Ministry of Health & Family Welfare
Government of India

NATIONAL GUIDELINES FOR MANAGEMENT OF DRUG RESISTANT TB

NATIONAL TB ELIMINATION PROGRAMME

CENTRAL TB DIVISION

MINISTRY OF HEALTH AND FAMILY WELFARE
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The National Guidelines for Management of Drug Resistant TB have been developed after a series of thorough meetings and deliberations with national experts from the Government of India (GoI) and technical partners including World Health Organization Country Office for India (WHO India).

The National Technical Expert Group (NTEG) on TB under the National TB Elimination Programme (NTEP) recommended key changes to the treatment of drug-resistant tuberculosis released in 2022, which include i) introducing a new 6-month (26 weeks) shorter oral MDR/RR-TB BPaLM regimen containing bedaquiline (Bdq), pretomanid (Pa), linezolid (Lzd), moxifloxacin (Mfx) under programmatic condition ii) introducing Bdq and delamanid (Dlm) in all age groups considering the unmet need of this population, and iii) replacement of ethionamide (Eto) with Lzd in 9-11 month shorter oral Bdq-containing MDR/RR-TB regimen.

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The guidelines are to be implemented across India to safely enhance treatment success, reduce mortality in TB patients and will be considered for refinement as new national and global evidence emerges in future.

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
aDSM	active Drug Safety Monitoring and Management
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ART	Anti-Retroviral Treatment
AST	Aspartate aminotransferase
Bdq	Bedaquiline
BPaL	Bedaquiline, Pretomanid, Linezolid
BPaLM	Bedaquiline, Pretomanid, Linezolid Moxifloxacin
C&DST	Culture and Drug Susceptibility Test
Cfz	Clofazimine
CHO	Community Health Officer
CP	Continuation Phase
Cs	Cycloserine
CSF	Cerebro-spinal Fluid
CTD	Central TB Division
DAIDS	Division of AIDS
DBT	Direct Benefit Transfer
DCGI	Drugs Controller General of ndia DDS District Drug Store
DDR-TBC	District Drug-Resistant Tuberculosis Centre
Dlm	Delamanid
DRT	Drug-Resistance Testing
DR-TB	Drug-Resistant Tuberculosis
DR-TBC	Drug-Resistant Tuberculosis Centre
DST	Drug Susceptibility Testing
DT	Dispersible Tablets
DT3C	Difficult-To-Treat Tuberculosis Clinic
DTG	Dolutegravir
DTO	District Tuberculosis Officer
E	Ethambutol
ECG	Electrocardiogram
EP-TB	Extra-Pulmonary Tuberculosis
Eto	Ethionamide
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
FL LPA	First Line-Line Probe Assay
FNAC	Fine Needle Aspiration Cytology
FQ	Fluoroquinolone
GoI	Government of India
H	Isoniazid
Hb	Haemoglobin
HF	Health Facility
H^h	Isoniazid High Dose
HP	Isoniazid and Rifapentine
Hr-TB	Isoniazid-resistant Tuberculosis
ICMR	Indian Council for Medical Research
IP	Initial Phase
IQR	Inter-Quartile Range
LC	Liquid Culture
LFT	Liver Function Test
Lfx	Levofloxacin
LPA	Line Probe Assay
LTFU	Lost-To-Follow-Up
Lzd	Linezolid
MDR-TB	Multi-Drug Resistant Tuberculosis
Mfx	Moxifloxacin
Mfx^h	Moxifloxacin high dose
MO	Medical Officer
MoHFW	Ministry of Health and Family Welfare
MO-TU	Medical Officer of TB unit (block medical officer)
MoU	Memorandum of Understanding
MTP	Medical Termination of Pregnancy
NAAT	Nucleic Acid Amplification Test
NDR-TBC	Nodal Drug-Resistant Tuberculosis Centre
NIRT	National Institute for Research in Tuberculosis

NPY	Ni-Kshay Poshan Yojana
NTEG	National Technical Expert Group
NTEP	National Tuberculosis Elimination Programme
P	Rifapentine
Pa	Pretomanid
PAS	Para-AminoSalicylic acid
Pdx	Pyridoxine
PDR	Poly-Drug Resistance
PLHIV	People Living with HIV
PMDT	Programmatic Management of Drug-Resistant Tuberculosis
PMTPT	Programmatic Management of Tuberculosis Preventive Treatment
PSM	Procurement and Supply Management
PTE	Pre-Treatment Evaluation
PvPI	Pharmaco-vigilance Programme of India
QTcF	QT prolongation (Fredericia's correction)
R	Rifampicin
RBS	Random Blood Sugar
RR-TB	Rifampicin Resistant Tuberculosis
SAE	Serious Adverse Event
SDS	State Drug Store
SLD	Second-Line anti-TB Drugs
SL DST	Second-Line Drug Susceptibility Testing
SLI	Second-Line Injectable
SL LPA	Second Line-Line Probe Assay
TAT	Turn Around Time
TB	Tuberculosis
TBI	Tuberculosis Infection
TPT	Tuberculosis Preventive Treatment
TU	TB Unit
TU-DS	TU Drug Store
ULN	Upper Limit of Normal
USAID	United States Agency for International Development
US FDA	United States Food and Drug Administration
WHO	World Health Organization
XDR-TB	Extensively-Drug Resistant Tuberculosis
Z	Pyrazinamide

DEFINITIONS

A second-line TB drug: This drug is reserved for the treatment of drug-resistant TB. First- line TB drugs used to treat drug-susceptible TB – ethambutol, isoniazid, and pyrazinamide may also be used in MDR-TB regimens (streptomycin is now a second-line TB drug and used only as a substitute for amikacin when amikacin is not available or there is confirmed resistance to it).

Bacteriologically confirmed TB: TB diagnosed in a biological specimen by smear microscopy, culture, or a WHO-endorsed rapid molecular test adopted by NTEP.

Disseminated TB: is defined as the presence of TB at two or more noncontiguous sites resulting from hematogenous and/or lymphatic dissemination of Mycobacterium tuberculosis, occurring because of progressive primary infection, reactivation of a latent focus with subsequent spread, or rarely through iatrogenic origin. Milliary TB is also a form of disseminated TB (1).

Drug-susceptibility testing: DST refers to in-vitro testing using either of the phenotypic

methods to determine susceptibility.

Drug resistance testing: DRT refers to in-vitro testing using genotypic methods (molecular techniques) to determine resistance.

Extensively drug-resistant TB (XDR-TB): TB caused by M.tb strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone (levofloxacin or moxifloxacin) and at least one additional Group A drug (presently to either bedaquiline or linezolid [or both]) (2).

Extensive or severe form of TB:

- Extensive TB disease in adults includes presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography & in children under 14 years, presence of cavity or bilateral disease on chest radiography.
- Severe EP-TB disease includes presence of TB-meningitis, or CNS TB, spinal/ skeletal TB, or disseminated TB (miliary TB or TB with multiorgan involvement). Severe EP-TB disease in children under 14 years, extrapulmonary forms of disease other than pleural effusion & lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression).
- In children, the occurrence of advanced malnutrition (defined by syndrome or by metrics) or advanced immunosuppression or positive tuberculosis (TB) bacteriology (smear, NAAT, culture) may also be considered when determining disease severity (3).

Isoniazid-resistant TB (Hr-TB): TB is caused by M.tb strains that are resistant to isoniazid, and resistance to rifampicin has been ruled out.

Mono-resistant TB (MR TB): TB caused by M.tb strains that are resistant to one first- line anti-TB drug only.

Multidrug-resistant TB (MDR-TB): TB caused by M.tb strains that are resistant to both H and R with or without resistance to other first-line anti-TB drugs. MDR-TB patients also include subsets of Pre-XDR and XDR TB.

Presumptive TB: This refers to a person with any of the symptoms/ signs or chest X-ray Abnormality suggestive of TB.

Presumptive DR-TB: It refers to the patient who is eligible for rifampicin-resistant screening at the time of diagnosis OR/and during treatment for DS-TB or H mono/poly DR-TB. [This includes all notified TB patients (Public and private), follow-up positive on microscopy including treatment failures on standard first- line treatment and H mono/poly DR-TB regimen and any clinical non-responder, including paediatric].

Pre-extensively drug-resistant TB (Pre-XDR-TB): TB caused by M.tb strains that fulfil the definition of MDR/ RR-TB and are also resistant to any fluoroquinolone (2).

Poly-drug resistant TB (PDR-TB): TB caused by M.tb strains that are resistant to more than one first-line anti-TB drug other than HR and RR.

Rifampicin resistant TB (RR-TB): TB caused by M.tb strains that are resistant to R, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R in the form of mono-resistance, poly-resistance, MDR-TB, or XDR-TB.

Serious adverse events: SAEs are those adverse events (AEs) classified as Grade 3 (severe), Grade 4 (life-threatening or disabling) or Grade 5 (death related to AE) or which led to the drug being stopped permanently. SAEs are otherwise often defined as AEs that either leads to death or a life-threatening experience; to initial or prolonged hospitalization; to persistent or significant disability; or to a congenital anomaly. The management of SAEs may require the termination of the drug suspected of having caused the event.

Universal DST: Refers to universal access to rapid DRT for at least rifampicin and further DST/DRT for at least fluoroquinolones among all TB patients with rifampicin resistance (preferably before initiation of treatment to a maximum within 15 days of diagnosis).

1 INTRODUCTION

1.1. Global and national recommendations on newer shorter oral regimens

In recent years, India has made far-reaching progress in the management of TB. For example, an injection-free fully oral treatment regimen for drug-resistant TB (DR-TB) has been implemented across the country. In 2023, among 25.52 lakh TB patients diagnosed, 24.38 lakh (95.5%) patients were put on treatment (4). The disaggregated treatment success rate of patients notified from the public and private sectors, with the current standard of care for drug susceptible TB i.e. 6-month regimen (two months initiation phase consists of isoniazid [H], rifampicin [R], pyrazinamide [Z], ethambutol [E] followed by four months HRE), are 85% and 87%, respectively (5).

The National TB Elimination Programme (NTEP) succeeded in retaining its focus on the goal of ending TB amidst the pandemic. The programme effectively utilized every opportunity of the integrated health system approach, the key to the resilience of India's health system during the pandemic (5).

The emergence of drug resistance is a major threat to global efforts to end TB (2)(3). Resistance to H and R – the two most effective first-line anti-TB drugs (FLDs)– is of greatest concern. For more than ten years, the best estimate of the proportion of people diagnosed with MDR/RR-TB among newly diagnosed TB has remained at about 3–4%, and among those diagnosed with previously treated TB has remained at about 18–21% globally (6). In 2023, five countries accounted for more than half of the global number of people estimated to have developed MDR/RR-TB in 2023: India (27%), the Russian Federation (7.4%), Indonesia (7.4%), China (7.3%) and the Philippines (7.2%). The estimates of MDR/RR-TB in India have reduced by 20% from 1.40 lakh in 2015 to 1.10 lakh in 2023, with an estimated proportion of new TB cases with MDR/RR-TB at 2.5% and of previously treated TB cases with MDR/RR-TB at 13% as per the WHO Global TB Report 2024 (7)(8).

India has made considerable progress in expanding diagnostic and treatment services for DR- TB in the last decade. In 2023, 63,929 MDR/RR-TB including 11,749 pre-XDR-TB and 114 XDR-TB patients; and 23,019 H-mono/poly DR-TB patients were diagnosed. The treatment success rate of MDR-TB patients has improved from 49% in the 2017 to 75% in patients in the 2021 (4). Treatment of XDR-TB presents multiple challenges to clinicians and national TB programmes (NTPs) because of the limited range of medicines available and the life-threatening nature of the disease. Patients with MDR/RR-TB and additional FQ resistance have typically experienced poor treatment outcomes since XDR-TB was first described in 2006 (9). With the introduction of newer drug-containing regimens, there has been a remarkable improvement in the treatment success of Pre-XDR-TB (erstwhile XDR-TB) patients, from 36% in the 2017 to 68% in the 2021. India reported a 73% treatment success rate in patients enrolled on longer oral M/XDR-TB regimens during 2021 (5). This has given better chances of survival to patients with MDR-TB.

1.1.1 WHO recommendations on new, shorter, oral regimens

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, need to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under programmatic conditions. The 2022 update of the DR-TB treatment guidelines added and prioritized a new 6-month regimen – BPaLM(7) , as a treatment of choice for eligible patients. (10).

In 2022, WHO recommended that all patients with MDR/RR-TB, including those with additional resistance to FQ, stand to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under programmatic conditions. The 6-month BPaLM regimen, comprising Bdq, Pa, Lzd (600 mg) and Mfx, may be used programmatically in place of 9-11 month or longer (≥ 18 months) regimens in patients (aged ≥14 years) with MDR/RR-TB who have not had previous exposure to Bdq, Pa and Lzd (defined as more than one month exposure)(9).

WHO recommended that the nine-month, all-oral, Bdq- containing regimens are preferred over the longer (≥ 18 months) regimen in adults and children with MDR/ RR-TB, without previous exposure to second-line treatment (including Bdq), without FQ resistance and with no extensive pulmonary TB disease or severe EP-TB and in patients where BPaLM cannot be given. In this regimen, two months of Lzd (600 mg) to be used as an alternative to four months of Eto (9).

Patients with XDR-TB or those who are not eligible for or have failed shorter treatment regimens will be considered for designing longer oral regimen (≥18 months) using the priority grouping of medicines recommended in current WHO guidelines (11).

1.1.2 Recommendations of the national technical expert group under NTEP

The national technical expert group (NTEG) under NTEP, considering the WHO recommendations, has recommended for developing a protocol with guidance document for (i) introducing BPaLM regiman under programmatic condition (ii) introducing Bdq and Dlm in all age groups considering the unmet need of this population, and (iii) adopting the 9-11 month shorter oral MDR-TB regimen with Lzd replacing Eto. In August 2024, the NTEG also recommended introducing CBNAAT M.tb/XDR test for rapid molecular detection of resistance to H, FQ, SLI and Eto at laboratories equipped with the technology.

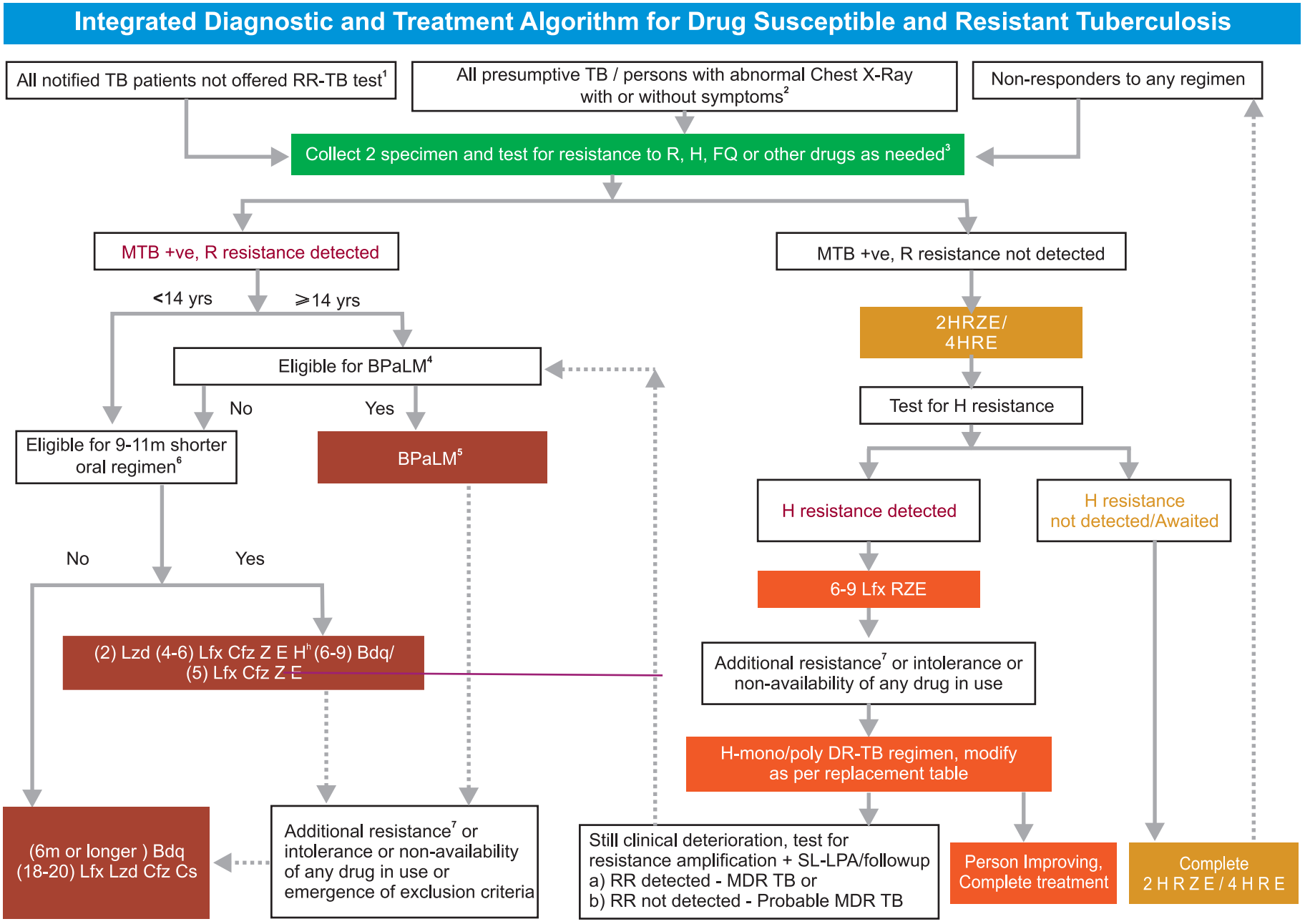
2 CASE FINDING AND DIAGNOSIS OF DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB

Early diagnosis and prompt treatment will prevent the patient from spreading the disease to others, developing resistance to more drugs, progressing to a chronic state of permanent lung damage and ultimately prevent mortality due to the disease. A patient is confirmed to have DR-TB when the results are from NTEP-endorsed and quality-assured NAAT or Culture and Drug Susceptibility Testing (C&DST) utilizing NTEP-endorsed testing method in public and private facilities.

