Z Lzd</td>
<td>1 GpA + 1 GpB / 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 SLI class)</td>
<td>XDR-TB</td>
<td>(6-12) Cm Eto Cs Z Lzd Cfx + (6) Bdq</td>
<td>(18) Eto Cs Lzd Cfx</td>
<td>0 GpA + 1 GpB / Z + add on 2 GpC + 1 GpD1 + 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 SLI class)</td>
<td>XDR-TB</td>
<td>(6-12) Mfx Cm Eto Cs Z Lzd Cfx E</td>
<td>(18) Mfx Eto Cs Z Lzd Cfx E</td>
<td>1 GpA / 2 + 1 GpB / Z + add on 2 GpC + 1 GpD1</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 / SLI + Lzd 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/SLI/ Lzd</td>
<td>(3-6) RE Z Cm Eto Lzd</td>
<td>(6) RE Z Eto Lzd</td>
<td>REZ + augment with 1 GpB / 1 + 2 GpC drug</td>
</tr>
<tr>
<td></td>
<td>MDR/RR-TB + FQ / SLI with Lzd or others.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 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
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
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. Use a minimum of 5 drugs and a maximum 8-9 drugs in the regimen

Once the baseline LC-DST results are available, the decision to modify the regimen by adding individual drugs in fluoroquinolones or second line injectable groups in the above DST guided regimen would be considered as below based on LC-DST results:

- If Mfx (2) is susceptible, then add Mfx\textsuperscript{h} and increase the frequency of ECG monitoring
- 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
- 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.

7.6.6 Non tuberculous mycobacterium (NTM)

**Treatment of NTM:**

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 NTP will be the prerogative of the NDR-TBCs. When questions about the clinical significance of an NTM isolate arise, expert consultation is strongly encouraged.

1. 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.
2. The 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 anti-mycobacterial 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.

3. Empiric therapy for suspected NTM lung disease is not recommended.

4. There are no 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).
- 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 and 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.

Points to note for treatment of NTM:

- The recommended initial regimen for most patients with nodular/bronchiectatic MAC lung disease is a thrice weekly regimen including clarithromycin 1,000 mg or Azithromycin 500 mg, ethambutol 25 mg/kg, and rifampicin 600 mg administered three times per week.
- The recommended initial regimen for fibro-cavitary or severe nodular/bronchiectatic MAC lung disease includes clarithromycin 500–1,000 mg/day or azithromycin 250 mg/ day, ethambutol 15 mg/kg/day, and rifampicin 10 mg/kg/day (maximum, 600 mg). An initial 2 months of ethambutol at 25 mg/kg/day is no longer recommended.
- Intermittent drug therapy is not recommended for patients who have cavitary disease, patients who have been previously treated, or for patients who have moderate or severe disease.
- The 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 mono-therapy for MAC because of the risk for developing macrolide-resistant MAC isolates.
• A macrolide with a single companion drug, ethambutol, may be adequate for nodular/bronchiectatic MAC disease but should not be used in patients with fibrocavitary 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.
• Expert consultation should be sought for patients who have difficulty tolerating MAC treatment regimens or who do not respond to therapy.

7.7 Drug Dosage and administration

The dosage of the drugs would vary as per the weight of the patients. The patients would be classified in the weight bands of <16 kg, 16-29 kg, 30-45 kg, 46-70 kg and >70 kg. All drugs in the regimen are to be given on a daily basis under observation. Injectable will be administered for six days/week (not on Sundays). All morning doses are to be supervised by the treatment supporter except on Sundays. 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 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 (two times a day).

The dosages for drugs used in various DR-TB regimens by weight bands for adults are enumerated in the table 7.6 below.

**Bedaquiline:** All patients eligible for BDQ will receive Tab. BDQ 400 mg once daily for the first 2 weeks and 200 mg three 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 the 24 weeks of BDQ administration for the RNTCP recommended duration of treatment. As mentioned above, the 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 Cfx 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.
- Week 25 (start of month 7) to end of treatment: Continue other second-line anti-TB drugs only as per RNTCP recommendations.
## Table 7.6: Dosage of DR-TB drugs for adults

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drugs</th>
<th>16-29 Kgs</th>
<th>30-45 Kgs</th>
<th>46-70 Kgs</th>
<th>&gt;70 Kgs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rifampicin*</td>
<td>300</td>
<td>450</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>2</td>
<td>Isoniazid*</td>
<td>200</td>
<td>200</td>
<td>300</td>
<td>450</td>
</tr>
<tr>
<td>3</td>
<td>Ethambutol</td>
<td>400 mg</td>
<td>800 mg</td>
<td>1200 mg</td>
<td>1600 mg</td>
</tr>
<tr>
<td>4</td>
<td>Pyrazinamide</td>
<td>750 mg</td>
<td>1250 mg</td>
<td>1750 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>5</td>
<td>Kanamycin</td>
<td>500 mg</td>
<td>500 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>6</td>
<td>Levofloxacin</td>
<td>250 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>7</td>
<td>Ethionamide</td>
<td>375 mg</td>
<td>500 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>8</td>
<td>Cycloserine</td>
<td>250 mg</td>
<td>500 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>9</td>
<td>Na-PAS (60% weight/vol)†</td>
<td>10 gm</td>
<td>14 gm</td>
<td>16 gm</td>
<td>22 gm</td>
</tr>
<tr>
<td>10</td>
<td>Pyridoxine</td>
<td>50 mg</td>
<td>100 mg</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>11</td>
<td>Moxifloxacin (Mfx)</td>
<td>200 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>12</td>
<td>High Dose Moxifloxacin (Mfx³)</td>
<td>400mg</td>
<td>600mg</td>
<td>800mg</td>
<td>800mg</td>
</tr>
<tr>
<td>13</td>
<td>Capreomycin (Cm)</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>14</td>
<td>Amikacin (Am)</td>
<td>500 mg</td>
<td>750 mg</td>
<td>750 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>15</td>
<td>High dose H (H³)</td>
<td>300 mg</td>
<td>600 mg</td>
<td>900 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>16</td>
<td>Clofazimine (Cfx)</td>
<td>100 mg</td>
<td>100 mg</td>
<td>200 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>17</td>
<td>Linezolid (Lzd)</td>
<td>300 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>18</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 BD (2 morning +1 even)</td>
<td>875/125 mg BD (2 morning +1 even)</td>
</tr>
</tbody>
</table>

*For mono-H resistant TB; †For Rifampicin Resistant TB in shorter MDR-TB regimen

† 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)

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).
The following **medications are disallowed** during the 24-week administration of BDQ and up to 1 month after the last dose of BDQ because of potential drug–drug interactions:

- The 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;
- The systemic use of strong CYP3A4 inducers, e.g. phenytoin, carbamazepine, phenobarbital, St. John’s wort and rifamycins (rifampin, rifabutin, rifapentine);
- The use of antiretroviral (ARV) medication (except for the triple nucleoside regimen AZT/3TC/ABC, or an NVP- or LPV/RTV-containing regimen (in combination with NRTIs);
- Cholesterol lowering medications of the “statin” class.

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

### 7.8 Treatment Duration for Various DR-TB regimen

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

**a. 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. 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.

**b. Conventional MDR-TB regimen:** Total duration of conventional MDR-TB regimen is 24 – 27 months, depending on the IP duration. IP should be given for at least six months. After 6th month of treatment, the patient will be reviewed and the treatment changed to CP if the 4th or 5th month culture result in solid or liquid culture is negative. If the 4th or 5th month culture result remains positive, the treatment is extended by 1 month. Extension of IP beyond 1 month will be decide on the results of subsequent culture results and the clinical/radiographic response. If the result of the 4th month culture is still pending after six months of treatment, the 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. 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, then the patient will be declared as “Failure”, re-evaluated as per the integrated DR-TB algorithm, re-classified as mixed pattern DR-TB and initiated on an appropriate DST guided regimen.

c. H mono-poly DR-TB Regimen: Total duration of H mono-poly DR-TB regimen is 9-12 months, depending on IP duration. IP should be given for at least three months. After 3rd month of treatment, if the result of microscopy is negative, then CP should be initiated. If the 3rd month smear result is positive then, IP is extended by one month. 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.

d. 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 (i.e., 2 consecutive negative cultures taken 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 six months up to a maximum of 12 months. In case of extension, the nodal DR-TR centre committee, which will be responsible for initiating and monitoring the regimen for XDR-TB, can decide on administering Capreomycin injection intermittently (3 times/week) for the months 7 to 12.

e. Regimen for Mixed pattern resistant TB

- H mono-poly + resistance to FQ/SLI1 with Lzd3 (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 monthly basis for the maximum period of three months. Total duration of IP is not more than six months. Duration of continuation phase (CP) is fixed for six months.

- MDR/RR-TB + resistance to FQ / SLI1 with Lzd3 or Failure of DR-TB regimen or patients who don’t fit in any of the above regimen (with or without newer drugs): This will be the same as for XDR-TB patients detailed above.

7.9 Patient Flow for DR-TB Patients

- DDR-TBC and NDR-TBCs should be involved actively in management of all DR-TB patients.
- District DR-TB centre will be the reporting unit for the respective district and will register all RR-TB and H mono/poly DR-TB patients of respective districts initiated on standard regimen based on CBNAAT or FL-LPA results in PMDT treatment register with issue of unique PMDT number. Patient details would be entered and regularly updated on NIKSHAY.

- NDR-TBC will be the reporting unit for the catering districts and will re-register all DR-TB patients of respective districts (who need DST guided regimen re-designing 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. Over accountability of all such patients would also be shared by the concerned district DR-TB centre and DTO.

- PMDT treatment card of DR-TB patients managed at the concerned DR-TB centre for pre-treatment evaluation will be opened by responsible staff of DR-TB centre at district or nodal level.

- After pre-treatment 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-TB centre 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.

- The DTO arranges for availability of the monthly IP drug box to the treatment supporter (via the TU staff) and the patient records at the identified treatment support centre with timely information to the respective MO-PHI.

- The MO-PHI is responsible for supplying the patient records and the drugs to the designated treatment supporter. The MO-PHI will need to make suitable arrangements during the intensive phase of the treatment for daily injections including free sterile needles and syringes.

- The patient’s information as per the 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.

The overall responsibility of monitoring the patient’s progress on treatment including follow up is with the MO-PHI where the patient is being treated.
7.10 Management of DR-TB patients with Treatment Interruptions and Loss 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 detail in Chapter 11. The following strategies apply in patient of treatment interruption.

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

- **Patients who interrupt treatment for less than 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 revised 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 the CP. The follow up cultures will be done as per the revised schedule.

- **Patients who are Loss to Follow up (interrupt treatment continuously for one month or more) and return back for treatment:**
  Such patients will be given an outcome of “loss to follow up”. The patient would be subjected to repeat 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 (e.g., no sputum smear conversion by 6 months or deterioration of clinical condition despite treatment) while the patient is on a shorter MDR-TB regimen, the patient should be considered for an appropriate DST guided DR-TB regimen.
- If patients **interrupt treatment continuously for one month or more** of shorter MDR-TB treatment then the episode is classified as “Loss 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 but on an appropriate DST guided DR-TB regimen. Patients need to be made aware of this.

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

DR-TB patients on Bdq containing regimen who interrupt treatment or are loss to follow-up or recurrent DR-TB:

BDQ: If a dose is missed during the first 2 weeks of treatment, one should not make up for the missed dose but should 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 3 times a week regimen.

Patients who interrupt treatment during the first 2 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.

• If interruption is more than 7 consecutive days, BDQ course will be re-loaded (started afresh) and a sputum sample will be collected for culture. The culture isolate must be stored for BDQ DST in future. In addition, serum sample will be collected and transported to the concerned lab within 6 hrs for BDQ levels for correlation with outcomes, wherever feasible and lab capacity is available.

Patients who interrupt treatment during 3-24 weeks of BDQ course and returns to resume the treatment:

• If interruption is up to 1 month, 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.

• If interruption is more than 1 months, BDQ will be permanently discontinued. Such patients will be given an outcome of “Lost to follow up” (LTFU) based on the duration of LTFU and managed as per DST guided treatment and registered afresh. A sputum sample will be collected for culture. The culture isolate must be stored for BDQ DST in future. In addition, serum sample will be collected and transported to the concerned lab within 6 hrs for BDQ levels for correlation with outcomes, wherever feasible and lab capacity is available.

Further treatment: If the patient has any indication of a treatment failure or recurrence, the NDR-TBC Committee will be contacted to discuss whether the
patient should be re-treated. The decision will be made on a case-by-case basis using all the available bacteriological and clinical data.

7.11 Transfers of DR-TB patients

It is important to note the patient’s address of the current residence, native place, occupation and the place of work to get a fair idea about the possible places that the patient could move. 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 he/she wishes to migrate. Transfer out should be brought to the notice of the district DR-TB centre by the concerned DTO.

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

If the patient is migrating to any other district that is not being served by the same DR-TB Centre; then the patient may be formally transferred out with seven days of drugs for transit period to a suitable treatment supporter at that place where he/she proposes to move in consultation with the DTO of that district and under intimation of the district DR-TB centre. This patient will be registered at the district DR-TB centre catering to the receiving district with a new PMDT TB number mentioning the old PMDT TB number in the remarks column for future reference. However, the NIKSHAY ID of the patient would remain the same and the 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, the copies of the 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-TB centre transferring the patient will be sent to the district DR-TB centre 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 along to the receiving DDR-TBC. The details of the patient will be updated in the PMDT treatment register at both the DR-TB centres for future reference. It is the responsibility of the receiving DTO and district DR-TB centre to send a feedback about the patient with the new PMDT TB number to the former district DR-TB centre to establish a link for future exchange of information.
about the interim reports, culture conversion and treatment outcomes of the patient.

7.12 Managing referrals from other sectors of patients for 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. As TB is a notifiable disease in India, DR-TB patients diagnosed or initiated on treatment in the private sector are also expected to be notified to RNTCP. As part of the public health action following notification, RNTCP would also offer DST to all notified TB patients if not already done. RNTCP will also offer treatment to all lab confirmed DR-TB patients diagnosed and classified as per the integrated DR-TB algorithm.

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 the machines.
- 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-TB centres 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 Palliative care

Palliative care is a multidisciplinary approach to medical care for people with serious illnesses. It focuses on providing patients with relief from the symptoms, pain, physical stress, and mental stress of a serious illness—whatever the diagnosis. WHO defines Palliative care as an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the 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 the patient and the family.

**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 also significant suffering associated with DR-TB illness and its treatment. These burdens add to the possibility that TB patients will not be able to adhere to treatment, and as a result treatment fails 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 show clearly 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. Improvements 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-centred 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 disease 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 most in need. Although clinical expertise in palliative care for patients who die in respiratory distress has developed considerably, individuals with DR-TB are not yet seeing 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 also be required in some patients when there are symptoms or other suffering during the treatment process too. 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 the patient is expected to be cured or fail treatment.

