UPDATED NATIONAL GUIDELINES ON DRUG RESISTANT TUBERCULOSIS (DR-TB) TREATMENT IN MYANMAR

National TB Program

Department of Public Health

Ministry of Health

March 2025

ACKNOWLEDGEMENTS

This guideline was developed by the National Expert DR-TB Committee, based on the “Guidelines for the Management of Drug-Resistant Tuberculosis (DR-TB) in Myanmar, July 2017”.

The National TB Program, department of Public Health, Ministry of Health, Myanmar would like to express our deepest gratitude to Professor Tin Maung Cho, Professor Ye Tun and Professor Yadanar Kyaw for their continuous encouragement and guidance; special thanks to Dr Zaw Myint for his continuous efforts and support; colleagues from WHO country office (Myanmar), Dr Shushil Dev Pant and WHO-CO team for coordination and technical support; and Dr. Muhammad Asif, the Senior Technical Advisor MDR-TB, NTP Myanmar for his technical support in the process of guideline revision and development. We are sincerely thankful to the core team revising the guidelines and other expert DR-TB committee members for their technical inputs and contribution.

The guidelines were initiated and devotedly revised by the core team members in 2020 and carried over by the final revising team. The team members on final revising of the guidelines includes, in alphabetical order: Dr Khin Zar Li Kyi Lay, Dr Mar Mar Htay, Dr. Muhammad Asif, Dr. Myint Myint Sein, Dr Nang Lay Nwe, Dr Thein Myint, Dr Thet Naing Oo, Dr. Wint Wint Nyunt, Dr. Zaw Myint. The principal source of financial support for the development and publication of these guidelines was the Global Fund to Fight against AIDS, Tuberculosis and Malaria.

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Abbreviations and acronyms

aDSM	Active TB drug-safety Monitoring and Management
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BMI	Body mass index
BPaL	Bedaquiline, pretomanid, linezolid
BPaLC	Bedaquiline, pretomanid, linezolid, clofazimine
BPaLM	Bedaquiline, pretomanid, linezolid, moxifloxacin
BHS	Basic Health Staff
CALHIV	Children and adolescents living with HIV
CB	Critical break point
CC	Critical Concentration
CI	Confidence interval
CNS	Central Nervous System
CPT	Cotrimoxazole preventive therapy
CXR	Chest X-ray
DOH	Department of Health
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment Short-Course Strategy
DR-TB	Drug-resistant tuberculosis
DRS	Drug resistance survey
DST	Drug susceptibility testing
ECG	Electrocardiography
FDC	fixed-dose combination (of medicines)
FLD	First-line drugs
FQ	Fluoroquinolone
GDF	Global Drug Facility
GDG	Guideline development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HA	Health assistant
HC	Health center
HCW	Health-care worker
HIV	Human immunodeficiency virus
HR	Isoniazid-rifampicin
HRZE	isoniazid–rifampicin–pyrazinamide–ethambutol
(H)RZE	(isoniazid optional)–rifampicin–pyrazinamide–ethambutol
Hr-TB	Rifampicin-susceptible, isoniazid-resistant tuberculosis
IC	Infection control

INGO	International nongovernmental organization
IPD	Individual patient data (or dataset)
IQR	Interquartile range
IR	Initial regimen
IV	Intravenous
LHV	Lady Health Visitor
LJ	Lowenstein-Jensen
LPA	Line probe assay
LTR	Longer treatment regimen
MDR-TB	Multidrug-resistant tuberculosis
MDR/RR-TB	Multidrug- or rifampicin-resistant tuberculosis
MIC	Minimum inhibitory concentration
MGIT	Mycobacterial growth indicator tube
MMA	Myanmar Medical Association
MO	Medical Officer
MS	Medical Superintendent
MSF	Médecins Sans Frontières
MTB	*Mycobacterium tuberculosis*
MTBC	*Mycobacterium tuberculosis* complex
NGO	Nongovernmental organization
NGS	Next generation sequencing
NHL	National Health Laboratory
NSAID	Non-steroidal anti-inflammatory drug
NTP	National Tuberculosis Programme
NTRL	National TB Reference Laboratory
OPD	Out-patient department
PCR	Polymerase chain reaction
PHS	Public Health Supervisor
PICT	Provider-initiated HIV counselling and testing
PLHIV	People living with HIV
Pre-XDR TB	Pre-extensively drug-resistant tuberculosis
PSI	Population Services International
PTB	Pulmonary tuberculosis
QA	Quality assurance
QTcF	Corrected QT interval by Fridericia
RR-TB	Rifampicin-resistant TB
R/S	Regional/State
R/S TBC	Regional/State Tuberculosis Centre
R/S TBO	Regional/State TB Officer
SNRL	Supranational Reference Laboratory
TAD	Treatment after default

TAF	Treatment after failure
THNO	Township Health Nurse Officer
TB	Tuberculosis
TBC	TB Center
TMO	Township Medical Officer
TPHO	Township Public Health Officer
TSH	Thyroid-stimulating hormone
UMTBL	Upper Myanmar TB Laboratory
UV	Ultraviolet
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

Anti-tuberculous drug Abbreviations

Amikacin	Am
Amoxicillin/clavulanate	Amx/Clv
Bedaquiline	Bdq
Clofazimine	Cfz
Cycloserine	Cs
Delamanid	Dlm
Ethambutol	E
Ethionamide	Eto
Imipenem/Cilastatin	Ipm/Cln
Isoniazid	H
Levofloxacin	Lfx
Linezolid	Lzd
Meropenem	Mpm
Moxifloxacin	Mfx
p-aminosalicylic acid	PAS
Pretomanid	Pa
Prothionamide	Pto
Pyrazinamide	Z
Rifabutin	Rfb
Rifampicin	R
Streptomycin	S

Main definitions used in guidelines

Pulmonary tuberculosis (PTB): Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.