Diagnosis of TB is difficult in certain key groups of the presumptive TB patients like extra-pulmonary, people living with HIV (PLHIV), children, smear -ve /NA with X-ray abnormalities suggestive of TB, and other vulnerable groups as defined in national guidelines and DR-TB contacts, hence, NAAT is offered upfront for diagnosis of TB among these presumptive TB patients. Currently the program follows upfront molecular testing for all presumptive TB.

Patients considered for inclusion in various regimens would be diagnosed using available rapid molecular tests and liquid C&DST for the drugs as specified in the integrated diagnostic and treatment algorithm for DS and DR-TB (Fig. 2.1).

Fig. 2.1: Integrated diagnostic and treatment algorithm for drug-susceptible and resistant tuberculosis.



Foot Notes to Diagnostic Algorithm:

1. Includes TB patients diagnosed based on smear microscopy, clinical/ radiological assessment, and histopathology on appropriate specimen
2. Presumptive TB includes a person with any of the symptoms, signs or any chest X-ray abnormalities suggestive of TB. States to accelerate upfront use of chest X-rays for screening and use of NAAT for TB diagnosis.
3. Sputum (two specimens), gastric lavage (GL), induced sputum (IS), broncho-alveolar lavage (BAL), other respiratory specimen and extra pulmonary specimen like fine needle aspiration cytology (FNAC) of peripheral lymph nodes (LNs) and cerebrospinal fluid (CSF), to be sent to NAAT site for M.tb/Rif, followed by
    i. NAAT for H, FQ resistance detection among M.tb detected using the same specimen, wherever the test is available and as per algorithm.
    ii. Until NAAT for H, FQ resistance detection is available for the district, send second specimen for FL-LPA for H resistance detection among M.tb detected followed by SL-LPA for FQ, SLI resistance detection among H or R resistance detected
    iii. Baseline culture to be done for specimen from MDR-TB patients received at C&DST lab for baseline liquid culture (LC) DST to Bdq*, Lzd, Pa*, Dlm*, Z, Mfx 1.0 (*whenever available) and for specimen from H mono/poly DR-TB patients received at C&DST lab for baseline (LC) DST to Mfx 1.0, Lzd, Z.
    iv. All EP-TB specimens except FNAC of peripheral LNs and CSF preferably to be sent directly to C&DST laboratory for further processing. (3).
    v. Start treatment based on NAAT for H, FQ resistance detection / LPA and modify based on LC-DST results whenever available.
    vi. InhA mutation is associated with Eto resistance and KatG mutation is associated with Hh resistance. If FL-LPA is done on culture isolates for patients with smear negative specimen, till the time the result of indirect FL-LPA is available, use other exclusion criteria to decide regimen. Results of Mfx, Am and Eto will be interpreted as per the mutation pattern of rapid molecular test/ LPA.
4. Eligibility criteria for BPaLM has been mentioned in the respective section of Chapter-3.
5. Implementation considerations/ Extension criteria for BPaLM (Details have been mentioned in section BPaLM respective section of Chapter-3).
6. Eligibility criteria for 9-11 month shorter oral MDR/RR-TB regimen have been mentioned in the respective section of Chapter-3)
7. At follow-up, offer LC-DST for Bdq*, Lzd, Pa*, Dlm*, Z, Mfx 1.0 (*whenever available).

- All states must ensure the availability of all NTEP-endorsed diagnostic technologies or appropriate linkages with public or private laboratories to ensure adequate diagnostic and follow-up capacity in consultation with CTD for all notified TB patients, including those seeking care in the private sector.
- In a new case, if M.tb detected is low or very low and RR-TB detected, NAAT to be repeated and an opinion from a microbiologist may also be sought. If there is a discordance in R resistance between NAAT and FL LPA, a second NAAT is to be performed at the C&DST laboratory using the decontaminated deposit, or fresh sample to be sent if culture deposits are not available. The final result will be on consensus of the 3 tests (2 NAAT and 1 LPA). If 2 of 3 are R resistant then the final result will be R resistant; if 2 of 3 are sensitive, then the final result will be sensitive to R and the treatment will be started as based on best of three results. Further, the C&DST report whenever available may be reviewed by N/DDR-TBC committee to decide on the treatment regimen. (3).

3 TREATMENT OF DRUG-RESISTANT TB

This chapter describes

I. Evidence on newer oral drugs and regimens for treatment of drug-resistant TB
II. Shorter regimens general considerations
III. The new 6-month shorter oral regimen BPaLM for the treatment of MDR-TB
IV. Highlights the key changes in 9-11 month shorter oral MDR/RR-TB regimen,
V. Highlights the key changes in18-20 month longer oral M/XDR-TB regimen,
VI. 6-month H mono/poly DR-TB regimen.
VII. Switching between regimens
VIII. Supply chain management
IX. Management of DR-TB in special situations
X. Adverse Events
XI. Treatment interruptions and follow ups

The decisions for enrolment on the BPaLM or 9-11 month shorter MDR/ RR-TB regimen or 18 month longer M/ XDR-TB regimen will be made by the nodal DR-TB centre (NDR-TBC) or district DR-TB centre (DDR-TBC) in consultation with respective N/DDR-TBC committee, as deemed necessary, based on the results of the molecular and/ or LC-DST (a single breakpoint concentration based for FQ) for second- line anti-TB drugs (SLD) for individual patient and the eligibility criteria. All DR-TB patients need to be assessed at the time of treatment initiation as per the guidance document for differentiated TB care.

Decisions on appropriate regimens should be made considering the results of DRT/ DST, clinical assessment, patient treatment history, risk of adverse events, severity, and site of the disease. To assess regimen effectiveness, all treatment services under NTEP should be delivered including patient- centered care and support, informed decision-making process where necessary, principles of good clinical practice, active drug safety monitoring and management (aDSM), and regular monitoring of patients (12).

3.1. Evidence on newer oral drugs and regimens for treatment of drug-resistant TB

- The NIX-TB trial (13) with three drugs Bdq, Pretomanid (Pa) and Lzd [BPaL] has shown 90% treatment success rate in patients with Pre-XDR-TB (erstwhile XDR-TB) patients and MDR-TB patients with treatment intolerance or nonresponse to standard treatment. The toxic effects of Lzd (1200 mg) include peripheral neuropathy (occurring in 81% of patients) and myelosuppression (48%), although common, were manageable, often leading to dose reductions or interruptions in treatment with Lzd.
- Two more studies viz, TB PRACTECAL trial (14) and ZeNix trial (15) were published and reviewed by the WHO guidelines development group (GDG). It was recommended the optimal dosing of Lzd is 600 mg daily to ensure optimal efficacy (91% treatment success rate), with the possibility of dose reduction

in the event of toxicity or poor tolerability (peripheral neuropathy occurred in 24%, myelosuppression occurred in 2%, and the Lzd dose was modified i.e., interrupted or reduced in 13%) (11).

- TB PRACTECAL trial (14) with the 6-month BPaLM regimen – comprising Bdq, Pa, Lzd (600 mg) and Mfx – showed favourable efficacy (treatment success rate 88.7%) and safety (19.4% grade > 3 adverse events as against 58.9% in the prevailing WHO standard of care) when compared with the regimens in the control arm of the TB-PRACTECAL trial. Evidence has largely revealed that the optimal dosing of Lzd is 600 mg daily. It also alleviated previous concerns on reproductive toxicities observed in animal studies (11).
- Modified BPaL (mBPaL) trial, a pragmatic randomized clinical trial, randomized participants to the three arms with Bdq, Pa and different Lzd doses; arm 1 had Lzd 600 mg for 26 weeks; arm 2 had Lzd 600 mg for 9 weeks & 300 mg for 17 weeks and arm 3 had Lzd 600 mg for 13 weeks & 300 mg daily for 13 weeks. At the end of the treatment, the effectiveness (cure) was similar across the three arms; 93% in BPaL in arm 1, 94% in BPaL in arm 2 and 93% in BPaL in arm 3. The study observed that the median (interquartile range) time for the occurrence of anemia was 4 weeks (2-6 weeks) and peripheral neuropathy was 11 weeks (4-16 weeks). Severe anemia (grade 3 or 4) was more in patients in arm 1 (13%) compared to arms 2 & 3 (4%, 6%). The anemia events were manageable in all the three arms. Grade 3 peripheral neuropathy was observed in 7 patients in arm 1 compared to one each in arms 2 & 3. The study showed that Lzd related toxicity could be reduced with structured dose reduction of Lzd from 600 mg to 300mg after 9/ 13 weeks while maintaining similar treatment effectiveness as Lzd 600mg when given along with Bdq and Pa for 26 weeks (16).
- The study for cost-effectiveness found that in most settings, BPaL-based regimens are cost-saving (17). It has been appreciated that BPaL would reduce workload and financial burden on the health care system, expressed concerns regarding BPaL safety (monitoring), long-term efficacy, and national regulatory requirements, and stressed the importance of addressing current health systems constraints as well, especially in treatment and safety monitoring systems (18).
- The Indian Council of Medical Research (ICMR) conducted Health Technology Assessment (HTA) for cost- effectiveness of BPaLM/ BPaL treatment regimen for MDR/RR-TB and following key observations were reported:
    i. Emerging global evidence suggests that 6-month Bedaquiline containing regimens BPaL and BPaLM are cost-effective, and improve compliance and clinical outcomes in drug resistant TB patients.
    ii. As compared with currently deployed treatment protocols, the BPaL/BPaLM regimens are cost effective.
    iii. Pragmatic uptake of the above regimen could improve treatment success rate for MDR/RR-TB and free up resources for investment in other areas of TB programme.
    iv. Introduction of BPaL and BPaLM regimens in the TB elimination mission merits consideration on priority.
- Routine data from the South African NTP for a 9-11 month shorter oral MDR/RR-TB regimen containing Bdq, FQ and Lzd (600 mg) combined with other medicines used in MDR/RR-TB patients without resistance to FQ without previous exposure to SLDs was compared with the existing recommended 9-11 month, all- oral, Bdq-containing regimen (which contains Eto instead of Lzd) or longer regimens in the same group of patients. It included mostly adult patients (96%) and a high proportion of PLHIV (67%). The data showed that replacing four – six months of Eto with two months of Lzd in this regimen resulted in similar treatment efficacy and safety. The outcomes were similar, irrespective of HIV status. (11).
- Based on data reviewed from TMC207-C211 and IMPAACT P1108 trials, corresponding the use of Bdq in children aged 5–18 years and aged 0–6 years, respectively, the WHO GDG concluded that in children 0–6 years of age, cardiac safety signals were not distinct from those reported in adults. Data from pediatric MDR/RR-TB individual patient data (IPD) were analyzed descriptively (24,231 records from all six WHO regions, the majority from India and South Africa) in April 2020, including 40 children aged below six years and 68 children aged 6–12 years who received Bdq as part of DR-TB treatment.

The moderately desirable effects of Bdq in all-oral regimens for children will allow the construction of regimens that are more child- and family-friendly, with shorter durations. The WHO GDG determined that the balance between desirable and undesirable effects probably favoured the use of Bdq in children aged below six years and was probably feasible to implement (19).

- On review of data on the use of Dlm in children from cohorts 1 (age 12–17 years), 2 (age 6–11 years), 3 (age 3–5 years) and 4 (age 0–2 years) for both protocols (protocol 242–12–232 and 233), the WHO GDG noted that exposures in the 0–2 year age group were lower than those of children aged three years and older, necessitating a modelling/simulation approach to dosing. No cardiac safety signals, distinct from those reported in adults, were observed in children 0–2 years of age. However, pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e. prolongation) would be unlikely in children under three years of age, even if higher doses were used to reach drug exposures comparable to those achieved in adults. The GDG concluded that the balance between desirable and undesirable effects probably favours the intervention (19).
- The chronology of events for introduction of Pa containing regimen in India can be found in annexure 1.

3.2 General consideration for treatment of drug resistant TB

- For MDR/RR-TB, in patients aged 14 years or more, 26-39 weeks BPaLM is the first preference and in patients aged <14 years 09-11 month shorter oral is first preference based on the eligibility criteria (described in the relevant section for BPaLM and 9-11 month shorter oral MDR/RR-TB regimen) (3).
- Patients who are not eligible for the BPaLM regimen should be assessed for the eligibility of the 9-11 month shorter oral MDR/RR-TB regimen, and if found ineligible, they should be considered for longer oral M/XDR-TB regimen based on the DST pattern.
- The DR-TB regimens will be provided by the N/DDR-TBC committee in the designated public sector facilities and engaged private sector facilities once the patient has been confirmed as eligible. Each of the N/DDR-TBCs must ensure that laboratory capacity and consultancy services from various specialists are available, either in-house, supported under institutional/ state government mechanisms or through an outsourced mechanism. The engagement with private facilities as per guidance document on partnerships 2019 should also be undertaken for investigations and specialist consultations that are not available in public health facilities (20).
- Selection of the treatment regimen is to be based on comprehensive analysis of lab report for NAAT/ LPA/ LC-DST, pre-treatment evaluation, Inclusion-exclusion criteria, past h/o drug use, absolute and relative contra-indication.
- All patients are to be assessed for selection of appropriate regimen and for hospital admission using differentiated TB care approach.

3.2.1 Pre-treatment evaluation

All MDR/RR-TB patients would be subjected to a thorough pre-treatment evaluation (PTE) at the N/DDR-TBCs as per table 3.1 below.

Table 3.1: The list of the PTE for MDR/RR-TB patients

Clinical evaluation	Laboratory-based evaluation
• History and physical examination (including previous drug use, alcohol/ substance abuse, family planning methods etc) • Previous history of ATT taken, especially Bdq, Pa, Dlm and Lzd (defined as more than one month exposure) • A thorough clinical examination • Assess nutritional status [Height (m), Weight(kg), BMI] • Neurological evaluation, if required • Ophthalmic evaluation, visual acuity, and color vision test	• Random blood sugar (RBS) • HIV testing following counselling • Complete blood count (Hb, TLC, DLC, platelet count) • Liver function tests# • Renal function tests • Serum electrolytes (Na, K, Mg, Ca) • Urine pregnancy test (in women of reproductive age group) • Chest X-ray • ECG

 # HBsAG and other viral markers (Hepatitis A, C and E) to be done in case of jaundice

- A brief peripheral neuropathy screening tool, annexure-3, is to be used to assess the peripheral neuropathy (21). "Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events" 2017, by National Institutes of Health, US Department of Health and Human Services, may be referred for grades of neuropathy and anemia (22).

3.2.2 Treatment initiation

- All patients diagnosed as MDR/RR-TB using various technologies will be evaluated and initiated on an appropriate regimen with eligibility criteria as per the integrated diagnostic and treatment algorithm for DS and DR-TB.
- Once a patient is identified as per the eligibility criteria, the N/DDR-TBC committee will start the patient on BPaLM or 9-11 month shorter oral MDR/RR-TB regimen or 18-20 months longer oral regimen.
- Till Bdq is available for the use in children below five years and evidences for the use of Pa among below 14 years, the other regimens as applicable will be used.
- The decision to initiate treatment will be taken by the nodal DR-TB centre (NDR-TBC) or district DR-TB centre (DDR-TBC) in consultation with respective N/DDR-TBC committee.
- All eligible patients will be offered thorough counselling along with educational material in the local language, which will give details of the nature and duration of treatment, including information on the BPaLM or 9-11 month shorter oral MDR/RR-TB regimen or 18-20 month longer oral regimen, the need for regular treatment, possible side effects of the drugs in the regimen, the drugs which are to be avoided and the consequences of irregular treatment or premature termination of treatment. Female patients in reproductive age-group will receive additional counselling on family planning. The patient-wise box with bottles and strips for the entire course will remain under the custody of the treatment supporter for the entire duration of treatment.
- As Bdq has a longer half-life (calculated half-life is 24 to 30 hours and terminal half-life of 5.5 months due to extensive tissue distribution post stopping BDQ), any interruption in treatment may lead to early washing out of other drugs while Bdq remains in the body leading to monotherapy with Bdq with higher

risk of Bdq resistance amplification. Hence, it is strongly recommended that all treatment regimens, including BPaLM doses are to be administered under direct observation (minimum 6 days per week) by a trained treatment supporter (health care provider, community volunteer) identified by the community health officer (CHO) of the respective Ayushman Arogya Mandir (AAM, erstwhile health & wellness centre, HWC). The treatment supervision may be supplemented by suitable digital adherence monitoring technology (3). It will be preferable for the treatment supporters to accompany the patient/ contacts for the screening and follow-up visits and liaise with the clinical staff.

Monitoring indicator:
Administer at-least 85% of doses under direct physical supervision by the treatment supporter.

- It is recommended to avoid taking magnesium supplements or magnesium-containing antacids for two hours before and two hours after taking any regimen as it can bind the FQs and make them ineffective (23).

3.3 BPaLM regimen

BPaLM regimen must be the first choice of treatment in eligible patients ≥14 years age with MDR/RR- TB regardless of their FQ resistance status or HIV status.

3.3.1 Eligibility criteria

The eligibility criteria for BPaLM regimen includes.