The 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:

1. **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 6. Morphine provides significant relief from respiratory insufficiency and should be offered according to established clinical protocols available in the medical literature.

2. **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.

3. **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.

4. **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.

5. **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.

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

7. **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 metre 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.

8. **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. Encourage patients to move their bodies in bed if able. Keeping beds dry and clean are also important.

9. **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, and provide emotional support, especially in settings in which strong stigma is attached to the disease.

10. **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. The healthcare providers should respect those beliefs and should not impose personal values and practices that prevent the patient to seek and find comfort in the 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, and anxiety of patients and their families, which typically accompanies these symptoms.

When patient isolation is done, strong measures to prevent loneliness, boredom and the sense of abandonment are needed to be in place. These consist 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 – HR and Infrastructure need**

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, the NDR-TBC staff can counsel and train the family members or care takers of the patient so that these services can be extended as home-based palliative care to the patients by the family members or care takers.

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

All health workers must receive training in palliative care to enable them extend support to the family members or care takers 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 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 (e.g. 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, the institution based palliative care should be minimized to a duration that is absolutely essential as per the decision of the NDR-TBC committee concerned and most of the palliative care must be provided home-based through a trained and counselled family member or care taker with regular visits by the health care workers and with psycho-social and spiritual support through local community based self-help groups or NGOs or panchayati raj institutes.
Chapter 8: 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 the treatment providers, and the prolonged adherence required by the patients. To add to these issues certain associated special situations make the treatment of MDR-TB more difficult.

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

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

8.1 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 fetus. There is a lack of experience in treating pregnant women with MDR-TB. Teratogenicity has been demonstrated with only some of the drugs used to treat MDR-TB. However, majority of the studies have demonstrated that it is common during first trimester. It is prudent to solicit the opinion of an experienced gynaecologist/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 MDR-TB drugs. Thus, for prevention of pregnancy the use of barrier methods (Condoms/diaphragms), IUDs (CuT) or depot-medroxyprogesterone (Depo-provera) are recommended based on individual preference and eligibility. Similarly, all women of child bearing age identified as presumptive DR-TB should be advised to use a reliable and appropriate contraceptive method till the results of culture and DST are available.

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

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

Further management of DR-TB patients who are pregnant prior to initiation of treatment or whilst on treatment are based on the 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 the mother and foetus. If the patient is willing, she should be referred to a Gynaecologist/Obstetrician for 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-TB Centre Committee.

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

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 becomes 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 MTP. If she is unwilling for MTP or have pregnancy > 20 weeks duration, the patient needs to be shifted to a modified conventional MDR-TB regimen.

Similarly, Km need to 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 summarised in the flow chart in Figure 8.1 below:
Pregnant DR-TB patients need to be monitored carefully both in relation to the treatment and the progress of the pregnancy. This approach should lead to good results, since the patient should be smear-negative at the time of parturition, and mother and infant do not need to be separated. Breast-feeding should be encouraged as long as the patient is sputum negative.

Avoid aminoglycosides as it is particularly toxic to the developing fetal ear. Moreover, ethionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies. If the injectable agents, ethionamide/prothionamide, 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 rifampicin, the use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving rifampicin treatment may choose between two options following consultation with a physician: (i) the use of an oral contraceptive pill containing a higher dose of estrogen (50 μg); or (ii) the use of another form of contraception.
8.2 DR-TB in Children

Principles of treatment of drug resistant TB in Children

- 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
- Don’t add a single drug to a failing regimen
- Treatment should be given for at least 12 months after *M. tuberculosis* cultures have converted to negative
- With HIV infection or cavitatory lesions treatment be extended to 24 months

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. Thus, children would be managed with regimen designs without newer drugs as in table 7.4 and 7.5, depending on the DST pattern and other parameters for mixed pattern DR-TB.

However, WHO also recommends that in children with less severe forms of DR-TB, a regimen free of SLI may be designed keeping in view of the principles. Thus, in such patients, the regimen design suggested in Table 7.4 and 7.5 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 pediatric DR-TB patients and the monitoring of DR-TB treatment in children are enumerated in the table below.

Table 8.1 Dosage of DR-TB drugs for children* (< 30 kg body weight)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Doses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin / Capreomycin</td>
<td>15-30 mg/kg</td>
</tr>
<tr>
<td></td>
<td>(SM 20-40 mg/kg)</td>
</tr>
<tr>
<td>Levofoxacin / Moxifloxacin</td>
<td>Lfx &lt;5 yrs: 15-20 mg/kg split dose</td>
</tr>
<tr>
<td></td>
<td>Lfx &gt;5 yrs: 10-15 mg/kg once day</td>
</tr>
<tr>
<td></td>
<td>Mfx 7.5-10 mg/kg</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10-20 mg/kg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-25 mg/kg</td>
</tr>
<tr>
<td>Pyrazinamide (Na-PAS )</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td></td>
<td>&lt;30 kg: 200-300 mg/kg</td>
</tr>
</tbody>
</table>
Table 8.2 Monitoring of DR-TB treatment in children

<table>
<thead>
<tr>
<th>Month</th>
<th>Clinical</th>
<th>Smear</th>
<th>Culture</th>
<th>DST</th>
<th>AST, ALT, Bilirubin</th>
<th>Cr, K</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Every 2 weeks</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4</td>
<td>Monthly</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>7</td>
<td>✓</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>✓</td>
<td></td>
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<tr>
<td>9</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>10</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>11</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Until end</td>
<td>Monthly</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.3 DR-TB with HIV co-infection

The presentation of MDR-TB in the HIV-infected patient does not differ from that of drug sensitive tuberculosis in the HIV-infected patient. However the diagnosis of TB in HIV positive persons can be more difficult and may be confused with other pulmonary or systemic infections. As the HIV disease progresses and the individual become more immunocompromised, the clinical presentation is proportionately more likely to be extra-pulmonary or smear-negative than in HIV-uninfected TB patients. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality. With the nation wide scale up of Intensified TB HIV Package, it is expected that more and more numbers of TB patients have known their HIV status and if found to be HIV positive, they 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 antiretroviral
treatment (ART), sound patient support, and strong infection control measures are all 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 the PLHIV person approaching ART centres. RNTCP guidelines are offering CBNAAT testing for all presumptive TB among PLHIV patients for early diagnosis of TB and DR-TB among PLHIV person. 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 knows their HIV status and many would have been diagnosed with the help of molecular test.

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

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

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

Co-trimoxazole can be provided to all patients with HIV according to WHO recommendations.

On the other hand undue delay in starting ART could result in significant risk of HIV related death amongst MDR patients.

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

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

If the patient already on Sensitive TB drug regimen, it should be switch over to appropriate DR-TB regimen by closing previous treatment with ‘regimen change’ outcome.

Periodic 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. Programme is monitoring treatment outcomes separately for HIV TB patients. Considering risk of development of primary DR-TB among susceptible close contacts, effective TB infection control measures is mandatory. If the patient shows signs of TB treatment failure, the 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 anti-HIV or other medicines: Rifampicin is not used in DR-TB treatment; they are used in the treatment of rifampicin-sensitive poly- and monoresistant TB, which has drug interaction with Protease Inhibitor (PI). Newer drugs like Delaminade and Bedaquiline metabolized by the CYP3A4 and have multiple drug interactions with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors (NNRTI). Avoid efavirenz and protease inhibitors along with Bedaquiline. More frequent monitoring of QT interval prolongation (every month) is required when Bedaquiline is recommended.
8.4 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 post-operative care are available. When unilateral resectable disease is present, surgery should be considered for the following cases:

- Absence of clinical or bacteriological response to chemotherapy despite six to nine months of treatment with effective anti-tuberculosis drugs;
- High risk of failure or relapse due to high degree of resistance or extensive parenchymal involvement;
- Morbid complications of parenchymal disease e.g. haemoptysis, bronchiectasis, broncho-pleural fistula, or empyema;
- Recurrence of positive culture status during course of treatment; and
- Relapse after completion of anti-tuberculosis 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. Linkages may be established with the existing institutions of excellence where the patients can be referred for the expert opinion and decisions may be taken to provide surgical options after a detailed review, to the patients. States need to identify institutes with capacity to conduct thoracic surgery and link up the DR-TB centres to such institutes with support to the patient to cover the cost involved for surgery through innovative mechanisms.

8.5 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. Consideration needs to be taken that MDR-TB patients require aminoglycosides for 6 months or more. Other drugs, which also might require dose or interval adjustment in presence of mild to moderate renal impairment, are: Ethambutol, Quinolones, Cycloserine and PAS. In the presence of severe renal impairment many other drugs may also require adjustments (Table 8.3).

In MDR-TB patients, blood urea and serum creatinine should be monitored prior to treatment initiation, monthly for three months after treatment initiation and then every three months whilst injection Kanamycin is being administered. In patients with mild renal impairment, the dose of aminoglycosides may be reduced. In the presence of severe renal failure, the aminoglycoside therapy should be discontinued and replaced with other potent non-nephrotoxic anti-tuberculosis drugs.
### Table 8.3 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>Prothionamide</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>PAS(^a)</td>
<td>4 g/dose, twice daily maximum dose(^d)</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;</td>
</tr>
<tr>
<td></td>
<td>For creatinine clearance &lt;20 ml/min dose 500 mg every 12 hours</td>
</tr>
</tbody>
</table>

\(^a\)source: Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis 2014.

**Estimated creatinine clearance calculations:**

**Men:** \(\text{Ideal Body Weight (kg) \times (140 – age)} / 72 \times \text{serum creatinine (mg/dl)}\)

**Women:** \(0.85 \times \text{Ideal Body Weight (kg) \times (140 – age)} / 72 \times \text{serum creatinine (mg/dl)}\)
8.6 DR-TB in patients with pre-existing liver disease

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

Once a patient on second line drugs develops hepatitis, other aetiologies should also be excluded such as viral hepatitis, alcoholic hepatitis, drug induced hepatitis by non-TB drugs etc. The further management should be on the same guidelines as in non-MDR-TB patients.

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

8.7 DR-TB in patients with seizure disorders

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

Among second line drugs, Cycloserine, Ethionamide and fluoroquinolones have been associated with seizures, and hence should be used carefully amongst MDR-TB patients with history of seizures. Pyridoxine should be given with Cycloserine to prevent seizures.

Cycloserine should however be avoided in patients with active seizure disorders that are not well controlled with medication. In patients where no other drug is appropriate, Cycloserine can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. The risk and benefits of using Cycloserine should be discussed with the patient and the decision on whether to use Cycloserine are made together with the patient.

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

8.8 DR-TB in patients with psychosis

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

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

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

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

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

8.9 Management of DR-TB in Extra Pulmonary TB patients

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

Investigations and pre-treatment evaluation

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

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

Initiation of Treatment

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

Monitoring progress during treatment and follow-up

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

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

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

   a. Weight Gain
   b. Decrease or increase in symptoms (e.g. healing of ulcer/scrofuloderma)
   c. Increase or Regression in size of nodes {possibility of Immune Reconstitution Inflammatory Syndrome (IRIS) should be considered and differentiated from disease progression}
   d. Appearance of new nodes
   e. If chest symptomatic, monthly sputum for AFB and chest X-ray (to rule out pulmonary involvement)
   f. Other Extra-pulmonary sites should be monitored (USG abdomen if necessary)
   g. Serum Creatinine – monthly for the first three months of treatment and then quarterly till the patient receives Kanamycin and further when clinically indicated
   h. Liver function test – as clinically indicated
   i. USG-abdomen – if necessary
   j. Monitoring for drug adverse reactions

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

8.10 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. (Morrison J, 2008;8(6)) All close contacts of MDR-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, he/she will be identified as a “Presumptive MDR-TB”. The patient will be initiated on Regimen for new or previously treated case based on their history of previous anti-TB treatment. Simultaneously two sputum specimens will be transported for culture and DST to a RNTCP-certified C&DST laboratory he/she should be evaluated for DR-TB status with molecular test. If the patient is confirmed to have MDR-TB, appropriate DR-TB
treatment should be provided. The patient will be admitted to the DR-TB Centre ward for pre-treatment assessment and initiation of Regimen for MDR-TB. Among asymptomatic contacts of patients with MDR-TB, rule out active TB by appropriate clinical examination and investigation. If TB is ruled out, the use of Isoniazid (fluoroquinolones…?) may reasonably be questioned as a chemoprophylaxis. Although alternative prophylaxis treatments have been suggested, there is no consensus regarding the choice of the drug(s) and the duration of treatment. Prompt treatment of MDR-TB in index case is the most effective way of preventing the spread of infection to others.

There are multiple opportunities to investigate contacts of MDR-TB patients

- **Patient:** Contact investigation starts with the education of the MDR-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 MDR-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 MDR-TB patient at the initiation of MDR-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 MDR-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 MDR-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 MDR-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 also directly interview the 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 MDR-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 MDR-TB infection:

- Early diagnosis and appropriate treatment of MDR-TB patients
- Screening of contacts as per RNTCP guidelines
- Further research into effective and non-toxic chemoprophylaxis in areas of high MDR-TB prevalence.
Chapter 9: Managing Adverse Reactions

MDR-TB can be deadly but the drugs used to treat the disease can be harmful in many ways. This chapter focuses on the measures to promote patient safety that contribute to improving quality of care during the treatment of 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
- 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 control programmes. Poor management of adverse effects increases the risk of default or irregular adherence to treatment, and may result in death or permanent morbidity. 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 9.1 Notable adverse reactions to drugs used for DR-TB patients

<table>
<thead>
<tr>
<th>COMMON OR RELEVANT ADVERSE EFFECTS OF DRUG-RESISTANT TB THERAPY</th>
<th>COMMON OR RELEVANT ADVERSE EFFECTS OF DRUG-RESISTANT TB THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Gastritis</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Hearing disturbances</td>
<td>Depression</td>
</tr>
<tr>
<td>Headache</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>Rash</td>
</tr>
</tbody>
</table>

Adverse effects are easy to recognised and usually reported by patients when they experience it. However, few effects may not be reported by patient in presence of other major adverse effect. 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 investigation is required on routine basis during the course of treatment to monitor the ADR.
Table 9.2 Baseline and routine monitoring for patients on DR-TB regimens

<table>
<thead>
<tr>
<th>MONITORING EVALUATION</th>
<th>RECOMMENDED FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>At baseline; then monthly if possible while receiving an injectable agent. Every one to three weeks in HIV infected patients, diabetics and other high-risk patients.</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>Monthly while receiving an injectable agent. 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. At baseline and then monthly if on Bedaquiline or Delamanid. 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 ethionamide/prothionamide and p-aminosalicylic acid (PAS). Every six months if receiving ethionamide/ prothionamide 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 1 Every six months if receiving ethionamide/ prothionamide for extended periods or for patients at risk for, or with symptoms of hepatitis. For HIV-infected patients monthly monitoring is recommended. For patients on Bedaquiline, monitor monthly. For patients with viral hepatitis, monitor every one to two weeks for the first month and then every one to four weeks.</td>
</tr>
<tr>
<td>HIV testing</td>
<td>At baseline, and repeat if clinically indicated.</td>
</tr>
<tr>
<td>Pregnancy tests</td>
<td>At baseline for women of childbearing age, and repeat if indicated.</td>
</tr>
<tr>
<td>Haemoglobin and white blood cell count</td>
<td>If on linezolid, monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use of linezolid. For HIV-infected patients on zidovudine, monitor monthly initially and then as needed based on symptoms.</td>
</tr>
<tr>
<td>Lipase</td>
<td>Indicated for work-up of abdominal pain to rule out pancreatitis in patients on linezolid, Bedaquiline, D4T, ddl or ddc.</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>Indicated for work up of lactic acidosis in patients on linezolid or antiretroviral treatment (ART).</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>If receiving gatifloxacin, monitor fasting blood glucose at baseline and monitor monthly. Educate/remind patients on signs and symptoms of hypoglycaemia and hyperglycaemia</td>
</tr>
</tbody>
</table>
Audiometry (hearing test) | Baseline audiogram and then monthly while on an injectable agent. Ask patients about changes in hearing at every clinic visit and evaluate their ability to participate in normal conversation.