Extrapulmonary tuberculosis (EPTB): Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs and tracheobronchial tree (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, meninges, etc.).

Extensive (or advanced) pulmonary tuberculosis disease: the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.[1]

Severe extrapulmonary TB: presence of miliary TB, TB meningitis, osteoarticular TB or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe.[1]

Drug susceptibility testing (DST): in vitro testing using either molecular or genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.[1]

Drug-resistant TB (DR-TB): TB disease caused by a strain of *Mycobacterium tuberculosis (M. tuberculosis)* complex that is resistant to any TB medicines.[1]

Rifampicin-resistant TB (RR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e., MDR-TB), or resistant to other first-line or second-line TB medicines.[1] In these guidelines and elsewhere, MDR-TB and RR-TB patients are often grouped together as MDR/RR-TB and are eligible for treatment with MDR-TB regimens.

Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin.[1]

MDR-TB: TB caused by a strain of *M. Tuberculosis* complex that are resistant to at least both rifampicin and isoniazid with or without resistance to other first or second-line TB medicines.

Pre-extensively drug-resistant TB (pre-XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).[1]

[1] WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Extensively drug resistant TB (XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).[1]

New patient: a person with TB disease who has never been treated for TB or has only previously ever taken TB drugs for less than 1 month.[1]

Previously treated patient: a patient who has received 1 month or more of anti-TB medicines in the past. Previously treated patients may have been treated with a first-line regimen for drug-susceptible TB or a second-line regimen for drug-resistant forms (e.g. shorter MDR-TB regimen).[2]

Second-line TB medicine (or drug): an agent used for the treatment of drug-resistant TB. Refer to table 3.5.

Serious adverse event: an adverse event that leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly. Serious adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.[1]

Treatment outcomes: the categories for treatment outcomes and their definitions used in these guidelines were adopted from Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update (see in Chapter 4: 4.5 Treatment Outcomes for DR-TB patients)

Operational research or implementation research: "the use of systematic research techniques for programme decision-making to achieve a specific outcome". In the context of this document, these terms are also applied to research that aims to develop the critical evidence base that informs the effective, sustained, and embedded adoption of interventions within a health system, to improve health or patient outcomes. Such research deals with the knowledge gap between efficacy, effectiveness, and current practice to produce the greatest gains in disease control. Operational research also provides decision-makers with information to enable them to improve the performance of their health programmes.[1]

Executive summary

WHO updated recommendations in December 2022 to inform National TB Programmes and other stakeholders about the key implications for treatment of MDR/RR-TB, pre-XDR TB, and XDR-TB in order to allow for transition to injection free regimens. WHO consolidated/operational guidelines 2022 provided recommendations on the overall treatment which is mainly shorter oral regimens which are BPaLM/BPaL and 9-month all-oral (9-Oral) as priority regimens among eligible patients and longer treatment regimen (LTR) as 2nd priority option where shorter regimens cannot be prescribed. WHO also recommended management of DR TB patients by adopting patient centered approach, care and monitoring of patients.

The Updated National Guidelines on drug-resistant tuberculosis (DR-TB) treatment in Myanmar (2025) take into account all WHO recent recommendations and international best practices to meet the international standards of care. These guidelines are stressing upon universal DST (molecular DST) for all TB patients and 2nd Line DST (both molecular DST and phenotypic DST) for all MDR/RR-TB patients as nationwide practice. As such practices will lead towards appropriate regimen selection and better treatment outcome. Moreover, policy guidance has been made on priority testing for INH resistant and treating them per DST results and previous treatment exposure.

Adverse drug safety monitoring & management (aDSM) has been emphasized in the guideline to be applicable to all MDR/RR-TB TB patients and its appropriate R&R per NTP protocols. Not only that but also all minor to major side effects of drugs to be monitored and managed for optimum patient care.

Moreover, a patient-centered approach through appropriate pre-treatment and during treatment counselling has been also strongly recommended in the guidelines. Mental health care including early detection of depression and anxiety and addressing such challenges through a team-based approach has been stressed.

Likewise, MDR/RR-TB and co-morbid conditions management is the crucial part of management of DR-TB that includes DM, HIV, mental health, alcohol and substance use, hepatitis, and renal disease. There is sufficient evidence that adequate management of co-morbid conditions in DR-TB leads to better outcomes and improves treatment success rate.

Adopting the WHO updated recommendations in the Myanmar context, these guidelines supersede the following chapters of “Guidelines for the management of drug resistant TB (February 2017)”. The other chapters remain valid and will be applied in the implementation of programmatic management of drug-resistant TB.