Inclusion Criteria

i. Person with age 14 years & above with new microbiologically confirmed MDR/ RR-TB requiring a new course of treatment or probable MDR-TB who failed H mono/ poly DR-TB treatment

ii. H/o of Drug Exposure: Person with exposure of less than one month intake of Bdq, Lzd and/ or Pa in the past

or

Person with exposure of more than one month intake of Bdq, Lzd and/ or Pa and documented sensitivity to these drugs

or

Person who had not failed treatment with Bdq or Lzd containing shorter or longer regimen, and sensitivity to these drugs are documented

iii. QTcF in ECG is ≤450 ms in males and ≤470 ms in females

or

when serum electrolytes are abnormal and QTcF is >450 ms in males & QTcF is >470 ms in females in baseline ECG, after correcting the electrolytes, QTcF in repeat ECG is ≤450 ms in males and ≤470 ms in females

iv. Non-lactating women, lactating women but not breast-feeding, non-pregnant women, pregnant women with <20 or <24 weeks gestation and who is willing for medical termination of pregnancy (as per latest MTP gazette notification, as applicable)

Exclusion criteria & Contra-indications

i. Person with age below 14 years
ii. Person with documented resistance to Bdq, Lzd and/ or Pa.
iii. Person with significant liver dysfunction [LFT (Liver enzymes and/ or total bilirubin); AST/ALT>3.0 x ULN and Total Bilirubin >2.0 x ULN]
iv. People with severe forms of extrapulmonary-MDR-TB like CNS TB, spinal/ skeletal TB, or disseminated TB (miliary TB or TB with multiorgan involvement)
v. Person with significant Cardiac conduction abnormalities in the heart- including structural heart disease, syncope, long QT syndrome, AV blocks, Reentry arrhythmias etc.
    i. Person currently having uncontrolled cardiac arrhythmia that requires medication
    ii. Person with history of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalemia, family history of long QT syndrome.
    iii. Baseline QTcF is >450 ms in males & QTcF is >470 ms in females in baseline ECG, and if electrolytes are normal.

    Or

    Baseline QTcF is >450 ms in males & QTcF is >470 ms in females in baseline ECG, electrolytes are abnormal and even after correcting the electrolytes QTcF in repeat ECG, is not ≤450 ms in males and ≤470 ms in females.

Note:

- In case of extensive pulmonary TB, BPaLM regimen may be given, if eligible.
- If at baseline, the results of the serum chemistry panel, hematology or urinalysis are outside the normal reference range (including above listed parameters), the patient may still be considered if the physician judges that the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable. Hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to a patient receiving any QTc prolonging drugs.

In addition to the eligibility criteria for BPaLM, the relative contraindications, requiring careful selection of patients after a detailed history of the patient (drug, comorbidity, concurrent use of any drugs, etc.), physical assessment in combination with PTE test, are detailed in Table 3.2.

Table 3.2: Relative contraindications for BPaLM

Relative Contraindications	Notes
Concurrent use of medications that have known interactions or overlapping toxicities with BPaLM	• Use of strong inhibitors or inducers of cytochrome P450 enzyme* • Drugs that prolong the QT interval (anti-fungals, antiarrhythmics, antipsychotics etc.) • Drugs that increase serotonin levels and other serotoninergic • Monoamine Oxidase Inhibitors (MAOIs) or prior use within two weeks of treatment • Currently on serotoninergic antidepressants/ tricyclic antidepressants or prior use within three days of treatment • Concomitant use of any drug known to induce myelosuppression • If a patient requires an oral magnesium-containing substance e.g. magnesium trisilicate, magnesium sulphate this must be dosed two hours separate from the fluoroquinolone.
Severe anaemia, thrombocytopenia or leukopenia	• Haemoglobin (Hb) level < 8.0 g/dL • Platelet count < 75 000/mm3 • Absolute neutrophil count < 1000/mm3
Severe renal failure	• Serum creatinine > 3.0 × ULN • Owing to limited experience with the use of this regimen, caution should be exercised in patients with severe renal failure
Severe neuropathy	• Peripheral neuropathy of grade 3 or grade 4

ALT: alanine transaminase; AST: aspartate transaminase; ULN: upper limits of normal.

** Exceptions may be made for patients that have received three days or less of one of these drugs or substances if there has been a wash-out period before administration of Bdq to at least five half-lives of that drug or substance.*

3.3.2 Regimen, dosage, and administration

- BPaLM regimen is to be administered orally with food (avoid magnesium supplements or magnesium -containing antacids before and after 2 hrs) and adequate water intake.
- Pyridoxine supplementation has been shown to reduce the incidence of neuropathy in patients, supporting its inclusion in treatment protocols to mitigate drug-induced neuropathy. Pyridoxine to be used in the BPaLM regimen to provide added protection against neuropathy.

- The dosages of the drugs in the regimen are as follows (14,16,24,25):

i. Bedaquiline
   - Weeks one to two: 400 mg once daily
   - Weeks three to 26/39*: 200 mg three times a week; plus

ii. Pretomanid:
   - Weeks one to 26/39*: 200 mg daily; plus

iii. Linezolid:
   - Weeks one to 26/39*: 600 mg once daily; plus

iv. Moxifloxacin:
   - Weeks one to 26/39*: 400 mg once daily

** Extension criteria has been described in subsequent section.*

Pyridoxine (Pdx) to be given as per weight band:

Body weight	16-29kg	≥30 kg
Dose	50mg	100mg

- All patients aged 14 years and above would receive the above standard dosage. There is no weight band wise dosing.

3.3.3 Dose Reduction of Lzd (16):

- All the efforts are to be made to continue the regimen with Lzd 600 mg throughout the course.
  i. If Lzd 600 mg can't be continued, because of grade 03/ grade 04 toxicity, up to 09 weeks, the regimen is to be declared as treatment failed.
  ii. The dose reduction of Lzd to 300 mg, because of grade 03/ grade 04 toxicity, can be considered only after 09 weeks.
  iii. If dose of Lzd is reduced to 300 mg the period of the regimen will be extended upto 39 weeks
- In the initial days of treatment, myelosuppression due to Lzd sets earlier compared to peripheral neuropathy. If, Hb falls less than 8g/dl and responds to blood transfusion, the patient can be continued with Lzd 600 mg with intensive monitoring.

3.3.4 Regimen Change as per DST:

- Since Bdq and Lzd resistance levels in India are low, the NTEG recommended that BPaLM regimen can be initiated in all the eligible MDR-TB patients while awaiting baseline DST to these drugs.
- In case the baseline DST shows resistance to any of the Bdq / Pa/Lzd, the outcome will be declared as "Treatment regimen changed" and the patient is considered for 18-20 months longer oral M/XDR-TB regimen, after assessment at N/DDRTBC.

3.3.5 Moxifloxacin in BPaLM:

- Mfx is a part of BPaLM regimen for full course, irrespective of resistance pattern to FQ at baseline or during the course of the regimen. The following are the supporting evidence for the continuation of Moxifloxacin in BPaLM regimen irrespective of FQ resistance pattern:

A. TB PRACTECAL study:

- TB PRACTECAL trial had 3 arms including BPaLM, BPaLC, BPaL compared with the WHO standard of care. In the BPaLM arm 32/138 participants (23%) were FQ resistant and Mfx continued throughout the treatment duration in all 138 patients irrespective of FQ resistance status.

- Culture conversion: Culture conversion at 12 weeks was observed for 99/121 (82%) patients for whom conversion could be defined in the standard care group and 107/120 (89%) patients in the BPaLM group (risk difference 7.3 percentage points [95% CI −1.5 to 16.2] (26). In stage 1 of the trial, the percentages of patients with culture conversion in liquid medium at 8 weeks after randomization were 77%, 67%, and 46% in the BPaLM, BPaLC, and BPaL groups, respectively. 78 of 99 patients in the standard-care group (79%) and 85 of 96 patients in the BPaLM group (88%) had culture conversion at 12 weeks (14).
- Comparable time to culture conversion: Median time to culture conversion was 56 days (IQR 28 to 83 days) in the standard care group and 55 days (IQR 28 to 57 days) in the BPaLM group (unadjusted hazard ratio 1.38 [95% CI 1.05 to 1.81] (26).
- Low recurrence and probable protection against amplification of bedaquiline resistance: In TB PRACTECAL trial, disease recurrence was observed in 5/115 (4%) participants in the BPaLC group, 4/111 (4%) participants in the BPaL group and 1/138 (1%) participants in BPaLM group. New resistance to bedaquiline was observed in three of four isolates from the participants with disease recurrence, all were in the BPaL group; of these, an isolate from one participant also showed resistance to clofazimine (26). At week 48, there were no recurrences of tuberculosis in the BPaLM group (14). Also sustained treatment success was observed with BPaLM at 108 weeks (94%) after randomization in patients resistant to FQ (26).
- Better treatment outcome: The network meta-analysis found successful outcomes in 55/62 (89%) patients treated with BPaLM compared with 46/60 (77%) patients of those treated with BPaL (absolute risk reduction 1.15 [95% CI 0.95–1.38]) (26).
- The safety outcomes also favoured BPaLM, with lower percentages of patients with adverse events of grade 3 or higher or serious adverse events for all outcomes (at week 72, at week 108, and during treatment) (14).
- The QTcF interval at week 24 was lower in the BPaLM group than in the standard-care group and more closely resembled the QTcF in the BPaL group. The QTcF in the BPaLC group was similar to that in the standard-care group. This finding corroborates evidence suggesting that clofazimine is a primary driver of QTcF prolongation in bedaquiline-containing regimens (14).

B. US programmatic data (27)

- CDC report compares patients who were initiated on the BPaLM regimen in the USA between 2019 and 2022, with patients receiving BPaL, a regimen previously documented to have uptake in US tuberculosis programmes, as a complement to the randomised TB-PRACTECAL study.
- 84/116 (72%) patients with BPaL regimen and 29/36 (81%) patients with BPaLM regimen completed treatment
- TB relapse reported was 3% in BPaL regimen and 0% in BPaLM regimen in the above cohort.
- TB death reported was 1% in BPaL regimen and 3% in BPaLM regimen in the above cohort.

3.3.6 BPaLM regimen implementation considerations/ extension criteria/ regimen modification

i. Folllow up cultures are to be done at the month 9,13, 18, 22, 26, and 39 in case of extension. However, if patients on BPaLM show clinical deterioration or no improvement by 9 weeks, send an additional specimen for smear, rapid molecular test, C&DST to all drugs at 9 weeks.

ii. At any point, after 9 weeks, if the patient is not improving clinically or radiologically, send sputum/ EPTB specimen for C&DST and refer the patient to N/DDR-TBC.

iii. Interruptions: All possible efforts should be made to support the patient and manage the adverse events to ensure uninterrupted treatment and intake of all medicines in the regimen. However, when severe toxicity occurs, the medicine should be stopped.

a. In case of treatment interruptions and extended treatment duration to make up for missed doses, it is necessary for patients to complete the 26 weeks of prescribed doses within 30 weeks and for patients in whom treatment is extended, it is necessary to complete 39 weeks of prescribed doses within 43 weeks.

b. If above conditions are not fulfilled, the patient may be declared as treatment failed and considered for an appropriate treatment regimen change at the N/DDR-TBC.

iv. Missed Doses: Patient must complete 26 weeks (182 days) / 39 weeks (273 days) of treatment period with all core medicines i.e., B, Pa, L. In case of missed doses in BPaLM regimen, the following general guidance should be considered:

a. Patient must be resumed and complete the BPaLM course by prolonging the treatment duration for number of missed doses of any core drugs in the regimen i.e., B, Pa, L in the following conditions:

- Consecutive treatment interruption of up to two weeks or
- Non-consecutive cumulative treatment interruption of up to four weeks

In the event of treatment interruption of the regimen, re-introduction of the regimen could be considered post-cessation within 4 weeks after re-assessment of the patient by the N/DDR TBC.

b. In following conditions of missed doses of any core drugs i.e., B, Pa, L, the regimen is not resumed.

- >2-weeks of consecutive treatment interruption; or
- >4-weeks cumulative of nonconsecutive treatment interruption.

Further,

- treatment outcome to be declared as treatment regimen changed.
- the patient to be sent for clinical review and assessment at NDR-TBC to consider for 18-20 months longer oral M/ XDR-TB regimen. The outcome of only the changed regimen would be reported.

v. Dose modification of Bdq, Pa, and Mfx is not recommended during treatment.

vi. For intolerance (grade 3-4) to FQ: Drop Mfx, complete the rest of the regimen as BPaL and extend the treatment to 39 weeks.

vii. For intolerance (grade 3-4) to LZD Dose: All efforts must be made to ensure that the dosage of Lzd **600mg daily to be continued for the entire duration of treatment.**

a. Within the first 9 weeks of treatment initiation, if Lzd (600 mg daily) need to be discontinued, due to severe/ grade 03 toxicity (myelosuppression and/or peripheral neuropathy or optic neuritis), despite efforts to restart Lzd at 600 mg, then discontinue the BPaLM regimen and declare the outcome as 'treatment failed'. The patient must be sent to the NDR-TBC for further evaluation and management.

b. For grade 03/ grade 04 toxicity/ intolerance due to Lzd (600 mg daily) in patients after 9 weeks of treatment initiation: -

- All efforts must be made to ensure that the patient consumes Lzd at full or lower dose up to at least 26-39 weeks of treatment.
- The patient must be sent to the N/DDR-TBC for detailed assessment regarding the temporary interruption, reintroduction of Lzd at full dose. If reintroduction at full dose is not possible, lower dose of Lzd to 300 mg.
- In case of reduction in the dose of Linezolid, the treatment must be extended upto 39 weeks and the patient must be followed up, more frequently by the physician clinically, radiologically and microbiologically.

In general, action for Lzd toxicity should be taken in the following manner:

- for optic neuritis diagnosed at any grade, permanent discontinuation of linezolid is indicated;
- for peripheral neuropathy Grade 2, reduce the dose of linezolid to 300 mg per day with a possible drug holiday for 1-2 weeks before dose reduction;
- for peripheral neuropathy Grade 3 or 4, in most cases permanent suspension of linezolid will be needed; in some cases, after a 1-2-week drug holiday and reversion to Grade 2, the linezolid can be restarted and tolerated, provided it does not revert back to a Grade 3 or 4 (caution is warranted with this approach because patients can be left with a severe painful and disabling permanent peripheral neuropathy); and
- myelosuppression (even of Grade 3 or 4) is often reversible with a short 1-to-2-week drug holiday followed by reducing the dose of linezolid to 300 mg per day; severe anaemia may need to be treated with transfusions or erythropoietin.

An example of changes in Lzd dosing within the BPaLM regimen are given in Box 3.1 below-

Box 3.1. Example of changes in linezolid dosing within the BPaLM regimen

A patient diagnosed with MDR/RR-TB (based on NAAT results) completes four weeks of treatment with BPaLM, with 600 mg of Lzd, when she/he experience symptoms of severe paresthesia in the feet, preventing her/his from completing daily life activities. This adverse event necessitates the cessation of Lzd within the first 9 weeks of therapy. Because permanent discontinuation of Lzd was needed, the entire regimen had to be discontinued, the treatment outcome to be declared as failed and a new regimen as applicable to be started.

viii. After all efforts, in case the side-effects are worsening, the regimen must be stopped and the patient must be shifted to longer oral M/XDR-TB regimen by the N/DDR TB Center. In the event of intolerance (grade 3 or 4) to Bdq, Pa or Lzd, when re-challenge is not possible within 4 weeks of de-challenge to address the intolerance or when resistance is detected, discontinue BPaLM regimen permanently and declare the outcome as 'treatment failed. Permanent discontinuation of Bdq, Pa or Lzd because of grade 3 or 4 ADR, drug resistance at any point of time, the patient must be declared as 'treatment failure' and referred to NDR-TBC for evaluation.

ix. Patients' screening for Lzd ADR: Patients must be actively screened for any early development of Linezolid induced adverse events especially myelosuppression and neuropathy.

   a. This is done more frequently in patients with any of the following high risk groups.
      - patients with co-morbidities like Diabetes mellitus, PLHIV, history of substance abuse, hypothyroidism, and abnormal baseline electrolytes.
      - low BMI < 18.5 kg/m2
      - pre-existing anemia (Hb <8 gm/dl).
      - nutritional deficiencies
      - Lack of gain in appetite or weight or weight loss.

   b. To screen peripheral neuropathy for neuromuscular weakness and neurosensory alteration and grade, "the DAIDS Table for grading AE & peripheral neuropathy screening tool in annexure-3" is to be referred. The table 3.3 has been suggested by the national experts for screening of peripheral neuropathy which can be used at the peripheral health institution/ community level.

   c. The indicator for myelosuppression:
      - >10% drop in hemoglobin from baseline or reduction in the TLC or platelet count should, prompt more frequent follow ups and additional monitoring of the patients.

Table 3.3 Signs/ symptoms for grading of peripheral neuropathy

Sr No.	Symptoms	Grade 1 / Mild	Grade 2 / Moderate	Grade 3 / Severe	Grade 4 / Potentially life-threatening
1.	Numbness, burning, prickly (pins and needles) feelings in the feet				
2.	Feel hurt when bed covers touch the skin				
3.	Cramps in the muscles of the leg or muscle weakness.				
4.	Inability to distinguish hot or cold water.				
5.	Worsening of symptoms at night or increase in leg pain while walking.				
6.	Slipping off of footwear without knowledge				
7.	Inability to place his soles on the ground.				
8.	Frequent sores or ulcers on the feet				
9.	Diminution in the vision				

x. Once a patient is declared as 'treatment failed', all attempts should be made to take opinion of state DT3C clinics and the person to be assessed for an longer oral M/XDR-TB regimen, appropriate modifications using replacement drug sequence (3).

xi. Extension Criteria:

   a. The dose reduction of the Lzd to 300, because of grade 3-4 intolerance, can be considered after 09 weeks. If dose of Lzd is reduced to 300 mg the period of the BPaLM regimen will be extended upto 39 weeks

   b. In case of grade 3-4 intolerance to Mfx, drop Mfx, complete the rest of the regimen as BPaL and extend the treatment up to 39 weeks.

   c. Extension of treatment upto 39 weeks should be done with strict clinical evaluation and smear and culture microbiological follow-up at monthly interval.

3.3.7 Follow-up monitoring

- Once the BPaLM regimen is started, the patient will be monitored with regular clinical, bacteriological, radiological, ECG, biochemical investigations and specialist consultation if needed, as shown in table 3.4.
- Monitoring neuropathy symptoms and Hb levels may help guide Lzd dosing to avoid toxicities. A decrease in Hb level of 10% or more after four weeks of treatment initiation, may help to identify those at high risk for severe anaemia.
- All patients initiated on BPaLM regimen need to be followed up as per the prescribed schedule. The results of the above follow-up assessments would be used to guide necessary modifications or change of the regimen.

