GUIDELINES
FOR USE OF DELAMANID IN THE TREATMENT OF DRUG RESISTANT TB
IN INDIA
2018

Revised National Tuberculosis Control Programme
Central TB Division, Directorate General of Health Services,
Ministry of Health & Family Welfare, Nirman Bhavan, New Delhi

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Contents

Acknowledgements

The Guidelines for use of Delamanid (Dlm) in the treatment of drug-resistant TB (DR-TB) in India (January 2018) has been developed as the end-product of a series of meetings and deliberations with national experts from government of India (GoI), WHO country office for India (WHO India) and key technical and developmental partners in 2017. The deliberations involved various stakeholders including members of the national expert committee on regulation of newer anti-TB drugs, extensive review of literature including global guidelines, recent evidences and aligning to the approval of its use by the Subject Expert Committee of Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services (DGHS), MoHFW, GoI. Based on this committee approval, the permission to import finished formulation of the new drugs was issued by Drugs Controller General of India (DCGI), CDSCO, GoI.

The guidelines development involved various stakeholders, extensive review of literature, aligning with emerging evidences to address the prevailing epidemiology of drug resistant TB in India from initiatives like i) the recently concluded first national drug resistance survey (2014-16), ii) the lessons learnt from the rollout of Bedaquiline containing regimen in 2016-17, iii) the revised technical and operational guidelines for TB, iv) the WHO PMDT Guidelines (2016) updates and recent WHO position statement on use of Delamanid in the treatment of multidrug-resistant (MDR) TB (2018), v) the national strategic plan for TB elimination in India (2017-25) which in turn is aligned with the WHO End TB Strategy.

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This document is consistent with the WHO interim policy guidance on the use of Delamanid in the treatment of MDR-TB (2014), WHO position statement on the use of Delamanid for multidrug-resistant tuberculosis (2018), WHO PMDT Guideline 2016, Companion Handbook to WHO Guidelines on PMDT and aligned with RNTCP PMDT Guidelines (2017) of India. The technical and operational aspects in this guideline are intended to complement the existing RNTCP Guidelines for PMDT in India (2017) for smooth introduction of Dlm under conditional access for management of DR-TB under RNTCP PMDT in India.

This guideline would be implemented by the initial identified seven states to gain and document experience on feasibility, safety monitoring and enhancement in interim treatment outcomes of DR-TB patients under RNTCP PMDT to further guide the country on its refinement and expansion to other states in India.

Abbreviations

AE	adverse event
ALT	alanine aminotransferase
Am	amikacin
Amx/Clv	amoxicillin/clavulanate
ARV	antiretroviral
AST	aspartate aminotransferase
BDQ	bedaquiline
CAP	Conditional Access Program
CBNAAT	Cartridge Based Nucleic Acid Amplification Test
Cfz	clofazimine
Cm	capreomycin
CP	continuation phase
Cs	cycloserine
CTD	Central TB Division
CUP	Compassionate Use Program
DAIDS	Division of AIDS
DCGI	Drugs Controller General of India
DDG	Deputy Director General
DDR-TBC	District drug resistant TB centre
DG	Director General
DGHS	Directorate General of Health Services
Dlm	delamanid
DOTS	Directly Observed Treatment Short-course
DR-TB	drug-resistant tuberculosis
DSMC	data safety monitoring committee
DST	drug susceptibility testing
E	ethambutol
Eto	ethionamide
FQ	fluoroquinolone
Gfx	gatifloxacin
GoI	Government of India
H	isoniazid
H^h	high dose isoniazid
ICH	International Conference on Harmonization
IP	intensive phase
Ipm	imipenem
IRL	intermediate reference laboratory
Km	kanamycin
LFT	liver function test

Lfx	levofloxacin
LPA	line probe assay
Lzd	linezolid
MDR-TB	multidrug-resistant TB
Mfx	moxifloxacin
MGIT	mycobacteria growth indicator tube
MoHFW	Ministry of Health and Family Welfare
NDR-TBC	Nodal drug resistant TB center
NIRT	National Institute for Research in Tuberculosis
NRL	national reference laboratory
OBR	Optimized Background Regimen
Ofx	ofloxacin
PAS	*p*-aminosalicylic acid
PK/PD	pharmacokinetic/pharmacodynamic
PLHIV	people living with human immunodeficiency virus
PMDT	programmatic management of drug-resistant tuberculosis
PQC	product quality compliance
PSM	procurement and supply management
Pto	protionamide
R	rifampicin
RNTCP	Revised National Tuberculosis Control Programme
RR-TB	rifampicin-resistant tuberculosis
SAE	serious adverse event
SLDST	second-line drug susceptibility testing
SLI	second-line injectables
STR	standardized treatment regimen
TB	tuberculosis
Thz	thioacetazone
Trd	terizidone
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
XDR-TB	extensively-drug resistant TB
Z	pyrazinamide

1. Introduction

The emergence of drug resistance is a major threat to global tuberculosis (TB) care and control. Multidrug-resistant TB (MDR-TB) is defined as TB with resistance at least to isoniazid (H) and rifampicin (R) with or without resistance to other first-line anti-TB drugs. Additional resistance to fluoroquinolones (FQs) and second-line injectables (SLIs), either alone or together i.e extensively drug resistant TB (XDR-TB), is considered to be advanced forms of MDR-TB.

1.1 Burden of Drug Resistant TB

About 4.1% of new TB patients and about 19% of previously treated patients in the world have MDR-TB including rifampicin resistant TB (RR-TB). The World Health Organization (WHO) estimates that 601 000 incident cases of MDR/RR-TB emerged in 2016, with cases of MDR-TB accounting for 82% (490 000) of the total. Among the notified TB patients, it is estimated that 350 000 (range, 330 000–370 000) MDR/RR-TB cases emerged in 2016. Nearly 47% of these patients were from India, China and the Russian Federation. By the end of 2016, XDR-TB had been reported by 123 countries. On average, an estimated 6.2% (95% CI: 3.6–9.5%) of people with MDR-TB have XDR-TB. The proportion of MDR-TB/RR-TB cases with resistance to any FQ for which testing was done – including Ofloxacin (Ofx), Levofloxacin (Lfx) and Moxifloxacin (Mfx) was 20% (95% CI:14–26%). Only 54% of MDR/RR-TB (2014 cohort) and 30% of extensively drug-resistant TB (XDR-TB) (2014 cohort) patients were successfully treated, largely as a result of high mortality and loss to follow up. At least 35 countries in Africa and Asia have introduced shorter regimens for treatment of MDR/RR-TB, with high treatment success rates (87–90%). As part of efforts to improve outcomes for MDR/XDR-TB, 89 countries and territories had started using Bedaquiline (Bdq) and 54 had used Delamanid (Dlm) by June 2017 (1).

The first national anti-TB drug resistance survey (2014-2016) conducted in India revealed MDR/RR-TB levels of 2.84% (2.28%-3.49%) in new cases and 11.60% (10.21-13.15%) in previously treated cases (1-3). Although the proportion is small, the number of persons with MDR/RR-TB is sizeable in numbers. WHO has estimated that in India, 147 000 incident cases of MDR/RR-TB including 84 000 (72 000–95 000) among the notified pulmonary TB cases emerged in 2016 (1). Although only 1.3% (0.36-3.30%) of MDR/RR-TB patients have XDR-TB, the proportion of patients with additional resistance to any Fluoroquinolones (Ofx, Lfx, Mfx) is observed to be 21.82% (17.33-26.87%) and any Second-line injection (Kanamycin [Km], Amikacin [Am], Capreomycin [Cm]) is observed to be 3.58% (1.80-6.32%) (2,3). Further, RR-TB patients almost have complete correlation with H resistant TB and hence such patients detected using WHO-endorsed rapid molecular tests are treated with the standard regimen for MDR-TB (2,3).

The Guidelines for Programmatic Management of Drug-resistant Tuberculosis (PMDT) in India (2017) offers an integrated drug-resistant tuberculosis (DR-TB) treatment algorithm to address the new epidemiological reality and provides evidence-based guidance for early diagnosis and appropriate treatment of various forms of DR-TB in India including the use of newer drugs in accordance with WHO Guidelines for PMDT (2016) and the End TB Strategy (2,4-6). In 2016, RNTCP was detected and treatment initiated in about 34016 patients of MDR-TB and 2476 patients of XDR-TB (1,7). The treatment success rate in the 2014 cohort of India is only 46% for MDR/RR-TB and is lower with additional FQ/SLI resistance and 29% for XDR-TB with a mortality of nearly 50%. (1,7) In earlier studies, adding Dlm to the optimized background regimen (OBR) had shown significant benefit in improving survival and treatment outcomes in such patients under clinical and programmatic settings (4-6,8-12).

1.2 Delamanid

Delamanid is one of two drugs developed specifically for the treatment of TB in the last 40 years. It is the first approved drug in the class of nitro-dihydro-imidazo-oxazoles for the treatment of MDR-TB. It has been developed by Otsuka Pharmaceutical Ltd. for the treatment of MDR-TB. Delamanid was first approved by the European Medicines Agency (EMA) in November 2014 and subsequently by regulatory authorities in Japan, Republic of Korea, Hong Kong, Turkey and Philippines (4-6,8-21).

Delamanid is indicated for use as part of an appropriate combination regimen for pulmonary MDR-TB in adult and adolescent (6-17 years) patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (15-17). It has the following characteristics (4,6,8-21):

- Chemical class: nitroimidazole
- Mechanism of Action: Bactericidal (Half-life: 36 hours)
    - By blocking the synthesis of mycolic acids (i.e., stopping the bacteria from creating building blocks important for their cell walls).
    - By poisoning them with nitric oxide, which the drugs release when metabolized
- Each film-coated tablet contains 50 mg Delamanid.
- Excipient with known effect: each film-coated tablet contains 100 mg lactose (as monohydrate).