	Chapter in 2017 guidelines	Updated Chapters of 2025 guidelines
1.	Chapter 2: Case finding strategies for MDR-TB	Chapter 1: Case finding strategies for DR-TB
2.	Chapter 3: Laboratory aspect of MDR-TB	Chapter 2: Laboratory aspect of DR-TB
3.1	Chapter 5: Treatment strategies for MDR-TB	Chapter 3: Treatment of DR-TB
3.2	Chapter 5.10 Adjunctive therapies in MDR-TB treatment	Chapter 6: Adjuvant therapies, interventions, care and support for DR-TB patients
4.	Chapter 8: MDR-TB treatment in special situations	Chapter 7: Treatment of MDR/RR-TB in special situation
5.	Chapter 9: MDR-TB and HIV co-infection	Chapter 7: Treatment of MDR/RR-TB in special situation
6.	Chapter 10: Management of side effects in MDR-TB patients	Chapter 8: aDSM
7.	Chapter 11: Monitoring of MDR-TB patients	Chapter 4: Monitoring and treatment outcome of DR-TB treatment
8.	Chapter 12: Treatment outcomes of MDR-TB patients	Chapter 4: Monitoring and treatment outcome of DR-TB treatment
9.	Chapter 13: Management to MDR-TB treatment failure	Chapter 3: Treatment of DR-TB
10.	Chapter 14: Management of XDR-TB	Chapter 3: Treatment of DR-TB
11.	Chapter 15: Treatment of mono and poly resistances	Chapter 5: Treatment of Hr-TB
		Chapter 9: Storage and supply chain management of medicines at field level
12.	Chapter 17: Information system and data management for DR-TB	Chapter 10: Information system and data management for DR-TB

1. Case finding strategies for DR-TB

Myanmar, a high TB/DR-TB burden country, its estimated TB incidence is 257,000 (475/100,000 population) and MDR/RR-TB incidence is 13,000 (24/100,000 population) cases for 2022[2]. In Myanmar, there were (2631) notified and (2512) treated DR-TB patients and achieved 47% of the NSP target (2021-2025) for DR-TB in 2023. Prior to 2022, DR-TB case finding was largely through screening of notified DS-TB patients, hence, notified DR-TB cases relied on DS-TB patients. As there is a yearly gap in treatment coverage (gap between notification and incidence) of DS-TB, which in turn has a DR-TB case finding gap.

In 2019, WHO recommended the use of the approved rapid molecular test (mWRDs) as the initial test to detect TB disease as well as resistance to several anti-TB agents before the initiation of appropriate therapy for all TB patients. Myanmar NTP has shifted its paradigm of case finding and diagnosis model by bringing CXR and Gene Xpert as point-of-care tests among TB presumptive. Case finding strategies should not be separately considered for DR-TB, rather it should be addressed as a holistic approach to find drug resistance among TB patients as one approach.

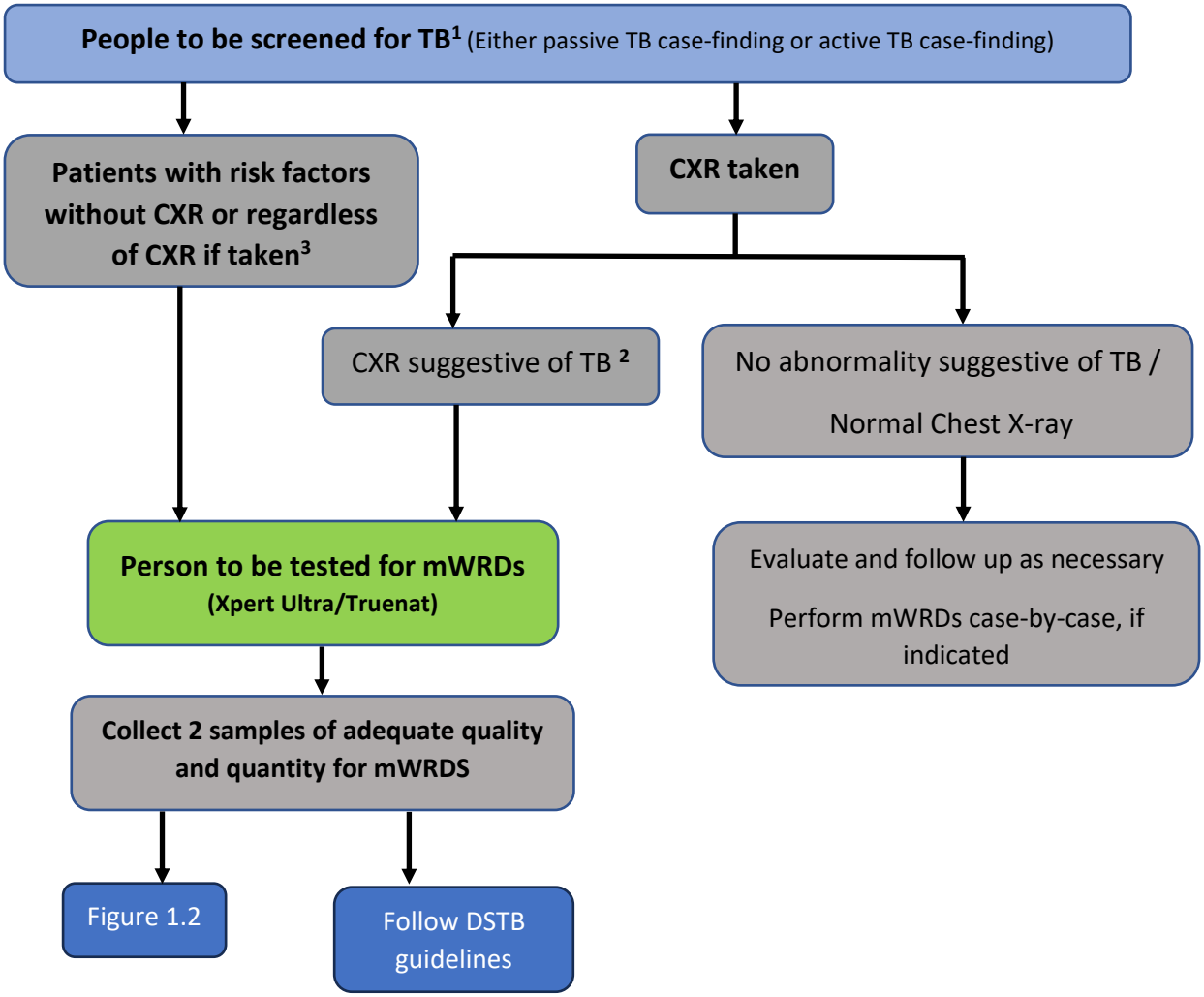
The focus of this chapter is case finding and algorithms for diagnosis of patients with TB and different forms of DR-TB that includes rifampicin-resistant TB (RR-TB), isoniazid-resistant TB (Hr-TB), polydrug resistant TB, multidrug-resistant TB (MDR-TB), pre-extensively drug-resistant TB (pre-XDR TB) and extensively drug-resistant TB (XDR-TB). The flow of TB case finding **(Figure 1.1)** starts with **people to be screened for TB** which include persons with any signs or symptoms of TB (cough, hemoptysis, weight loss, fever, or night sweats), systematic screening and medical check-up. After screening with CXR and/or symptoms, screen positive persons are to be further tested with mWRDS (Xpert Ultra/Truenat) for TB diagnosis **(Figure 1.2).**