Table 3.4: List and frequency of follow-up assessments for patient initiated on BPaLM regimen

Follow-up assessments	Timeline
Duration	26 weeks (extended up to 39 weeks)
Clinical review, including weight and BMI, concomitant medication, adherence, signs/ symptoms suggesting adverse events	Monthly
CBC (with Hb, platelets)^, and ECG	Day 15, 30, then monthly till month six, and more frequently if clinically indicated
Visual acuity, and color vision test	Week 09, 13, 26 and more frequently if clinically indicated
Smear microscopy@	With culture at the C&DST lab
Culture@	Monthly from month two onwards (i.e., at month 2, 3,4,5,6). If the culture results of month four or later are positive, collect one repeat specimen immediately and send it for culture to rapidly ascertain bacteriological conversion or reversion and if the repeat specimen is culture negative, then collect and send the subsequent monthly or end-of- treatment specimen.
DST@	NAAT for H, FQ resistance detection or FL and SL LPA (Lfx, Mfx, Am, Eto) and LC-DST Bdq*, Lzd, Pa*, Dlm*, Z, Mfx 1.0 (*whenever available) if culture +ve at the end of month four, end of Rx and as and when clinically indicated during treatment
Urine pregnancy test	As and when clinically indicated
Chest X-Ray and LFT#	At the end of month three, the end of treatment, as and when clinically indicated
S. Electrolytes (Na, K, Mg, Ca)	As and when clinically indicated in case of any QTcF prolongation
Specialist (Ophthalmic, Neurological) consultation	As and when clinically indicated
Surgical evaluation	After culture conversion
Long term follow-up	At 06, 12, 18, and 24 months after completion of treatment (Clinical, CXR, Smear and C&DST, if symptomatic) and whenever the patient returns to the health system

^ Lzd containing regimen to rule out bone marrow suppression and optic neuritis

@ During clinical follow-up if the patient deteriorates or shows no improvement at month two, send an additional specimen to the C&DST lab for a smear, set up a culture if smear is positive and test for amplification of resistance. All positive cultures of this time point should be preserved for such patients. Update the test results in Ni-Kshay on the same day.

** DST whenever available*

 # HBsAG and other viral markers (Hepatitis A, C and E) to be done in case of jaundice

- Sociological/ psychological evaluation for treatment adherence, reasons for non-adherence, mental health status, quality of life, motivation and counselling are to be done. Referral services for care and rehabilitation will be provided if required.

3.3.8 Management of patients found to be ineligible for BPaLM regimen

- Patients who cannot be initiated on a BPaLM regimen will be assessed for and be managed with a 9-11 month shorter oral MDR/RR-TB regimen if eligible.
- If the patient is ineligible for both shorter regimens, then the patient will be managed with longer oral M/XDR-TB regimen with appropriate modifications based on the decision of the N/DDR-TBC committee.
- If a clinical decision support is still needed, the state/national difficult to treat TB clinic (DT3C) may be consulted on a case-to-case basis (3).

3.4 9–11-month shorter oral MDR/RR-TB regimen

- 9-11 month shorter oral MDR/R-TB regimen is to be used in eligible persons as per integrated algorithm.
- In patients 14 years or above with MDR/RR TB, BPaLM is first preference.
- The 9-11 month shorter oral MDR/RR-TB regimen is to be preferred over 18-20 months longer M/XDR-TB regimen in adults and children with MDR/RR-TB.
- Till Bdq is available for the use in children below five years, Bdq is replaced by inj Amikacin, and other modifications as per the PMDT guidelines 2021.
- Access to rapid DRT/ DST for ruling out FQ resistance is required before starting a patient.
- The program has adopted 9-11 month shorter oral regimen "with Lzd" for two months replacing "4 months of Eto" in IP phase, the rest of the medicine and duration of treatment remains same as earlier.

3.4.1 Eligibility criteria:

The eligibility criteria for the 9-11 month shorter oral MDR/RR-TB regimen is mentioned below:

i. Rifampicin resistance detected.
ii. MDR/RR-TB with FQ resistance not detected.
iii. No history of exposure to previous treatment with second-line medicines in the regimen (Bdq, Lfx, Cfz or Lzd as applicable) for more than one month (unless susceptibility to these medicines is confirmed)
iv. No extensive TB disease
v. No severe forms of extra-pulmonary MDR - TB like CNS TB, spinal/ skeletal TB (miliary TB or TB with multiorgan involvement or disseminated TB)
vi. As Eto has been replaced by Lzd in the regimen therefore the 9-11 month shorter oral MDR/RR- TB regimen with Lzd can be given to pregnant women irrespective of the gestational age with appropriate safety monitoring in consultation with the patient (3). Further, if Z resistance is detected during initial phase (IP), the patient will be switched to longer oral M/XDR-TB regimen.
vii. For the Lzd containing regimen, thyroid function test is not required in pre-treatment evaluation.
viii. InhA mutation and/or KatG mutation:
    - Lzd containing shorter oral MDR/RR-TB regimen can be given even in case of both KatG & InhA mutations are present.
    - In case of both KatG & InhA mutation, Eto containing shorter oral MDR/RR-TB regimen cannot be given
ix. Non-lactating women, non-pregnant women, pregnant women with <20 or <24 weeks gestation and who is willing for medical termination of pregnancy (as per latest MTP gazette notification), if Eto is to be used.

3.4.2 Regimen, dosage, and administration

- The regimen with Lzd or Eto would be as follows:

(2) Lzd (4-6) Lfx Cfz Z E Hh (6-9) Bdq	(5) Lfx Cfz Z E
(4-6) Lfx Cfz Eto Z E Hh (6-9) Bdq	(5) Lfx Cfz Z E

Table 3.5 The dosage of Lzd is 600 mg for 14 years & above. Table 3.5 Lzd dose for children <14years is as per weight band as given below:

Medicine	Weight-based Daily dose	Formula-tion	Weight bands among patients under 15 years old							Usual upper Daily dose
			5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg	
Linezolid	15 mg/kg od in 1–15 kg	20 mg /mL susp	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	600 mg
	10–12 mg/kg od in >15 kg	600 mg tab	0.25	0.25	0.25	0.5	0.5	0.5	0.75	

- Clinical and haematological monitoring are crucial to detect early Lzd-associated AEs, particularly sudden or significant drop in Hb(>10%), neutrophils or platelets.
- If sputum smear microscopy is positive by the end of the month 04, then FL-LPA and SL-LPA, culture & DST should be offered and the IP should be extended. IP can be extended to month 05 or 06 based on smear results at the end of month 04 or 05 of treatment. This will be done for a maximum of 2 months (i.e., total duration of IP is not more than 6 months).
- If additional resistant to Z is detected in the baseline sample on C&DST or FQ/InhA & KatG mutation is detected in month 04 sample, the patient needs to be reassessed at N/DDR-TBC for stopping shorter oral Bedaquiline-containing MDR/RR-TB regimen and initiation of longer oral M/XDR-TB regimen, immediately on receiving the report

Table 3.6 Dosage of drugs 9-11 month shorter oral MDR/RR-TB regimen for adults

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	High dose H (H^h)	300 mg	600 mg	900 mg	900 mg
2	Ethambutol (E)	400 mg	800 mg	1200 mg	1600 mg
3	Pyrazinamide (Z)	750 mg	1250 mg	1750 mg	2000 mg
4	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
5	Bedaqulline (Bdq)	Week 0-2 Bdq 400 mg daily Week 3-24: Bdq 200 mg 3 times per week			
6	Clofamizine (Cfz)	50 mg	100 mg	100 mg	200 mg
7	Ethionamide (Eto)*	375 mg	500 mg	750 mg	1000 mg
8	Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

**Drugs can be given in divided doses in a day in the event of intolerance*

3.4.3 Baseline and follow-up monitoring

While using the 9-11 month shorter oral MDR/RR-TB regimen with Lzd, the following modification would be considered in baseline and follow up monitoring:

- Ophthalmic evaluation, including visual acuity and colour vision test, need to be done at baseline and week 09, 13, 26 and more frequently if clinically indicated.
- CBC, including Hb and platelets, needs to be done at baseline followed by week 2, week 4 and week 8
- If Eto is not used, there would be no need for monitoring TSH
- Repeat NAAT for H, FQ, SLI, Eto resistance detection or FL and SL LPA (Lfx, Mfx, Am, Eto) and LC DST (Mfx 1.0, Lzd, Z, Bdq, Pa*, Dlm*) (*whenever available) if culture is positive at the end of month three or later and end of treatment or smear is positive at the end of IP, end of extended IP and end of treatment

3.4.4 Regimen modification

Based on the recent evidence, the following regimen modifications are permissible in the modified 9-11 month shorter oral MDR/RR-TB regimen with Lzd (23):

i. Bdq is usually given for six months but can be extended to 11 months, particularly if IP is extended from four to six months due to a positive sputum smear result at month 4.

ii. Lzd is only given for two months (instead of 4-6 months of Eto). In case of missed doses of Lzd upto 14 days, the missed doses may be added at the end of 2 months if resistance to FQ, Hh, Z has been ruled out.

iii. To reduce the severity of AEs, Lzd dose should not be reduced to less than 600 mg.

iv. In case of Lzd intolerance leading to permanent discontinuation of Lzd 600 mg within the initial two months period, replace Lzd with four-six months of Eto to complete the regimen, Suppose person has consumed Lzd for six weeks and develops intolerance, Eto needs to be started. The period for Eto will be 04 months minus 6 weeks, i.e period of Eto (4 months) minus the period of Lzd(6weeks) consumed at the time of replacement. Still if the regimen cannot be continued because of any reason, declare the outcome as “treatment failed” and switch to longer oral M/XDR-TB regimen without Lzd after reassessment.

v. If, for any reason, a patient is unable to tolerate Z or E, then drop one (but only one) of these drugs during CP and complete the treatment duration. If two or more of these drugs or any of the other drugs (Bdq, Lfx/Mfx, Lzd/Eto, or Cfz) are stopped due to intolerance or emergence of drug resistance, declare the outcome as “treatment failed” and switch the patient to longer oral M/ XDR-TB regimen after reassessment.(3).

3.5 18-20 months longer oral M/XDR-TB regimen

- (6 or longer) Bdq (18-20) Lfx Lzd Cfz Cs
- To be given to eligible person as per integrated algorithm in chapter 2.
- The patients who cannot be initiated on BPaLM or 9-11 month shorter oral MDR-TB regimen due to reasons of ineligibility, additional resistance, intolerance, non-availability of any drug in use or emergence of exclusion criteria will be managed with longer oral M/XDR-TB regimen modified in accordance with the replacement sequence.
- After month 06 of treatment, the patient must be reviewed based on month 05 culture results. If month 05 culture result is not available at the end of month 06, decision to taper the dose of Lzd to 300 mg will be based on month 04 culture result. If the month 05 or 04 culture result (whichever applicable) remains positive, after initial 06 months, Lzd 600 mg may be extended by one month and maximum for two months based on month 06, month 07 culture reports and clinical/radiographic response. If the 8th month culture is positive, declare the outcome as treatment failed, subject the culture isolate to FL-LPA, SL-LPA and C&DST. If any additional resistant to Group A, B or C drugs in use is detected, the patient needs to be reassessed at N/DDR-TBC for modification of longer oral M/XDR-TB regimen immediately on receiving the report.

- The duration of Bedaquiline is limited to 6 months. Extension beyond 6 months is to be considered in patients in whom an effective regimen cannot otherwise be designed if only 2 of 5 drugs are available from Groups A & B and adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST.
- Maximum duration of treatment is not more than 20 months.
- Till the Bdq use is approved for use in children below five years in India, the existing guideline for management of MDR TB in children below five years will be followed, Bdq is replaced by Dlm)
- Repeat NAAT for H, FQ, SLI, Eto resistance detection or FL and SL LPA (Lfx, Mfx, Am, Eto) and LC-DST Bdq*, Lzd, Pa*, Dlm*, Z, Mfx 1.0 (*whenever available) if culture is positive in sample collected at the end of month 06 or any time beyond.
- For XDR-TB patients the duration of longer oral XDR-TB regimen would be for 20 months.(3).

Table 3.7 Dosage of M/XDR-TB drugs for adults in longer oral M/XDR-TB regimen (with replacement drugs)

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
2	Moxifloxacin (Mfx)	200 mg	400 mg	400 mg	400 mg
3	High dose Mfx (Mfxh)	400mg	600mg	800mg	800mg
4	Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			
5	Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
6	Cycloserine (Cs)[3]	250 mg	500 mg	750 mg	1000 mg
7	Linezolid (Lzd)	300 mg	600 mg	600 mg	600 mg
8	Delamanid (Dlm)	50 mg twice daily (100 mg) for 24 weeks in 6-11 years of age 100 mg twice daily (200 mg) for 24 weeks for ≥12 years of age			
9	Amikacin (Am)[1]	500 mg	750 mg	750 mg	1000 mg
10	Pyrazinamide (Z)	750 mg	1250 mg	1750 mg	2000 mg
11	Ethionamide (Eto)[3]	375 mg	500 mg	750 mg	1000 mg
12	Na - PAS (60% weight/vol)[2,3]	10 gm	14 gm	16 gm	22 gm
13	Ethambutol (E)	400 mg	800 mg	1200 mg	1600 mg
14	Imipenem-Cilastatin (Imp-Cln)[3]	2 vials (1g + 1g) bd (to be used with Clavulanic acid)			
15	Meropenems (Mpm)[3]	1000 mg three times daily (alternative dosing is 2000 mg twice daily) (to be used with Clavulanic acid)			
16	Amoxicillin-Clavulanate (Amx-Clv) (to be given with carbapenems only)	875/125 mg bd	875/125 mg bd	875/125 mg bd	875/125 mg bd
17	Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

[1] *For adults more than 60 yrs of age, dose of SLI should be reduced to 10mg/kg (max up to 750 mg)*

[2] *Patients receiving PAS with 80% weight/volume the dose will be changed to 7.5gm (16-29 kg); 10 gm (30- 45 Kg); 12 gm (46-70 Kg) and 16 gm (>70 kg)*

[3] *Drugs can be given in divided doses in a day in the event of intolerance*

3.6 Isoniazid (H) mono/poly drug-resistant TB regimen

- Regimen - (06) LxREZ, to be given to eligible persons as per integrated algorithm in chapter 2.
- H mono/poly DR-TB regimen is of 06 or 09 months with no separate IP/CP. In exceptional situations of unavailability of loose drug R or E or Z, the use of 4 FDC (HREZ) with Lfx loose tablets may be considered as an option for starting the H mono/poly DR-TB regimen.
- It can be extended directly to 9 months in certain conditions. In patients with extensive disease; uncontrolled comorbidity; extra- pulmonary TB; if smear at the end of month 4 is found positive and when regimen is modified, the treatment may be directly extended to 9 months. There would be no monthly extensions in this regimen.
- The patients not responding or failing in the H mono/poly DR-TB regimen demonstrating & no additional resistance to R will be considered as 'probable MDR TB case' and further evaluated for treatment with the MDR-TB regimen in the preferred order of BPaLM if eligible, 9-11 month shorter oral MDR/RR-TB regimen if eligible or longer oral M/ XDR-TB regimen with appropriate modification as per the programme guidelines.

Table 3.8 Dosages for drugs used in H mono/poly DR-TB regimen by weight bands for adults

S.N	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	Rifampicin (R)	300mg	450mg	600mg	750mg
2	Ethambutol (E)	400 mg	800 mg	1200 mg	1600 mg
3	Pyrazinamide (Z)	750 mg	1250 mg	1750 mg	2000 mg
4	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg

Table 3.9 Replacement sequence of drugs to modify Hr-TB regimen

Situation	Sequence of using replacement drugs
1. If Lfx or Z can't Be Used	Replace with Lzd. If Lzd also cannot be given, replace with Cfz* + Cs.
2. If both Lfx and Z can't be used	Add 2 drugs of the 3 – Lzd, Cfz*, Cs in order of preference based on resistance, tolerability & availability.
3. If R resistance	Switch to appropriate shorter or longer oral regimen.

**whenever DST is available*

3.7 Switching between treatment regimens

This section describes the management of patients while switching between shorter and longer regimens (23).

- Patients who are required to be shifted from BPaLM or 9-11 month shorter oral MDR/RR-TB regimen to longer oral M/XDR-TB regimen due to reasons of resistance, tolerability, availability, Interruptions and the emergence of exclusion criteria, need to be re-evaluated for necessary modification of longer oral M/XDR-TB regimen and initiated on a full course of longer oral M/XDR- TB regimen after discussion with state difficult-to-treat TB clinic.
- Similarly, patients who are placed on a longer oral M/XDR-TB regimen based on the history of exposure to SLDs for more than one month awaiting DST results and later found to be eligible for the BPaLM or 9-11 month shorter oral MDR/RR-TB regimen (and in whom resistance is not detected on baseline specimen to H, i.e. both InhA and KatG or to FQ or Z, Bdq, Pa*, Dlm*) can be switched to any of these shorter regimens, provided that treatment has not lasted for more than one month. If patients are

switched in this way, the BPaLM or 9-11 month shorter oral MDR/RR-TB regimen is given for the full duration without any changes to its composition or duration.