1.3 WHO recommendations on use of Delamanid

In 2014, WHO issued interim policy guidance on the use of Dlm for the treatment of MDR-TB. The interim policy guidance stated that 'Dlm may be added to a MDR-TB regimen in adult patients with pulmonary TB' conditional upon: i) careful selection of patients likely to

benefit; ii) patient informed consent; iii) adherence to WHO recommendations in designing a longer MDR-TB regimen; iv) close monitoring of clinical treatment response; and v) active TB drug-safety monitoring and management (aDSM) (4,6,15). The guidance recommends that Dlm may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB under the following conditions:

- When an effective treatment regimen containing four second-line drugs in addition to pyrazinamide (Z) according to WHO recommendations cannot be designed;
- When there is documented evidence of resistance to any FQ or second-line injectable drug in addition to MDR.
- When there is higher risk for poor outcomes (eg. drug intolerance or contraindication, extensive or advanced disease)

The WHO interim policy guidance was based on evidence available at the time from a phase IIb trial and an observational study conducted by the manufacturer (6,8-10,15). This evidence was considered to be of very low certainty based on GRADE evidence assessment (22), and the interim policy was subject to review once phase III trial data became available (17,18).

In 2016, the Dlm interim policy was extended to children aged 6-17 years following a review of data from a 6-month safety, efficacy, and pharmacokinetic trial of paediatric patients (16). These data were also considered to be of very low certainty based on GRADE evidence assessment (22). Delamanid has been added to the WHO's Essential Medicines List for adults in 2015 and for children in June 2017 (1).

In mid-October 2017, Otsuka Pharmaceutical communicated the final results of Trial 213 to the public during the annual UNION World Conference on Lung Health in Mexico. Detailed aggregated data were subsequently submitted to WHO as an Electronic Common Technical Document (eCTD) in late November 2017 (18). WHO conducted an expedited external expert review of the data on Trial 213 data in early December 2017 in order to assess the implications of the results on the 2014 and 2016 interim policy guidance (17).

Trial 213 was designed as a phase III, multi-centre, randomized, double-blind, placebo-controlled clinical trial comparing two regimens for treatment of MDR-TB in adult pulmonary TB patients. The test regimen consisted of an optimized background regimen (OBR) consistent with WHO and national guidelines, plus Dlm given as 100 mg twice a day for two months, followed by 200 mg once a day for four months; after six months, participants in the test arm continued to receive OBR for a total treatment duration of 18-24 months. The control regimen consisted of OBR plus an identical appearing placebo for six months, followed by OBR for the remaining duration of therapy. Participants in the Dlm arm achieved culture conversion on average six to 13 days earlier than the placebo arm. This was statistically significant. However, there was no clinically relevant or statistically significant

difference observed between the Dlm and placebo study arms in treatment success, all-cause mortality, two- or six-month culture conversion and treatment-emergent adverse events (TEAE) (17-18).

WHO will conduct an extensive review of its MDR-TB policy guidelines in mid-2018, which will include consideration of data from observational studies on Dlm. Until then the current interim and conditional guidance on Dlm remains in place. However, national TB programmes and other stakeholders are advised to **only add Dlm to a longer MDR-TB regimen when it cannot be composed according to WHO recommendations. When an effective and well-tolerated longer MDR-TB regimen can be otherwise composed, the addition of Dlm may not be warranted.** Use of Dlm in the shorter MDR-TB regimen under programmatic conditions is not recommended by WHO given the lack of data. (17)

The decision to use Dlm in such regimens should be made by treating clinicians based on individual patient assessment and well-established considerations for composition of MDR-TB regimens including drug susceptibility profiles, drug intolerability and safety, risk-benefit and ethics. The inclusion of sufficient medicines to ensure effectiveness and avert acquisition of resistance in such regimens is particularly important. Although the data from Trial 213 were limited, Dlm may have a protective role in preventing the emergence of additional drug resistance. Hence, the conditions for Dlm use in individual patients remain the same. Dlm should be retained in country guidelines, national essential medicine lists and procurement options. (17)

1.4 Progress on introduction of Delamanid in India

Since 2016, the following efforts have been made to introduce Delamanid for the treatment of MDR-TB in India:

- A series of high level consultations took place between officials from GoI (Sec-DHR & DG-ICMR, DGHS, DCGI, DDG-TB), WHO India, M/s Otsuka Pharmaceuticals Ltd., M/s Mylan Pharmaceuticals Ltd. and eminent national experts on fast-tracking regulatory approval of Delamanid in India.
- Regulatory approvals were obtained from stringent regulatory authority in India as detailed in the next chapter. (23, 24)
- A MoU is being established between RNTCP and M/s Otsuka Pharmaceuticals Ltd. through M/s Mylan Pharmaceuticals Ltd. for necessary mutual cooperation to introduce Dlm in India.
- Dlm DST has been standardized at 4 supra-national reference laboratories (SNRL) and will be introduced through national reference laboratories (NRLs) with support of M/s Otsuka Pharmaceuticals (19). Hence, Dlm would be considered with other drugs like Z, Cfz, Bdq for policy in future, whenever available, standardized & WHO endorsed.

- The national expert committee for regulation of newer anti-TB drugs in India recommended RNTCP to introduce Delamanid through the PMDT framework in alignment with the WHO guidelines (2) and with technical support from WHO India. The recommendations of the committee guided the development of this guideline.
- 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 in the year 2015-2016. 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 Newer drugs (Bdq & Dlm), Shorter MDR-TB Regimen and DST guided treatment (25).

Delamanid has been available to individual patients under “compassionate use” (12,14,15) with pre-approval of Drugs Controller General of India (DCGI) upon request from the treating physician, who submits patient details for accessing the drug from M/s Otsuka Pharmaceuticals Ltd.

2. Approval for use of Delamanid

Delamanid has been given approval for use along with the background regimen under conditional access through the Revised National Tuberculosis Control Programme (RNTCP) PMDT services in India. However, Dlm will continue to be available for "compassionate use" in the country till such time that the expanded access programme is rolled out under RNTCP.

2.1 Recommendations of the Subject Expert Committee

The Subject Expert Committee (Antimicrobial & Antiviral) under the Ministry of Health and Family Welfare in its 34th meeting has approved the use of Dlm under RNTCP PMDT through conditional access (23).

The approval dated 14 June 2017 reads as follows:

"Drug name: Delamanid (50 mg);

Indication: Indicated in adults aged 18 or over 18 years as part of combination therapy of pulmonary tuberculosis (TB) due to multi-drug tuberculosis (MDR) *Mycobacterium tuberculosis*;

***Technical Committee* recommendations:** The committee noted that the firm has applied for grant of permission to import and market of Delamanid 50 mg tablet indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability and requested for local clinical trial waiver.

Based on the examination of the data on global clinical trials conducted and approval by European Union (EU) and Japan for this drug, and risk benefit analysis, **the committee recommended for waiver of local clinical trial as Delamanid is required as an unmet need in emergency for the treatment of MDR/XDR-TB in adult. Further, the Committee recommended for approval of the drug in the conditional access programme through RNTCP.** It was also recommended that the firm shall submit the data of monitoring after 3 years for further review by office of DCGI.

2.2 Permission to import finished formulation of the new drug

Following the subject expert committee approval, the DCGI granted an import license (IMP-ND-136-2017) dated 02 August 2017, F.No. 12-27/2017-DC under rule 122A of the Drugs and Cosmetics Rules, 1945 to M/s Mylan Pharmaceuticals Ltd., the local partners of M/s Otsuka Pharmaceuticals Ltd., that reads **"Delamanid film coated tablets 50 mg is indicated for use as part of an appropriate combination regimen of pulmonary multidrug-resistant tuberculosis in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability."** (24)

The label on the immediate container of the drug as well as the packing in which the container is kept should have the following warning;

WARNING: For use in the Revised National Tuberculosis Control Programme (RNCTP).

The drug has been approved for conditional access, i.e. it shall be used under RNTCP framework for conditional access through the PMDT programme for treatment of MDR/XDR-TB patients only. The firm has been directed to do post-marketing surveillance for periodic safety review and submit the data of monitoring after 3 years for further review by the office of DCGI (24).

3. Delamanid introduction in India

Seven states have been identified as initial sites for the introduction of DLM under the RNTCP PMDT through conditional access. All identified nodal DR-TB centres (NDR-TBC) have the capacity to manage complicated DR-TB patients and laboratory support for first- and second-line drug susceptibility testing (DST) as per WHO standards through the attached intermediate or national reference culture-drug susceptibility testing (C-DST) laboratory.

These centres are as follows:

Location	Nodal DR-TB Centre	Laboratories
Punjab Chandigarh	• GMCH 32, Chandigarh • TBH, Patiala • GMC, Amritsar • GGSMC, Faridkot	• PGIMER, Chandigarh • IRL, Punjab
Rajasthan	• SMS, Jaipur (1 & 2) • JLNMC, Ajmer • SNMC, Jodhpur • RNTMC, Udaipur • GMC, Kota • SPMC, Bikaner	• SMS, Jaipur • IRL, Ajmer • C-DST lab, Jodhpur
Karnataka	• RGICD, Bangalore • KIMS, Hubli • PKTB & CDH, Mysore • DGH, Gulbarga • VIMS, Bellary • District Wenlock Hospital, Mangalore	• NTI, Bangalore • IRL, Bangalore • KIMS, Hubli
Odisha	• SCB, Cuttack • MKCG, Behrampur • VSS, Burla	• RMRC, Bhubaneswar • IRL, Cuttack
Kerala Lakshadweep	• ICD & GMC, Trivandrum • ICD & GMC, Kozhikode	• IRL, Trivandrum

The physicians at these NDR-TB centres are responsible for the management and safety monitoring of patients who would be treated using Dlm. NDR-TB centres should make available or have referral linkages with a consultant cardiologist for stringent ECG/cardiac monitoring and with a general laboratory for close monitoring of haematological and biochemical parameters for management of adverse events and safety monitoring requirement for Dlm containing regimen.

However, domicile would not be considered as criteria to offer Dlm to the eligible patient.

4. Criteria for patients to receive Delamanid

Proper patient selection is one of the five conditions recommended by WHO for introduction of Dlm in any country (4,6,15,17,19,21). The selection criteria are detailed in this section.