DR-TB case detection requires bacteriological confirmation of TB and testing for drug resistance using rapid molecular tests, culture methods or sequencing technologies. Overall, an effective process for TB/DR-TB case finding requires:

- **Universal access to drug-susceptibility testing (DST)** for all TB patients (newly detected as well as previously treated)
- Proper evaluation of TB patients by **using WHO endorsed rapid diagnostic methods** for TB and DR-TB diagnosis
- A reliable surveillance system including **Recording and Reporting of DR-TB patients** as per NTP criteria.

[2] Global tuberculosis report 2023. Geneva: World Health Organization; 2023

Figure (1.1): TB case-finding flow



Footnote

[1] People to be screened for TB include persons with any signs or symptoms of TB (cough, hemoptysis, weight loss, fever, or night sweats), systematic screening (screening health centers attendee, screening in prison, contact screening, mobile outreach screen, etc.) and medical check-up

[2] CXR suggestive of TB includes ones with active or suspected, and healed lesions. In case of healed lesion, only patients with TB signs or symptoms are recommended to test with mWRDs

[3] The following groups are recommended for mWRDs regardless of CXR. They include high-risk groups and/or situations which CXR cannot be taken as described below:

- High risk of progression to TB disease – PLHIV with TB symptoms
- High risk of exposure to DR-TB - MDR/RR TB contact with TB signs and symptoms if CXR is not available
- Pregnancy with TB symptoms when CXR is not feasible to take
- Presumptive TB patients in areas where CXR is not available, samples to be tested using mWRDs (Xpert Ultra/Turenat) preferred if resources are allowed or microscopy as alternative. Sputum AFB positives are to be further sent and tested for mWRDs.
- Presumptive pulmonary TB children <10 years with independent risk factors which are < 2 years old, PLHIV, severe acute malnutrition is recommended Xpert test (Stool specimen of presumptive TB children will be tested with Xpert ultra as a pilot)
- Extra-pulmonary samples (CSF, lymph node aspirate) and gastric aspirate

NTP has fair geographical coverage of smear and Xpert MTB/RIF testing facilities nationwide and will be further expanded as per National Strategic Plan for TB (2021-2025). Currently, NTRL and other BSL3 Labs with the support of NHL and NTP are performing Drug Susceptibility Testing (DST) for 1st and 2nd Line drugs including rapid molecular testing prioritized with Xpert MTB/RIF, Xpert MTB/XDR, and Line probe assays (LPAs); with recent introduction of Xpert MTB/XDR modules. However, phenotypic DSTs both for FLD and SLDs are also performed by NTRL/BSL3 laboratories.

The major objective of early case finding is that patients should be initiated on an appropriate treatment regimen as soon as possible. Prompt treatment initiation will have a positive effect on patient outcomes and survival, while the treatment regimen can be modified/refined when additional testing results become available. It will have a substantial impact on disease transmission.

1.1 Case finding for DR-TB

1.1.1 Case finding of MDR/RR-TB

Xpert MTB/RIF, particularly Xpert MTB/RIF Ultra is the preferred initial diagnostic test for TB and RR-TB among presumptive TB clients (WHO 2020). The molecular testing methods (Xpert MTB/RIF and line probe assays) have been found to have a high sensitivity and specificity for detection of rifampicin and INH resistance (MDR/RR-TB). A negative result generally excludes rifampicin resistance and no further testing to confirm negative results is required. However, rarely, when a patient is strongly presumed to have RR-TB even after a negative molecular test, it may be useful to send samples for phenotypic culture-based DST for rifampicin and other drug resistance resulting from a small number of mutations occurring outside the *rpo*B hotspot region. **Diagnosis of MDR/RR-TB is determined by a single positive result (RR: rifampicin resistant detected) for high-risk patients** such as retreatment cases, non-converter, PLHIV, contact of MDR-TB and diabetes patients. The new patients without risk factors and if **Xpert MTB/RIF** result is RR TB with very low MTB detected, such results should be repeated by requesting fresh quality samples. (TB/DR-TB Diagnosis Algorithm, footnote 5).