Vision tests | For patients on long-term ethambutol or linezolid 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.

Educational, psychological and social consultation | At baseline by personnel trained in health education, psychological and social issues relevant to TB management; during treatment and repeat as indicated. Refer to social worker, psychologist or psychiatrist when indicated.

ECG | An ECG should be obtained before initiation of treatment with bedaquiline or delamanid, and at least 2, 4, 8, 12, and 24 weeks after starting treatment. Monitoring ECGs should be done monthly if taking other QT prolonging drugs (i.e. moxifloxacin, clofazimin).

### 9.1 Management of Adverse Drug Reactions

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

Training of all the health staffs will be done to identify and manage ADRs. Close monitoring of patients is necessary to ensure that the adverse effects of the drugs are recognized quickly by health-care personnel. The ability to monitor patients for adverse effects daily is one of the major advantages of treatment supporter over self-administration of treatment. Treatment supporter should be trained to screen patients regularly for symptoms of common adverse effects: rashes, toxic epidermal necrolysis, gastrointestinal symptoms (nausea, vomiting, diarrhoea), psychiatric symptoms (psychosis, depression, anxiety) jaundice, ototoxicity, peripheral neuropathy, symptoms of electrolyte wasting (muscle cramping, palpitations), and convulsions. Treatment workers should also be trained to identify ADRs and refer the patient to the MO PHI for minor ADRs and to the DTO for major ADRs. Most of the ADRs could be managed by the DTO/chest physician of the district hospital. If required, hospitalisation could be done at the districts where inpatient facility is available or referred to a referral hospital for admission. Symptom based approached
should be followed to manage minor ADR where patient usually able to tolerate ATT drugs and continue the medication with symptomatic treatment. Patient with major adverse effect should be manage at hospital level and may require admission.

The nodal/District DR-TB Centre Committee would be consulted to take decisions regarding reduction/termination of any drug. If any drug is withheld / terminated due to ADR, it would be replaced with the appropriate substitute drug as per the DR-TB Centre Committee. Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen, and if and when they occur, to notify a health-care provider. Proper management of adverse effects begins with pretreatment patient education. Depending on the severity of ADRs the following actions may be indicated: If the adverse effect is mild and not serious, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option. Most of the adverse effects of a number of second-line drugs are dose-dependent. Reducing the dosage of the offending drug or terminating the offending drug is another method of managing adverse effects.

Psychosocial support is an important component of the management of adverse effects. This may be provided through patient education and motivation by treatment supporter, patient support groups like patients association/organization or through group discussions while in the hospital. The recommended schedule for ADR management is detailed in the below.

**Gastro-intestinal symptoms (nausea and vomiting)**

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

**Giddiness**

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

**Ocular toxicity**

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

**Renal toxicity**

Prior to starting treatment, all patients will have renal function evaluated. During treatment of MDR-TB, if the patients presents with symptoms and/or signs of renal impairment (oliguria, anuria, puffiness of face, pedal oedema), all the drugs should be withheld, renal function tests should be done and, if required, opinion of nephrologist should be sought. Re-introduction of drugs will be undertaken by the DR-TB Centre committee in consultation with a nephrologist, along with frequent monitoring of renal parameters. Common offending drug is an aminoglycoside. During treatment, blood urea and serum creatinine should be done every month for the first three months after treatment initiation and then every three months thereafter whilst injection Kanamycin is being administered. Silent renal toxicity may be picked up by these routine follow-up biochemical examinations. If at any time, the blood urea or serum creatinine becomes abnormal, treatment should be withheld and further management decided upon in consultation with the DR-TB Centre committee.

**Arthralgia**

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

**Cutaneous reactions**

Hypersensitivity reactions such as pruritus or rash, can occur with any of the drugs used, and are commonly managed with anti-histamines. For severe reactions which do not respond to anti-histamines, an attempt will be made to identify the offending drug by challenging with individual drugs. The dose of the offending drug may be reduced or the drug terminated if required. For severe hypersensitivity reactions the offending drug may need to be stopped. If there is a generalized erythematous rash,
especially if it is associated with fever and/or mucous membrane involvement, all drugs should be withheld immediately. When the rashes subside, the medications can be restarted one by one, at intervals of 2-3 days. The order of reintroduction will be Ethambutol, Cycloserine, Ethionamide, Fluoroquinolone, Kanamycin and lastly Pyrazinamide. After identification, the offending drug will be terminated.

**Hepatitis**

This could be due to the combined effect of potentially hepatotoxic drugs such as Isoniazid, Rifampicin, Pyrazinamide, Ethionamide, Fluoroquinolones, PAS and Bedaquiline. If a patient presents with symptoms/signs of hepatitis (anorexia, nausea, vomiting, abdominal discomfort, and/or dark coloured urine), he/she will be examined for clinical jaundice and liver enlargement. PAS induced hepatitis is also associated with rash and fever. Blood will be drawn for liver function tests. Patients will be questioned carefully regarding symptoms suggestive of biliary tract disease and exposures to other potential hepatotoxins, including alcohol and hepatotoxic medications. If there is icterus, anti-TB drugs will be withheld and the patient reviewed with the results of the liver function tests. If the results are abnormal, Ethionamide and Pyrazinamide are to be withheld, and the other drugs continued. If the results of the liver function tests are normal, the treatment will be resumed. Patients with abnormal liver function will be reviewed at weekly intervals and liver function repeated when jaundice subsides clinically. The regimen will be resumed after the liver function become normal. If the jaundice recurs after reintroduction of the allocated regimen, further management of the patient will be decided by the DR-TB Centre committee.

**Neurological symptoms**

- **Peripheral neuropathy:**

  The common offending drugs are Linezolid, Isoniazid, Cycloserine, Kanamycin, Amikacin, Capreomycin, Fluoroquinolones and rarely Prothionamid/ Ethionamide, Ethambutol. To prevent the occurrence of such adverse reaction, all patients on an RNTCP Regimen for MDR-TB should receive daily Pyridoxine 100mg. If peripheral neuropathy develops, an additional 100mg Pyridoxine will be given. The commonest offending agent is Linezolid, almost 60-70% of the patients on Linezolid 600 mg/day develop neuropathy and pyridoxine does not help in preventing Linezolid induced neuropathy. Early recognition of neuropathy symptoms and early dose reduction of Linezolid 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. Other neurological complications are headache, dizziness, drowsiness and restlessness, the offending drugs could be cycloserine, fluroquinolones and less commonly isoniazide. Insomnia is caused by fluroquinolones.
• **Seizures:**

If patient gets seizures, the offending drugs could be either Fluroquinolones, Cycloserine or Isoniazide. The offending drugs should be stopped, anticonvulsants to be given under neurologist guidance.

**Psychiatric disturbances**

The common offending drugs are Cycloserine, Fluoroquinolone and/or Ethionamide. In patients of suicidal tendencies and other psychiatric disturbances, the first offending drug is Cycloserine, followed by Ethionamide and Fluoroquinolone. Cycloserine induced psychological and emotional disturbances include excitement, anxiety, aggression, confusion, depression, night mares, negative thoughts, suicidal ideation and psychosis. These drugs will be withheld and further management of the patient will be done in consultation with the psychiatrist.

**Vestibulo-auditory disturbances**

Offending drug is usually the Aminoglycosides. Patient may present with tinnitus, unsteady gait or loss of hearing. Auditory disturbance with cochlear toxicity (tinnitus) leads to loss of hearing occurs for high frequency first. Patient can develop permanent deafness, if offending drug continues. Vestibular toxicity includes vertigo, dizziness, nausea and incoordination. Health workers should do symptoms screening for auditory symptoms and get audiometry done in symptomatic patients. Aminoglycoside will be withheld and patient referred for a specialist opinion. Lower dosage of aminoglycoside should be considered in patients above age of 50 years.

**Hypothyroidism**

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

**9.2 Specific toxicities due to Bedaquiline:**

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

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.

**AST and/or ALT elevations**

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

- Grade 1 (>1.0 to <2.0 x ULN) or Grade 2 (>2.0 to <3.0 x ULN) AST or ALT elevation: Patients may continue BDQ. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.
- Grade 3 (>3.0 to <8.0 x ULN) or Grade 4 (>8.0 x 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 2 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.

- Grade 1 (>1.0 to <1.5 x ULN) or Grade 2 (>1.5 to <2.0 x ULN): Patients may continue BDQ and should be carefully evaluated and followed closely.
- Grade 3 (2.0 to <5.0 x ULN) or Grade 4 (> 5.0 x 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 – myalgia**

- Grade 1 (mild with no limitation of activity): Patients may continue BDQ and should be carefully evaluated and followed closely.
- Grade 2 (muscle tenderness at site other than injection site or with moderate impairment of activity), Grade 3 (severe muscle tenderness with marked
impairment of activity) or 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 2 weeks, then every 2 weeks for 3 months and then monthly. ECGs should be done at least weekly throughout the BDQ course if other QT prolonging drugs like FQ (Mfx, gatifloxacin [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 the use of QT prolonging drugs with BDQ. If it is absolutely necessary to include a QT prolonging drug, 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.

- Grade 1 (asymptomatic) or Grade 2 (asymptomatic, transient rhythm abnormality not requiring any treatment) cardiac rhythm disturbances: Patients may continue BDQ and should be carefully evaluated and followed closely.
- Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4 (unstable dysrhythmia requiring hospitalization and treatment) 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.

- A value greater than 440 ms is considered prolonged but does not need action until >450 ms.
- A value between 450 – 480 ms: Rule out other causes of prolonged QTc, before deciding to withhold BDQ.
- A 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 the 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 ECGs to confirm that the QTc interval is stable.

- If the QTc interval is > 500ms (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 ECGs at least weekly to confirm that the 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 the QTc interval normalizes (even though the drug is no longer being given).

**If a QTcF of greater than 500 ms is recorded and is confirmed by a repeat ECG,** it is recommended that BDQ and all other QTc-prolonging drugs must 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-TB centre 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, the AE or laboratory toxicity poses a 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 [18].

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.
## Table 9.3 Management of adverse drug reactions

<table>
<thead>
<tr>
<th>ADVERSE EFFECT</th>
<th>SUSPECTED AGENT(S)b</th>
<th>SUGGESTED MANAGEMENT STRATEGIES</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| Rash, allergic reaction and anaphylaxis | Any drug | 1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols.  
2. Eliminate other potential causes of allergic skin reactions (like scabies or other environmental agents).  
3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include  
   • Antihistamines  
   • Hydrocortisone cream for localized rash  
   • Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful  
   • Phototoxicity may respond to sunscreens, but these can also cause rash  
   • Dry skin may cause itching (especially in diabetics), liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine.  
4. Once the rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last.  
   Consider not reintroducing even as a challenge any drug that is highly likely to be the cause.  
5. Suspend permanently any drug identified to be the cause of a serious reaction. | 1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card.  
2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flushes, itching, palpitations can be caused with isoniazid and tyramine containing foods (cheese, red wine). If this occurs advise patients to avoid foods that precipitate the reaction.  
3. Any of the drugs can cause hives (urticaria). To identify the drug, introduce the drugs one at a time. In the case of hives a desensitization attempt can be made (methods are described elsewhere (6).  
4. Any drug that resulted in anaphylaxis or Stevens–Johnson syndrome should never be reintroduced, not even as a challenge. |
| Nausea and vomiting | Eto, Pto, PAS, Bdq | 1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis. Initiate rehydration | 1. Nausea and vomiting are universal in early weeks of therapy and usually abate with time on |
H, E, Z, Amx/CIV, Cfx, Dlm therapy if indicated and correct any electrolyte disturbances. If there is blood in the vomit, check haemoglobin and treat for possible bleeding ulcers.

2. Initiate a step-wise approach to manage nausea and vomiting.
   • Phase 1: Adjust medications and conditions without lowering the overall dose:
     — Give Eto/Pto at night
     — Give Eto or PAS twice or thrice daily
     — Give a light snack (biscuits, bread, rice, tea) before the medications
     — Give PAS two hours after other anti-TB drugs.
   Phase 2: Start antiemetic(s):
     — Metoclopramide 10 mg, 30 minutes before anti-TB medications.
     — Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used.) For refractory nausea give 24 mg, 30 minutes before the dose can be tried.
   Phase 3: Decrease dose of the suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.

1. Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent.
2. If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth

1. Severe gastritis, as manifested by blood in the vomit or stool is relatively rare, but should be always treated to facilitate adherence to treatment.
2. If antacids must be used, they should be carefully timed so as to not interfere with the absorption of fluoroquinolones (take two hours

1. Gastritis and abdominal pain
   | PAS, Eto, Pto, Cfx, FQs, H, E, and Z | 1. Severe gastritis, as manifested by blood in the vomit or stool is relatively rare, but should be always treated to facilitate adherence to treatment.
   | | 2. If antacids must be used, they should be carefully timed so as to not interfere with the absorption of fluoroquinolones (take two hours
   | | 2. Creatinine and electrolytes should be checked if vomiting is severe. Give intravenous fluids and replace electrolytes as needed.
   | | 3. Another strategy is to stop the responsible medicine for two or three days and then add it back gradually increasing the dose (advise the patient that the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated).
   | | 4. Ondansetron is a serotonin 5-HT3 receptor antagonist and considered to have strong antiemetic properties. It is on the WHO essential drug list. A number of other antiemetics from this class of serotonin 5-HT3 receptor antagonists exist. Trying different antiemetics, even if from the same class may be helpful for some patients.
   | | Odansetron prolongs the QT interval; avoid the use of odansetron with bedaquiline or delamanid.
   | | 5. For patients particularly anxious about the 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 the intake of anti-TB drugs.
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 the use of antacids as they decrease absorption of fluoroquinolones.