4.1 Basic criteria

The criteria for patients to receive Dlm as approved by the subject expert committee and national expert committee on regulation of newer anti-TB drugs in India (23,24) are:

Inclusion criteria:

- Adults (≥18 yrs), including people living with HIV (PLHIV), not eligible for a shorter MDR-TB regimen for reasons of resistance, contraindication or tolerability
  - MDR/RR-TB with resistance to any/all FQ OR any/all SLI
  - XDR-TB
  - Mixed Pattern DR-TB including patients who are failing any DR-TB regimen or have drug intolerance or contraindications or who return after interruption or emergence of any exclusion criteria for shorter MDR-TB regimen or with extensive or advanced disease and others deemed at higher baseline risk for poor outcomes.
- Special caution: HIV+ (in consultation with ART centres), 65yrs+, patients with diabetes, hepatic or severe renal impairment, those with serum albumin <2.8 g/dL or those who use alcohol or substances.

Additional considerations:

- Delamanid may be considered with caution by the NDR-TBC committee under specialist consultation in patients with baseline serum albumin <2.8 g/dL. Very frequent monitoring serum albumin need to be done in such patients.
- Electrolyte imbalances (Serum K, Mg, Ca) to be corrected before initiating Delamanid.
- Females should not be pregnant, or should be using a birth control method. 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.

- Delamanid film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption can be considered after obtaining specialist consultation.

Exclusion Criteria:

- Children under 6 years.
- Pregnant & breastfeeding women (20).
- Patients with repeated demonstration of a QT interval >500 ms, history of torsades de pointes or cardiac ventricular arrhythmias
- Hypersensitivity to the active substance or to any of the excipients

Special Considerations:

A. Cardiac Risk Factors:

Treatment with Dlm should not be initiated in patients with the following risk factors unless the possible benefit of Dlm is considered to outweigh the potential risks. Such patients should receive very frequent monitoring of ECG throughout the full Dlm treatment period (13).

- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval or QTc > 500 ms.
- History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
- Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):
    - Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
    - Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive agents.
    - Certain antimicrobial agents, including:
        - macrolides (e.g. erythromycin, clarithromycin)
        - fluoroquinolones (e.g. moxifloxacin, sparfloxacin)
        - triazole antifungal agents
        - pentamidine
        - saquinavir

- Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
- Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.

Prolongation of QTc Interval

- ECG should be monitored before initiation, at day 15 of treatment and then monthly during the full course of treatment with Dlm in patients with normal ECG at baseline.
- Very frequent ECG monitoring needs to be done where risk of QTc interval prolongation is high (e.g. patients with baseline ECG abnormalities put on treatment with cardiologist's advice, if Qtc interval exceeds 450/470 ms for male/female patients during Dlm treatment, use of other Qtc prolonging drugs, known cardiac risk factors).
- Correct electrolyte imbalances (especially serum potassium) that can predispose to cardiotoxicity.
- Stop all Qtc prolonging drugs if a QTcF > 500 ms is observed.

Actions to minimize the risk of the development of Dlm-resistant MTB strains:

- Delamanid must only be used in appropriate combination regimen for MDR-TB treatment as recommended by WHO.
- Delamanid must never be added to a failing regimen.

B. Extra-pulmonary TB:

Although, there is no regulatory approval for use of these drugs in EP MDR-TB patients as the evidence is still evolving, there is no absolute contraindication for use in EP MDR-TB patients if benefits offset any potential harm. Effectiveness of Dlm in central nervous system TB is yet unestablished. (15,17,19,21)

C. Children & Adolescent (6-17 years):

Although, WHO has issued an interim guideline in 2016 for the use of Delamanid in this age group with a dosage of 50 mg BID (6-11 years) and 100 mg BID (12-17 years) for 6 months (16), it is yet under process of approval by regulatory authorities including India. Once regulatory approvals for use of Delamanid in children and adolescent (6-17 years) are obtained, they would be considered in the inclusion criteria.

D. Caution to be exercised with baseline laboratory abnormalities important for choosing other second-line drugs:

Patients with following laboratory abnormalities (DAIDS Grading) would also be considered for treatment with caution for choosing second-line drugs in the regimen (28):

- Albuminaemia below 2.8 g/dL
- Creatinine grade 2 or greater, i.e. >1.5 times the upper limit of normal (ULN);
- Hemoglobin grade 4 (<8.0 gm/dL);
- Platelet count grade 4 (≤ 80,000/mm3);
- Absolute neutrophils count grade 4 (≤ 1000/mm3);
- Aspartate aminotransferase (AST) grade 2 or greater (>2.5 times ULN);
- Alanine aminotransferase (ALT) grade 2 or greater (>2.5 times ULN);
- Total bilirubin grade 2 or greater (>1.6 times ULN);
- Lipase / Amylase grade 2 (with no signs or symptoms of pancreatitis) or greater (>1.5 time ULN).

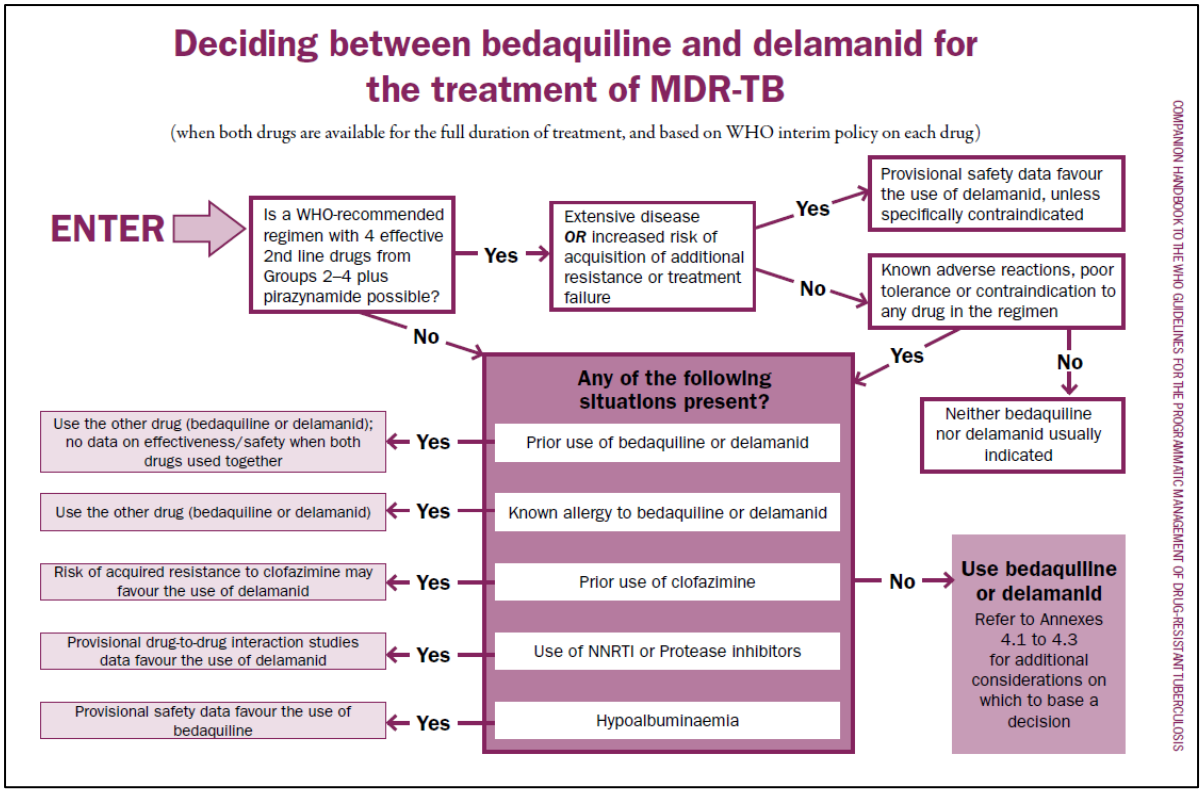
If the results of the serum chemistry panel, haematology or urinalysis are outside the normal reference ranges (including the above listed parameters), the patient may still be considered for treatment if the physician judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable. Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to a patient receiving Dlm. Patients who could not be initiated on a Dlm containing regimen would be managed as per the appropriate regimens given in the Guidelines for PMDT in India (2017) (2).

4.2 Delamanid access to patients seeking care in private/other sector:

PMDT services including newer drugs like Delamanid would be available through regulated access from RNTCP and can be provided to the patient seeking services in private/other sector. Again, priority providers should be mapped by every state for partnership. The mechanism for access to PMDT services including newer drugs for patients seeking care in the private sector are detailed in Chapter 7 of the Guidelines for PMDT in India (2017) (2).

4.3 Choosing Bedaquiline or Delamanid for treating MDR-TB:

In future, there would be situations when some states may have access to both the new drugs i.e. Bdq and Dlm. While waiting for evidence and WHO recommendations on use of both drugs in combination with a background regimen, the choice between Bdq and Dlm can be guided by the following decision framework available from the Companion handbook to WHO PMDT Guidelines (2014) (6):