In near future NTP may install **Truenat** technology (newly approved technology by WHO in 2019 to detect TB and RR-TB simultaneously) in hard-to-reach areas as this tool does not require air conditioning and can be powered by batteries with minimal training and in addition no annual calibration requirements.

When interpreting the laboratory results from molecular methods, it is pertinent that patient details such as **treatment history and risk factors for drug-resistant TB** should always be considered for treatment decision making.

As per updated NTP policy and updated diagnostic algorithm, following patients are to be tested with Xpert MTB/RIF Ultra or Truenat for enhanced and rapid molecular diagnosis of MDR/RR-TB.

1. Chest X-ray abnormality showing suggestive of TB (diagnosis purpose of sputum microscopy will no longer be done in these cases)
2. All notified PTB patients
3. Sputum smears positive at the follow-up sputum examination of DS-TB or during Hr-TB treatment (no conversion or reversion)
4. TB patients with diabetes mellitus
5. Close contact of MDR/RR-TB with TB signs and symptoms
6. PLHIV with TB signs and symptoms
7. Other cases to be considered individually by DR-TB committee

As per new NSP 2021-2025 NTP has already adopted and is striving to replace smear microscopy with a new diagnostic model which includes chest X-ray and Xpert MTB/RIF Ultra as a primary test among TB presumptive persons.

1.1.2 Case finding of pre-XDR TB

Xpert MTB/XDR or SL-LPA are recommended rapid molecular tests to be used for case finding of pre-XDR TB and additional resistance. The purpose of early case-finding for pre-XDR TB and knowing additional resistance is to design appropriate regimens which will result in better treatment outcome.

Followings are prioritized groups for Xpert MTB/XDR testing.

1. All notified MDR/RR-TB patients at baseline (to exclude H, FQs, Eto and second-line injectable drugs resistance)
2. Non-responders of MDR/RR-TB treatment patients who showed no improvement clinically or bacteriologically by month 4 or bacteriological/radiological deterioration during MDR-TB treatment
    - Lack of conversion by month 6 of MDR-TB treatment (observing culture up to 4 month) or
    - Culture reversion after culture conversion to negative
3. Failure/Relapse/LFU of MDR/RR-TB treatment
4. Previous history of treatment > 1 month with group A and group B drugs (to exclude FQ resistance)
5. Other - close contact of pre-XDR/XDR-TB patients, people who have indeterminate Xpert MTB/XDR results, patients as requested by the expert DR-TB committee or technical working group
6. Non-responders/failures of Hr-TB treatment (repeat testing with Xpert MTB/RIF to exclude RR and perform other tests as mentioned above)

All RR-TB specimens from patients diagnosed as MDR/RR-TB must be transported to the assigned culture and DST laboratory (or) to Xpert MTB/XDR site to get tested by Xpert MTB/XDR TB modules.

1.1.3 Case finding of XDR-TB patients

Phenotypic DSTs are to be used for case finding of XDR-TB among pre-XDR patients or MDR-TB patients with poor treatment response. Regular monitoring of culture during MDR/RR-TB or pre-XDR TB treatment is critical for detection of XDR-TB cases. MDR/RR-TB/pre-XDR treatment failure cases and follow-up culture results positive at month 4 and beyond are to be tested phenotypic second-line liquid DST especially for bedaquiline and linezolid. The turnaround time of SL pDST is about 2 to 2.5 months. Ideally all notified RR-TB are to be tested by pDST as baseline if resources allow.

1.1.4 Case finding of rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB)

TB strains resistant to isoniazid (Hr-TB), hampers the effectiveness of TB treatment as INH being one of the most potent drugs in TB treatment. Among non-converters and previously treated TB patients when RR-TB has been excluded by Xpert MTB/RIF, it is also important to rule out Hr-TB by requesting rapid molecular assays Xpert MTB/XDR or 2nd priority FL-LPA. An estimated 1.1 million people had TB disease caused by MTBC with resistance to INH and susceptibility to RIF (referred to as Hr-TB), which is largely undetected. Globally about 7% INH resistant TB has been reported (WHO TB report 2018) and patients with confirmed isoniazid resistance had worse outcomes – i.e., higher treatment failure (11% vs 1%); relapse (10% vs 5%); as well as higher rates of acquired drug resistance 8% vs 0.3% (Gegia et al 2017). While in Myanmar the estimated mono + poly-INH resistant-TB was 10.2% (8.7% -12%) among new and 20.8% (14.8% -28.5%) among retreatment TB patients.[3]

To detect INH resistant among TB patients **after ruling out RR-TB**, following categories should be tested Xpert MTB/XDR or FL-LPA directly from smear or indirectly from culture isolates:

1. Close contacts of Hr-TB patients who are CXR positive and/or have presumptive TB symptoms
2. Non-converter of DS-TB treatment, and RR-TB has been excluded.
3. Failure of DS-TB treatment, with Xpert MTB/RIF result “T or TI” (smear positive at 5th month of DSTB treatment should be first tested by Xpert MTB/RIF and then if it is negative for RR, then the Xpert MTB/XDR will be considered)
4. Others as per physician’s clinical judgment

NOTE: point 1,2,3 are the priority patients for testing with Xpert MTB/XDR or FL-LPA, while others depend upon resources available for testing.