3. For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days).
4. Lower the dose of the suspected agent, if this can be done without compromising the regimen.
5. Discontinue the suspected agent if this can be done without compromising the regimen.

before or three hours after anti-TB drugs).

3. Stop any nonsteroidal anti-inflammatory drugs the patient may be taking.
4. Diagnose and treat for Helicobacter pylori infections.
5. Severe abdominal distress has been reported with the use of clofazimine. Although these reports are rare, if this occurs, clofazimine should be suspended.

### Diarrhoea and/or flatulence

| PAS, Eto/Pto | 1. Encourage patients to tolerate some degree of loose stools and flatulence.  
2. Encourage fluid intake.  
3. Treat uncomplicated 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.  
4. Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe.  
5. 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. |
| 1. Consider other causes of diarrhoea:  
• Pseudo-membranous colitis related to broad-spectrum antibiotics (such as the fluoroquinolones) 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.  
2. Loperamide can be used in children over two years of age. |

### Hepatitis

| Z, H, R, Pto / Eto, PAS, FQ, BDQ | 1. 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, fluoroquinolone and cycloserine). If hepatitis worsens or does not resolve with the three-drug regimen, then stop all drugs. |
| 1. History of previous drug hepatitis should be carefully analysed to determine the most likely causative agent(s); these drugs should be avoided in future regimens.  
2. Viral serology should be done to rule out other aetiologies of hepatitis if available, especially to |
2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis being the two most common causes) and treat any that is identified.
3. Consider suspending the most likely agent permanently. Reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely agent is not essential consider not reintroducing it.

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Eto/Pto, PAS</th>
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</table>
| 1. Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner:  
• Young healthy adults can be started on 75–100 mcg daily  
• Older patients should begin treatment with 50 mcg daily  
• Patients with significant cardiovascular disease should start at 25 mcg daily.  
2. Monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions. |
| 1. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate.  
2. Do not start treatment unless TSH is above 1.5–2.0 times of the upper normal limit.  
3. It is completely reversible upon discontinuation of PAS and/or ethionamide/protonamide.  
4. The combination of ethionamide/protonamide with PAS is more frequently associated with hypothyroidism than when each individual drug is used. |

<table>
<thead>
<tr>
<th>Arthralgia</th>
<th>Z, Bdq, Fluoroquinolones</th>
</tr>
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</table>
| 1. Initiate therapy with nonsteroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day).  
2. Lower the dose of the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen.  
3. Discontinue the suspected agent if this can be done without compromising the regimen. |
| 1. Symptoms of arthralgia generally diminish over time, even without intervention.  
2. Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present it should be used.  
3. If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc. |

<table>
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<tr>
<th>Tendonitis and tendon rupture</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
</table>
| 1. If significant inflammation of tendons or tendon sheaths occur:  
• Consider stopping fluoroquinolones |
| 1. Tendon rupture with fluoroquinolone use is more likely in patients doing new physical activities and more common among older patients |
1. Give a non-steroidal anti-inflammatory drug (ibuprofen 400 mg four times daily)
2. Rest the joint.
3. If treatment failure is likely without the fluoroquinolone
4. Reduce dose if possible
5. Ensure joint is strictly rested
6. Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the fluoroquinolone.

| Electrolyte disturbances (hypokalaemia and hypomagnesaemia) | Cm, Km, Am, S | 1. Check potassium.
2. If potassium is low, also check for magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all patients of hypokalaemia).
3. Replace electrolytes as needed. Dose oral electrolytes apart from fluoroquinolone as they can interfere with fluoroquinolone absorption. Also see Annex 7 – Management of electrolyte Disturbances

| Nephrotoxicity (renal toxicity) | S, Km, Am, Cm | 1. Discontinue the suspected agent.
2. Consider using capreomycin if an aminoglycoside had been the prior injectable drug in the regimen.
3. Consider other contributing aetiologies (non-steroidal anti-inflammatory drugs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated.
4. Follow creatinine (and electrolyte) levels closely, every one to two weeks.
5. Consider dosing the injectable agent two to three times a week if the drug is essential to the regimen and the patient can tolerate (close monitoring of creatinine). If the

1. If severe hypokalaemia is present, consider hospitalization.
2. Amiloride, 5–10 mg daily, or spironolactone, 25 mg daily, may decrease potassium and magnesium wasting, and thus useful in refractory patients.
3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.
4. See Annexes 4.1 and 4.2 for management of hypokalaemia when the patient receives bedaquiline or delamanid.

1. 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.
2. An example of how to calculate a creatinine clearance based on the serum creatinine is provided in Chapter 7, Box 7.2.
3. Renal impairment may be permanent.

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2. An example of how to calculate a creatinine clearance based on the serum creatinine is provided in Chapter 7, Box 7.2.
3. Renal impairment may be permanent.
Creatinine continues to rise despite twice/thrice a week dosing, suspend the injectable agent.
5. Adjust all TB medications according to the creatinine clearance (see Chapter 7, Table 7.2 and Box 7.2).

<table>
<thead>
<tr>
<th>Vestibular toxicity (tinnitus and dizziness)</th>
<th>S, Km, Am, Cm, Cs, FQs, H Eto, Lzd</th>
</tr>
</thead>
</table>
| 1. If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen.  
2. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. This is one of the few adverse reactions that cause permanent intolerable toxicity and can necessitate discontinuation of a class of agents. | 1. Ask the patient about tinnitus and unsteadiness every week.  
2. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity.  
3. A degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, H or linezolid. 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. |

<table>
<thead>
<tr>
<th>Hearing loss (also see vestibular toxicity above)</th>
<th>S, Km, Am, Cm, Clr</th>
</tr>
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</table>
| 1. Document hearing loss and compare with baseline audiogram if available. (Some degree of hearing loss occurs with most patients starting with high frequency loss.)  
2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen.  
3. Discontinue the 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. Also see Annex 7 – Management of hearing loss | 1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy.  
2. Hearing loss is almost always permanent. Continuing the injectable agent despite hearing loss almost always results in irreversible deafness.  
3. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use. |

<table>
<thead>
<tr>
<th>Peripheral neuropathy</th>
<th>Cs, Lzd, H, S, Km, Amk, Cm, H, Fluoroquinolones,</th>
</tr>
</thead>
</table>
| 1. Correct any vitamin or nutritional deficiencies. Increase pyridoxine to the maximum daily dose (200 mg per day).  
2. Consider whether the dose of cycloserine can be | 1. Patients with comorbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these |
rarely Pto/Eto, E

reduced without compromising the regimen. If isoniazid is being used (especially high dose isoniazid), consider stopping it. If possible, switching the aminoglycoside to capreomycin may also be helpful.

3. Initiate medical therapy:
   • Nonsteroidal 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 anti-depressant drugs.
   • Carbamazepine, an anticonvulsant, at 100 to 400 mg twice daily can be tried.
   • Gabapentin (used off-label) at 300 mg thrice a day; it can be used at a maximum dose of 3600 mg/day in three or four divided doses.

4. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.

<table>
<thead>
<tr>
<th>Headache</th>
<th>Cs, Bdq,</th>
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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. Consider low dose tricyclic antidepressants for refractory headaches.

1. Headaches are common during the initial months of MDR-TB therapy. They can present as migraine or cluster headaches.
2. To minimize headaches at the start of therapy, cycloserine can be started at lower doses of 250–500 mg and gradually increased over one to two weeks to achieve the target dose.
3. Headaches due to cycloserine and Bedaquiline are usually self-limited.
4. Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurotoxicity. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.
| Depression | Psychological and socioeconomic circumstances, chronic disease, Cs, fluoroquinolones, H, Eto/Pto | 1. Assess and address underlying emotional and socioeconomic issues (see Chapter 12 on Social support).  
2. Assess patients for coexisting substance abuse and refer to treatment if appropriate.  
3. Initiate individual counselling (or group counselling if the patient is smear and culture negative).  
3. When depression is more significant, initiate antidepressant therapy (amitriptyline, fluoxetine or similar).  
Tricyclic antidepressants and selective serotonin reuptake inhibitors should be given together and should not be given to patients on linezolid.  
4. Lower the dose of the suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and ethionamide to 500 mg daily to see if the depression is lessened is a common strategy).  
5. Discontinue the suspected agent if this can be done without compromising the regimen. | 1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression.  
2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated.  
3. History of previous depression is not a contraindication to the 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 cycloserine, if possible.  
4. Question the patient regarding suicidal ideation any time the depression is judged to be more than mild. |
|---|---|---|---|
| Suicidal ideation | CS, H, Eto/Pto | 1. Hospitalize the patient and put under 24-hour surveillance.  
2. Discontinue cycloserine.  
3. Request psychiatric consultation.  
4. Initiate antidepressant therapy.  
5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable. | 1. Keep the patient in the hospital until risk of suicide has passed.  
2. If no improvement occurs after holding cycloserine, hold H and/or Eto/Pto. |
| Psychotic symptoms | Cs, H, fluoroquinolones | 1. Stop the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control.  
The most likely drug is cycloserine followed by high dose isoniazid.  
2. If moderate to severe symptoms persist, initiate antipsychotic therapy (haloperidol). | 1. Some patients will need to continue antipsychotic treatment throughout MDR-TB treatment (and discontinued upon completion of treatment).  
2. Previous history of psychiatric disease is not a contraindication to cycloserine, but its use may increase the likelihood of psychotic symptoms. |
<table>
<thead>
<tr>
<th>Seizures</th>
<th>Cs, H, fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hold cycloserine, fluoroquinolones and isoniazid pending resolution of seizures.</td>
<td>1. An anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent is discontinued.</td>
</tr>
<tr>
<td>2. Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used).</td>
<td>2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient’s seizures are well controlled and/ or the patient is receiving anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available.)</td>
</tr>
<tr>
<td>3. Increase pyridoxine to the maximum daily dose (200 mg per day).</td>
<td>3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy.</td>
</tr>
<tr>
<td>4. Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride.</td>
<td>5. Always check creatinine in patients with new onset seizures. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may</td>
</tr>
<tr>
<td>5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.</td>
<td>developing during treatment.</td>
</tr>
<tr>
<td>3. Some patients will tolerate cycloserine 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 only be done when there is no other alternative.</td>
<td></td>
</tr>
<tr>
<td>4. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.</td>
<td>5. Always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.</td>
</tr>
</tbody>
</table>

### Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others.

### Increase pyridoxine to the maximum daily dose (200 mg per day).

### Lower the dose of the suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising the regimen.

### Discontinue the suspected agent if this can be done without compromising the regimen.

### Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered off. If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist trained in the adverse effects of second-line anti-TB drugs.
**Optic neuritis**

| E, Lzd, Eto/Pto, Cfx, rifabutin, H, S |

1. Stop ethambutol and linezolid. Do not restart.
2. Refer patient to an ophthalmologist.

1. The most common drug responsible is ethambutol and it usually reverses with cessation of the drug.
2. Improve diabetes control in Diabetic patients.

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**Metallic taste**

| Eto/Pto, Clr, FQs |

1. Encourage the patient to tolerate this side effect.
2. Sucking hard candy or chewing gum can be helpful.

1. Normal taste returns when treatment is stopped.

---

**Gynaecomastia**

| Eto/Pto |

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

1. Resolution occurs after treatment is stopped.

---

**Alopecia**

| H, Eto/Pto |

1. Hair loss can occur or there can be significant thinning of the hair, but this is temporary and not progressive during treatment.
2. Encourage patients to tolerate this side effect.

1. Significant cosmetic change has not been reported.

---

**Superficial fungal infection and thrush**

| Fluoroquinolones and other antibiotics with antibacterial properties |

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

1. Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.

---

**Lactic acidosis**

| Lzd |

1. Stop linezolid if lactic acidosis occurs.

1. Lactic acidosis can be monitored with a blood test that measures lactic acid.

---

**Dysglycaemia and hyperglycaemia**

| Gfx, Eto/Pto |

1. Stop gatifloxacin and replace with different later generation fluoroquinolone like moxifloxacin.
2. Treat diabetes as needed. Good glucose control is important during treatment.

---

**QT prolongation**

| Bdq, Dlm, fluoroquinolones, clarithromycin clofazimine |

Any patient found to have a QTc value greater than 500ms should be managed carefully.
- Repeat ECG and confirm the prolongation.
- Bedaquiline and delamanid are drugs that should be stopped for QTc value greater than 500ms. Consider stopping other drugs that prolong the QT interval.
- Check potassium, calcium and magnesium levels.

1. The 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. A normal QTc is generally <440ms.
2. Values above QTc 440ms are referred to as
Electrolyte levels should be maintained in the normal range in any patients with an elevated QT interval.  
• It is suggested to maintain potassium levels of more than 4 mEq/l and magnesium levels of more than 1.8 mg/dl.  
• Avoid other drugs that increase the QT interval. Monitor the patient’s renal and hepatic function and adjust the dose of fluoroquinolones if impairment is present.  
Consider suspension of fluoroquinolone if risk of torsades de pointes outweighs the benefits of the drug. Also see Annexes 4.1 and 4.2 for more information on QT interval monitoring with bedaquiline and Delamanid prolonged. Patients with prolonged QTc are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life threatening. Patients with QTc greater than 500ms are at the greatest risk for developing these arrhythmias.  
3. The fluoroquinolones cause prolongation of the QTc. Moxifloxacin and gatifloxacin cause the greatest QTc prolongation, while levofloxacin and ofloxacin have a lower risk.  
4. Currently, ECG monitoring prior to initiation and during MDR-TB therapy is only required with the use of bedaquiline, delamanid, or when two drugs known to prolong QT (e.g. moxifloxacin, clofazimine) are combined in the same regimen.