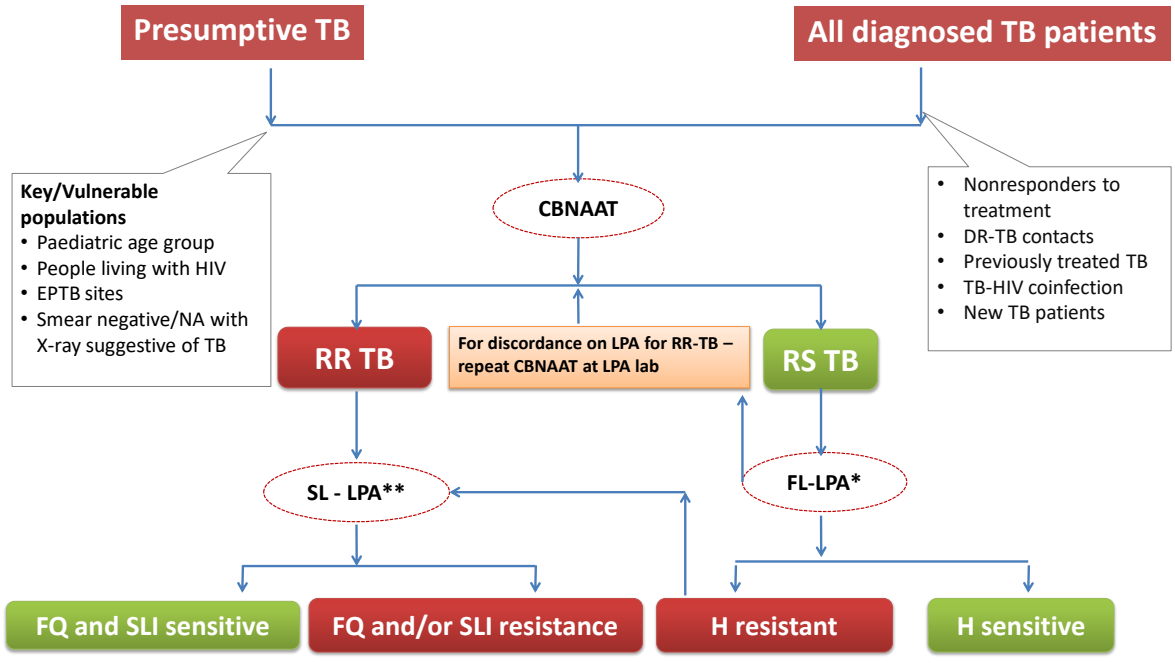

Deciding between bedaquiline and delamanid for the treatment of MDR-TB
(when both drugs are available for the full duration of treatment, and based on WHO interim policy on each drug)
ENTER
Is a WHO-recommended regimen with 4 effective 2nd line drugs from Groups 2–4 plus pirazynamide possible?
Yes
Extensive disease OR increased risk of acquisition of additional resistance or treatment failure
Yes
Provisional safety data favour the use of delamanid, unless specifically contraindicated
No
Known adverse reactions, poor tolerance or contraindication to any drug in the regimen
Yes
No
Neither bedaquiline nor delamanid usually indicated
No
Any of the following situations present?
Prior use of bedaquiline or delamanid
Known allergy to bedaquiline or delamanid
Prior use of clofazimine
Use of NNRTI or Protease inhibitors
Hypoalbuminaemia
Yes
Use the other drug (bedaquiline or delamanid); no data on effectiveness/safety when both drugs used together
Yes
Use the other drug (bedaquiline or delamanid)
Yes
Risk of acquired resistance to clofazimine may favour the use of delamanid
Yes
Provisional drug-to-drug interaction studies data favour the use of delamanid
Yes
Provisional safety data favour the use of bedaquiline
No
Use bedaquiline or delamanid
Refer to Annexes 4.1 to 4.3 for additional considerations on which to base a decision
COMPANION HANDBOOK TO THE WHO GUIDELINES FOR THE PROGRAMMATIC MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

5. Diagnosis of DR-TB

Diagnosis of MDR/RR-TB will be done in accordance to the integrated DR-TB diagnostic algorithm as per the Guidelines for PMDT in India (2017) (2) as shown below (Figure 5.1).

All patients diagnosed as MDR-TB/RR-TB as per the algorithm would be offered baseline SL-LPA to facilitate decision on patient selection for Dlm. DST to Mfx (2.0), Km, Cm and Lzd will be set up on liquid culture using the decontaminated deposits only for patients who are found to be resistant to FQ and/or SLI class. The results of the LC-DST for individual FQ and second line SLI will be provided based on a single breakpoint concentration and decisions on modification of regimen will be made by the NDR-TBC committee based on the results of LC-DST for each individual patient as detailed in the guidelines later. DST to Z, Cfz, Bdq and Dlm would be considered for policy in future, whenever available, standardized and WHO endorsed. All culture isolates will be stored for all patients put on Dlm containing regimen and DST for Dlm (phenotypic or molecular) will be performed on all culture positive isolates at baseline and follow up once it becomes available to the programme (2).

Figure 5.1 DR-TB diagnostic algorithm



*Offer molecular testing for H mono/poly resistance to TB patients prioritized by risk as per the available lab capacity
**LC DST (Mfx 2.0, Km, Cm, Lzd) will be done only for patients with any resistance on baseline SL-LPA. DST to Z, Cfz, Bdq & Dlm would be considered for policy in future, whenever available, standardized & WHO endorsed.

6. Pre-treatment evaluation

All eligible patients would be subjected to a thorough pre-treatment evaluation at the NDR-TB centres as per the Guidelines for PMDT in India (2017) (2).

The summary of the pre-treatment evaluations are as below:-

SN	Pre-treatment evaluations
1	Detailed history (including screening for mental illness, seizer disorder, drug/alcohol abuse, etc.)
2	Previous history of ATT taken especially SLI/FQ
3	Weight & Height
4	A thorough clinical examination
5	Complete Blood Count with haemoglobin & platelets count
6	Blood sugar to screen for Diabetes Mellitus
7	Blood Urea and S. Creatinine to assess Renal function
8	Urine examination – Routine and Microscopic
9	UPT (for all women in the child-bearing age)
10	Chest X-Ray
11	HIV Counselling and Testing*
12	Audiogram
13	Liver Function Tests#
14	TSH levels to assess the thyroid function
15	Psychiatric evaluation
16	Surgical evaluation
17	ECG (if Mfx^{h}, Bdq, Dlm, Cfz used)
18	Serum electrolytes – sodium, chloride, potassium, magnesium, calcium
19	Serum albumin and total proteins, uric acid
20	Ophthalmologist opinion to rule out chorioretinitis /uveitis

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

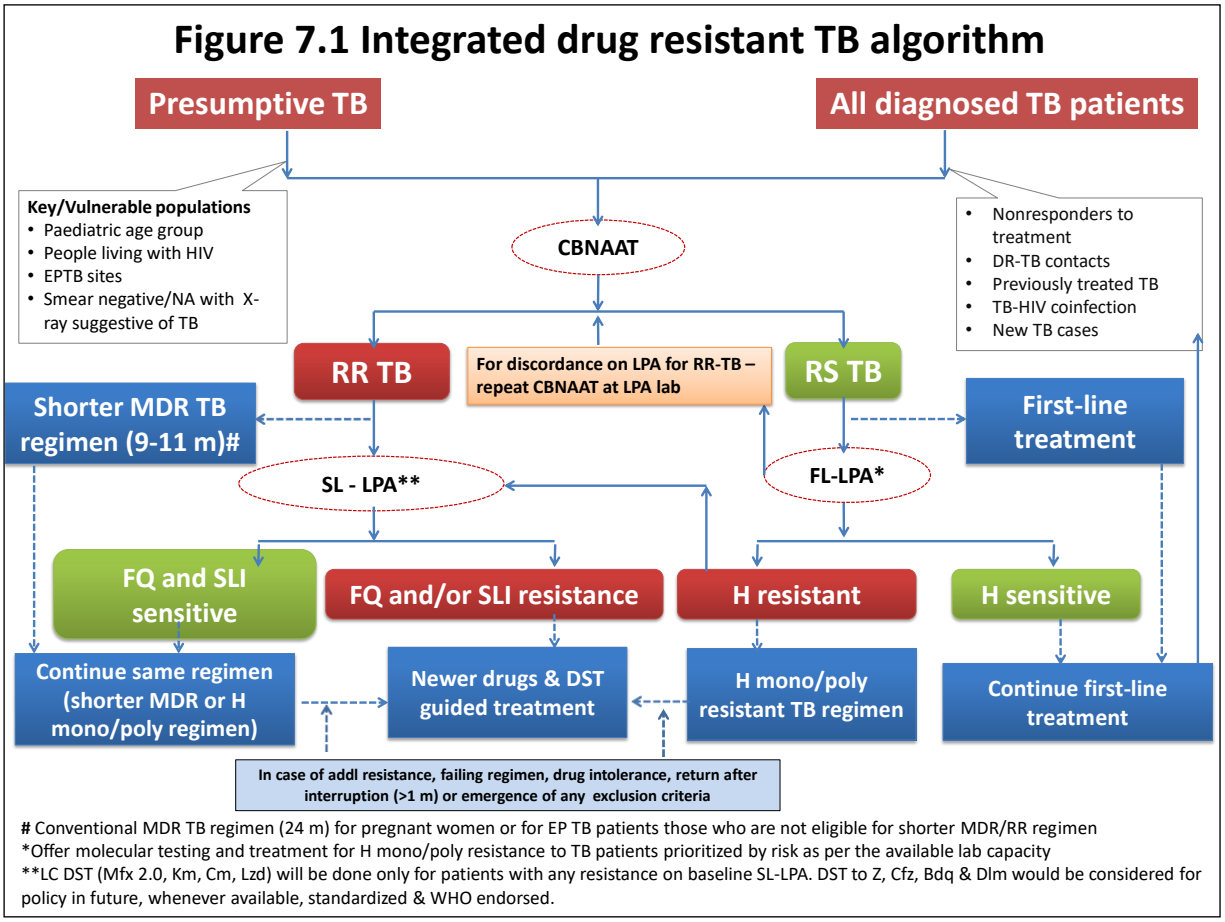
 # including HBsAg at baseline

Every NDR-TB centre must ensure that the necessary laboratory capacity and consultancy services from various specialists are available in the sites, either in-house or through an outsourced mechanism supported under institutional/state govt. mechanisms (2).

7. Treatment initiation

While waiting for the results of baseline SL-LPA as detailed above, all patients diagnosed as MDR-TB/RR-TB using various technologies will be initiated on an appropriate MDR-TB regimen as per Guidelines for PMDT in India (2017) (2) as shown below (Figure 7.1). Once the results of baseline SL-LPA are available, the patients eligible to be treated with Dlm containing regimen will be identified and an appropriate regimen will be designed by the NDR-TBC committee as described in the next chapter.

Figure 7.1 Integrated drug resistant TB algorithm



Conventional MDR TB regimen (24 m) for pregnant women or for EP TB patients those who are not eligible for shorter MDR/RR regimen
*Offer molecular testing and treatment for H mono/poly resistance to TB patients prioritized by risk as per the available lab capacity
**LC DST (Mfx 2.0, Km, Cm, Lzd) will be done only for patients with any resistance on baseline SL-LPA. DST to Z, Cfz, Bdq & Dlm would be considered for policy in future, whenever available, standardized & WHO endorsed.