[3] Fourth Nationwide Anti-TB Drugs Resistance Survey in Myanmar (2019-2020)

Most FL-LPA testing can be performed directly with smear positive samples or indirectly from culture isolates in smear negative samples. In case, INH resistant results are coming through culture and phenotypic DST which may take 4-6 or more weeks, then it is important to test again with Xpert MTB/RIF before enrolling on Hr-TB treatment. Likewise, Hr-TB patients should also be tested by Xpert MTB/XDR or SL-LPA to identify resistant to FQ (and SLIs). (See more details in Chapter on treatment of Hr-TB)

1.2 TB/DR-TB case finding in children

It is generally believed that attempting to diagnose TB microbiologically in children is difficult and meticulous and diagnostic evaluations using body fluids and tissue samples is challenging and not a common practice. As a result, TB patients amongst children may be missed and this deprives them of early treatment. Similarly, diagnosing MDR/RR-TB in children is also a challenge due to difficult to obtain samples and pauci-bacillary nature of disease.

Negative laboratory test results cannot reliably exclude TB in this age group. Therefore, clinical diagnosis continues to play an important role in the management of childhood TB. Physical examination, clinical history, contact history, radiography, response to treatment, and other assessments together can lead to a confident, empirical diagnosis of TB in young children and should be paired with available laboratory diagnostic testing to support and confirm a TB diagnosis where feasible. However, it is important to consider that the drug resistance pattern of a child case will be similar to the index case and a similar treatment regimen can be considered according to the DST of source case and other parameters.

The Xpert MTB/RIF and Xpert MTB/RIF Ultra have been recommended by WHO in 2021 to be used in children to test sputum, gastric aspirate, nasopharyngeal aspirate, and stool specimens for detection of pulmonary TB. However, all children suspicious of TB/RR-TB should be tested with stool samples by Xpert ultra. There are developing data to show that Xpert MTB/RIF testing done on stool after simple decontamination procedures can have a diagnostic yield closer to gastric aspirate and is also not invasive. Sputum induction should be performed in a properly ventilated area and requires specific infection control and biosafety measures to reduce the risk of MTB transmission that could result from aerosolization during the procedure. Xpert testing with cerebrospinal fluid (CSF), lymph node aspirate, lymph node biopsy for EPTB are recommended as the initial diagnostic test for TB and rifampicin-resistance detection rather than smear microscopy/culture and phenotypic drug-susceptibility testing.

Testing presumptive TB children with stool samples by Xpert MTB/RIF Ultra will be a priority. However, for sputum samples, most young children will not be able to produce adequate sputum specimens upon request and following practices may be adopted to obtain samples from children.

- Sputum induction with nebulized hypertonic saline may facilitate collection of

tracheobronchial secretions, especially in children who have a dry cough or no cough.

- Gastric lavage is the most common procedure for collecting specimens for Xpert MTB/RIF or culture and DST, especially early in the morning before the child has had anything to eat or drink.
- Fiber-optic bronchoscopy may be the best next step if gastric aspirates fail, in settings with appropriate facilities and technical expertise.
- Fine needle aspiration or biopsy should be considered where the anatomic location of disease includes sites outside the pulmonary parenchyma. It is important to note that such specimens should also be sent for pathology to rule out other diseases.
- Recent studies have demonstrated that TB detection is substantially improved when molecular WHO-recommended diagnostics (mWRD) are used to test more than one specimen per pediatric patient or with the combination of different samples.

Collecting the respiratory specimen at optimal times is important to enhance the yield e.g. early morning fasting gastric aspirate, before mobilization; induced sputum after fasting 2-4 hours; expectorated sputum early morning. Of note, sputum (induced or expectorated) should be minimum 3 ml, gastric aspirate 5 ml, gastric lavage 10 ml, bronchial-alveolar lavage (BAL) 3 ml, nasopharyngeal aspirate 2 ml.

In addition to that there are extra pulmonary samples useful to test by Xpert MTB/RIF or MTB/RIF Ultra to get diagnosis in children and can be obtained any time, e.g. CSF. For testing purposes CSF 2 ml and stool 5 gm is enough. Serosal fluids include pleura, pericardium, peritoneum, and synovium may also be helpful in diagnostics, but bacteriological yield is higher in tissues than fluids.

Children suspected of having pulmonary TB but with a single Xpert MTB/RIF negative result should undergo further diagnostic testing and evaluation, and **a child with high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.**

1.3 TB/DR-TB case finding in extra-pulmonary TB

It is recommended by WHO that whenever an extra-pulmonary sample is available it is pertinent that such samples should be tested by Xpert MTB/RIF and even now with more sensitive test Xpert MTB/RIF/Ultra. As per recent WHO recommendations in adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF or Xpert MTB/RIF Ultra may be used in CSF, lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens as the initial diagnostic test for the corresponding form of extrapulmonary TB and for RR-TB detection rather than smear microscopy/culture and Phenotypic DST.

1.4 TB/DR-TB case finding in HIV patients

TB/DR-TB and HIV co-morbid conditions are associated with high mortality and if TB/DR-TB patients are not detected early; the risk of disease transmission is high.

Early detection of MDR/RR-TB in PLHIV is being improved by using Xpert MTB/RIF and Xpert Ultra in diagnosis of TB in all presumptive TB patients among PLHIV. (See section on use of Xpert MTB/RIF). Myanmar NTP is using Xpert MTB/RIF and Xpert Ultra as the initial diagnostic test for TB in all presumptive patients of all PLHIV patients. Hence early detection of MDR/RR-TB is much enhanced in this population. Moreover, NTP with close collaboration with NAP will also be using Urinary LAM to assist in diagnosing TB followed by Xpert MTB/RIF.

In line with WHO recommendations in HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF Ultra may be used in blood, as a diagnostic test for disseminated TB.