<table>
<thead>
<tr>
<th>Haematological abnormalities</th>
<th>Lzd</th>
</tr>
</thead>
</table>
| Stop linezolid if myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs. Consider restarting with a lower dose of linezolid (300 mg instead of 600 mg) if myelosuppression resolves and if linezolid is considered essential to the regimen. Consider nondrug related causes of the haematological abnormality. Consider blood transfusion for severe anaemia. | 1. 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.)  
2. There is little experience with prolonged use of linezolid. |
ADR management is crucial to improve treatment compliance of DR-TB patients. Majority of side effects and ADR management is possible with 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 9.4 Drugs used in management of adverse event

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Suggested Drugs to manage the ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting, upset Stomach</td>
<td>Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate, donperidone</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, risperide (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>

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

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

9.4 Pharmacovigilance in TB control programme

Pharmacovigilance is defined by the World Health Organization (WHO) as the “science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”. The overall objective of pharmacovigilance programme is to improve patient care by assessment of harm of benefit received from drug. More than 100 ADR Monitoring Centers (AMC) currently collecting ADR related information at various levels. Pharmacovigilance Programme of India (PvPI) is a national programme for surveillance of ADR related information. DR-TB management is inclusive of newer drugs which required robust system of monitoring and reporting of ADR related information to build the guideline for safe use of drugs.

Under the PvPI, reporting of any adverse event (AE) or serious adverse event (SAE) is done using a suspected ADR reporting format. However, since newer drugs like BDQ are still under Phase III clinical trials, WHO recommends active drug safety monitoring as one of the five conditions countries should meet for introducing new drugs. Hence, RNTCP in collaboration with PvPI and support from WHO India developed the comprehensive cohort event monitoring system for active pharmacovigilance for patients initiated on Bedaquiline (newer drugs) containing regimen. A drug safety monitoring committee periodically monitors the occurrence of AE/SAE including deaths of patients while on newer drugs containing regimen for necessary signalling and guidance to the programme on their safety and efficacy.

It has been decided that suspected ADR reporting format of PvPI (Annexure 7) would be used for aDSM in patients put on any DR-TB regimen. However, the CEM formats (Annexure 8, 9) will be continued only at the initial 6 DR-TB Center where BDQ conditional access programme is implemented till further guidance from the programme.
9.5 Adverse Event Monitoring and Reporting for New Drugs (Bdq, Dlm)

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

Adverse event definitions and classifications

**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 unfavorable 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 per 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. (The 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 were 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;
- is medically important.*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

**Non-serious adverse drug reaction (ADR)** (associated with the use of the drug): Any untoward medical occurrence that does not meet the above criteria to be serious and also is considered associated with the use of the drug.
**Life threatening:** Any event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

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

**Attribution definitions:**

Causality assessment will be done by the physician at DR-TB centre. There are five categories as mentioned below. The drug safety monitoring committee (DSMC) for BDQ conditional access will review and confirm the causality of all serious events/reactions in relation to the therapy [20].

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

ii. **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.

iii. **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.

iv. **Probable:** An AE that might be due to the 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).

v. **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 very suggestive, e.g. it is confirmed by de-challenge and re-challenge.

**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, (i.e. non-serious adverse events which are possibly, probably or very likely related to the administration of BDQ) that fit the definition as detailed later related to detailed formats for AE reporting and pregnancy occurring during the programme must be reported by the physician to RNTCP as they occur. If pregnancy occurs during BDQ treatment, BDQ must be stopped and OBR must be modified as per the 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 25) should be undertaken. It is recommended that the patient be questioned before the 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 active pharmacovigilance is implemented by all the NDR-TBC and district physicians for ambulatory patients.

The flowchart 1 on ADR management and data capturing format related to Pharmacovigilance is shown below.

Flowchart 1: ADR management and data capturing related to pharmacovigilance for BDQ
Once the relevant forms CEM, Suspected ADR forms are filled in NIKSHAY and Vigiflow by Technical Associate from PvPI in coordination with statistical assistance of DR TB centre. The sites need to ensure reporting of SAE within 24 hours to Central TB Division using NIKSHAY followed by email to ddgtb@rntcp.org and bdq@rntcp.org. Records need to be maintained in hard copies at respective sites.

The CEM data will be analysed at CTD periodically. The relevant information will be shared with DSMC on monthly basis as a routine. The data on action required on immediate basis will be shared with DSMC by CTD.

The data related to suspected ADR format will be analyzed by PvPI using Vigiflow and shared with CTD, on monthly 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 the DAIDS (Division of AIDS) criteria during treatment and follow-up [18].
9.4 Preparation for Implementation of DR-TB patients management with newer drugs

In India, RNTCP programme has access for one new drug Bedaquiline, while is preparing to introduce the second drug Delamanid through conditional approval from DCGI as detailed earlier. WHO has recommended these drugs for the DR-TB patients for specified group. Within programme for the DR-TB patient, define selection criteria are applied to access eligibility for newer drugs. Pre-requisites for introduction of newer drugs Bedaquiline and Delamanid are the drugs currently available for RNTCP under conditional access programme. These drugs are not available to open market in India and so there are few pre-requisites proposed for providing access under RNTCP programme. Once the NDR-TBC gets access to newer drugs they have to comply with all the requirements listed below.

- Lab aligned should have capacity and is certified to do extended DST for all required second line drugs.
- Implementing district must have completed training for required cadre.
- All requirements like ECG, follow up lab investigation during treatment course should be made available.
- Drugs availability and logistic arrangement need to be ensured.

**Bedaquiline (BDQ)** Bedaquiline is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). It has a novel mechanism of action. It binds to Mycobacterium tuberculosis ATP synthase, an enzyme that is essential for the generation of energy in M. tuberculosis. Inhibiting ATP synthesis results in bactericidal activity. The drug is not active against non-mycobacteria. There are few exclusion criteria for providing Bedaquiline drug. Doses for BDQ containing regimen: Week 0 to 2: 400 mg (4 tables of 100 mg) daily 7 day per week + OBR Week 3 to 24: 200 mg (2 tables of 100mg) 3 times a week (at least 48 hrs apart) for total 600 mg per week + OBR Week 25 to end of treatment: continue OBR as per RNTCP recommendation.

A dose is irrespective of weight. BDQ should be administered along with food but avoid milk and fatty food. This drug retain within body up to 5.5 months even after discontinuation of drug. This requires more frequent and more intense monitoring during and post-treatment which includes strict monitoring of adverse event occurs during treatment. ECG and few lab investigations require during follow up which is essential to monitor adverse event. Most important ADR is QT prolongation.

**Delamanid** As per Interim policy guidance document release by WHO in 2014, delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB. (WHO, 2014). This recommendation is subject to following conditions.
1. Proper patient inclusion: The current recommendation for the use of delamanid applies to adults (≥18yrs) with pulmonary MDR-TB disease, including people living with HIV. Use of the drug in children and in pregnant and breastfeeding women is not currently advised due to a lack of evidence on safety, efficacy and proper dosing in these groups. Because delamanid is shown to cause prolongation of the QT interval, patients with a QTcF>500ms should not receive the drug.

2. Regimen should be designed as per the WHO recommendation of use of Z with at least 4 second-line drugs. Delamanid should not be added alone to a failing regimen. The recommended dose of delamanid in adults is 100mg twice a day preferably after a meal, irrespective of body-weight, for a period of six months. higher doses in not effective but causing more ADR.

3. Consent should be obtained from the patient initiated on treatment .Close monitoring of treatment including Active pharmacovigilance and proper management of adverse
Chapter 10: Monitoring and Outcome Definitions

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

10.1 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 D/NDR-TBC, at monthly intervals during the IP, and at 3-monthly intervals during the CP until the end of treatment. The responsible medical officer at D/NDR-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 the adverse effects are recognized early by the Treatment Supporter. This makes it possible to closely monitor patients. Patients should be encouraged to volunteer if they experience any adverse effects, though patients should not be asked any leading question to elicit any adverse reaction. However, if the patient makes any complaint, s/he should be interrogated in detail and the 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 the 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 the D/NDR-TBC or any institute as per the 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.

10.2 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 10.1 below:
Table 10.1 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 (for NDR-TBC other than Six centers in BDQ-CAP)</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></td>
<td></td>
<td></td>
<td></td>
<td>Monthly in IP, Quarterly in CP</td>
</tr>
<tr>
<td>Smear Microscopy®</td>
<td>Monthly till end of IP, Monthly in extended IP only if previous month S+ve</td>
<td></td>
<td></td>
<td>With culture at C-DST labs</td>
<td></td>
</tr>
<tr>
<td>Culture®</td>
<td>Quarterly at months 3, 6, 9, end of Rx</td>
<td></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>
</tr>
<tr>
<td>DST®</td>
<td>Repeat DST on LPA and MGIT as per diagnostic algorithm if culture +ve at any time from end of IP till end of Rx</td>
<td></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>Audiology</td>
<td>As and when clinically indicated till SLI course is completed</td>
<td></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/platelets*</td>
<td>As and when clinically indicated</td>
<td></td>
<td></td>
<td>Monthly in IP, Quarterly in CP</td>
<td></td>
</tr>
<tr>
<td>CXR®, TSH &amp; LFT*</td>
<td>As and when clinically indicated</td>
<td></td>
<td>At end of IP, as and when clinically indicated</td>
<td>CXR also at end of treatment</td>
<td></td>
</tr>
<tr>
<td>ECG$</td>
<td>As and when clinically indicated</td>
<td>At 2 wks, monthly in IP, as and when clinically indicated</td>
<td>As and when clinically indicated</td>
<td>At 2 wks, monthly in IP, as and when clinically indicated</td>
<td></td>
</tr>
<tr>
<td>S. Electrolytes (Na, K, Cl)</td>
<td>As and when clinically indicate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. Mg, Ca, Amylase Lipase</td>
<td>As and when clinically indicated</td>
<td></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>Quarterly in IP, as and when required</td>
<td></td>
</tr>
</tbody>
</table>

@ After completion of treatment the patients should be followed up at the end of 6, 12, 18 and 24 months and if found symptomatic any time, the patient will be retrieved for clinical evaluation, CXR, smear and culture. DST would be repeated if culture is positive.

* CBC/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
$ Increase frequency of ECG monitoring as and when clinically indicated particularly in regimen containing Mfxh, Bdq and Cfx.
The most important objective evidence of response to DR-TB treatment is the conversion of sputum smear and culture to negative. Good quality sputum specimen is essential to get reliable results that form the basis of monitoring bacteriological response to treatment.

Smear examination would be used on 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 (3m IP) and Shorter MDR-TB regimen (4m IP). It would be continued on monthly basis if IP need to be extended if the previous month smear is positive up to a maximum of 6 months in both regimens.

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 of more than one year duration, sputum culture

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 the date of the first of these two negative consecutive cultures (the date of sputum specimens are collected for culture should be used).

Arrangements can be made to collect the 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 the supply of conical tubes for follow up sputum culture examination should be ensured.

Wherever available, as per the laboratory decision based on resources available, follow-up sputum culture should be done using liquid culture for all IP follow-up cultures and for the last 6 months of CP. For the rest of the follow up cultures and wherever liquid culture is not available, solid media will be used for follow up. In case of extension of IP, the follow up culture months will shift by every month of extension of IP till the maximum limit of IP set for all regimen classes.

Follow up evaluation schedule for Six NDR-TBC currently in BDQ-CAP:

Once the BDQ-containing regimen is started, the patient will be monitored for QTc prolongation which will prompt a regular ECG and other safety monitoring as shown in the table below. A cardiologist must be available for expert interpretation of ECG. All patients enrolled on BDQ-containing regimen would be closely monitored by the DR-TB Centre or district hospital physician as per the schedule in Table 10.2 below.
Table 10.2 Follow up schedule for Newer Drug containing regimen

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 wk</th>
<th>1 m</th>
<th>2 m</th>
<th>3 m</th>
<th>4 m</th>
<th>5 m</th>
<th>6 m</th>
<th>7 m</th>
<th>9 m</th>
<th>12 m</th>
<th>15 m</th>
<th>18 m</th>
<th>21 m</th>
<th>24 m</th>
<th>30 m</th>
<th>36 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evaluation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Weight</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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*ECG to be done daily (first 2 weeks), weekly (for 3 months) then monthly.
*HBsAg at baseline, other viral markers (HEP A,C & E) on signs of jaundice during treatment

This intensified follow up evaluation schedule would be continued only at the six NDR-TBC implementing the BDQ – CAP till further guidance from the programme.
10.3 Treatment outcomes

The treatment outcome definitions would vary with the duration of treatment. The treatment outcomes are defined for patients on longer term regimen beyond one year in section 10.3.1 and for regimen on shorter term regimen up to one year in section 10.3.2

10.3.1 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 are negative after the intensive phase

**Treatment completed:** Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase

**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 intensive phase or
- Microbiological reversion in the continuation phase after conversion to negative or
- Evidence of additional acquired resistance to fluoroquinolones or second line injectable drugs or
- Adverse drug reactions (ADR)

**Conversion and reversion:** Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion. Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

**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

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

**Regimen Changed:** A TB patient need for permanent regimen change of at least one or more anti-TB drugs prior to being declared as failed
10.3.2 Outcomes for H mono- / poly DR-TB patients and RR-TB patients put on Shorter MDR-TB Regimen

**Cure:** A microbiologically confirmed TB at the beginning of treatment who was culture-negative in the last month 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 the end of the intensive phase or
- Microbiological reversion in the continuation phase after conversion to negative or
- Evidence of additional acquired resistance to fluoroquinolones or second line injectable drugs or
- Adverse drug reactions (ADR)

**Died:** A patient who dies for any reason during the course of mono- / poly-DR-TB treatment

**Lost to follow up:** A patient whose treatment was interrupted for one month or more for any reasons.

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

Treatment outcome is defined by reviewing her/his PMDT Treatment Card. The treatment outcome and the date the patient stopped treatment is written in the appropriate column in the Tuberculosis 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 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 Drug Resistant TB, poses a greater challenge due to its longer course. It is observed that approximately 50% of MDR-TB patients do not complete treatment, often due to loss to follow up or death. Early detection of drug resistance through rapid diagnostics facilitates early initiation of treatment and favours good prognosis. Adverse drug reactions, comorbidities, social neglect and catastrophic expenditures are the 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 program customised for each DR-TB patient.

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

- Minimise patient travel
- Minimise delay in treatment initiation and follow up
- Minimise Catastrophic expenditure
- Minimise infection in transit
- Maximise patient satisfaction
- Maximise adherence to treatment
- Maximise 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 tuberculosis including DR-TB. Some may need total support including social, nutritional, financial, and residential support and special support for management of substance abuse, co-morbidity etc. Even though the patient is in need of support, he may not request for it since he may not be aware that such supports could be availed through his healthcare team. Hence the need for support should be assessed and process of providing support should be 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 affected with DR-TB; these need to be addressed in their training. All patients need to be provided with a feedback form with rating scales for Staff behaviour, health facility cleanliness, and details of costs incurred. These feedback should be collected on a monthly basis and monitored at the district. 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 endorsements.