- If a new episode of treatment is being started while switching over from BPaLM or 9-11 month shorter oral MDR/RR-TB regimen to longer oral M/XDR-TB regimen or vice versa, and if Bdq is sensitive or the patient is not exposed to Bdq for more than one month, Bdq needs to be continued in the new regimen till the treatment duration is completed.
- At the time of switching between regimens, if the loading dose of Bdq (first 14 days)
  i. is still ongoing with no dose interruption, then complete the loading dose and shift to the thrice-weekly doses after 14 days to complete the treatment duration.
  ii. is over, there is no need to repeat the loading dose. Start Bdq with a fresh bottle/strip with the thrice-weekly doses along with the first dose of other medicines in the new regimen and continue the thrice-weekly doses to complete the treatment duration.
- In all the above situations, the remaining drugs (except a bottle of Bdq) of the regimen stopped should be returned for reconstitution, and a new box of the changed regimen should be initiated.
- In such patients with a change in regimen from BPaLM or 9-11 month shorter oral MDR/RR-TB regimen to longer or vice-versa in the initial months either due to delay in receiving the baseline DST results or before any definitive treatment outcome can be applied, the outcome the "Treatment regimen changed" needs to be reported. The patient needs to be removed from the denominator of the previous regimen while assessing the treatment outcome.

3.8 Supply chain management of anti-TB drugs and logistics

This section describes procedures and supply chain management of second-line anti-TB drugs.

3.8.1 Drug procurement

NTEP will supply patient courses of drugs for the DR-TB regimens to the respective treatment initiating sites through the respective state drug store (SDS), district drug store (DDS), TB unit drug store (TUDS) along with the routine supply of rest of the drugs. The procurement and supply management (PSM) will be through the regular mechanisms of NTEP, like other FL and SLDs, and will be monitored using Ni- Kshay (https://nikshay.in/) / Ni-Kshay Aushadhi (https://nikshayaushadhi.in/) online portals.

3.8.2 Supply chain management

- The drugs of the DR-TB regimens will be supplied to the SDSs, DDSs and subsequently to identified treatment initiating sites (DR-TB centres) through NTEP as a part of regular drug supply.

3.8.2.1. BPaLM regimen

- Pa 200 mg tablet is packaged in either white, round, high-density polyethylene bottles with polypropylene child-resistant closure or child-resistant blister packages consisting of a polyvinyl chloride film with foil and paper backing.
- The tablets dispensed outside the container should be stored in a tight, light-resistant container with an expiry date that should not exceed three months. It will have a shelf-life of 24 months and will need to be stored at 25 °C (15–30 °C).
- BPaLM regimen will be issued as a complete box containing 26 weeks course. One Bdq bottle contains 24 weeks course of 100 mg x 188 tablets plus 12 loose tablets or Bdq 100 mg is available in strips 10 tablets in a single strip, thus leading to a need of 20 strips to complete the 26 weeks course, One Pa bottle contains 200 mg x 26 tablets & Lzd is available in 600 mg X 10 tablets per strip, and Mfx is available in 400 mg X 10 tablets per strip.

- Since there are no weight bands, the patient-wise boxes (PwB) with 26 weeks' complete duration of the drugs in the regimen will be prepared by the SDS and issued to the DDS as per the stocking norms and subsequently to identified treatment initiating sites (DR-TB centres) on a caseload basis. The composition of a PwB for the entire BPaLM course of 26 weeks is given in table 3.10, and for its extension of 27-39 weeks (13 weeks) is given in table 3.11.

Table 3.10: Composition of one PwB for the entire BPaLM course of 26 weeks

Drug	Strength	Total tablets	No. of bottles/ strips/ tablets
Bedaquiline (Bdq)	100 mg	200	One bottle plus 12 loose tablets /20 strips
Pretomanid (Pa)	200 mg	182	7 bottles / 19 strips
Linezolid (Lzd)	600 mg	182	18 strips plus 2 tablets
Moxifloxacin (Mfx)	400 mg	182	18 strips plus 2 tablets
Pyridoxine (Pdx)	50/100 mg	182	18 strips plus 2 tablets

- PwB has a Bdq pouch with 12 tablets (which needs to be taken for the first 3 days of loading doses) and a Bdq bottle with 188 tablets. The batch number and expiry date are to be mentioned on the pouch.
- Pyridoxine (Pdx) will be administered for the entire duration of treatment.
- The complete PwBs will be stored at the DDS and issued as per the monthly case load basis to the N/DDR TBC respectively. At the time of treatment initiation, the N/DDR TBC will open a fresh complete PwB to initiate the treatment with using Bdq loose drugs available from the zip-lock pouch for the first three days (12 loose tablets) and the rest of the drugs directly from the PwBs.
- If the treatment is initiated on an out-patient basis, the first dose of all medicines will be given under observation at the N/DDR TBC, and the rest of the PwB will be provided to the treatment supporter or the patient. The patient is counselled to take 2nd and 3rd day dose from the pouch (pouch has 12 tablets for 3 days). Further treatment supporter and the patient will be directed to utilize remaining Bdq doses from the Bdq bottle provided in the PwB from day four onwards to continue the Bdq daily loading dose upto day 14 and shift to thrice-weekly dose from day 15 till the end of 26 weeks.
- Pa (200 mg), Lzd (600 mg) and Mfx (400 mg) are to be taken as one tablet per day for the entire duration of treatment.
- After treatment initiation, respective DTO to be informed by the N/DDR-TBC and sr. DR-TB TB-HIV supervisor/ STS is responsible for handing over treatment box from the patient/relative to the trained treatment supporter.
- If the N/DDR-TBC directs to reduce the dose of Lzd 300 mg once daily dose, half a tablet of 600 mg will be consumed by the patient, and the remaining half to be discarded.
- In case of an extension of treatment beyond 26 weeks, an additional PwB to cover the drug requirement from 27-39 weeks (13 weeks) will be issued from the DDS based on the decision conveyed by N/DDR-TBC. These additional drug requirements will be covered using loose drugs supplied from SDS to DDS and may be adjusted against the drugs returned from the patients who died, LTFU or whose regimens were changed.
- The patient should be encouraged to submit empty bottles to the health facility and eventually store them at DDS. If required, a new bottle of Bdq or Pa may be opened for reconstitution.

Table 3.11: Composition of One extension PwB for the BPaLM course of 27-39 weeks (13 weeks)

Drug	Strength	Total tablets	No. of bottles/ strips/ tablets
Bedaquiline (Bdq)	100 mg	78	One reconstituted bottle with 78 tablets / 8 strips
Pretomanid (Pa)	200 mg	91	Three full bottles (26 tablets per bottle) and one reconstituted bottle with 13 tablets
Linezolid (Lzd)	600 mg	91	9 strips plus one tablet
Moxifloxacin (Mfx) (if indicated)	400 mg	91	9 strips plus one tablet
Pyridoxine (Pdx)	50/100 mg	91	9 strips plus one tablet

- In case the patient has been continued BPaL regimen, all Mfx (400 mg) tablets will be removed by the SDS/DDS before issuing the PwB or by the respective treatment supporter/supervisor from the ongoing PwB during an immediate home visit and the patient as well as treatment supporter informed about the change in the daily dosing. The remaining Mfx (400 mg) tablets will be returned to the concerned DDS/SDS for reconstitution. The change should be reflected in the dispensation module of Ni-Kshay by the N/DDR-TBC or concerned treatment supervisor as per advice of the N/DDR-TBC.

3.8.2.2 9 -11 month shorter oral MDR/RR-TB regimen

- The constitution of the IP box of the 9-11 month shorter oral MDR/RR-TB regimen will be the same as detailed in respective section (3), except replacement of four months of Eto with two months of Lzd in the IP, as applicable. Thus, 63 tablets of Lzd (600 mg) to cover the initial nine weeks are to be added to the initial monthly PwBs in place of the entire quantity of Eto(3).
- A child-friendly formulation of Bdq (20 mg scored uncoated dispersible tablet [DT]) is approved by DCGI for children and adults. Indirect bioequivalence testing of Bdq 20 mg DT child friendly and Bdq 100 mg adult formulations showed that both tablets have the same bioavailability and can be used interchangeably at the same total dose. Findings from the Bdq crush study also showed that the bioavailability of Bdq tablets suspended in water was the same as for tablets swallowed whole (28)(29).
- If any regimen modification is advised by N/DDR-TBC in accordance with section 3.4.4., the patient as well as treatment supporter/supervisor must be informed about the change in the daily dosing while the next month's PwB will be modified and issued by the respective DDS/SDS for the respective patient. The remaining drugs will be returned to the concerned DDS/SDS for reconstitution by the treatment supporter/supervisor. The change should be reflected in the dispensation module of Ni-Kshay by the N/DDR-TBC or concerned treatment supervisor as per the advice of the N/DDR-TBC.

3.8.2.3 Longer oral M/XDR-TB regimen

- Patients who cannot be initiated on BPaLM or 9-11 month shorter oral MDR-TB regimen due to any reasons will be managed with longer oral M/XDR-TB regimen modified in accordance with the replacement sequence.
- PwBs of the longer oral M/XDR-TB regimen with appropriate modifications will be prepared and issued by DDS to the concerned N/DDR TBC (3).
- Delamanid 25mg DT was approved by DCGI for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children, and infants with a body weight of at least 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (30). However, adult Dlm tablets can be split, crushed or dissolved to ease administration in children without potentially altering bioavailability (28)(31).

- All the drugs in the PwB issued to be consumed by the patient as per the dosing schedule of the respective regimen till the end of treatment. The patient should be advised to visit the N/DDR-TBC for end of treatment evaluation and further actions including updating the treatment outcome on Ni-Kshay.
- If MERM boxes are being used, the empty box and the device need to be returned to the concerned DDS/SDS for resetting and reissuing the box to a new patient.

3.9 Management of special situations

This chapter deals with the management of patients eligible for BPaLM or 9-11 month shorter oral MDR/RR-TB regimen and longer oral M/XDR-TB regimen in special populations.

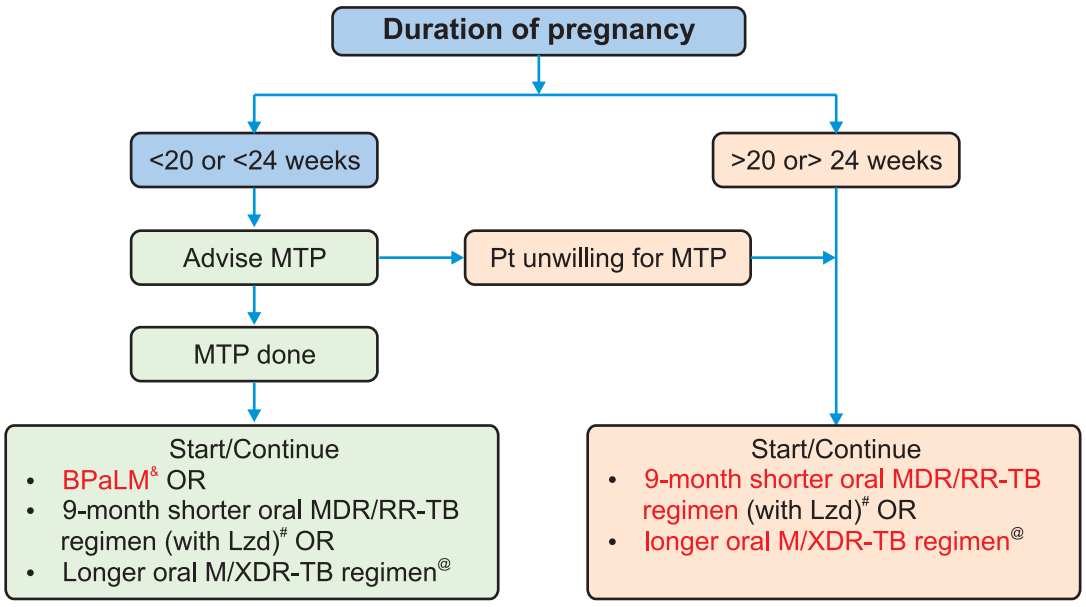
3.9.1 Pregnancy and lactation

- Pregnancy is not a contraindication for the treatment of drug-resistant TB but poses a great risk to both the mother and foetus.
- SLIs are contraindicated throughout the pregnancy due to their effect on the 8th cranial nerve of the foetus. Eto is contraindicated during the first 32 weeks of pregnancy due to teratogenic effects.
- There is an experience of using Lzd during pregnancy. For pregnant and lactating women, it is therefore recommended to use the regimen with Lzd instead of Eto in the 9-11 month shorter oral MDR/RR-TB regimen.
- The use of Bdq in pregnancy has been shown to be associated with infants born with a lower mean birth weight when compared with infants whose mothers did not take Bdq; however, when infants were followed up over time, no other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in infants until one year of age were observed (32).
- Pa is not recommended during the lactating period unless the mother is willing to replace breastfeeding with formula feed. Thus, the recommendation of the BPaLM regimen doesn't apply to pregnant and breastfeeding women. It is prudent to solicit the opinion of an obstetrician while treating such patients.
- All women of childbearing age who are awaiting results of C&DST as well as those receiving DR-TB treatment, should be advised, and counselled intensively to use birth control measures because of the potential risk to both mother and foetus. It should be remembered that oral contraceptives might have decreased efficacy due to vomiting and drug interactions with DR-TB drugs.
- All women of childbearing age should be tested for pregnancy as part of the PTE and whilst on treatment. DR-TB patients found to be pregnant prior to treatment initiation or whilst on treatment must be evaluated in consultation with an obstetrician, considering factors such as risks and benefits of DR-TB treatment; severity of DR-TB; gestational age, and potential risk to the foetus.
- In pregnant women, strict counselling needs to be done for MTP, especially regarding the risk of delaying treatment, potential effects of new drugs on the foetus, including foetal abnormalities (if MTP is not opted) and the need for more intense maternal-foetal-neonatal follow-up. Appropriate counselling and an informed decision-making process for consent need to be undertaken in each case with electronic data management in Ni-Kshay, including aDSM.
- Pregnant women with MDR-TB should be jointly managed by an obstetrician and a pulmonologist or physician at DR-TBC. Management of DR-TB patients who are pregnant prior to initiation of treatment or whilst on treatment is based on the duration of pregnancy and regimen being considered as follows:

1. BPaLM regimen may be considered if the pregnant women with <20 or <24 weeks gestation and who is willing for medical termination of pregnancy (as per latest MTP gazette notification)
2. As Lzd is an option in place of Eto, all pregnant women would be eligible for the 9-11 month shorter oral MDR/RR-TB regimen after considering other eligibility criteria. Eto based regimen may be considered after 32 weeks' gestation, if Lzd based regimen can't be used.

3. If the pregnant woman is not eligible for both above regimens, the 18-20 month longer oral M/XDR-TB regimen may be considered. Modify regimen if one or more drugs cannot be used due to reasons of resistance, tolerability, contraindication, availability etc.
   - in the order of Z E PAS
   - Eto may be considered after 32 weeks' gestation, if required
   - Am may be considered in post-partum period only. Am can not be considered as a replacement drug in the final 12 months of treatment

- In women of reproductive age who have been initiated on BPaLM or 9-11 month shorter oral MDR/ RR-TB regimen or longer oral M/XDR-TB regimen and who become pregnant, the risk to the mother and foetus needs to be explained clearly. If the pregnancy is < 24 weeks, the decision to continue the BPaLM regimen would depend upon the willingness of the patient to opt for an MTP as per MTP (amendment) act, 2021.
- Lactating mother should be encouraged for breastfeeding, if she is smear/ culture negative and not on Pa containing regimen.
- If she is unwilling for MTP or has a pregnancy > 24 weeks duration, she needs to be treated with or shifted from BPaLM (if already initiated), based on eligibility and in the given order of preference, to 9-11 month shorter oral MDR/ RR-TB regimen or longer oral M/XDR-TB regimen. In such patients, the risk to the mother and foetus needs to be explained clearly, and the pregnant DR-TB patients need to be monitored carefully, both in relation to the treatment and progress of the pregnancy. This approach should lead to good results since the patient should be smear/culture negative at the time of parturition, and the mother and infant do not need to be separated.



& *Regimen: 6-9 Bdq, Pa, Lzd, Mfx*
# *Regimen: 4-6 Bdq, (6m or longer) Lfx/Mfx, Cfz, Lzd (2m), Hh, Z, E / 5 Lfx/Mfx, Cfx,Z, E Lzd can be replaced with Eto if required post MTP or only after 32 weeks' gestation*
@ *Regimen: 18-20 Lfx, Bdq (6m or longer) Lzd, Cfz, Cs. Modify regimen if one or more drug cannot be used due to reasons or resistance, tolerability, contraindication, availability etc*
- *in the order or Z E PAS*
- *Eto may be considered after 32 weeks' gestation, if required*
- *Am may be considered in post-partum period only. Am will not be started in the final 12 months of treatment*

- The following additional monitoring is recommended for pregnant women managed with any MDR-TB regimens:
  i. These mothers should deliver in a tertiary care institute or at least at a place where a pediatrician is available.
  ii. CBC, including Hb, need to be monitored monthly and more frequently if clinically indicated.
  iii. USG foetal anomalies scan at 18 weeks and USG growth scan at 32 weeks. A fetal echo is to be done only if there is an abnormality on the scan.
  iv. More frequent ECG and serum electrolytes may be considered as clinically indicated.
  v. The option of 2nd trimester MTP can be considered if the mother is fit for it, based on a fetal scan of 2nd trimester.
  vi. Strict aDSM is to be done.
  vii. ANC registration and obstetrician follow-up are to be done regularly.
  viii. If Eto is considered in the regimen, and if the basal TSH in PTE is deranged, then TSH must be done monthly and once it is normal (less than 2.5), then quarterly during treatment. Check the infant for early evidence of hypothyroidism.
  ix. In case para-aminosalicylic acid (PAS) and Eto are given (which cause hypothyroidism) and Lzd (which causes myelosuppression) to a newborn who has been exposed to a cocktail of drugs, certain baseline investigations at birth like CBC and TSH should be done.

3.9.2 Children

- Safety and effectiveness of BPaLM regimen with Pa in children < 14 years have not been established. Thus, children below 14 years should be treated with 9-11 month shorter or longer oral regimens as per eligibility in consultation with the paediatrician available or linked to the N/DDR-TBC.
- Bdq has been approved by the regulatory authority for use in children 5 years and above. Bdq may be used in shorter or longer regimen in children less than 5 years of age whenever approved by the regulatory authority.