All eligible patients need to be offered counselling along with a patient education booklet for Delamanid (Appendix 1) which will give details of the nature and duration of treatment including information on Dlm; need for regular treatment; possible side-effects; drugs to be avoided with Dlm and the consequences of irregular treatment or premature termination of treatment. Female patients will receive special counseling on family planning.

Pretreatment counselling must serve as an informed decision-making process that enables patients to make a duly informed decision regarding the use of all anti-TB drugs including newer drugs like Dlm. This activity must be recorded in the counsellor's register, PMDT

treatment card and treatment book of the patient before initiating treatment. Once the patient has taken an informed decision during pre-treatment counselling, this will be documented as above and administration of Dlm containing regimen will be considered (2).

Once Dlm containing regimen is initiated, the patient will be registered on the RNTCP PMDT treatment register and entered on Nikshay by the concerned NDR-TBC. The patient would be registered in this updated register and all necessary records would be maintained in accordance to the recording and reporting systems of the Guidelines for PMDT in India (2017) (2).

All patients eligible for Dlm containing regimen would be managed in an in-patient setting preferably for a period of two weeks (15 days) to observe for tolerance of the patients to the regimen. In exceptional patients who are not seriously ill, it is important to have all pretreatment evaluations within normal limit and for those who are ambulatory or residing close to the NDR-TBC and are willing to visit NDR-TBC for periodic ECG and clinical monitoring, the NDR-TBC Committee may decide to manage the patient on an ambulatory basis (2). The final decision of further duration of in-patient management rests with the NDR-TBC Committee and must be well-documented for every patient. After discharge, treatment will be continued on ambulatory basis with strict adherence to treatment supplemented with ICT based adherence monitoring and follow-up schedule.

All measures for airborne infection control must be implemented as per the national AIC guidelines while managing all TB patients (2, 26).

8. Dosage, regimen, administration and missed doses management

The principles of designing a WHO-recommended MDR-TB regimen will be adhered to. Such a regimen is typically composed of at least pyrazinamide and four second-line drugs that are considered to be effective based on drug susceptibility test and/or previous use and/or drug resistance surveillance data (2,4,15,17,19,21).

Dlm 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, patients who meet the inclusion criteria detailed in chapter 4 will be considered for Dlm containing regimen.

Delamanid containing regimen in context of MDR-TB for the above patients would contain Dlm (group D2) with pyrazinamide (group D1) and at least four second-line drugs considered to be effective (group A or B based on SL-LPA results and group C). The choice of drugs should be based on DST pattern and in accordance to the principles for designing a WHO recommended regimen (2,4,15,17,19,21).

8.1 Dosage:

All patients will receive Tab. Delamanid 100 mg (two tablets of 50 mg) orally twice a day for 24 weeks (6 months) in combination with an optimized background regimen (OBR). The OBR will be continued beyond the 24 weeks of Dlm administration for the RNTCP recommended duration of treatment. As mentioned above, the OBR will be designed as per Guidelines for PMDT in India (2017) and WHO recommendations for designing an OBR for use with Dlm.

- Week 0–24: Delamanid 100 mg (two tablets of 50 mg) orally twice a day + OBR
- Week 25 (start of month 7) to end of treatment: Continue other second-line anti-TB drugs only as per RNTCP recommendations. (2,4,15,17,19,21)

8.2 Regimen:

The regimen designing/modification will be the prerogative of the NDR-TBC committee. The decision on drugs to be included in OBR would be based on the following conditions (2):

Resistance Pattern	DST Guided Regimen class	Intensive Phase	Continuation Phase	Principle of regimen design
Regimen with New drugs for MDR-TB + FQ / SLI resistance:				
MDR/RR + resistance to FQ class OR SLI[1] class	MDR/RR + res to FQ class	(6-9) Km Eto Cs Z Lzd[3] Cfz + (6) Dlm	(18) Eto Cs Lzd[3] Cfz	0 GpA + 1GpB + 2 GpC + Z + add on 2 GpC + 1 GpD2
	MDR/RR+ res to SLI[1] class	(6-9) Lfx Cm[1] Eto Cs Z Lzd[3] Cfz + (6) Dlm	(18) Lfx Eto Cs Lzd[3]	1 GpA + 1 GpB[1] + 2 GpC + Z + add on 2 GpC + 1 GpD2
Regimen with New drugs for XDR-TB:				
XDR-TB (res to both FQ and SLI[1] class)	XDR-TB	(6-12) Cm[1] Eto Cs Z Lzd[3] Cfz E + (6) Dlm	(18) Eto Cs Lzd[3] Cfz E	0 GpA + 1 GpB[1] + 2 GpC + Z + add on 2 GpC + 1GpD1 + 1 GpD2
Regimen with New drugs for Mixed Pattern DR-TB:				
Mixed pattern DR-TB	MDR/RR-TB + res to FQ / SLI[1] + Lzd[3] or more	Modify the Regimen with New drugs for XDR-TB as per the footnotes		

1. If only Km resistant (at eis mutation), then add Cm in IP upfront in the regimen design
2. In patients with MDR/RR + FQ Class resistance, XDR-TB and Mixed pattern resistance where a new drug is not considered in the regimen for any reason, Mfx[h] would be added upfront in the regimen design and the decision to continue or replace it would be taken based on LC-DST results to Mfx (2.0) by NDR-TBC
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

8.3 Administration:

It is important that Dlm be taken daily preferably after a standard meal to improve bioavailability (4,15,17,19,21). After their last dose of Dlm, all patients will continue to take their OBR in accordance with Guidelines for PMDT in India (2017) (2). Patients should not consume milk-containing products at the same time, as calcium 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). Sputum culture should continue as per schedule and DST results should be used to guide necessary changes in the OBR. Patients who could not be initiated on a Dlm containing regimen (either found ineligible or did not take an informed decision) would be treated with an appropriate regimen in accordance to the Guidelines for PMDT in India (2017) (2).

8.4 Management of patients with missed doses:

If the patient misses one or more doses of Dlm during treatment up to a maximum of one month, one should not make up for the missed dose but should continue the usual dosing schedule. Patients who return after treatment interruption of one month or more will be declared as “loss to follow up”. Such patients would not be considered eligible for administration of Dlm anymore (2,4,15,17,19,21). The NDR-TBC committee would re-evaluate the patient and manage them as per the Guidelines for PMDT in India (2017).

9. Follow-up monitoring

Once the Dlm containing regimen is initiated, the patient will be monitored for QTc prolongation which will prompt a regular ECG and other safety monitoring as shown in the table below (2,4,15,17,19,21). A cardiologist must be available for expert consultation and interpretation of ECG. All patients enrolled on Dlm containing regimen would be closely monitored by the NDR-TB Centre or DDR-TBC as per the schedule below.

Clinical + Weight	As suggested by treating clinician, at least monthly in IP and quarterly in CP
Smear Microscopy	With culture at C-DST labs
Culture	Monthly from 3m till the end of IP if converted, monthly in extended IP only if the previous month culture +ve, quarterly in CP, 2 consecutive monthly if any culture +ve from 12m onwards
DST	SL-LPA if C+ve at end of IP &/or extended IP or any time in CP & expanded DST if any resistance on SL-LPA
S. Creatinine	Monthly till 3m, then every 3m till SLI course is completed
Audiometry	As and when clinically indicated till SLI course is completed
CBC/Hb/platelets*	Monthly in IP, Quarterly in CP
CXR, TSH & LFT[#]	At end of IP, as and when clinically indicated CXR also at end of treatment
ECG[$]	At 2 wks, monthly in IP, as and when clinically indicated
Serum Electrolytes (Na, K, Cl), Mg, Ca, Proteins[@]	Quarterly in IP and as and when clinically indicated
S. Uric Acid, UPT, Specialist consultation - As and when clinically indicated	
Long term follow up at 6, 12, 18, 24 months after completion of treatment (Clinical, CXR, Sm, C-DST if symptomatic)	

* CBC/Hb/Platelets done to rule out bone marrow suppression and anemia only if Linezolid is included in the regimen

HBsAg and other viral markers (Hepatitis A, C & E) to be done on signs of jaundice during treatment

$ In patients with baseline ECG abnormalities, ECGs must be done on daily basis for the first 15 days if patient is managed with regimen containing Mfx[h], Dlm, Bdq, Cfz and further frequency as advised by cardiologist. Repeat ECG after an hour if abnormal at any time to reconfirm with long lead II for one minute.

@ Serum albumin and total proteins must be done more frequently (monthly) in patients with serum albumin <2.8 g/dL.

Sociological/psychological/nutritional evaluation for treatment adherence, reasons for non-adherence, depression status, quality of life, motivation and counselling will be done**.** Referral services for care and rehabilitation will be provided if required. Refer the Guidelines for PMDT in India (2017) for further details (2).

10. Drug procurement, supply and quality assurance

10.1 Drug procurement

RNTCP will obtain patient courses of DLM through M/s Otsuka Pharmaceuticals Ltd. via M/s Mylan Pharmaceuticals Ltd. and supply to the selected states. Rest of the drugs in the background regimen will be from RNTCP. The procurement and supply management (PSM) will be through the regular mechanism of RNTCP like other second-line drugs (2).

10.2 Product quality compliance

Product quality compliance (PQC) is defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or drug delivery system. Timely, accurate and complete reporting and analysis of PQC information are crucial for the protection of patients, investigators and the company, and are mandated by regulatory agencies worldwide. M/s Otsuka Pharmaceuticals Ltd. via M/s Mylan Pharmaceuticals Ltd. has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. All initial PQCs must be reported to RNTCP and M/s Otsuka Pharmaceuticals Ltd. via M/s Mylan Pharmaceuticals Ltd. as soon as possible after being made aware of the event. If the defect is combined with an adverse event (AE), the physician must report the PQC according to the AE reporting timelines in the relevant section on AEs. A sample of the suspected product should be maintained for further investigation.

10.3 Supply chain management

Delamanid will be supplied to the state drug stores (SDS). It has a shelf-life of 5 years and requires to be stored at 25 ºC (15–30 ºC). The drug would be dispensed in the form of strips, supplied in box of 48 film-coated tablets in aluminium / aluminium packing.