11.3 Diagnosis and Treatment Initiation

When the presumptive DR-TB patients are identified at the PHI/ private health facility, they should then be counselled by the MO-PHI/ treating physician regarding their status as presumptive DR-TB and the 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 that they receive the eligible financial support from the program provision.

The Lab Technician should communicate the result of DST to the MO-PHI/ treating physician, patient and the DR-TB centre at the earliest possible time and convenience of the patient. In case the result indicates Drug resistance the patient will be asked to visit the nearest DR-TB centre. In the DR-TB Centre the PTE and any inpatient care should be completely free of cost. In case the service is chargeable the same needs to be availed from the financial support given 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 date of result, then tracking action should be initiated by the DR-TBC counsellor in co-ordination 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, which will assist in tracking. Patients referred for treatment initiation or further management to the DR-TB Centre, should be advised to report to the DR-TB Counsellor. The patient should be provided with the contact details of the necessary staff at the DR-TB Centre. Once the patient reports to the DR-TB Counsellor, they should counsel the patient about DR-TB drugs and treatment regimen, Adverse Drug Reactions, follow-up and access to services.
In the DR-TB Centre all patients needing in-patient care should be admitted under a committee member designated as nodal clinician responsible for DR-TB management. The patients who do not need in-patient care the nodal clinician will co-ordinate consultations and referral to other members of the committee or other clinical care. In-case the services needed are not available under the same institution the DR-TB counsellor should co-ordinate the same under the guidance of the nodal clinician. To minimise the delays in pre-treatment clinical evaluation, the 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 the members, will initiate treatment on the appropriate regimen. In no case, patient should be kept waiting for beds, consultation with specialists and eligible enablers.

11.4 Domiciliary, ambulatory and inpatient care

The patients on ambulatory care and patients stabilised after in-patient care will be referred to the concerned PHI through a filled PMDT - Referral for Treatment form. The patient will carry their copy of the Treatment book. The DR-TB counsellor should counsel the patient on the various drugs that he has been initiated on and their adverse events. Patients should be provided with a list of Adverse Drug Reactions and necessary actions to be taken. The counsellor should train the patient the use of an adverse event monitoring tool. The DR-TB counsellor should intimate the referral and relevant details of treatment in advance to the MO-PHI or treating clinician to arrange drugs and necessary support.

All patients may not need in-patient 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 in-patients. 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 for at least the first two weeks, by a trained treatment supporter. Further treatment supervision may be provided through any of the various options available, such as family observation of treatment, Electronic Pill Box (Annexure 10), ICT support, based on the collective decision of the patient and the MO-PHI.
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 co-ordinate 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. Counselling need 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, follow-up specimen collection and record the details of the same in relevant sections of the treatment book.

At no point during diagnosis, pretreatment, treatment and follow up, should the patient incur any direct cost to avail any service. 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 is expected to be provided to the patient by a Direct Beneficiary Transfer system.

11.7 Patient support for Co-morbidities

Many of the 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 co-morbidities are made available to the patient without interruption.

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 support. Occasionally these support may have to be locally initiated and financed. Social interventions with the stewardship of the community have been found to be effective in promoting treatment adherence.

11.9 Treatment support for the 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 counsellors should educate the patients on potential adverse reactions, their signs and symptoms, necessity of timely reporting and their recording in the ADR diary provided with the treatment book. The field staff 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-TB centre immediately. The MO should fill a referral for 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-TB Centre. 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.

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.

11.11 Patient helpdesk

At all service provision levels there are possibilities where 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 a feedback is received the District TB officer should categorise the feedback based on level at which the feedback is related to and whether it needs action or not. Even if it does not require an action, the message should be responded. If it needs further action the DTO will assign a competent authority to address the request/grievance and a 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, patient should be informed of the status of their submission and patient should have the ability to confirm that the grievance was addressed. The turnaround time of various types of grievances and successful resolution should be monitored and should be included as a part of the quality assessment of Tuberculosis care in the country.
Chapter 12: RNTCP PMDT Reporting & Recording System

This chapter describes the importation system for patients that fall under RNTCP PMDT, with the objective of recording and reporting drug resistant patient information which are needed to monitor resistant trends and programme performance. This chapter also describes both paper-based as well as electronic reporting and recording system.

12.1 Aims of the information system

The aims of the information system are:

1. To allow the managers at different levels in RNTCP to follow overall programme performance through following:
   a. The distribution and trend in DR-TB notification.
   b. The response to treatment in DR-TB patients treated with RNTCP regimen

2. To aid the staff in the treatment units in providing adequate management of the individual patient.

3. To enable real-time monitoring of the patients and real-time generation of reports.

There is e-NIKSHAY 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.

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 the RNTCP.

The 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 of the detailed information that the treatment units may need to manage the individual patient: this is contained in the clinical record and other special forms used in the wards or clinics and depends on the local requirements and practices.
12.3 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.

12.3.1 RNTCP Request Card for Examination of Biological Specimen for TB

All individuals who are suspected of having Drug sensitive or Drug resistant TB are required to have a sputum or extra-pulmonary specimen examination for diagnosis. The comprehensive Request card for examination of biological specimen for TB (Annexure 11) (ToG Annexure 15 A) 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), test requested and result of sputum smear microscopy. Back page is for the laboratory to report the results of CBNAAT, LPA, DST and any other tests requested.
12.3.2 RNTCP Laboratory Register for Culture, CBNAAT and Drug Susceptibility Testing

The RNTCP laboratory register for Culture, CBNAAT and DST (Annexure 12) (ToG Annexure IV) is used to record CBNAAT, LPA and culture and DST examination results. This register should be compared regularly with the RNTCP PMDT treatment register to ensure that all DR-TB patients to be started on Various DR-TB regimen are entered in the PMDT treatment register to ensure each case diagnosed is accounted for monitoring indicators and report generation. The lab NIKSHAY number is a unique number, given to a patient first time his/her specimen comes the lab. On all subsequent specimen sent to the lab, the same NIKSHAY number is retained for the patient, but the new specimen is provided with a new lab number. This gives an opportunity to easily extract the test results of all the specimen provided by the patient and there by track his/her response to the treatment.

12.3.3 RNTCP PMDT Referral for Treatment Form

The RNTCP PMDT referral for treatment form (Annexure 13) (ToG Annexure 15H) has to be filled for all confirmed DR-TB patients that are referred from one centre to another centre. The form has to be filled by the doctor of the referring centre in duplicate and one copy sent along with the copy of the current treatment card to the referred centre. This form can be used for referring the patient at various points in time during the management of the patient between the PHI, DTC and DR-TB Centre for reasons like initiation of treatment, adverse drug reaction, transfer out, ambulatory treatment or any other reason. In patients that are transferred out, a copy of the updated PMDT treatment card must also be sent along with the referral for treatment form.

12.3.4 RNTCP PMDT Treatment Card

The RNTCP PMDT Treatment card (Annexure 14) (ToG Annexure 15E) is a key instrument for the treatment supporter administrating drugs daily to the patient. The card will be initiated at the D/NDR-TB Centre when the patient is initiated on treatment either on outpatients or indoor basis. The card should be updated daily, ticking off the administration of drugs by the treatment supporter. The card is the source to complete and periodically update the PMDT register. The original treatment card will be maintained at the DR-TB Centre and a copy will be kept at treatment supporter. Accountable systems have to be developed locally for updating cards at all levels. When or if the patient moves from the DR-TB Centre to his/her district of residence a copy of the card, must follow the patient. A copy of this card may be used as a notification form and to inform about final outcome of treatment.

The card contains the following sections:
Basic demographic information: Name, sex, age, address, telephone number, state, DR-TB Centre, district, TU, PHI and details of the treatment supporter.

PMDT TB number: This is a new unique patient identification number given to the patient at the DR-TB Centre on initiation of treatment. The PMDT TB number should include the following – S.No./Name of the DR-TB Centre code/year of initiation of treatment. E.g. PMDT TB number of the first patient started on treatment at Nagpur DR-TB Centre in 2012 will be 1/NGP/2012. Every year the PMDT TB number will be started at 1. This would remain as a transitory system till such point in time that most of the DR-TB patients are entered on NIKSHAY and it is time to completely transition from paper-based registers to auto-generation of electronic registers from NIKSHAY PMDT modules directly.

NIKSHAY ID / CDL NIKSHAY ID / PMDT NIKSHAY ID: NIKSHAY ID refers to the unique ID which is generated after registering a TB patient at TB unit level. CDL NIKSHAY ID refers to the unique ID generated after registering a patient at Culture DST Lab which includes IRL/C-DST as well as CBNAAT laboratories. PMDT NIKSHAY ID refers to the unique ID generated after registering a DR-TB patient at DR-TB Centre. Eventually, all these IDs would be submerged into a NIKSHAY ID.

As per RNTCP TOG, all TB patients are to be notified at the time of diagnosis. This information is recorded in Notification register. Notification of all DR-TB patients diagnosed either at CBNAAT lab or C&D DST labs is also entered in the notification register with Notification ID. The notification register is maintained at the PHI level that includes the facilities where these labs are located. DR-TB patients notified from private sector directly on NIKSHAY are also available as additional source of information. NIKSHAY ID would be generated for the patient with a unique ID. In the same unique ID, all subsequent events happening for diagnostic and treatment pathway would be added. So it's the life cycle approach where multiple events can happen for the single patient to complete the diagnosis and treatment pathways. All the relevant information of a particular patient would be available with the same NIKSHAY ID, which would be, updated as and when information is available in different point in time. With > 7 million TB patients entered in NIKDSHAY to date, most of the patients would already have a NIKSHAY ID and with the real-time entries from CBNAAT and C-DST labs on all diagnosed TB/DR-TB patients into the NIKSHAY laboratory module, NIKSHAY ID should become a universal unique ID. Once the patient is notified in Notification the treatment details would be captured in PMDT treatment register maintained at DDR-TBC / NDR-TBC.

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

**HIV Testing:** This section lists the date of testing, PID no, date of starting CPT and ART (Wherever applicable). As per the national policy, the information sharing on the HIV status of the patients should be restricted within the health care facilities based on the concept of “Shared Confidentiality”. Hence, this information must not be written on the copy of the card held by the Treatment Supporter.

**Contact tracing:** This section details the no of household contacts screened, no of presumptive TB patients identified, no of presumptive TB patients evaluated, no diagnosed with TB and no of DR-TB diagnosed.

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 for Bedaquiline containing regimen are recorded in this section.

**Drugs and dosages:** This section details the drugs and dosages used including status of eligibility and consent for Bedaquiline containing regimen.

**DR-TB Centre Committee meetings:** There should be periodic meetings of the DR-TB Centre -committee, with the caregivers involved with the DR-TB patients, in which the progress of the individual patient is reviewed. This section provides a space to record any major changes by the Committee like extension of IP; change of IP to CP; completion of treatment; severe adverse reactions; change of treatment, declaring treatment outcome etc.

Page 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.

**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 Bedaquiline 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 the 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. The CP should be documented on new line.

Page 7 of the treatment card:

**Date and details of the retrieval action** taken should be recorded in the relevant section

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

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

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

**12.3.5 TB Notification register**

A TB notification register (Annexure 15) (ToG Annexure 15I) 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. It will also incorporate those cases initiated on first line treatment and offered drug susceptibility testing and results are awaited. The registration data is based on the date on which a TB patient is diagnosed.
If patient is put on treatment in area of facility where s/he is diagnosed then information on treatment and follow up is recorded in the same TB notification register. If patient is treated in area other than where h/she is diagnosed then information on treatment and follow up is recorded in TB notification register of health facility where patients is residing.

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.

For every patient, status of treatment should be recorded. The status of treatment for any patient would one of the following

1. Initiated on First line treatment in the same Health Facility
2. Initiated on second line treatment in the same Health Facility
3. Initiated on treatment outside Health Facility
4. Treatment initiated outside RNTCP
5. Incomplete/ incorrect address
6. Died
7. Migrated & untraceable
8. Repeat diagnosis
9. Patient already on treatment/ Follow up patient
10. Wrong diagnosis
11. Referred for treatment with pending feedback
12. Other

12.3.6 RNTCP PMDT Treatment register

This register is maintained at DDR-TBC and NDR-TBC. While TB notification register captures the details about the notified DR-TB patients as well, the RNTCP PMDT TB register (Annexure 16) is restricted to patients who have actually started on a second-line TB treatment regimen. Date of registration will be date on which a patient is initiated on second-line treatment. The patients should be entered consecutively by their date of registration.

The following is recorded in the PMDT treatment register:

**LEFT PAGE:**

**PMDT TB No:** This is a unique patient identification number for patients that are initiated on treatment for DR-TB. It has been described earlier. Every year the PMDT TB number will be started at 1.

**PMDT NIKSHAY ID:** This is a unique ID generated for a patient on registering him/her in NIKSHAY at DR-TB centre.
CDL NIKSHAY ID: This is a unique ID generated at the C&DST lab once a patient whose is subjected to C&DST is registered in NIKSHAY.

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. Codes to be used as mentioned below the page.

Site of disease: Whether pulmonary or extra-pulmonary is mentioned in this column.

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

DST details: Type of test (LJ / 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 drugs whose DST might be done in future.

RIGHT PAGE

Type of DR-TB patient: Type of the patient, whether RRTB / MDR-TB / XDR-TB is mentioned here.

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

Culture and DST results at initiation and during DR-TB treatment: 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 RNTCP PMDT Treatment Book

RNTCP PMDT Treatment Book (Annexure 17) (ToG Annexure 15F) 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 treatment card is filled out. This Treatment book will be kept by the patient and should be brought whenever s/he comes to DR-TB Centre 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-TB Centre, District and State
- Information about Initial home visit, by whom it has been done and on what date
- Information about NIKSHAY ID, CDL NIKSHAY ID, PMDT NIKSHAY ID and PMDT TB number
- Essential information about Reason for Testing, which are as follows:
  - Whether New or Previously treated case
  - Whether Presumptive TB, Private referral or Presumptive NTM
  - Whether Presumptive MDR-TB at diagnosis or due to contact of MDR/RR TB or follow-up smear positive at end of IP or it is a private referral
  - Whether Presumptive H mono/poly resistant TB
  - Whether Presumptive XDR-TB case due to MDR/RR-TB at diagnosis, or 4 months culture positive or culture reversion or Failure of MDR/RR-TB regimen or recurrent case of 2nd 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 case 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 conventional and Shorter MDR-TB Regimen
- Information about the 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 1st and 2nd line anti-TB drugs done in different months [with date of specimen collection & type of DST (LJ/LC/LPA/CBNAAAT)]
• 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 6 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 complain, which includes the following:
  o Date of visit o Chief complaints made by the patient o Major findings of clinical examination
  o Different types of investigations done
  o What treatment provided
  o Counselling notes
• Information about treatment outcome of the patient with date
• Information about Post-treatment follow up clinical & sputum examination (Result with date) done at interval of 6, 12, 18 and 24 months after the end of treatment.