3.9.3 Older people

- Clinical studies of the combination regimen of Pa, Bdq, and Lzd did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Hence, health status and underlying co-morbidities must be assessed carefully before considering patients aged 65 years and over for BPaLM regimen, and if included, they would need much closer monitoring.

3.9.4 People living with HIV

Management of DR-TB patients in people living with HIV should be done in consultation with ART centre. BPaLM regimen can be given to eligible MDR/RR-TB and Pre-XDR-TB regardless of their HIV status and CD4 count provided they fulfil all other eligibility criteria. However, care should be taken when CD4 counts are below 100 cells/mm3. It is important to consider drug–drug interactions when administering TB and HIV medications in combination with respect to the following points.

i. Efavirenz induces metabolism of Bdq, so its co-administration with Bdq may result in reduced Bdq exposure and loss of activity; therefore, co-administration is to be avoided. Efavirenz also reduces Pa exposures significantly; therefore, an alternative antiretroviral agent (potentially dolutegravir (DTG), although there is currently insufficient evidence for this) should be used if the BPaLM regimen is considered.

ii. Ritonavir may increase Bdq exposure, which could potentially increase the risk of Bdq-related adverse reactions; however, increased risk has not been noted in studies administering both drugs concurrently. Individuals who are prescribed both Bdq and ritonavir should be monitored closely for adverse events, including QTc prolongation.

iii. Zidovudine (no longer commonly used or recommended for HIV treatment in adults and adolescents) should be avoided, if possible, because both zidovudine and Lzd may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity (23).

These cases should be managed through consultation between the ART Centre and DR-TB Centre.(3).

3.9.5 People with renal insufficiency

- Generally Bdq, Lnz and Mfx are considered safe in renal insufficiency
- Renal insufficiency may be caused by TB infection itself or by previous use of aminoglycosides. Patients with renal insufficiency and initiated on BPaLM or 9-11 month shorter oral MDR/RR-TB regimen or longer oral M/XDR-TB regimen may develop severe anaemia and electrolyte imbalance.
- Patients with renal insufficiency should be carefully evaluated before the start of any MDR/RR-TB regimen if the PTE rules out the exclusion criteria. Owing to limited experience with the use of this regimen, caution should be exercised in patients with severe renal failure.

3.9.6 People with liver disorders

- In various DR-TB regimens under NTEP, R, H, Z, PAS, Eto, Bdq and Pa are potentially hepatotoxic drugs. Hepatitis rarely occurs with the FQs.
- The potential for hepatotoxicity is increased in the elderly, alcoholics, malnourished and in patients with pre-existing liver disease. In general, most SLDs can be safely used in the presence of mild hepatic impairment, as they are relatively less hepatotoxic than FLDs.
- For patients on BPaLM regimen, routine liver function test (LFT) is recommended at month three in all patients and then as and when clinically indicated. DR-TB patients having deranged LFT during PTE should be strictly monitored and more frequently as clinically indicated while on treatment. Once a patient on SLDs develops hepatitis, other etiologies should be excluded, such as viral hepatitis, alcoholic hepatitis, drug- induced hepatitis by non-TB drugs etc.
- Close monitoring of liver enzymes is recommended, and the drugs may need to be stopped if significant liver inflammation is apparent.

3.9.7 People with diabetes mellitus

- Blood sugar levels may be difficult to control in patients with MDR/RR-TB and diabetes, and insulin may be required to gain adequate blood sugar control during treatment.
- Patients with diabetes are also at increased risk of peripheral neuropathies, which may be further exacerbated following exposure to Lzd and Hh. These patients must be counselled to report symptoms of peripheral neuropathies early because such symptoms may necessitate a change in regimen – either to the Eto-containing 9-11 month shorter oral MDR/RR-TB regimen (bearing in mind this will still include Hh in the IP), or longer oral M/XDR-TB regimen without Lzd.
- The concomitant use of metformin at high doses and Lzd may increase the risk of lactic acidosis. Also, the long-term use of Lzd, Hh and cycloserine (Cs) in patients with diabetes can lead to an increased risk of peripheral neuritis. Baseline optic neuropathy or retinopathy or maculopathy may worsen after Lzd use; hence, eye evaluation is recommended before and during treatment. Regarding potential baseline renal damage in diabetics, Am or Sm should be used with caution. Patients with DR-TB and diabetes may need close follow-up and support, with quick identification of drug–drug interactions and adverse events (23).

3.9.8 People with anaemia

- Patients with TB commonly have anemia of chronic disease. Many patients with TB also suffer with nutritional deficiencies, and low Hb may also be a result of iron deficiency and low iron stores. This deficiency may resolve naturally once effective TB treatment (even including Lzd) leads to resolution of TB symptoms and improvement in the patient's anaemia, diet and appetite.
- Extended use (≥ 2 weeks) of Lzd has been associated with reversible myelosuppression and requires intensive monitoring.
  - Therefore, the Lzd-containing regimen must not be offered to patients with a pretreatment serum Hb below 8 g/dL that cannot be rapidly corrected (i.e. with blood transfusions) before starting MDR/RR- TB treatment.
  - Some patients respond well to an initial blood transfusion that raises their Hb above 8 gm/ dL and allows them to at least start a Lzd-containing regimen. Lzd will not necessarily cause myelosuppression in patients with baseline anaemia.
  - Although blood transfusions may help to reverse anaemia following withdrawal of Lzd, they may not resolve Lzd-induced myelosuppression with ongoing exposure to the drug. Therefore, if Lzd toxicity leads to a drop in Hb below 8 g/dL during the first two months of treatment, Lzd should be withdrawn, and the regimen switched appropriately.
  - More research is needed on the role of iron supplementation to treat anaemia during MDR/RR- TB treatment; however, oral supplementation of iron is often not well tolerated and is not immediately effective at the start of treatment, at a time when the pill burden can be overwhelming and the risk of multiple drug side- effects is high (23).
- Similarly, owing to the morbidity associated with severe neutropenia and thrombocytopenia, the Lzd-containing regimen is not suitable in patients with neutrophils below 0.75 × 109/L (or 750/mm3) or platelets below 150 × 109/L (or 1,50,000/mm3) before starting treatment. Some patients respond well to an initial blood transfusion that raises their Hb above 8 gm/ dL and allows them to at least start a Lzd-containing regimen. Lzd will not necessarily cause myelosuppression in patients with baseline anaemia, although a baseline Hb below 10.5 g/dL has been reported as a risk factor for Lzd-induced anaemia.
- If Lzd toxicity leads to a drop in Hb below 8 g/dL during the first two months of treatment, Lzd should be withdrawn, blood transfusions may help to reverse anaemia. The Lzd reintroduction may be tried after Hb is above 9 g/dL. More research is needed on the role of iron supplementation to treat anaemia during MDR/RR- TB treatment; however, oral supplementation of iron is often not well tolerated and is not immediately effective at the start of treatment, at a time when the pill burden can be overwhelming and the risk of multiple drug side- effects is high (23).

3.10 Adverse events

- Identification of adverse drug reactions (ADR) should be a part of patient interaction at the time of treatment initiation as well as treatment supporters should be involved in sensitization sessions for common ADR. N/DDR- TBC initiating the treatment should be informed immediately once any ADR is reported by the patient in the field.
- If the treatment is stopped in the field due to any reason, the N/DDR-TBC should be informed immediately to take the necessary action to reintroduce the treatment, modify or replace the regimen and/or manage the ADR.
- The most common adverse reactions observed in patients treated with Pa in combination with Bdq and Lzd are peripheral neuropathy, hematological abnormalities, visual impairment and cardiotoxicities.
- Other adverse reactions included acne, nausea, vomiting, headache, increased transaminases, dyspepsia, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyl transferase, lower respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, hypoglycemia, abnormal loss of weight, and diarrhoea (33).

- New data on the safety of Pa based on hormone evaluations in four clinical trials and a paternity survey were also assessed; these data have largely alleviated previous concerns on reproductive toxicities observed in animal studies, suggesting that adverse effects on human male fertility are unlikely. A study assessing semen in men undergoing treatment that includes Pa is in progress and will address any remaining concerns (9)(12).
- Management of patients experiencing QT prolongation and hepatotoxicity during MDR-TB treatment with newer regimens is detailed in annexure 2 & 3.
- Pyridoxine (Pdx) will be administered for the entire duration of treatment as per weight band (3).
- Pyridoxine supplementation has been shown to reduce the incidence of neuropathy in patients, supporting its inclusion in treatment protocols to mitigate drug-induced neuropathy.
- Pyridoxine to be used in the BPaLM regimen to provide added protection against neuropathy.

3.11 Management of treatment interruptions and lost to follow-up

- Interruption and missed doses in BPaLM regimen has been detailed in a separate section 3.3.6.
- All efforts must be made to ensure that the DR-TB patients do not interrupt treatment or are not LTFU. Action should be taken to promptly retrieve patients who fail to come for their daily dose by the treatment supporter/ supervisor.
- All possible efforts should be made to support the patient and manage the adverse events to ensure uninterrupted treatment and intake of all medicines in the regimen; however, when severe toxicity occurs, the medicine should be stopped.

3.11.1 Patients who miss doses

All missed doses during IP (wherever applicable) must be completed prior to switching the patient to CP. Similarly, all missed doses during CP must be administered prior to ending treatment.

3.11.2 Patients who interrupt treatment for less than 9 weeks

When the patient returns to resume treatment, the treatment will be continued, and the duration of treatment will be extended to complete the regimen. The follow-up smear or cultures will be done as per the schedule.

a. Consecutive treatment interruption (of all medicines in the regimen) of up to two weeks needs to be made up and added to the treatment duration.

b. Non-consecutive missed doses of all medicines in the regimen up to a cumulated total of four weeks need to be made up and added to the treatment duration.

c. In case of tolerances is exceeded for anyone of the above two conditions, general guidance is to consider clinical review, declare outcome as treatment failed if the interruption is due to ADRs or lost to follow up and switch to longer oral M/XDR-TB regimen.

An additional culture may be considered if the DR-TB patient returns between four to nine weeks of treatment and has clinically deteriorated. If the culture is positive, repeat FL/SL LPA and LC DST need to be done as per the integrated algorithm. If additional resistance is detected to any component drugs, the outcome will be declared as 'treatment failed', the patient will be sent to NDR-TB centre for clinical, radiological and microbiological review and be switched to longer oral M/XDR-TB regimen with a fresh PTE.

3.11.3 Patients who interrupt treatment continuously for 9 weeks or more and return for treatment

- Such patients will be given an outcome of LTFU. The patient would be revaluated as per the integrated algorithm to restart with appropriate treatment. (This is not applicable to BPaLM)
- If there are signs of impending treatment failure for any MDR/RR-TB patient with or without additional resistance to SLDs, the patient should be switched to longer oral M/XDR-TB regimen and evaluated further to modify appropriately based on DST results if required.

3.11.4 For patients who interrupt Bdq during the first two weeks of the Bdq course and return to resume the treatment

- If the interruption is up to seven days, Bdq will be continued to complete the doses, and the duration of treatment will be extended to complete first two weeks of loading dose and the compensation to be done before starting Bdq 200mg thrice weekly. Follow-up cultures will be done as per the revised schedule, and
- If the interruption is more than seven consecutive days, the Bdq course will be reloaded (started afresh with a new bottle and the old bottle sent for reconstitution after adjusting for the additional tablets required for reloading). And a fresh specimen collected for culture and the culture isolate must be stored for Bdq DST in the future. Follow-up cultures will be done as per the revised schedule.

3.11.5 Patients who interrupt Bdq during 3-26 weeks of the Bdq course and return to resume treatment

During the maintenance phase of Bdq dosing, Bdq can be reinitiated with the loading dose if the interruption, if any, is up to nine weeks. If Bdq is interrupted for

i. less than two consecutive weeks, no reloading is required. Resume the thrice-weekly dosing schedule and complete the treatment duration.

ii. more than two weeks (but less than eight weeks), Bdq should be reloaded at the higher daily dose of 400 mg for seven days before resuming the thrice-weekly dosing schedule.

iii. more than eight consecutive weeks, then declare the outcome as 'LTFU' and the patient and treatment plan should be reassessed to consider longer oral M/XDR-TB regimen (23). (This is not applicable to BPaLM)

4 PATIENT SUPPORT DURING DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB

The CHO, HF and TU staff will be responsible for screening all contacts of the patient for TB (either symptom screening and/or chest X-ray) and, if eligibility to provide TPT, ensuring treatment support, adherence monitoring, regular follow-up assessments, identifying and referring patients experiencing adverse events for aDSM, Ni-Kshay entries, declarations of final treatment outcome. The final treatment outcome of DR-TB patients will be given in consultation (preferably teleconsultation) with a HF doctor or the concerned N/DDR- TBC if the patient is unable to visit the facility for any reasons. All patients should be subjected to long-term follow-ups at months 6, 12, 18 and 24.

4.1 Ambulatory care

After treatment initiation, while referring the patient back to the HWC or HF of the public or private sector for ambulatory treatment, patients should be referred after updating all relevant information in Ni-Kshay for TB.

In the case of MDR-TB patients, the patient should be referred with the remaining PwB initiated at N/ DDR-TBC for the entire duration of treatment and a copy of the PMDT treatment book and referral form under intimation of the district TB officer (DTO). The respective DTO or MO-TU or HF doctor or CHO or private health care provider should be informed by the concerned staff of N/DDR-TBC on the referral of patients for ambulatory care in advance by means of the NTEP PMDT referral for treatment process via Ni-Kshay, email or mobile phone. Confirmation that the patient has reported to the concerned HF doctor or CHO or private health- care provider from the respective N/DDR-TBC must be received by N/DDR-TBC including acceptance by the current HF of the district as soon as the patient reaches home and is initiated on ambulatory care with a patient turnaround time (TAT) of within one week of referring the patient.

4.2 Counselling

Health education and counselling to the patients and their family members about the disease, the mechanism of transmission and the necessity of taking regular and adequate treatment is of utmost importance. Effective counselling for all patients and their family members from the time of treatment initiation with DS-TB is found to be effective in preventing the development of drug resistance. In all circumstances, counselling should start at the initial point of contact as soon as the diagnosis is established and continued during all visits by the patient to a health facility as well as by the healthcare workers to the patient's home or through the national TB call centre (Nikshay Sampark). The trained counsellors at the NDR-TBC would be responsible to ensure regular counselling of all DR-TB patients under care of the respective N/DDR-TBC as well as coordinate with the supervisors to retrieve patients who interrupt treatment and extend them all necessary care and support they need till the end of treatment.

4.3 TB aarogya saathi mobile app

All patients and their care takers should be encouraged to use the TB aarogya saathi mobile app **(https://play.google.com/store/search?q=tb+aarogya+sathi+app&c=apps&hl=en)** linked to their Ni-Kshay patient ID to keep track of information pertaining to their care, including treatment adherence monitoring and enablers. Digital adherence technology, including reporting on TB aarogya saathi mobile app, will be deployed to ensure adherence monitoring with signals to Ni-Kshay to document daily treatment adherence rate and prioritized home visits to treatment interrupters for prompt retrieval.

4.4 Nutritional assessment and support

Nutritional assessment is important to be done during PTE and at every follow-up visit. Holistic nutrition assessment, nutrition-specific counselling, nutrition support by linkages and nutrition supplementation should be offered. This can also be self-assessed by the patients and caretakers using TB aarogya saathi mobile app.

Patients with severe malnutrition (HB <7 g/dl, BMI <16 kg/m2 with pedal oedema, MUAC < 16 cm) need to be hospitalized, if required, for appropriate management. Patients with severe or moderate acute malnutrition (SAM or MAM) may need to be appropriately managed to provide adequate nutritional support with reference to the Guidance Document for Nutritional care and support to TB patients in India 2017 (34).

The significant burden of TB in India is compounded by the dual existence of food insecurity and undernutrition, signifying the necessity of facilitating nutritional support to TB patients. Under the Ni-Kshay Poshan Yojana (NPY), all patients are eligible for Rs 1000 per month as nutritional support for the entire duration of their TB or DR-TB treatment. All patient data must be entered into Ni-Kshay on a real-time basis. The patients and providers would be eligible for Direct Benefit Transfer (DBT) and enablers as applicable.

4.5 Community support to TB patients under “Pradhan Mantri TB Mukt Bharat Abhiyan”

It becomes imperative to strengthen collaboration with the community and the existing institutions in society that can play a critical role in filling gaps and addressing social determinants. CTD has initiated this with the objective of providing additional patient support to improve treatment outcomes, augment community involvement in meeting India’s commitment to end TB by 2025 and leverage the avenues for corporate social responsibility towards ending TB. Under this initiative, the programme is facilitating a mechanism to enable the elected representatives, non-governmental organizations, individuals, institutions (both public and private), corporates and partners to support efforts to end TB as Ni-Kshay Mitra. The support to TB patients is envisaged through the adoption of blocks or urban wards or districts or even individual or groups of patients for effecting a better response against TB to complement government efforts. In this regard, all active TB patients need to give consent to be part of this programme and DTOs will link them to avail this the support from Ni-Kshay Mitra through Ni-Kshay.

5 TREATMENT OUTCOME

The progress of the patient on treatment would be monitored using interim as well as final treatment outcomes, which are detailed below. The following definitions are the most recent outcome definitions recently revised by WHO and would apply to all forms of TB patients (3).

5.1 Interim outcomes

5.1.1 Bacteriological conversion

After bacteriological confirmation of TB, at least two consecutive cultures (applicable for DR-TB and DS-TB) or smears (applicable for DS-TB only) taken on different occasions at least seven days apart are found to be negative.

5.1.2 Bacteriological reversion

At least two consecutive cultures (applicable for DR-TB and DS- TB) or smears (applicable for DS-TB only) taken on different occasions at least seven days apart are found to be positive either after the initial conversion or for patients without bacteriological confirmation of TB.

For defining treatment failed, bacteriological reversion is considered only when it occurs in the continuation phase.