As a matter of fact, diagnosis of TB in HIV-infected people is more complex and may be confused with other pulmonary or systemic infections. PLHIV are more likely than HIV-negative persons to have smear-negative TB or extra-pulmonary TB.

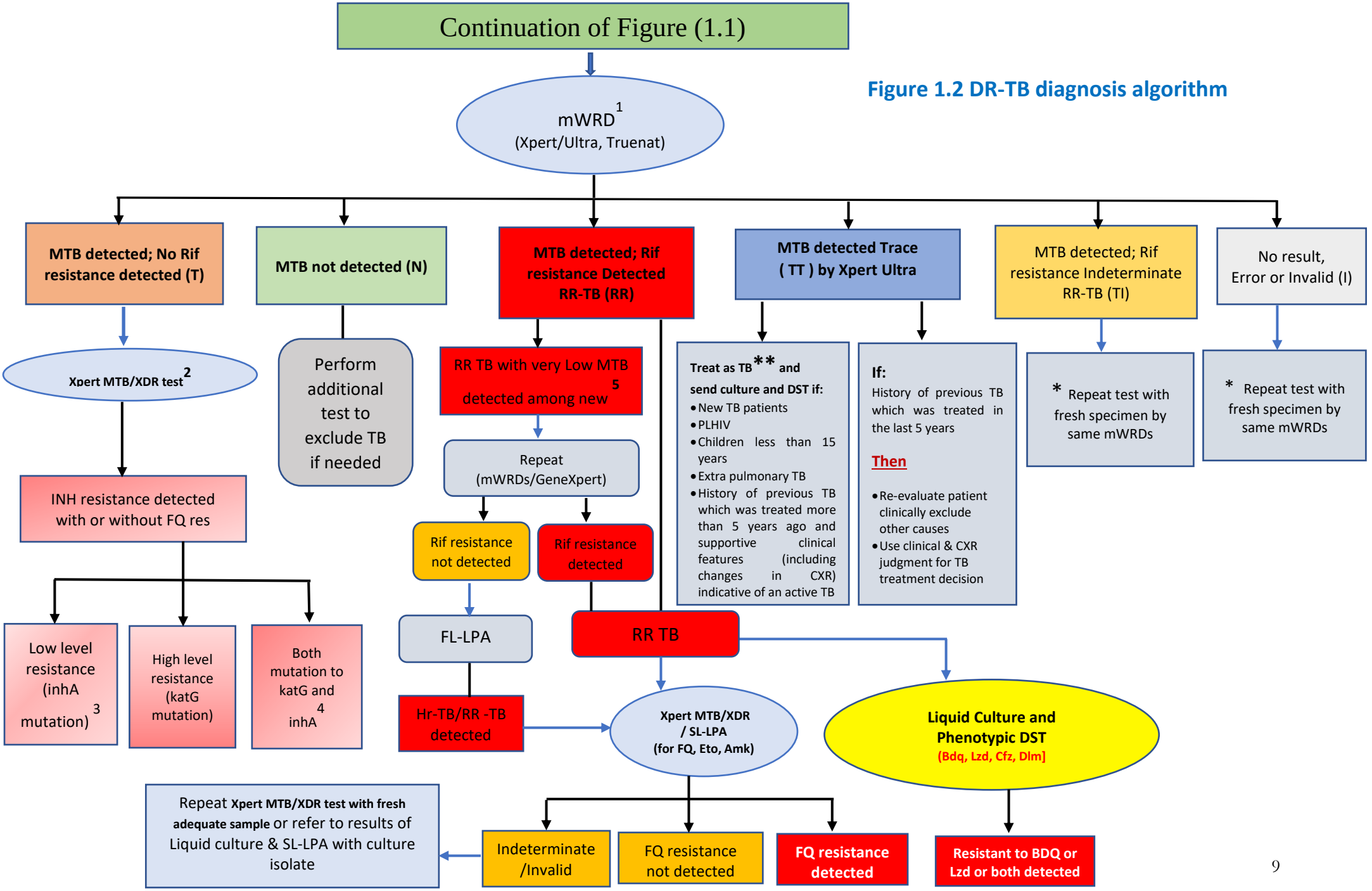


Figure 1.2 DR-TB diagnosis algorithm

Footnote:

1. Molecular WHO-recommended rapid diagnostic test (mWRD) - (Xpert= Xpert MTB/RIF assay; Ultra=Xpert MTB/RIF Ultra assay; Truenat or other centralized Dx platforms). In future, only Xpert MTB/RIF Ultra and Truenat will be used for initial tests.
2. Priority patients to perform Xpert MTB/XDR Test or FL-LPA to detect INH resistant are non-converter or failure of DS-TB patients when RR-TB has been excluded with Xpert MTB/RIF result "T or TI" and close contacts of Hr-TB patients who are CXR positive and/or have presumptive TB symptoms
3. High dose INH is likely to be effective; Eto is unlikely to be effective.
4. Both high dose INH and Eto are unlikely to be effective.
5. Do not repeat the test in new patients with close contact to MDR TB, PLHIV, TB/DM if MTB detected very low with RR detected.

*In case of inconclusive result (TI/I), repeat test with same mWRDs, and then proceed to LPA if repeated one is also inconclusive.