12.3.8 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:

12.3.8.1 Patient Education Booklet for BDQ-containing regimen under PMDT (RNTCP) and Informed Consent Form

A detailed patient education booklet has been developed for educating the patient on the use of BDQ (Annexure 23) and for obtaining informed consent (Annexure 24).

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.

The informed consent must be filled with signature / thumb impression of the patient after educating the patient with counselling before initiation of treatment with BDQ containing regimen. The consent form must be maintained in the patient folder.

12.3.8.2 Cohort Event Monitoring Form:

The standard formats for cohort event monitoring (Annexure 8, 9) as prescribed in the WHO Guidelines would be used at all the sites. Every AE or SAE including death needs to be promptly reported by the sites to RNTCP using the standard format. The data of CEM form will be entered into NIKSHAY on a real-time case to case basis. Hard copies need to be maintained at each of the sites in the individual patient folders of records. The process of data entry and analysis for active pharmacovigilance and event based ADR reporting using NIKHSAY and Vigiflow has been described in details 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 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 the 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 historical cohorts, only 6 months, 12 months and treatment outcome reports would be prepared for those quarters for which case finding was given till 4Q2016.

12.5 Computerized systems

All the reports will be available in both paper and electronic versions. To facilitate better quality of the information as well as data analysis, NIKSHAY for real time monitoring of DR-TB patients through Dashboards and monitoring indicators will be used and 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 sites using the information system, are fundamental to maintaining good quality of information.
12.7 Cohort analysis

All patients that are identified with DR-TB and are 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 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 of the DR-TB patients to be either continued on standard regimen or re-classified to a DST guided regimen with or without newer drugs based on SL-LPA and LC-DST detailed earlier, for analytical purposes, the cohort definition would be done 3 months after the last day of the quarter for the case finding report. For example, for 1st quarter (Jan – March), the cohort definition will be done in 1st week of July to enable accounting of the patients in the respective standard or DST guided regimen with or without newer drugs only once and avoid double counting of DR-TB patients in the same quarter due to change in the regimen. This will also 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. Reports for specific periods or cohorts could also be generated online through NIKSHAY. 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 regimen. Final analysis should be performed thirty-six months after the last patient enrolment date in the cohort.

Patients still on treatment at the end of a designated cohort treatment period must also be explicitly identified as such, and whether they were culture-positive or negative at the time of the cohort analysis; this is an interim status until a final outcome is available. Interim status should be assessed at six months and twelve months of treatment to monitor patient progress.
Chapter 13: Supervision, Monitoring & Evaluation on PMDT

In this chapter, participants will learn about the guidelines for supervision, monitoring and evaluation systems that need to be operationalized 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 and the requisite tools to do so have been developed that are detailed in this chapter.

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 program activities this 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 programme monitoring indicators in cohorts of patients.

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

13.1 Organization of SME for PMDT

SME will be driven by 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. To help each staff engaged in PMDT to supervise, monitor and evaluate the activities, a set of job aides are also developed. These job aides are ready-reference tools to aid the staff to take the appropriate action at each step of PMDT. Various registers and reports on PMDT related services will be extracted from the Nikshay / eNikshay. Adherence score of individual patient based on automated ICT enabled system like pill box (Annexure 10) or 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 (D/NDR-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 assess 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 priorities 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 here that supervision promotes successful implementation of the program policies and processes and M&E ensure that the implementation progresses in the right direction to achieve the desired targets, objectives and goals.

**Objectives of supervision:**

The following are the objectives of supervision.

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

Since PMDT is not a standalone activity within RNTCP, all the functionaries responsible for the implementation 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 the NIKSHAY / e-NIKSHAY. (Refer to PMDT supervisory check-lists for various levels). The actions taken and pending from the previous supervisory visit must also be reviewed during every visit. Review of previous reports is useful for identifying the priority areas to be focused during the supervision. The existing documents like RNTCP Supervisory Registers placed at all health institutions may be used for recording observations on 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, the processes involved in the recording & reporting, drugs & logistics and supply chain management, tracking of transportation of sputum specimens to the CBNAAT and C-DST Laboratory, status of data update on NIKSHAY / e-NIKSHAY, referral of diagnosed DR-TB patients to the D/NDR-TBC etc. have to be examined in detail.

Modalities of Supervision

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

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

Extensive checklists and monitoring tools have been developed for use by all supervisory staffs. These are to be put to use. All visits to the district and sub district levels by district and State level officials have to, mandatorily include supervision of PMDT activity. 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>
<tbody>
<tr>
<td>DTO</td>
<td>- Conduct interview with health staff and RNTCP key staff involved in PMDT</td>
<td>- Visit all TUs every month and all DMCs every quarter.</td>
</tr>
<tr>
<td></td>
<td>- Interact with community and local opinion leaders and mobilize their support to help DR-TB patients with diagnosis</td>
<td>- Visit all CHCs and Block</td>
</tr>
</tbody>
</table>
and treatment.
- Randomly interview patients on treatment, their Treatment Supporter, family members and community leaders.
- Inspect records of the DTC, TU, DMCs, PHI and Treatment Center, NIKSHAY entries and stock of Drugs.
- Check the status of card updating and ensure that the original card at the DR-TB Centre is updated at least once monthly along with digitalization of adherence data in Nikshaw either by manually or ICT supported mechanism.
- Ensure prompt identification of presumptive DR-TB and the transport of sputum specimens to the Lab as per guidelines maintaining cool chain
- Physically verify the stock of PWBs at District, TU and PHI stores.
- Ensure uninterrupted supply of medicines
- Liaise with State TB Cell, DR-TB Centre and the designated C-DST Lab

**MO – DTC**
- 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 and treatment.
- Randomly interview patients on treatment, their Treatment Supporter, family members and community leaders.
- Inspect records of the DTC, TU, DMCs, PHI and Treatment Center, NIKSHAY entries and stock of drugs.
- Check the status of card updating at District, TU, PHI and Treatment Supporter

**MO-TC**
- Interview the MO I/C Block PHC/CHC/PHC./Private/NGO hospitals regarding implementation of PMDT activities
- Randomly interview patients, their Treatment Supporter, family members and community leaders.
- Interact with community and local opinion leaders and mobilize their support to help MDR-TB patients with diagnosis and treatment
- Inspect records of the TU, DMCs, PHI and Treatment Center, NIKSHAY entries and stock of Drugs.
- Check the status of updating treatment card, booklet and NIKSHAY / e-NIKSHAY entries
- Ensure drug availability for all DR-TB patients during the treatment course.

**District DR-TB TB-HIV Supervisor (this section deals only**
- Assist DTO in organizing direct observation of treatment for DR-TB patients and DR-TB drug logistics management
- 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

PHCs in the district every quarter, one sub-centre from each Block PHC area and a proportion of treatment observation centres every quarter.
- Conduct supervisory visits at least 3-5 days a week.
- Visit at least three patients at their homes per visit including one DR-TB patient on treatment
### STLS
- In consultation with the DTO and MO-TC, put systems in place to ensure that all Presumptive DR-TB are diagnosed at the earliest – facilitate the transport of sputum specimens of these Presumptive DR-TB to the designated RNTCP-certified lab for C-DST.
- Visit all microscopy centres, review laboratory 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.
- Impart hands on training and guidance to LTs on
- Visit all microscopy centres in the jurisdiction of the TU at least once a month.
- Visit all sputum collection centres at least once a month.

### STS
- Interview MPHS / MPWs at the PHC sub-centre regarding implementation of PMDT activities.
- Interview Treatment Supporters of patients on DR-TB treatment
- Help the DTO in identifying and training suitable Treatment Supporters for diagnosed MDR-TB patients to be initiated on DR-TB treatment.
- Verify records, Cards and Tuberculosis Laboratory Register. Ensure that the treatment cards at the 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 patients on treatment. Ensure that 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
- 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
- Visit all PHIs at least once every month and all Treatment Centers once every quarter.
- Visit all diagnosed DR-TB patients at their home within one month of treatment initiation.
- Conduct supervisory visits at least 5 days a week

### with the PMDT responsibilities
- Identification and training of Treatment Supporters for MDR-TB patients and maintenance of a directory of such Treatment Supporters at the TU and district levels.
- Maintain the district level PMDT records and reports.
- Ensure that the records and NIKSHAY entries of all DR-TB patients in the district are updated regularly.
- Supervise all PMDT treatment observation centres once in a quarter.
- Coordinate with field staff to ensure drug availability for all DR-TB patients receiving various regimen.
- Update the treatment cards and NIKSHAY entries at the DDR-TBC.
- Assist the DTO for providing training to the staff of health facilities under his/ her jurisdiction to carry out PMDT related activities.
- Establish liaison with private practitioners, NGOs and other sector dispensaries / hospitals to provide PMDT services as per the programme guidelines.

- Interview MPHS / MPWs at the PHC sub-centre regarding implementation of PMDT activities.
- Interview Treatment Supporters of patients on DR-TB treatment
- Help the DTO in identifying and training suitable Treatment Supporters for diagnosed MDR-TB patients to be initiated on DR-TB treatment.
- Verify records, Cards and Tuberculosis Laboratory Register. Ensure that the treatment cards at the 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 patients on treatment. Ensure that 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
- 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
- Visit all PHIs at least once every month and all Treatment Centers once every quarter.
- Visit all diagnosed DR-TB patients at their home within one month of treatment initiation.
- Conduct supervisory visits at least 5 days a week

- Visit all microscopy centres in the jurisdiction of the TU at least once a month.
- Visit all sputum collection centres at least once a month.
identification of Presumptive DR-TB and transport of their sputum specimens to the Lab as per guidelines with proper documentation.

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 the disease, the evolution of trends and the description of those groups in the population at increased risk of TB and unfavourable prognosis. It is an essential element in monitoring the 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, socio-economic, geographic, spatial characteristics to enable better understanding of the local epidemiology and trend of tuberculosis.

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

NIKSHAY / e-NIKSHAY will play a pivot role in surveillance of DR TB cases by capturing important information at source and disseminate it with various levels to have quality patient wise information.

Objectives:

1. Evaluate the epidemiological characteristics of TB in the population over time and geography, both within the states, regions and across the country as a whole.

2. Monitor the performance of TB control activities and feed this information into the decision-making cycle to allow for appropriate interventions to upgrade the districts, state and national TB plans.

3. Identify and describe vulnerable populations at increased risk of TB and unfavourable prognosis to which targeted public health activities should be addressed.
Strategies/actions

1. Evaluate the epidemiological characteristics of TB
   a. Strengthen nationwide surveillance systems and other sources of data collection, and reinforce the use of standard reporting and definitions including DR-TB patients in order to gather reliable data that are comparable within and between states, and internationally over time.
   b. Develop the use of enhanced laboratory techniques such as DNA fingerprinting and molecular typing to evaluate the spread of DR-TB patients and identify outbreaks.
   c. Integrate laboratory, clinical and epidemiological data on TB patients, at district, state and national levels.
   d. Create algorithms for the detection of local outbreaks and clusters.

2. Monitor TB control activities
   a. Expand drug-resistance surveillance activities to monitor and improve case management.
   b. Collect TB patients with laboratory information on co-morbidity status to improve care such as joint management of TB/HIV co-infected patients, TB/DM management etc.
   c. Enhance the 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.

3. Identify and describe vulnerable populations for TB
   a. Analyse routine surveillance data and perform ad hoc surveys to identify vulnerable populations.
   b. Enhance or implement TB surveillance in migrants, prisoners and other vulnerable populations according to the particular situation in the district/state.

4. Establish TB Surveillance system from district to National levels
   a. TB Surveillance units at district level in DTC, at State level in STDC and National level at NTI
   b. Sentinel surveillance units at medical colleges
   c. Laboratory surveillance units at all IRLs and NRLs
   d. Use of 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. NIKSHAY envisages establishing ICT enabled state-of-art surveillance system with system utilization by 100% stakeholders and ensuring 100% notification of TB patients at diagnosis (microbiologically confirmed & clinically diagnosed). The programme also envisions continuous monitoring and treatment adherence for all TB patients registered with e-NIKSHAY, enable tracking of all registered TB patients across TB control lifecycle, geographies, transfers and referrals.
First step is to ensure complete data entry in all the formats of R&R. Dashboard functions to track activities and on-line monitoring indicators with graphical and geo-mapping displays in NIKSHAY / e-NIKSHAY would be helpful in programme monitoring provided data completeness of data entered is ascertained.

13.5 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 program 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 programs is of paramount importance for ongoing program 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 program activities.

A. Monitoring indicators

Various components of programme service delivery are feed in NIKSHAY from where various input, process, and outcome indicators drawn for different levels of health facilities. Analysis of these indicators will help in monitoring improvement in program performance. List of monitoring indicators is placed at Annexure 18

13.6 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 - 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 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 state of Gujarat and Maharashtra and gradually scaled up across the country by the 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 applications, web applications, tablets and call centre on real time basis. This will also change and improve the reporting structures to be more agile and efficient by providing relevant reports at relevant levels without the delays 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 which will aid the staff to prioritize the tasks at various levels. ICT enabled adherence mechanisms i.e., 99 DOTS, MERM, etc. will feed the 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 program by providing real time information on referral of patients for treatment initiation and ADR management. This will aid the program to manage referral and provide feedbacks thereby decreasing the lost to follow up and improved tracking of the patients across the country.

- e-NIKSHAY will also 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, geographies and periods. This will aid the supervisors and programme managers in identifying the 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 the patients, providers and supervisors for actions to promote favourable outcome and improve the programme management efficiency. The indicators shall also be projected as interactive tables and maps to promote information driven monitoring at all levels.
Chapter 14: Supply Chain Management in PMDT

This chapter constitutes guidance regarding procedures for inventory management of the 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 regimen shall be supplied through a centralized procurement system at Central TB Division, MoHFW, GoI. An advance intimation of all drug supplies shall be communicated to the States for the 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 re-pack the loose drugs into 1 monthly patient wise boxes of Type A (Core oral drugs), Type B (IP Plus boxes) and supplies to the districts for treatment. SDS shall be preparing ‘standardized drug boxes’ for the following standard regimen and supplies to the districts:
1. Shorter MDR/RR TB regimen;
2. Conventional MDR-TB regimen and
3. Regimen for H mono/poly DR-TB.

SDS shall supply additional loose quantity of SLD to the 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 district including dedicated full time human resource support at district drug store level, entire exercise of preparation of patient wise boxes shall need to be conducted at DDS under guidance and supervision of DTO.