Time-to-culture conversion is calculated as the interval between the date of treatment initiation and the date of the first of these two negative consecutive smears or cultures taken seven days apart (date of sputum specimens collected for culture should be used).

5.2 Final Outcomes

5.2.1 Treatment failed

A patient whose treatment regimen needs to be terminated or changed permanently to a new regimen option or treatment strategy. The reason for the changing the regimen permanently include:

a) No clinical response and/ or no radiological response

b) No bacteriological response (no bacteriological conversion achieved or bacteriological reversion after initial conversion; bacteriological reversion is considered only when it occurs in the continuation phase)

- For BPaLM regimen: “bacteriological reversion” would be considered only during the period between 26-39 weeks in cases where treatment duration has been extended to 39 weeks. It will not be considered in BPaLM regimen of treatment duration of 26 weeks).

c) ADRs,

d) Evidence of additional drug resistance to medicines in the regimen.

Failure outcome definitions for BPaLM: Failure will include

i. The culture of sample collected at month 04 or later is positive for M.TB.

ii. Amplification of resistance to B, Pa and or L

iii. No clinical response

5.2.2 Cured

A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response[1] and no evidence of treatment failed.

5.2.3 Treatment completed

A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition of cure or treatment failed.

5.2.4 Died

A patient who died[2] before starting or during the course of treatment.

5.2.5 Lost to follow-up

A patient who did not start treatment or whose treatment was consecutively interrupted for one month or more. (not applicable to BPaLM)

5.2.6 Not evaluated

A patient for whom no treatment outcome was assigned[3]

5.2.7 Treatment regimen changed:

The patients who has been initiated on treatment, in case of baseline resistance to the drugs in the regimen (when available) is found, the treatment need to be changed to an appropriate regimen and the outcome to be given as "treatment regimen changed". The patient needs to be moved out of the denominator of the previous regimen. The outcome of only the changed regimen needs to be reported. The same would be applicable for patients who switched between the DS-TB and the DR-TB regimens.

Treatment regimen changed outcome definitions for BPaLM: Treatment regimen changed will include:

i. Discontinuation of B, Pa or Lzd because of intolerance, toxicity at any point of time

ii. Baseline DST resistance to B/Pa/L when available

The treatment regimen changed because of intolerance and baseline DST resistance are to be recorded in Ni-kshay and analyzed separately.

5.2.8 Sustained treatment success

An individual assessed at six months (for DR-TB and DS-TB) and at 12 months, 18 months and 24 months (for DR-TB only) after successful TB treatment who is alive and free of TB (36).

5.3. Long term follow-up

Patients who completed TB treatment remain at risk of TB recurrence (re-infection or relapse). TB patients require regular follow-up starting from the treatment initiation until two years after successful treatment completion to achieve the desired outcome of recurrence-free survival. Hence, the programme introduced patient assessment at 6, 12, 18 and 24 months after completion of treatment (35).

[1] *Bacteriological response – bacteriological conversion with no reversion.*

[2] *Patients died for any reason*

[3] *This includes cases "transferred out" to another treatment unit whose treatment outcome is unknown and excludes LTFU.*

6 RECORDING, REPORTING AND MONITORING

6.1 Recording and reporting in Ni-Kshay under NTEP

The entire cascade of patient care from diagnosis through treatment outcome as well as post-treatment follow-up needs to be updated in Ni-Kshay in appropriate modules and meticulously. In this vein, sequential data entry points made need to be noted solemnly. The suggestive ones are as noted below:

- Enrolment is needed before generating any test request, and the first point of contact of the patient is expected to do the enrolment via the available mechanisms like CHO or patient provider support agency (PPSA) if applicable.
- Test requests may need to be generated by the health facility requesting the test.
- Test details may need to be updated by the testing facility.
- Treatment initiation need to be updated by the initiating the treatment.
- Treatment outcomes need to be updated by the where the patient has completed the treatment and final assessment(s).(3).
    - PTE module will be made available in Ni-Kshay in due course of time.
    - Adverse drug reaction monitoring is currently available in Ni-Kshay as per the questionnaire per the pharmaco-vigilance programme of India (PvPI) format, which will be made more nuanced in the coming days.
    - Albeit newer treatment regimens are anticipated to be made available in the regimen selection section in Ni-Kshay, the greater emphasis is expected to be on further utilization of the dispensation module, which would enable any treatment changes within a given instance of the disease.
    - Transfer of patients, when needed, would be effected via the transfer module of Ni-Kshay.
    - Reports and case-based data would accordingly be updated for the information on newer regimens as well for monitoring purposes.

The aDSM data extracted from Ni-Kshay will be analyzed at CTD with support from WHO India. The relevant information will be shared with the sub-group of NTEG on a monthly basis as a routine for drug safety monitoring. The data on action required on an immediate basis will be shared with the sub-group of NTEG by CTD.

The sub-committee of NTEG would evaluate periodically (quarterly and more frequently if required) accumulated data for patient safety, progress and continuation and make a recommendation to CTD concerning further refinement of the guidelines.

Physical copies of any records or document(s), like treatment card(s), and register(s) if required, may be printed from Ni-Kshay, in inevitable circumstances only.

Detailed training materials on various modules of Ni-Kshay can be accessed from the following link: https://nikshay.zendesk.com/hc/en-us

6.2 Programme monitoring

The following two indicators will be used for monitoring purposes (3):

No.	Indicator	Numerator	Denominator
Diagnosis			
1	Coverage of DST to H and FQ among bacteriologically confirmed TB patients with Rif resistance not detected Number or proportion of bacteriologically confirmed TB patients with Rif resistance not detected and valid results available for H and FQ resistance	Number of bacteriologically confirmed TB patients with Rif resistance not detected, and valid results available for H and FQ resistance	Total number of bacteriologically confirmed TB patients with Rif resistance not detected
Process indicators			
2	Sustained treatment success at six and 12 months, 18 months and 24 months post-treatment Number or proportion of successfully treated TB patients who are alive and free of TB Disaggregate by after six months of treatment completion or after 12 months of treatment completion, by DS-TB or DR-TB pattern, by regimen	Number of successfully treated TB patients who are alive and free of TB	Total number of TB patients initiated on treatment

7 ANNEXURES

Annexure 1:

Chronology of events for the introduction of pretomanid-containing regimen in India

Post approval by the United States Food and Drug Administration (US FDA) in 2019, a series of high-level consultations between TB Alliance, M/s Viatris (erstwhile M/s Mylan), officials from the Ministry of Health and Family Welfare, DCGI, officials from NTEP, Indian Council for Medical Research (ICMR) and WHO Country Office for India on fast-tracking regulatory approval and modalities of the introduction of BPaLM regimen in India.

In January 2020, the Subject Expert Committee of the Central Drugs Standard Control Organization (CDSCO) approved Pa to be used only as conditional access under the NTEP. The committee noted that there is an unmet need for the drug in a patient with XDR-TB (erstwhile definition). The use of Pa in combination with Bdq and Lzd is reported to be advantageous in respect of the reduction of the duration of treatment from 20 months to six months. However, the drug should be used under the restricted conditions to prevent its misuse and development of resistance etc. In July 2020, DCGI issued permission to manufacture the drug.

In September 2020, based on WHO recommendations and a series of deliberations on concerns of high toxicity with 1200mg of Lzd in the regimen, NTEG recommended that a BPaL research proposal may be considered with the flexibility to adapt to anticipated results of ZeNix trial with four arms of reduced dosage and duration of Lzd in BPaL; and in exceptional cases, BPaL can be considered as a last resort by NTEP under prevailing ethical standards in individual patients for whom the design of an effective regimen is not possible as per WHO recommendations.

NIRT, Chennai, in collaboration with CTD and WHO India, developed a multicentric study protocol that was converted into a pragmatic three arm clinical trial to "evaluate the effectiveness, safety and tolerability of various doses of Lzd in combination with Bdq and Pa in adults with Pre-XDR, or MDRTI/NR (treatment intolerant/ non-responsive) pulmonary TB in India" based on recommendations from experts in National Operational Research Committee (NORC). In June 2021, M/s Viatris agreed to donate 400 courses of Pa (200mg tablet) to Central TB Division for the modified BPaL (mBPaL) regimen. The study is funded by USAID through the UNION. In October 2021, the enrolment of eligible patients commenced and was expected to be completed in 2022. The study is expected to be completed with post-treatment 12 months follow-up of all enrolled patients by the end of 2024. The results have been described in the respective section above (16).

In 2022, based on WHO recommendation, the NTEG recommended CTD to prepare a protocol with a guidance document on the proposed technical recommendation of utilizing BPaLM for the treatment of MDR-TB as per the indications and implement to gain local experience and generate evidence in selected geographies across India with regular safety and efficacy monitoring by CTD to guide NTEP on the further expansion.

In August 2024, the ICMR completed the health technology assessment and submitted a report to NTEP, MoHFW recommending BPaLM as a cost-effective and cost-saving strategy. The NTEG recommended introduction of BPaLM under programmatic setting.

Annexure 2:

Standard operative procedure for collection, transportation and processing of extra-pulmonary specimens

Introduction

Extra pulmonary specimens are divided in two groups based on the site and mode of collection and extent of contamination.

- Aseptically collected specimens, usually free from other microorganisms (sterile) – fluids like spinal, pleural, pericardial, synovial, ascitic, blood, bone marrow, tissues (lymph node, tissue biopsies) and fine needle aspirates (FNAs).
- Specimens contaminated by normal flora or specimens not collected aseptically (not sterile) – gastric lavage, bronchial washings, urine, pus and stool (in case of disseminated TB in HIV infected patients and infants).

Collection of extra-pulmonary specimens

Body fluids (spinal, pleural, pericardial, synovial, ascitic, bone-marrow) should be aseptically collected in a sterile container by the physician using aspiration techniques or surgical procedures. Specimens should be transported to the laboratory as quickly as possible.

i. Pleural fluid

Considered a suboptimal specimen as tubercle bacilli are mainly in the pleural wall and not within the fluid. The minimum volume for pleural fluid required for processing for culture is 20–50ml. The fluid is collected using pleural tap or thoracocentesis.

ii. Pericardial fluid

Should be collected using ultra sonogram.

iii. Blood

Blood as a specimen for isolating M. tuberculosis should be generally discouraged for the low diagnostic yield and high possibility of contamination with respect to the technique required for its culture.

iv. Tissues

The aseptically collected tissues are placed by the physician in sterile containers preferably without fixatives or preservatives. If the specimen is to be shipped, it should be protected from drying by adding sterile saline maintaining a temperature of 4-15oC. Specimens should be transported to the laboratory as quickly as possible.

v. Swabs

Swabs are always sub-optimal specimens and not recommended because of risk of infection for specimen collector. They may be useful in children and patients who cannot produce sputum or may swallow it. A sterile absorbent cotton swab should be used for collection. The best time for the collection is early morning before food and drinks are taken. The swab should be placed in a screw capped container containing normal (0.9%) saline to prevent drying. Swabs except for laryngeal swabs or from discharging sinus should be avoided.

vi. Urine

Among specimens expected to be contaminated, urine is the most common. To minimize excessive contamination of urine specimens, special instructions for collecting urine with adequate cleansing of external genitalia to prevent contamination by commensals should be given. Early morning sample should be collected in 500 ml screw capped sterile containers. Once received in the laboratory, urine must be immediately processed or centrifuged and the pellet refrigerated for further processing. As excretion of tubercle bacilli in urine is intermittent, it is advised to collect three early morning specimens on different days.

vii. Bronchial secretions

Other respiratory specimens that can be submitted to the laboratory for mycobacteria culture are bronchial secretions (minimum volume: 2- 5ml) and bronchial alveolar lavage (BAL) (minimum volume of 20 – 50 ml). Trans-bronchial and other biopsies should be collected under sterile conditions and placed in 0.5-1.0 ml of sterile normal (0.9%) saline to prevent drying during transportation to the laboratory.

viii. Gastric lavage

In children, who rarely produce sputum, the aspiration of the early morning (gastric content) may be used for TB diagnosis. This is done as an in-patient procedure. This should be transported immediately to the lab and processed (not more than 4 hours) to prevent the killing action of the acid content in the gastric lavage on the tubercle bacilli. In the event of delay, the sample can be neutralized using 1-2 ml of sterile 10% sodium bicarbonate solution depending on the volume of gastric aspirate. If facilities are available for aseptic neutralization, it may be carried out at the periphery. Else, specimens are to be sent to the C&DST laboratory without addition of any reagent along with an indication that the specimen has not been neutralized. The laboratory would perform neutralization prior to processing.

Note:

- Samples for culture should never be collected in formalin;
- If histopathological examination is required, two samples should be collected. No preservative should if being sent for TB culture; and
- Necessary instructions are to be given to the concerned staff for sending the biopsy specimen in normal saline for culture and not in formalin.

Transportation of extra pulmonary specimens

As for pulmonary specimens, extra pulmonary specimens will need to be transported in cool boxes (below 200°C) to be compatible for liquid culture systems as well as molecular methods. Triple packing system should be used for transportation. All precautions that are followed for transporting pulmonary specimens should be followed for EP specimens too.

When sending out specimens or when receiving them, check that:

- Test request form is placed separately in a self-sealing pouch;
- Containers are labelled not on the cap but on the wall of the container; and
- Date of dispatch and particulars of the health centre are on the accompanying list.

i. Specimens and request forms

All specimens transported to the laboratory must be accompanied by the request form. Tests must be performed only upon written request of authorized persons and oral requests without follow up written instructions should not be allowed. It is also important that specimen request forms are kept separate

from the specimens themselves. Forms that have been contaminated by specimens should be sterilized by autoclaving. If mistakes in filling request forms and labelling of specimens are found, reject specimens and mention the reasons for rejection in the register. Document the time of specimen receipt in the laboratory and note any delays in delivery in the remarks column of the register.

Registration of samples

i. Receipt of incoming specimens

For safety reasons, specimens should be received in the registration area of the laboratory.

To minimize risk of infection, the following procedures should be applied:

- The specimen box received should be opened only in a biosafety cabinet inside the laboratory. (Do not open on an open bench at the lab reception).
- Before opening the package, inspect the delivery box for signs of breakage or leakage; if there is gross leakage evident, discard the package following biomedical waste management.
- If on gross inspection there is no leakage, proceed for sample opening.
- Open the package carefully and re-check for any leakage. In case of leakage, discard the entire contents following biosafe precautions. Rejection/ leakage of samples, to be informed to the respective DTOs immediately to enable re-collection of specimen.
- Check labelling of specimens in the specimen container and test request form.
- Register the samples in LIMS and proceed for processing by the appropriate method.
- Document the date of the receipt of the specimen, patients name, age, sex and address, the name of the referring health centre, the reason for testing and volume of the specimen in the C&DST lab register.

ii. Decontamination of extra-pulmonary samples

Most of the extra-pulmonary specimens are paucibacillary in nature. Hence, they require milder decontamination.

Processing of EP specimens for MGIT960

Isolation of M. tuberculosis by MGIT system requires the final inoculum to be in an ideal condition that will not interfere with the fluorescence.

Pus and other muco-purulent specimens

- Thick pus of volume >10 ml is decontaminated using the NALC – NaOH method as sputum.
- If the volume is < 10 ml, either aliquot and process only 10 ml by NALC–NaOH method or concentrate the initial volume by centrifugation for 15–20 minutes and re-suspend the pellet in 5 ml of sterile distilled water. If the pus is too thick, add about 50-100 mg of NALC powder; mix well and decontaminate using NaOH. Re-suspend the final pellet in buffer to reduce the Ph.
- If the pus is not thick, decontaminate using 2-4% NaOH. The concentration of NaOH can be changed based on the expected level of contamination in the specimen which depends on the site of collection.

Gastric aspirates

- Distribute the volume in smaller aliquots and centrifuge the tubes at 3000 x g.
- Pool the deposits, add 5ml distilled water and decontaminate it using NALC-NaOH or 2-4% NaOH.

Bronchial washings

- Process using NaLC-NaOH like sputum.
- If the specimen is >10 ml in volume, process the whole specimen.
- If <10ml, concentrate the specimen by centrifugation (3000x g, 15-20 minutes).
- Add 5 ml sterile water to the pellet and decontaminate as for sputum.

Laryngeal Laryngeal swabs

- Transfer the swab into a sterile centrifuge tube and add 2 ml sterile water.
- Add 2 ml of NaLC-NaOH solution and mix well in a vortex mixer.
- Let it stand for 15 minutes. Remove the swab with forceps, squeezing the liquid out of the swab and discarding it.
- Fill the tube with phosphate buffer and mix.
- Centrifuge at 3000xg for 15–20 minutes.
- Discard the supernatant fluid and re-suspend the sediment in 1–2 ml sterile buffer. Use this suspension for smear and culture.

Tissue

- Homogenize the tissue in a tissue grinder with a small quantity of sterile saline or water (2–4 ml).
- Decontaminate the homogenized specimen using NaLC-NaOH procedure as in sputum.
- Re-suspend the sediment with phosphate buffer.
- If the tissue grinder is not available, use a mortar and pestle.
- Tissue may also be placed in a petri dish with sterile water (2–4 ml) and be torn apart with the help of two sterile needles.

Urine

- Isolation of mycobacteria from urine specimens using MGIT has not been validated.
- Aliquot the entire volume in several centrifuge tubes.
- Concentrate the specimen by centrifugation for at least 20-25 minutes
- Re-suspend the pellet in each tube with 1–2 ml of sterile water and pool together.
- Decontaminate using 4% NaOH as for sputum.

Other body fluids (CSF, synovial fluid and pleural fluid)

As these fluids are collected usually under aseptic conditions, they require only milder decontamination.

- If the specimen volume is more than 10 ml, concentrate by centrifugation at about 3000x g for 15–20 minutes.
- Liquefy thick or mucoid specimens prior to centrifugation by adding NALC powder (50– 100 mg).
- Re-suspend the sediment in about 5 ml of saline.
- Mix and decontaminate as for sputum.