Delamanid strips will be issued by the SDS along with the other second-line drugs through the NDR-TB centers as loose drugs where the patient is initiated on treatment. From the SDS, on initiation of treatment patient's one month drugs requirement will be managed. On discharge, the patient will be handed over the drugs for the rest of the month, e.g. if 15 days of drug is consumed by the patient at the NDR-TBC then the remaining 15 days (of the one month's course) will be handed over to the patient under information to District TB Officer, Senior Treatment Supervisor, Senior District DR-TB & HIV supervisor for management of this patient through the treatment supporter.

Delamanid stock will be issued by SDS to the District Drug Store (DDS) as and when the NDR-TBC gives intimation to the district about discharge of this patient and his/her treatment. The monthly Type B box for the intensive phase containing other second line drugs issued from the DDS to the treatment supporter will also include the monthly quantity of Dlm. The Type B box will be issued on a monthly basis till the end of IP along with the Type A with monthly quantities of Dlm. In the last month (6^{th} month), the box would contain 72 tablets in place of 120 as Dlm is to be given for 24 weeks. The details are explained below:

Delamanid will be administered with other second line drugs for a duration of 24 weeks. Each tablet consists of 50 mg of Dlm, hence patients need to take 4 tablets a day. There are 8 tablet in each strip and 6 strips in each box. In a month, the patient will receive 120 tablets (15 strips) through Type B Box. To complete the full course, in the 6^{th} month, the patient will require only 72 tablets (9 strips). Hence, only 72 tablets of Dlm will be provided in the 6^{th} month. The table below provides the diagrammatic representation of the same:

	Week	Daily Dosage	Strips to be included in the box
1 Month	4	120	15 Strips
2 Month	4	120	15 Strips
3 Month	4	120	15 Strips
4 Month	4	120	15 Strips
5 Month	4	120	15 Strips
6 Month	4	**72**	**9 Strips**
Total	24	672	84 Strips

In the event of loss to follow up or death or discontinuation of Dlm for any reason, the leftover tablets will also be returned back to the DDS. These drugs would be taken back in stock and used under the supervision as per Batch No. & expiry. Batch No. & expiry need to be labelled properly on the box. The existing records and reporting formats for second-line drug supply chain management will be used to enter details about Dlm storage, issue and reconstitution in conjunction with other second-line drugs.

11. Adverse events of Delamanid

As per the Phase IIb trial results, many adverse events with Dlm had similar frequency as the placebo group. The most frequently observed adverse drug reactions in patients treated with Dlm (i.e. incidence >10%) are nausea (38.3%), vomiting (33%), and dizziness (30.2%). AE's were lower in 100 mg arm compared to 200 mg arm. Prolonged QTc interval was the most prominent safety concern although no clinical manifestations such as syncope or arrhythmia observed. (4,6)(8-21)

In the phase III trial (Trial 213), the following observations were made (17,18):

- There was no significant difference in treatment-emergent adverse events (TEAEs) between participants receiving Dlm and those receiving placebo. No previously unknown TEAEs were recorded. Serious TEAEs were recorded in 89/341 (26.1%) of participants in the Dlm arm and in 47/170 (27.6%) of those in the placebo arm (RR 0.944; 95%CI 0.698 - 1.276). **Contrary to earlier trial results, increased Dlm toxicity in patients with lower albumin levels was not confirmed in Trial 213.** Hepatotoxicity was recorded in 6.5% (22/341) of participants on Dlm and 7.1% (12/170) of those on placebo (RR 0.914; 95% CI 0.464 - 1.802).
- No new or significant drug-drug interactions between Dlm and antiretroviral (ARV) drugs were observed, although the number of participants receiving dual treatment was low and results should be interpreted with caution. Overall, 12/32 participants with HIV co-infection (37. 5%) in the Dlm group experienced one or more serious TEAEs compared to 5/16 (31.3%) in the placebo group (RR 1.2; 95%CI 0.51-2.82).
- There was no clinically relevant or significant difference in the prolongation of the Fridericia-corrected QT interval (QTcF) between participants receiving Dlm and those receiving placebo. New-onset QTcF >500 ms was recorded in 7/341 (2.1%) of the participants who received Dlm and in 2/170 (1.2%) of those who received placebo (RR 1.761, 95% CI 0.362 - 8.568). QT prolongation (>60 ms from baseline) was observed in 10.3% (35/341) of participants receiving Dlm and 7.1% (12/170) of those on placebo (RR 1.454; 95% CI 0.775 - 2.728).

11.1 Specific toxicities

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. The most frequently occurring adverse drug reactions (ADRs) in patients treated with Dlm include nausea, vomiting and dizziness. (4,6)(8-21)

Management of patients with QTc interval prolongation, gastrointestinal system disorders or other toxicities is enumerated below (4,6)(8-21)(27,28).

i. QTc interval prolongation:

Electrocardiogram (ECG) QTc interval prolongation has been identified as the most prominent safety concern of treatment with Dlm. Therefore, ECGs should be obtained before initiation of treatment and monthly during the full course of treatment with Dlm. Treatment should not be started or should be discontinued if a QTcF > 500 ms is observed either before the first dose of Dlm or during Dlm treatment.

Some of the medicines recommended for the treatment of MDR-TB by the WHO guidelines, such as the fluoroquinolones, can cause QTc interval prolongation. If possible, avoid the use of QT prolonging drugs with Dlm. If it is absolutely necessary to include a QT prolonging drug like fluoroquinolone in order to construct an adequate treatment regimen for MDR-TB etc., very frequent monitoring of ECGs is recommended throughout the full Dlm treatment period in consultation with cardiologist.

QT interval monitoring: An ECG should be obtained before initiation of treatment and in patients with baseline ECG abnormalities put on Dlm containing regimen after consultation with a cardiologist, it should be monitored on a daily for the first 2 weeks. However, in patients with normal baseline ECG, the next ECG would be done on day 15. Then ECG would be done on monthly basis till the end of Dlm course. ECGs should be done at least weekly throughout the Dlm course if other QT prolonging drugs like FQ etc. are included in the regimen.

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 Dlm use.

- **Grade 1 (asymptomatic) or Grade 2 (asymptomatic, transient rhythm abnormality not requiring any treatment) cardiac rhythm disturbances:** Patients may continue Dlm 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 Dlm.

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 in males and >470 ms in females.

- A value between 450 – 480 ms: Rule out other causes of prolonged QTc, before deciding to withhold Dlm.
- 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 Dlm 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** Dlm and all other QTc-prolonging drugs in the regimen.

Dlm and all other QTc-prolonging drugs are to be discontinued if the patient develops a clinically significant ventricular arrhythmia. If Dlm is stopped for QTc prolongation, monitor ECGs at least weekly until the QTcF interval has returned to baseline. **If syncope occurs, obtain an ECG to detect QT prolongation.**

If a QTcF of greater than 500 ms is recorded and is confirmed by a repeat ECG, it is recommended that Dlm 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. Only after repeated demonstration of Qtc < 450 ms, the Qtc prolonging drugs could be reintroduced under consultation of the cardiologist and close monitoring with frequent ECG.

ii. 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 Dlm treatment should be discussed with the DR-TB centre committee.

iii. Other toxicities

- **Grade 1 or 2:** Patients who develop grade 1 or 2 AE or laboratory toxicity may continue intake of Dlm.
- **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 Dlm 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 [28].

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.

11.2 Drug-Drug Interactions:

Delamanid has minimal drug interactions and can be co-administered with drugs commonly given to MDR-TB patients. When introducing Dlm into a regimen, there is also potential for its interaction with other medications administered concurrently, with additive or synergic adverse effects (4,6,8-21).

Other second-line drugs that are likely to be administered with Dlm, notably FQs and Cfz may potentially increase the risk of cardiotoxicity. Also, some antiretroviral medications can cause modest QT prolongation, especially ritonavir-containing regimens. Therefore, monitoring of patients for cardiac dysrhythmias or QT interval prolongation (i.e. using ECG), and for electrolyte imbalances (especially serum potassium) that can predispose to cardiotoxicity is imperative.

Drug-drug interaction studies of Dlm with tenofovir, efavirenz and lopinavir/ritonavir, respectively, suggested that no dose adjustments were needed when Dlm was used with any of these anti-retroviral agents. No new or significant drug-drug interactions between Dlm and ARV drugs were observed in Trial 213, although the number of participants receiving dual treatment was low and results should be interpreted with caution. (17,18). Therefore, PLHIV who will be receiving Dlm as part of DR-TB treatment should have their ART regimens designed in close consultation with HIV clinicians and ART specialists.

12. Adverse event monitoring and reporting

Timely, accurate, and complete reporting and analysis of Dlm-related adverse events are required to be reported under the programme. This is crucial for the protection of the patients (4,6,8-21,27-28)

12.1 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 to be associated with the use of the drug, if the attribution is possible, probable or very likely.

12.2 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) 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 dechallenge. 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 dechallenge and rechallenge.

12.3 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.

12.4 Reporting of adverse events, serious adverse events and pregnancy

All SAEs and AEs, (i.e. non-serious adverse events which are possibly, probably or very likely related to the administration of Dlm) 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 Dlm treatment, Dlm must be stopped and OBR must be modified as per the Guidelines for PMDT in India (2017) (2).