Modification/ change in regimen may be required during course of treatment based on 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 re-classified to. For regimen containing Bedaquiline (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, to be included in the first monthly Type B box for the intensive phase containing SLI and oral drugs in IP only that is issued to the treatment supporter. The bottle will remain under custody of the treatment supervisor 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 patient from DR-TB Centre, the stock shall be entered in the stock register at District Drug Store and handed over to the treatment supporter. District DR-TB TB-HIV Supervisor shall be the link for passing information to district drug store keeper.
regarding BDQ stock supplies to treatment supporter. District drug store keeper shall keep record of patient wise stock of BDQ in district drug stock register.

**Figure 14.1 Flow Chart of Second Line Drugs Supply Chain Management**

- Supplies PWB for Type A, Type B & Type C for SR, CR & regimen for INH Mono resistance
- Supplies loose drugs for modification of boxes

At DTC/ District drug store
- Stock of Type A, B and C boxes held
- Loose drugs for modification of regimen
- Stock of BDQ to be entered in DDS stock register as patient wise

1. Boxes supplied to TU as per monthly consumption report
2. Stock of Type A, B and C boxes held at TU with buffer

At DRTC
- Loose drugs supplied to the DR-TB Centre to maintain adequate stock for a month of treatment, plus buffer
- On Discharge, patient given a maximum of 7 Days drugs to cover transfer period
- BDQ Pt. carry the bottle for entire course and hand over to treatment supporter in

1. a) Patient reports to the DTO
2. b) PWB supplied to DP
3. c) Training of MO-PHI

Type A, B and C boxes received by the DOT Centre

1-monthly Type A, B and C boxes issued immediately to the respective treatment supporter

14.2 Technical specification of patient wise box

The technical specifications of the monthly patient wise box for DR-TB patients is detailed in Annexure 19. 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
For CP: Type A box of same weight band

These drug boxes will be prepared at the SDS for five standard weight band and regimen constituted for DR-TB Patients as given in the table below:

**Table 14.1 Guidance for regimen formulation and weight band**

<table>
<thead>
<tr>
<th>Weight Bands</th>
<th>Intensive Phase (IP) Box</th>
<th>Continuation Phase (CP) Box</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16kgs</td>
<td>Type A + Type B</td>
<td>Type A</td>
</tr>
<tr>
<td>16 - 29 Kgs</td>
<td>Type A + Type B</td>
<td>Type A</td>
</tr>
<tr>
<td>30 - 45 Kgs</td>
<td>Type A + Type B</td>
<td>Type A</td>
</tr>
<tr>
<td>46-70kgs</td>
<td>Type A + Type B</td>
<td>Type A</td>
</tr>
<tr>
<td>&gt;70kgs</td>
<td>Type A + Type B</td>
<td>Type A</td>
</tr>
</tbody>
</table>
14.3 Constitution of patient wise boxes and role of various drug stores

At State Drug Store level

SDS shall formulate drug boxes (both Type A and Type B) for Shorter MDR-TB regimen, Conventional MDR-TB regimen and regimen for H mono/poly DR-TB and supplies to linked districts.

Table 14.2 Standard drug box for shorter MDR-TB regimen

<table>
<thead>
<tr>
<th>Type A (Core oral drug box)</th>
<th>Type B (IP Plus box)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin – high dose (Mfx(^h))</td>
<td>Kanamycin (Km)</td>
</tr>
<tr>
<td>Clofazimine (Cfx)</td>
<td>Isoniazide – high dose (H(^h))</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>Ethionamide (Eto)</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td></td>
</tr>
</tbody>
</table>

Table 14.3 Standard drug box for conventional MDR-TB regimen

<table>
<thead>
<tr>
<th>Type A (Core oral drug box)</th>
<th>Type B (IP Plus box)</th>
</tr>
</thead>
<tbody>
<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>Pyrazinamide (Z)</td>
<td></td>
</tr>
</tbody>
</table>

Table 14.4 Standard drug box for regimen for H mono/poly DR-TB

<table>
<thead>
<tr>
<th>Type A (Core oral drug box)</th>
<th>Type B (IP Plus box)</th>
</tr>
</thead>
<tbody>
<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-TB Centre, District drug store 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 district drug store for carrying out entire exercise of preparing standardized patient wise drug boxes decentralized at DDS level. Dedicated full time district drug store 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 of treatment and special situation respectively.

14.4 Packing Instructions

1. Packaging of loose drugs into Type A & B boxes should be done under guidance of the STO/Medical Officer/Drug logistics In-charge at the State level and district level.
2. One monthly pouch of Cap. Cycloserine & Tab. Ethambutol each should be made from plastic bag with zip lock facility in which 1 gm. pouch of silica gel desiccant should be kept. In each Type A box, one pouch of silica gel desiccant of 4 gm. weight should also be kept.
3. Each Type A & B box should be numbered consecutively at the SDS. The record of the serial no. of the box should be maintained at the State, District & Sub-district (TU) Drug Stores and it would be of help while tracking a particular box.
4. 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 the boxes – would be the 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 in English/ Hindi/ local regional language for ensuring adequate precautions in storage of the drugs, especially at the Treatment Supporter level. Some suggested messages are:-

Store in a cool and dark place preferably in a clean cup board. Do not expose to direct sunlight. Keep away from children/unauthorized persons. Box to be closed properly every time after withdrawal of drugs. Prototype of label is suggested in Annexure 20.
1. Re-packaging process for utilizing MERM system
2. Barcoding and real time tracking system

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

The management cycle of second-line anti-TB drugs comprises six elements: drug selection; quantitative assessment of drug requirements; management of procurement; distribution protocol; assurance of drug quality; and ensuring rational drug use. Accurate demand forecasting of second-line anti-TB drugs, i.e. correct quantification of the drug needs for a specific period of time, is one of the elements that guarantees an uninterrupted drug supply.

Inventory Management: Procedures for on-going tracking and replenishment of the inventory of 2nd line anti-TB drugs at the State Drug Store (SDS) and all subordinate stocking points ensures that these are maintained at or close to the stocking norms presented below:

Table 14.5 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>(Monthly consumption x2) – (existing stock in PHI at end of the month)</td>
</tr>
<tr>
<td>TU drug store</td>
<td>0 months</td>
<td>1 months</td>
<td>(Quarterly consumption/ 3) x 3 – (existing stock in TU including PHI drug stores at end of the quarter)</td>
</tr>
<tr>
<td>DTC drug store</td>
<td>0 month</td>
<td>2 months</td>
<td>(Quarterly consumption/ 3) x 5 – (existing stock in DTC drug store including TU &amp; PHI drug stores at end of the quarter)</td>
</tr>
<tr>
<td>SDS</td>
<td>0 months</td>
<td>3 months</td>
<td>(Quarterly consumption/ 3) x 8 – (existing stock in SDS including stocks at all districts at end of the quarter)</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 loose drugs as well as details of the monthly Type A & B boxes, as at the last day of each calendar month in the prescribed format. The MSS shall be sent to the STO by the 7th of every month, by all the SDSs, in the state. The statement shall facilitate determination of drug stocks available with SDS(s) within
the state. MSS shall thereafter be forwarded to CTD through the STO, by the 10th of every month. In the case of more than one/multiple SDSs within the state, all the MSSs shall be forwarded to CTD within the timelines stated above.

**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. SDS 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 21. The DTC shall send the boxes to its implementing TU in a similar manner on monthly basis & 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 the supply of monthly drug boxes of Type A & B from the respective PHI to the Treatment centre. STS shall identify of the Treatment supporter in consultation with the 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-TB Centre:** Issuance of loose drugs to DR-TBC (including District DR-TBC) from SDS shall be based on the Monthly Stock Statement submitted by the DR-TB Centre, to ensure adequate stocks for a month of treatment plus a buffer of 1 month. On discharge from DR-TB Centre, 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 shall earmarked for each enrolled patient and handed over to treatment supporter in supervision of District DR-TB TB-HIV Supervisor.

**Distribution from DDS to TB drug stores:** Buffer stock equivalent to 1 month will be kept at the TU. The drug boxes will be supplied from the TU to the PHI. The drug box will be transferred from the TU to respective PHI on instruction of the DTO as per monthly consumption report submitted by TU.

**Distribution from TB 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 the PHI to the Treatment centre / Treatment supporter. 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.
Scenario 1: Modification in regimen  If NDR-TBC committee decides on modification of regimen, DDS shall prepare a modified Type A or Type 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 the IP of the patient is required to be extended, the respective DR-TB Centre Committee shall inform the DTO who will intimate the same to the MO-PHI and the respective TU. The PHI will release 1 Type A 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 the 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-TB Centre Committee decides to change the regimen then the 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/transferred out/treatment stopped patients, the 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 at the DDS & issued as per FEFO principles to either the DR-TB Centre or be used for repackaging into the monthly Type A or B boxes.
- Partially used BDQ bottle shall be sent back to State drug stores and repackaging shall be done there only. All loose drugs remaining in the bottle received back shall be accounted for in the Reconstitution Register at the SDS & to be used for repackaging. Upon reconstitution, bottle shall be accounted for in the Stock Register (loose tablets to be mentioned in remarks column) and to be issued as per FEFO principles. If the expiry of the remaining loose drugs is less than 6 months, the drugs shall be consumed at the NDR-TBC for admitted patients and adjusted from the new bottle when they are discharged.
14.8 Guidelines for storage of 2nd line anti TB drugs for State and District Drug Store

Storage Space

Requirements 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 would form the basis for quantification and storage space will need to be worked out separately for each SDS and DDS.

Specifications for drug stores

1. The Drug Store should preferably comprise one large room. Where multiple rooms already exist, they should be contiguous or proximate to each other.
2. Preferably separate space for storage, handling and re-packing into Type A & B boxes.
3. Ceiling to have a height of at least 3 metres.
4. A lockable door.
5. At least one window with grill.
6. Proper lighting.
7. An even-level, ‘pukka’ floor.
8. Plastered walls and ceiling with whitewash without any kind of seepage in the room.
9. In case of a situation where separate room for storing 2nd line drugs is not possible, an attempt to demarcate and enclose a specified area for storing 2nd line drugs should be made within the larger store to ensure required temperature control for 2nd line drugs.
10. Architects should be consulted for suitable modifications in the existing drug store/construction of a new drug store for the same.
11. A signage board with instructions in local language should to be put near the entrance of the store to remind the concerned officials regarding good storage practices.
12. Ideally, Vacuum de watered flooring (VDF) should be used for the Drug Stores. However depending on the feasibility, such flooring may be done at the State Drug Store level.
13. In case it is feasible at the State Drug Store level, separate areas should be demarcated for receiving and dispatching the drugs.
14. Contract for Pest Control should be entered into by the State to ensure drug stores free from pests, rodents etc.
Shelves, Racks & Storage Arrangements

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

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

3. Typically, five rows of shelves to be fabricated, one on top of the other into racks. A single rack to usually be long enough to accommodate upto a minimum of three cartons on each shelf.

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

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

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

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

Stacking Arrangement

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

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

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

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

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

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

**Control of Humidity and Temperature**

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

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

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

**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 the 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.

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

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

3. The purpose of information provided in the above sub-paras is to emphasise that the drugs should be stored in cool & dark place for proper efficacy. However,
after the drug boxes are moved outside temperature controlled (AC) environment till it is consumed by the patients all efforts must be made to store the drug boxes in cool and dry place.

14.9 Quality Assurance of Drugs

The quality assurance component of the RNTCP drug supply system makes certain that each drug used by a patient is safe, efficacious, and has appropriate standards of quality. As per the protocol developed by Central TB Division (CTD), specimens of 2nd Line Anti TB Drugs shall be picked up on random basis from various levels in the field and sent for testing by an independent drug testing laboratory contracted by CTD to find out any change in the quality of these drugs. This should be done based on communication sent by CTD to the concerned states and districts.

14.10 Waste Disposal Guideline

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

14.11 Guidelines for Recording, Reporting of SLD

The recording and reporting system for drug stock management from the State Drug Store to the DR-TB Centre and to the Districts, TB Units and PHIs has been recently revised to suit the 1 monthly patient wise boxes system. Formats for Drug Logistics Management of 2nd line drugs under PMDT are described in Annexure 21.

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 has been identified and soon be implemented under RNTCP. Bar code reader, scanner & printer shall be provided up to district level.
Chapter 15: Infection Control Measures

Infection control in DR-TB: Evidence indicates that DR-TB is similar in transmissibility to DS-TB in early stages of mutation. Thus, infection control policies and strategies are not much different for DR-TB. However, it does demand that every programme attempting to treat multidrug-resistant TB (MDR-TB) must comply to adequate infection control measures. Ensuring implementation of infection control policy in all health-care facilities, at public/private/household level, and in congregate settings (correctional facilities, military barracks, homeless shelters, refugee camps, student dormitories, nursing homes, among others) is essential to prevent transmission before diagnosis up-to initial stages of treatment till the patient has culture converted and turned non-infectious. Airborne infection control (AIC) (including TB) requires action at national and subnational level to provide managerial direction, and at health facility level to implement airborne infection control measures.

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 that includes human resource requirements 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, including engagement of civil society.
- Monitor and evaluate the set of TB infection control measures.
- 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, and develop a facility plan (including human resources, and policies and procedures to ensure proper implementation of the controls listed below) for implementation.

1. Adequate ventilation (ACH >12 per hrs) should be maintained for high priority health facility like DR-TB wards, ART centre etc.
2. Beds should be arranged with 6 feet distance in between
3. 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.
4. Availability of different size of N 95 particular respirators
5. Rethink the use of available spaces and consider renovation of existing facilities or construction of new ones to optimize implementation of controls. Sitting position rearrangements within 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.
- Participate in research efforts.

National guideline for infection control in all health care settings including DR-TB care settings includes to have integrated implementation of administrative, environmental and personal protective equipment

15.2.1 Administrative controls

- Promptly identify people with TB symptoms (triage), separate infectious patients, control the spread of pathogens (cough etiquette and respiratory hygiene) and minimize time spent in health-care facilities.
- Linen and waste management
- Cleaning and disinfection of patient-care equipment
- Provide a package of prevention and care interventions for health workers.
- Standard precautions combine the major features of Universal Precautions, Body Substance Isolation, and Airborne Precautions.

15.2.2 Environmental controls

- Use ventilation systems including mechanical ventilation system.
- Use ultraviolet germicidal irradiation fixtures, at least when adequate ventilation cannot be achieved.

15.2.3 Personal protective equipment

- Use particulate respirators (N95 or equivalent) for staff
- Use of simple surgical mask or cloth to cover the cough for source control at the patient level
References

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Annexures