Blood

- Isolation of mycobacteria from blood specimens by MGIT 960 has not been evaluated thoroughly. A few published studies have used blood after lysis centrifugation. Ideally BACTEC Myco/F Lytic medium is recommended for isolation of mycobacteria from blood samples.

Annexure 3:

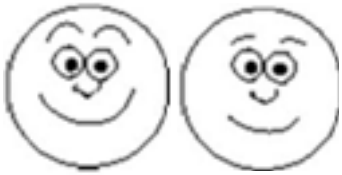
Peripheral Neuropathy

Symptoms/ signs of neuropathy:

- Numbness, Burning, prickly (pins and needles) feelings in the feet
- Feel hurt when bed covers touch the skin.
- Inability to distinguish hot or cold water while bathing
- Slipping off the footwear without knowledge
- Inability to place his soles on the ground.
- Frequent sores or ulcers on the feet.
- Worsening of symptoms at night or increase in leg pain while walking

Brief peripheral neuropathy screening tool (21)

<table>
<tr><th colspan="5">Patient Initials:</th><th colspan="5">Patient ID:</th></tr>
<tr><td>1. Visit (Circle One)</td><td>All Subjects</td><td>Baseline</td><td>Week 4</td><td>Week 8</td><td>Week 12</td><td>Week 16</td><td>Week 20</td><td>Week 26</td></tr>
<tr><td></td><td></td><td colspan="2">3 Month</td><td>6 Month</td><td>12 Month</td><td colspan="3">24 Month</td></tr>
<tr><td></td><td>9 Month Treatment Only</td><td colspan="3">Week 30</td><td colspan="2">Week 34</td><td colspan="2">Week 39</td></tr>
<tr><td></td><td>Other</td><td colspan="3">Early Withdrawal</td><td colspan="5">Unscheduled (For New or worsening peripheral neuropathy during treatment)</td></tr>
<tr><td>2. Date of assessment</td><td colspan="8"></td></tr>
<tr><td colspan="9">Interference with Walking or Sleeping</td></tr>
<tr><td colspan="7">3. In the last 2 weeks, have pain, aching or burning in your feet interfered with your walking or sleeping? (Check one)</td><td>Yes</td><td>No</td></tr>
<tr><td rowspan="3">3a.</td><td colspan="8">If yes, ask the patient to rate the level of interference (1 to 10) to his walking or sleeping caused by this pain, ache or burning (circle one)</td></tr>
<tr><td colspan="3">Minimal (Grade 1)</td><td colspan="3">Modest (Grade 2)</td><td colspan="3">Severe (Grade 3)</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
<tr><td colspan="9">Subject Elicited Symptoms</td></tr>
<tr><td colspan="9">• Using the faces below, ask the patient to rate the severity of the symptoms for the questions 4, 5, 6 on a scale of 1 (mild) to 10 (severe) for both feet. If the severity is different between the left and right foot, record the severity of the most affected foot.
• Enter a score for each symptom
• If a symptom has been present fin the past, but not since the last visit, enter ’00 – currently absent’
• If a symptom has never been present, enter ’11 – Always been Normal’</td></tr>
</table>

<table>
<tr><td colspan="2">  </td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
<tr><td>00
Very Happy, No Symptoms</td><td>02
Just a little bit</td><td>04
A little more</td><td>06
Even More</td><td>08
A whole lot</td><td>10
Worst</td></tr>
<tr><td colspan="2" rowspan="3">During the last 14 days, have you experienced:</td><td colspan="2">4. Pain, aching or burning in feet or legs?</td><td></td><td></td></tr>
<tr><td colspan="2">5. “Pins and needles” in feet or legs?</td><td></td><td></td></tr>
<tr><td colspan="2">6. Numbness (lack of feeling) in feet or legs?</td><td></td><td></td></tr>
<tr><td colspan="6">Perception of Vibration
• Press the ends of a 128 Hz tuning fork together so the sides touch and let go. Place the vibrating tuning fork on the bony prominence on the patient’s wrist to be sure that they can recognize the vibration or “buzzing” quality of the tuning fork.
• Again, press the ends of the tuning fork hard enough so that the sides touch and let go. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of the great toe and begin counting the seconds. Instruct the Subject to tell you when they stop feeling the vibration or “buzzing”. Repeat for the great toe on the other foot.
Vibration Perception Grade Scale:
0– Vibration felt for > 10 seconds (normal) 1– Vibration felt for 6-10 seconds (mild loss)
2– Vibration felt for 5 seconds or less (moderate loss)
3– No feeling of vibration (severe loss) 9 – Unable to evaluate or did not assess</td></tr>
<tr><td colspan="4" rowspan="2">Measured vibration grade of great toe DIP joint</td><td>Right</td><td>Left</td></tr>
<tr><td></td><td></td></tr>
<tr><td colspan="6">Deep Tendon Reflexes
• The examiner uses one hand to press upward on the ball of the foot, dorsiflexing the Subject’s ankle to 90 degrees. Using the reflex hammer (preferably long handled), the examiner strikes the Achilles tendon.
• The tendon reflex is felt by the examiner’s hand as planter flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck.
Ankle reflex grade scale: 0– Absent
1– Hypoactive
2– Normal Deep Tendon Reflexes
3– hyperactive deep tendon reflexes (eg. With prominent spread of toes) 4- Clonus
9 – Unable to evaluate or did not assess</td></tr>
</table>

8. Measured ankle reflex grade			Right		Left	
Comments						
Name of Person Completing Form		Name of Clinician (if required)				
Signature of Person Completing Form		Signature of Clinician (if required)				
Date		Date				

Peripheral Neuropathy: DAIDS criteria (22)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Neuromuscular Weakness (includes myopathy and neuropathy) Specify type, if applicable	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) Specify type, if applicable	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

Medical treatment of Peripheral neuropathy

- Usually occurs later in treatment, while hematological abnormalities occur earlier in treatment
- Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms
- Pregabalin (75 mg) + methylcobalamine (750 mg) twice a day also used (take care of giddiness/sleepiness). Pregabalin dose upto 150-300 mg twice daily
- Gabapentin has been helpful for many individuals. Adults should be treated initially with a single dose of 300 mg on Day 1, increased to 300 mg twice a day on Day 2, and 300 mg 3 times a day on Day 3.
- Tab Gabapentin NT (a combination of Gabapentin 100 mg and Nortriptyline 10 mg) once daily, to be taken in the evening. May be increased upto Gabapentin/Nortriptyline (Tab Gabapentin NT 300 mg/10 mg)
- Treatment 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 (to be avoided with Bdq as mild MAO inhibitor: may cause Serotonin syndrome).
- Duloxetine:
  - Initiate Cap Duloxetine 20 mg twice daily (BD) for 30 days, followed by once daily (OD) for the next 30 days.
  - If no relief is seen with the BD dose within the first 15 days, increase the dose to 20 mg three times daily (TDS).
- Avoid Duloxetine with Linezolid as it may cause Serotonin syndrome
- Refer to Nodal DR-TB center and to specialist for further management (may delay the treatment)

Annexure 4:

Management of patients experiencing QT prolongation and hepatotoxicity during MDR-TB treatment

QT Prolongation

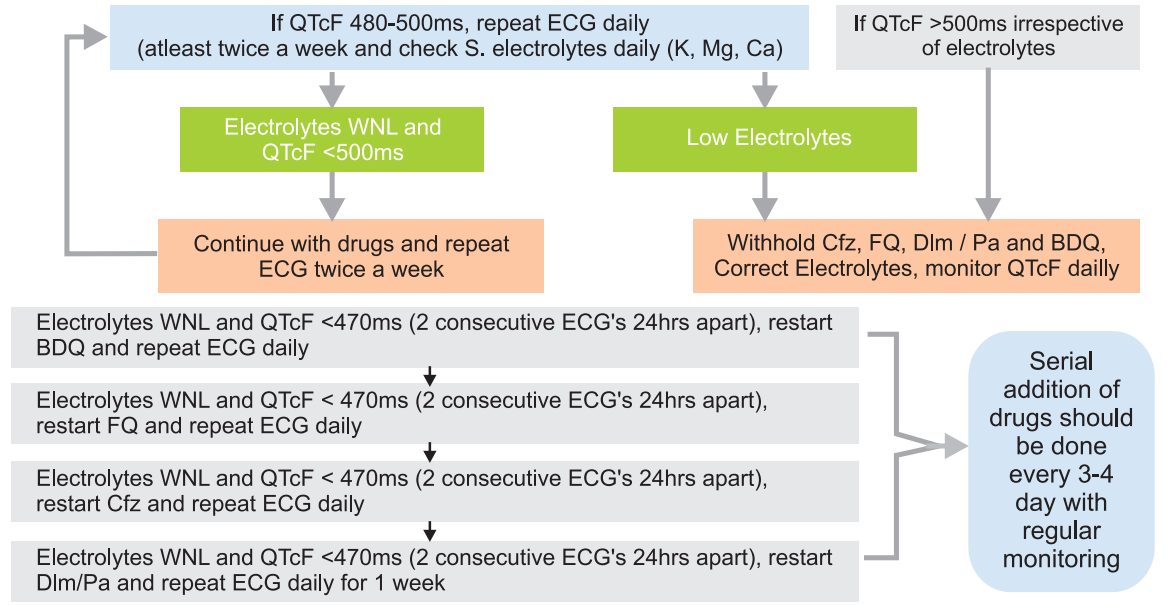
Suspected agent(s): Mfx, Dlm, Pa, Bdq, Cfz Suggested management strategies:

- QT interval is measured from the start of the QRS complex to the end of the T wave on a standard
- ECG. The QT is corrected for heart rate, which is referred to as the QTc and is calculated by most ECG machines. Values above QTc Fridericia correction (QTcF) 450 ms in males and 470 ms in females are referred to as prolonged. Patients with prolonged QTcF are at risk for developing cardiac arrhythmias like torsade's de pointes, which can be life-threatening. Bdq, FQ, Cfz, Pa and Dlm may cause prolongation of the QTcF. Among FQs, Mfx cause the greatest QTcF prolongation, while Lfx has a lower risk. Currently, ECG monitoring prior to initiation and during DR-TB treatment is only required with the use of Bdq or when two drugs known to prolong QTcF (e.g. Mfx, Cfz, Pa, Dlm) are combined in the same regimen.
- Low serum levels of potassium, calcium and magnesium are associated with QTc prolongation. Electrolyte levels should be maintained in the normal range in any patient with an elevated QT interval. Also, avoid other drugs that increase the QT interval. The patient's renal and hepatic function should also be monitored.
- QT prolongation can result in ventricular arrhythmias (Torsade's de Pointes) and sudden death. It is, therefore, imperative that ECGs be used to monitor the QT interval regularly during the use of the suspected drugs.
- Management of increased QTcF entails looking at the algorithm for the reintroduction of anti-TB drugs (Mfx, Dlm, Pa, Bdq, Cfz) once prolonged QTc has normalized as shown in table and figure below:

Management of prolonged QTcF during treatment with BPaLM/Shorter/Longer oral MDR-TB Regimen

Instruction applying for the whole algorithm if **QTcF** is **450** or above

1. Check S. Potassium (K), Calcium (Ca), Magnesium (Mg) corrected for albumin
2. Consider abnormalities for thyroid function
3. When QTcF does not remain to 470ms even after discontinuation of the QTcF prolonging drugs or increased after re- introduction, decision to continue the suspected drug or regimen is in the purview of DR-TB committee. Evaluate the patient for malnutrition, diabetes, LFT, RFT, etc prior to taking decision.



Management of QT prolongation by grade of severity of ADR

Normal Value	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
QTcF M: < 450 F: < 470	M: 450-480 ms F: 470-480	481-500 ms	> 500 ms on two separate ECGs	> 500 ms and life threatening consequences
Condition	Asymptomatic	Asymptomatic, transient rhythm abnormality	Recurrent, persistent, symptomatic arrhythmia	Unstable dysrhythmia
Action	Check electrolytes and correct them, as necessary Monitor ECG more closely	Check electrolytes. If abnormal, hold all QTcF prolonging drugs and correct the electrolytes before restarting them. Monitor ECG more closely	Consider hospitalization, hold QTcF prolonging drugs and correct electrolytes as necessary Repeat ECG after 24 hours and reintroduce the drugs if QTcF remains below 500 ms	• Hospitalize and replete electrolytes as necessary • Stop the offending drug • Repeat ECG after 24 hours

Hepatotoxicity

Suspected agent(s): Z, H, R, Eto, PAS, Bdq, Pa

Hepatotoxic drugs in the shorter/ longer MDR/RR-TB regimen are Z, H, R, Eto, PAS, Bdq, Pa. Hepatitis occurs rarely with the FQ. The potential for hepatotoxicity is increased in the elderly, alcoholics, malnourished and in patients with pre-existing liver disease. In general, most second-line drugs can be safely used in the presence of mild hepatic impairment, as they are relatively less hepatotoxic than first-line drugs.

Once a patient on second-line anti-TB drugs develops hepatitis, other etiologies should be excluded such as viral hepatitis, alcoholic hepatitis, drug induced hepatitis by non-TB drugs etc. Further management should be on the same line as in non-DR-TB patients. MDR/RR- TB patients having deranged liver function test (LFT) during pretreatment evaluation should be strictly monitored as clinically indicated while on treatment.

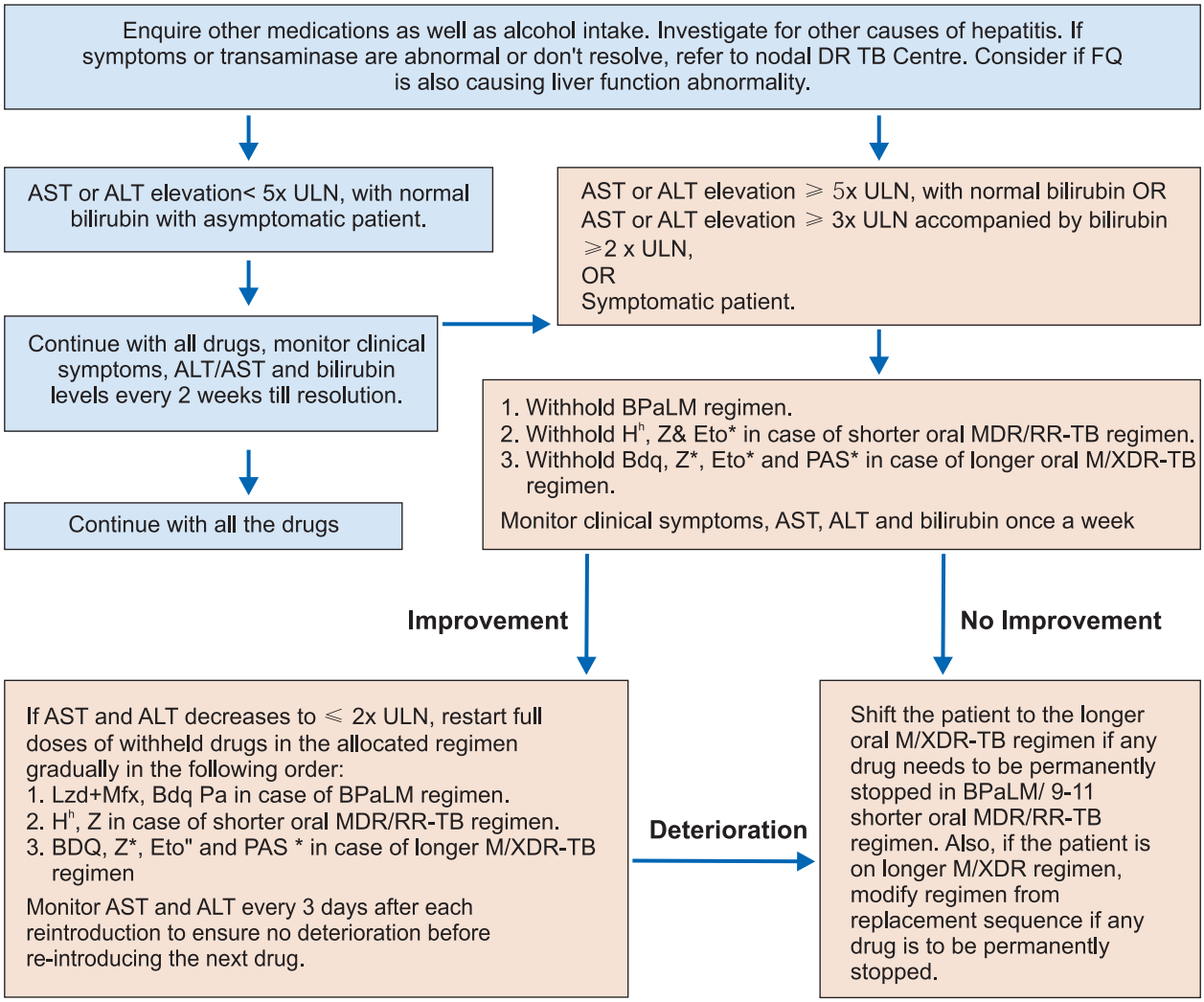
Suggested management strategies:

- In cases where the patient is very sick, i.e., meningitis, sputum smear grade 3+, administer ATT, e.g. Amikacin, FQ and Cs. Where the patient is not seriously ill, and one can wait, the introduction of ATT can be done once enzyme levels are near within 2 times of normal;
- If enzymes are more than five times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non-hepatotoxic medications (for example, the injectable agent, FQ and Cs). If hepatitis worsens or does not resolve with the three-drug regimen, then stop all drugs;
- eliminate other potential causes of hepatitis (viral hepatitis and alcohol-induced hepatitis being the 2 most common causes) and treat any that are identified; and
- once enzyme level improves, reintroduce remaining drugs, one at a time, with the least hepatotoxic agents first, while monitoring liver function by testing enzymes every three days. If the most likely agent is not essential, consider not reintroducing it.

Points to note

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

Management of hepatotoxicity during treatment with DR-TB regimen is described figure below:



**If used, introduction can be tried from lower doses of each drug with gradually increasing to full dose while monitoring the LFT and symptoms*

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