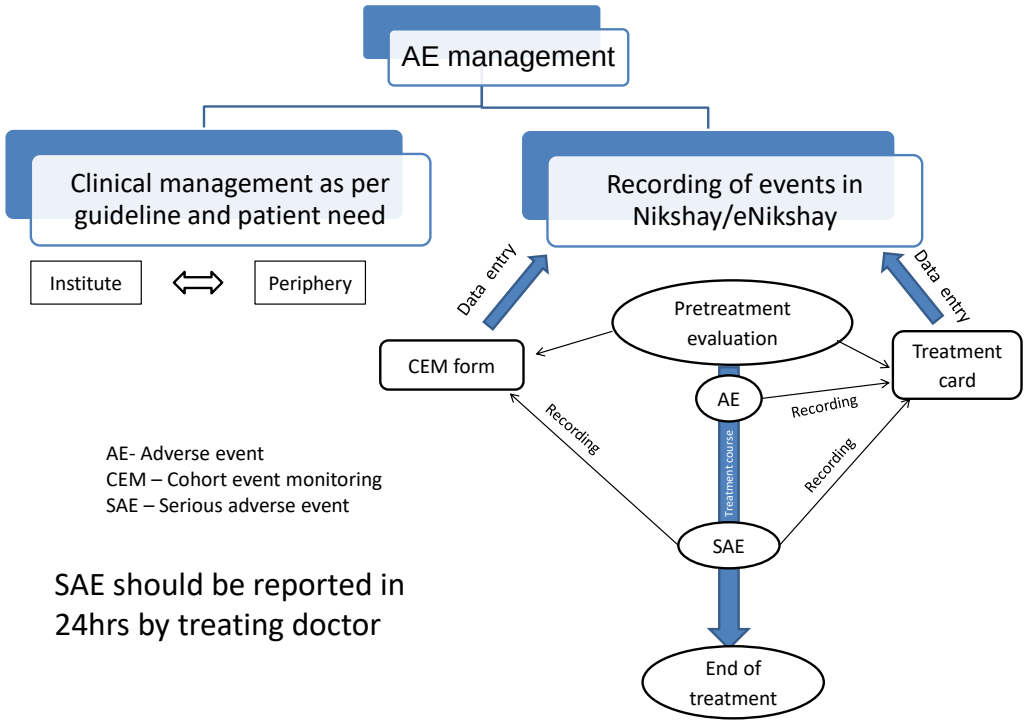
Any death of a patient occurring during treatment in a Dlm containing regimen, regardless of causality, must be reported as SAE and a verbal autopsy should be undertaken.

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 cohort event monitoring - treatment initiation form need to be maintained for every patient and uploaded on Nikshay.

RNTCP will ensure that strict active drug safety monitoring (aDSM) is implemented by all the NDR-TBCs, DDR-TBCs and doctors at the peripheral health institutes for ambulatory patients.

ADR management, recording and reporting mechanism is shown in figure 12.1 below.

Figure 12.1 ADR management recording and reporting



The treating physician at N/DDR-TBC and doctors at periphery will observe patients for any adverse events (spontaneous reporting by patient and active screening) and will manage as per laid down criteria in document. The N/DDR-TBC will collaborate with the ADR monitoring center (AMC) of the pharmacovigilance programme of India (PvPI).

Cohort event monitoring (CEM) is no longer a requirement. Active drug safety monitoring (aDSM) is the standard of care now for patients on new or repurposed drugs or novel regimens. The recording and reporting activities of aDSM primarily target the serious adverse events (SAEs) as a basic requirement. The appropriate and timely management of ADRs is an integral component of aDSM and patient care (29).

The recording of events has been divided in to two components.

1. Active drug safety monitoring (aDSM) (erstwhile CEM) will follow the patient pathway from registration to the treatment outcome. The patient details will be captured as baseline (before starting treatment) using the aDSM – treatment initiation form and will get updated for all SAEs using aDSM – treatment review form after it is appropriately managed.

2. Any AE will be captured additionally using RNTCP PMDT treatment card.

The primary responsibility of filling up of above forms will be with treating physician and doctors in the periphery.

All information about AE and SAE need to be updated on Nikshay immediately after the event is appropriately managed by the N/DDR-TBC concerned. The formats to be used are the same as detailed in the Guidelines for PMDT in India (2017) (2).

Once the relevant information is uploaded in NIKSHAY it will seamlessly flow to Vigiflow software of PvPI through the electronic bridge that is functional. 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 dlm@rntcp.org. Records need to be maintained in hard copies at respective sites. (2)

The aDSM data will be analyzed at CTD. The relevant information will be shared with drug safety monitoring committee (DSMC) on regular basis. The data on action required on immediate basis will be shared with DSMC by CTD.

The primary role of DSMC would be to evaluate periodically, the accumulated data for patient safety and make recommendation to CTD concerning use of Dlm.

13. Outcome and aDSM indicators

Interim and final treatment outcome definitions as well as monitoring indicators will conform to the Guidelines for PMDT in India (2017) (2). The final treatment outcomes of the patients would be reported after the end of continuation phase with a background regimen.

Apart from these, monitoring indicators specific for aDSM in patients initiated on Dlm containing regimen will be applied. These indicators cover measures of aDSM coverage, sputum culture conversion, case fatality while on treatment, SAEs, AEs and discontinuation of Dlm. The following table details these indicators, their definitions and data source:

Indicator	Numerator	Denominator	Data source
Indicators on aDSM coverage			
1. *Proportion of DR-TB patients on Dlm included in aDSM*	Number of DR-TB patients registered on Dlm containing regimen included in aDSM	Number of DR-TB patients registered on Dlm containing regimen during the period of assessment	PMDT TB register/ Nikshay /aDSM format
Indicators on sputum culture conversion			
2. *Proportion of DR-TB patients with sputum culture conversion by the end of Dlm containing phase of treatment regimen*	Number of DR-TB patients registered on Dlm containing regimen who achieved sputum culture conversion by the end of Dlm containing phase of treatment regimen	Number of lab confirmed DR-TB patients registered on Dlm containing regimen during the period of assessment	PMDT TB register/ Nikshay
Case fatality indicators			
3. *All-cause case fatality rate by the end of full DR-TB treatment course*	Number of DR-TB patients registered on Dlm containing regimen who died due to any reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on Dlm containing regimen during the period of assessment	PMDT TB register/ Nikshay / aDSM treatment review format
4. *Dlm attributable* case fatality rate by the end of full DR-TB treatment*	Number of DR-TB patients registered on Dlm containing regimen who died due Dlm attributable* reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on Dlm containing regimen during the period of assessment	PMDT TB register/ Nikshay / aDSM treatment review format

Indicators on Serious Adverse Events (SAEs)			
5. *All-cause SAEs rate by the end of full DR-TB treatment course with Dlm containing regimen*	Number of DR-TB patients registered on Dlm containing regimen who reported SAEs due to any reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on Dlm containing regimen during the period of assessment	PMDT TB register/ Nikshay / aDSM treatment review format
6. *Dlm attributable* SAEs rate by the end of full DR-TB treatment course with Dlm containing regimen*	Number of DR-TB patients registered on Dlm containing regimen who reported SAEs due Dlm attributable* reason by the end of full DR-TB treatment course	Number of DR-TB patients registered on Dlm containing regimen during the period of assessment	PMDT TB register/ Nikshay / aDSM treatment review format
Indicator on discontinuation of Delamanid			
7. *Proportion of DR-TB patients in whom Dlm was stopped permanently before completion of Dlm containing phase of treatment course*	Number of DR-TB patients in whom Dlm was stopped permanently before completion of Dlm containing phase of treatment course	Number of DR-TB patients registered on Dlm containing regimen during the period of assessment	PMDT TB register/ Nikshay / aDSM treatment review format
8. *Mean time taken for stopping Dlm permanently before completion of Dlm containing phase of treatment course*	Sum of difference in days between the date of start and date of stopping for all the DR-TB patients for whom Dlm containing regimen was permanently stopped before completion of Dlm containing phase of treatment course	No of the DR-TB patients for whom Dlm containing regimen permanently before completion of treatment	PMDT TB register/ Nikshay / aDSM treatment review format

* Attribution will include causality assessment grades of definite or probable.

The above indicators would be measured using the severity grading of SAE as defined by the DAIDS (Division of AIDS) criteria during treatment and follow-up (28).

14. Salvage regimen

Salvage regimens may be needed for patients who receive Dlm under RNTCP but fail treatment. A standardized salvage treatment strategy may not be feasible, as all these patients have already been treated for DR-TB using second-line drugs. Salvage regimens will be DST-guided treatment regimens based on expanded panel of standardized DST for all available first- and second-line drugs (Refer to Regimen for mixed pattern resistance in chapter 8). Given that the number of drugs that could be used for salvage regimens is limited and that these reserve drugs are less potent, drugs of uncertain effectiveness may be included. Further details of anti-tuberculosis drugs that may be used for salvage regimens should follow the Guidelines for PMDT in India (2017). This would guide careful selection of sensitive first- and second-line drugs including group D2 and D3 drugs to scientifically design an appropriate regimen wherever possible. In patients requiring surgical intervention, the feasibility of surgery should be evaluated. (2)

15. Records, reports & monitoring

The recently updated records, reports and monitoring indicators detailed in the Guidelines for PMDT in India (2017) (2) will be applied to patients who would be managed with a Dlm-containing regimen. For every patient enrolled on a Dlm-containing regimen, a separate folder of all patient records as listed below must be maintained at the NDR-TB centres.

15.1 PMDT records, reports and monitoring indicators

The following records, reports and monitoring indicators from the Guidelines for PMDT in India (2017) (2) would also be used for patient put on Dlm containing regimen:

Annex 12A: Active drug safety monitoring (aDSM) – Treatment initiation form
Annex 12B: Active drug safety monitoring (aDSM) – Treatment review form
Annex 15A: RNTCP request form for examination of biological specimen for TB
Annex 15E: RNTCP PMDT treatment card
Annex 15H: RNTCP PMDT referral for treatment form
Annex 15I: RNTCP TB notification register
Annex 15J: RNTCP PMDT treatment register
Annex 15K: TB laboratory register
Annex 15L: RNTCP laboratory register for CBNAAT and CDST
Annex 15M: RNTCP PMDT treatment book
Annex 15N: DR-TB counselling register
Annex 16: PMDT monitoring indicators
Annex 18: Labels of second-line drugs (SLD) patient-wise boxes (PWB)
Annex 19: Monthly stock statement for second-line formats
Annex 20: Stock Register
Annex 21: Reconstitution Register

15.2 Patient Education Booklet for Dlm-containing regimen

A detailed patient education booklet has been developed for educating the patient on the use of Dlm (Appendix 1). The patient education booklet for Dlm (Appendix 1) must be provided to the patient along with the RNTCP PMDT treatment book that contains the list of drugs contraindicated or to be used with caution with Dlm. The patient must be motivated to carry these documents at every visit to any health care provider throughout the treatment course.

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Appendix 1: Patient Information Booklet on Delamanid

Revised National Tuberculosis Control Programme
Central TB Division, Directorate General of Health Services
Ministry of Health & Family Welfare,
Nirman Bhawan, New Delhi

Patient Information Booklet on TB, Drug-resistant TB and Delamanid

NATIONAL INSTITUTE FOR RESEARCH IN TUBERCULOSIS

DOTS Pure course, Pakka ilaaj

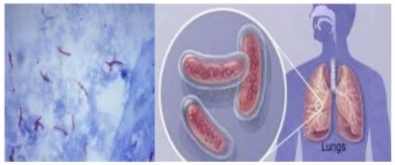
World Health Organization India

This guide is meant for MDR-TB patients to understand all you need to know about tuberculosis and MDR-TB. We hope this will help you clarify all your doubts and fears about this disease as well as enable you to cope with this illness, complete treatment as required and help you lead a healthy lifestyle during the treatment and thereafter.

TB is a curable disease and treatment is available free of cost. Yet in India we have 2.8 million cases of TB. MDR-TB has emerged as a public health problem. India is one of the countries with highest burden of MDR-TB. India accounts for 147 000 MDR-TB patients of the 600 000 MDR patients estimated in the world.

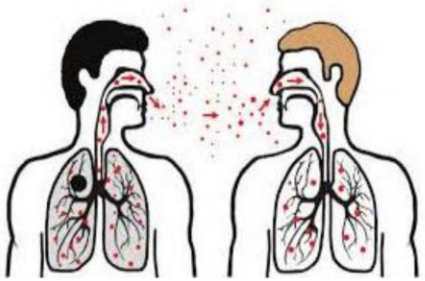
What causes tuberculosis?

Tuberculosis (TB) is caused by bacteria (*Mycobacterium tuberculosis*) that most often affect the lungs.



How does it spread?

It spreads through the air when a person with TB (whose lungs are affected) coughs, sneezes, spits, laughs or talks.



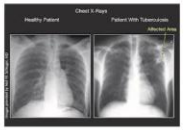
Symptoms of tuberculosis:

The symptoms of active TB include any of the following:

- *Cough for 2 weeks*
- *Fever for more than a month*
- *Blood in sputum anytime*
- *Loss of weight*
- *Loss of appetite*
- *Night sweats.*

Diagnosis of tuberculosis:

Tuberculosis is diagnosed by finding *Mycobacterium tuberculosis* bacteria in sputum which can be seen with the help of a microscope.

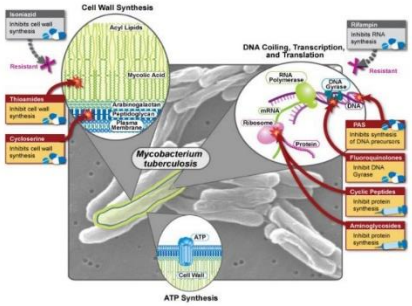


Tuberculosis treatment:

- Treatment is available is all government health facilities.
- Treatment is free of cost.
- Duration of treatment is as short as 6 to 8 months.
- Treatment has to be continued for the prescribed period.

What is multidrug-resistant TB?

- **Multidrug-resistant** tuberculosis (**MDR-TB)** is defined as a form of TB infection caused by bacteria that is resistant to treatment with at least two of the most powerful first-line anti-TB drugs, isoniazid (H) and rifampicin (R).



How does drug resistance develop?

- Use of inadequate regimen and inappropriate treatment adherence leads to increase in drug resistance levels in the community.
- MDR-TB is treated by second-line drugs. Incomplete and erratic treatment for MDR-TB leads to worsening of resistance and XDR-TB.
- All patients of MDR-TB cough out bacteria that are drug-resistant. These can infect another person with the same resistant bacteria. This is how MDR-TB spreads fast.

Who is at risk for getting MDR TB?

Drug-resistant TB is more common in people:

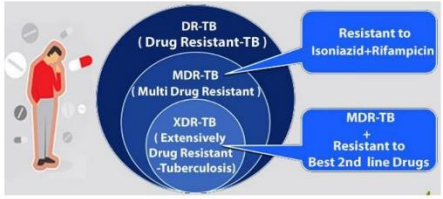
- who do not take their TB drugs regularly;
- who relapse with TB after being irregularly treated for TB in the past and are initiated on re- treatment regimen for 8 months;
- who are exposed to drug-resistant TB patients from known MDR patient;
- who are health workers working among MDR-TB patients;
- TB patients who are dependent on alcohol and habituated smokers and do not complete treatment.

Conditions to suspect MDR-TB:

- When people continue to have symptoms of TB even after 2 months of initiating treatment;
- Those TB patients who do not complete the full course of treatment;
- When a patient becomes sputum smear positive again after initial conversion at 2 months.

How to diagnose MDR-TB?

- MDR-TB can be detected at special laboratory which test the bacteria for sensitivity to the drugs or detect resistance patterns.
- These tests can be molecular in type or else culture-based.

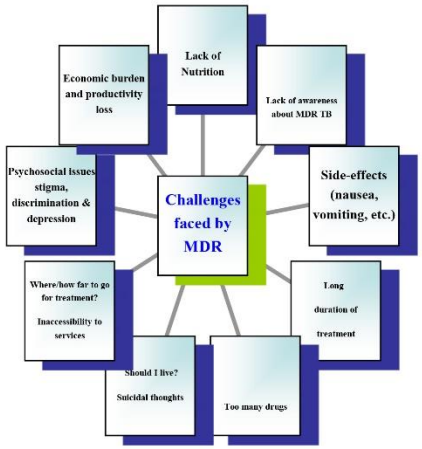


Management of MDR-TB:

- The total duration of treatment is 9-11 months with 4-6 months of injections and 6 oral drugs namely moxifloxacin, ethionamide, clofazimine, high-dose isoniazide, ethambutol and pyrazinamide. Some patients may need up to 24-27 months of treatment.

Challenges faced by MDR-TB patients:

Treating MDR-TB is a challenging task, and there are challenges at every level.



Patients have to follow:

1. Patients must fully adhere to TB treatment
2. Family members of an MDR patient have to be investigated for TB
3. Children below 6 years of age in the same house of an MDR-TB patient, if negative for TB, need to be initiated on drugs to prevent TB.
4. Patients have to take timely, affordable and nutritious food.
5. Patients have to avoid consumption of alcohol, smoking and other addictive substances
6. Patients have to follow preventive steps to avoid spreading the infection, such as covering the mouth while coughing.
7. Patients need to follow healthy lifestyle practices like exercise, yoga and positive thinking.
8. If a patient experiences any side-effects to the drugs, e.g. nausea, vomiting, giddiness, irritability, palpitations, depression, nightmares, suicidal thoughts, etc. they should inform the doctor immediately. These side-effects can be managed and there is no need to panic or discontinue treatment.
9. The patient MUST complete the full course of treatment and cannot afford to be irregular. The consequences of irregular treatment can be dangerous and unmanageable.

INFORMATION ON DELAMANID FOR PATIENTS

Some facts about Delamanid:

- It is a new drug which has shown much promise in the treatment of TB, especially TB which is resistant to treatment by usually available medications.
- For maximum benefits, it is mostly given in combination with other drugs used to treat TB.

How do you take Delamanid?

- It is in tablet form and is easy to swallow.
- You will receive Delamanid for 24 weeks (6 months) with treatment of MDR-TB.
- The drug comes as 50 mg tablets.
- The dose is 100 mg twice daily.

Take 100 mg (2 tablets) two times a day, daily for 24 weeks (6 months).

 **morning**

 **evening**

- It should be taken after a standard meal.
- It can be taken as the same time with other drugs for the treatment of MDR-TB.

What are the possible side effects?

- As all other drugs, Delamanid also causes some unwanted, unpleasant and sometimes harmful side effects.

The most common-side-effects are:

- nausea
- vomiting
- dizziness
- tremors
- anxiety

Does it have any serious side effect?

Yes, in few patients, Delamanid can have some potentially serious side effects.

- Heart rhythm changes (changes in ECG – QT interval prolongation).

What do I do when I have problems?

- You should tell your health-care provider immediately about any side-effect that you experience while taking Delamanid.
- The treating doctor regularly does blood tests and ECG to monitor if the drug is having any side effect, and gives appropriate treatment.

Benefits:

- There is a greater chance that you will be cured of tuberculosis
- You will possibly become better sooner than if you only took the standard medicines for treatment of MDR-TB.
- Also, it is probably less likely that the drugs you are taking will develop resistance if you are taking Delamanid

What do women need to know?

- All women must avoid getting pregnant while taking Delamanid. If you are a woman able to become pregnant (i.e. not sterilized or less than 2 years since menopause), you should use 2 methods of birth control. Breastfeeding must also be avoided.

What do I do in case of pregnancy during treatment?

- Inform the health care provider immediately
- After evaluation in consultation with Obstetrician/gynecologist you may be required to either terminate the pregnancy (MTP), get modified regimen without Delamanid. You and the baby both may be evaluated for longer duration post treatment

What do men need to know?

- All men should avoid fathering a child while on treatment with Delamanid. This is advised as the effects of the medication on your sperm are unknown.

What should I avoid with Delamanid?

- You should not drink alcohol while taking Delamanid.
- There are some medications that cannot be taken safety with Delamanid.
- Make sure to inform your doctor if you are taking medicines or if medicines are recommended to you by a health-care practitioner for some other illness while you are on treatment for TB with Delamanid.
- If you do not know the names of the medicines please ensure that you show the prescriptions to the DR-TB center doctor.

Drugs not be taken along with Delamanid

- Alcohol, Fluoroquinolones, Clofazimine, ritonavir, strong inducers of CYP3A4
- Class 1a or Class III antiarrhythmics (amiodarone, sotalol, procainamide, dysopyramide and quinidine)
- tricyclic anti-depressants (amitriptyline, doxepin, desipramine, imipramine, clomipramine)
- non-sedating antihistamines (astemizole and terfenadine)
- Frequent ECG to be done if the above drugs cannot be avoided.

Name & Contacts of DR-TB Center

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MDR-TB can be cured provided regular and uninterrupted treatment is taken by the patient

END THE GLOBAL TB EPIDEMIC

Let us all work together to overcome the scourge of MDR-TB

A WORLD FREE OF TB

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