** Perform additional testing (Culture/DST, LPAs) to rule out RR TB/FQ resistant, consider treating as MDR/RR-TB if close contact of MDR/RR-TB

Action Points

- Case finding strategies should not be separately considered for DR-TB, rather it should be addressed as holistic approach to find drug resistance among TB patients as one approach
- Chest X-ray suggestive of TB and person eligible for mWRDs as per National policy should undergo Xpert MTB/RIF or Xpert Ultra testing and if RR TB is reported further to be tested by Xpert MTB/XDR test before treatment initiation
- Diagnosis of MDR/RR-TB is determined by a single positive result (RR: rifampicin resistant detected) for high risk patients such as retreatment cases, non-converter, PLHIV, contact of MDR-TB and diabetes patients. Those patients without risk factors if **Xpert MTB/RIF** result is RR TB with very low MTB detected, such results should be repeated by requesting fresh quality samples.
- The Xpert MTB/RIF and Xpert MTB/RIF Ultra have been recommended by WHO in 2021 to be used in children to test sputum, gastric aspirate, nasopharyngeal aspirate, stool specimens for detection of pulmonary TB. Stool specimen to be a priority testing for children if sputa sample not available
- To detect INH resistant among TB patients after ruling out RR-TB, all high risk for INH resistant to be tested by by Xpert MTB/XDR test preferably before treatment initiation.
- Always monitor and ensure that quality sample is being collected and referred for testing.

2. Diagnosis of DR-TB and role of laboratories in PMDT

Since DR-TB diagnosis is based on microbiological (phenotypic and molecular) confirmation, the quality-assured laboratory results play an essential role in the management of DR-TB patients. DR-TB diagnosis can be done by isolating the bacteria by culture, identifying it as belonging to the *M. tuberculosis* complex (MTBC), and conducting drug susceptibility testing (DST) using solid or liquid media or by performing molecular tests to detect DNA of Mycobacterium tuberculosis and mutations associated with resistance.

Testing for drug resistance allows the use of appropriate treatment regimens for patients from the beginning, which improves treatment results and controls TB transmission. Spread of drug-resistant TB strains and the management of patients diagnosed with DR-TB are among the most challenging tasks faced by national TB control programme.

In recent years, in addition to MOH contribution substantial laboratory support came from The Global Fund while technical support came from Supra-national TB Reference Laboratory (Chennai, India) through WHO. Bio- safety level-3 (BSL-3) laboratories have been established in Yangon and Mandalay since 2010. Taunggyi State TB Laboratory has been upgraded to BSL-3 laboratory in 2017 and another BSL-3 laboratory in Yangon has been opened in 2018. Mawlamyaing State TB Laboratory has been promoted to BSL-3 facility in 2019 and rapid TB diagnostic tools have been started since June 2020. The new rapid molecular DST platform Xpert MTB-XDR has been scaled up nationwide in 2022.

The full monitoring requirements of patients clinically, bacteriologically, and for adverse effects are described in other Chapters. This chapter addresses only laboratory aspects of diagnosis of DR-TB and Laboratory (microbiological) monitoring DR-TB management.

2.1 General definitions for the laboratory and drug susceptibility testing (DST)

The following are definitions of the laboratory aspects in relation to DST discussed in this chapter:

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

- Genotypic DST (molecular DST): Genotypic testing detects the genetic mutation in *M. tuberculosis* bacterium/ genome responsible for or associated with the resistance. (Note: genotypic testing is also used to detect the presence of the TB bacterium itself).
- Cross-resistance: Mutations that confer resistance to one anti-TB drug may also confer resistance to some or all the members of the drug family and, less commonly, to members of different drug families.
- Direct testing: Direct testing refers to testing directly from a clinical sample (most commonly a sputum specimen). In direct DST the clinical sample (after processing) is used directly to inoculate the media or as the clinical sample in a molecular test.
- Indirect testing: Indirect testing refers to testing performed on culture isolates of *M. tuberculosis* that has been grown from a clinical sample.

2.2 Sputum collection and transport system

Good quality specimens are essential for proper laboratory diagnosis of TB and drug- resistant TB. However, collecting sputum, the most frequent specimen for pulmonary TB testing, represents a significant hazard as coughing produces potentially infectious aerosols. Therefore, specific measures must be taken to minimize exposure. Wherever possible, sputum specimens should be collected in specified sputum collection booths or **open air,** away from other patients, where infectious droplets are rapidly diluted and UV rays can inactivate TB bacilli. Sputum specimens should not be collected inside laboratories, toilets, waiting rooms, reception rooms, or any other enclosed space. Collecting a good specimen in a safe manner also requires **trained staff** to provide the patient with effective instructions (**Annex 2**: Sputum collection and Transportation) as well as with adequate material and procedures.

The quality of sputum is also important to get the quality assured laboratory results. Specimens should be collected in wide-mouthed containers that are clear, and leak-proof. Specimens should be promptly transported to the laboratory in leak-proof containers surrounded by absorbent material in a shock-resistant outer package. Patient information should be written on the container (not on the lid).

Prior to transport, specimens should be kept in a cool place, preferably in a refrigerator at **+4°C**. If travelling time is long, cold boxes should be used during the transportation.

It is preferable to transport specimens rather than have the patient travel long distances to provide a specimen. The logistics of the transport system are described in Annex 2. If the patient lives close to the TB diagnostic center, he or she can present themselves for a sputum collection where should be outside of the laboratory at a separate safe designated place.

2.3 Procedures and recommendations for genotypic DST, culture & phenotypic DST and smear microscopy

2.3.1 Genotypic DST (molecular tests)

Genotypic methods have considerable advantages when PMDT is being scaled up, in particular with regard to their speed, the standardization of testing, their potential high throughput and reduced requirements for biosafety. Nucleic acid amplification technologies, which can amplify either DNA or RNA, use polymerase chain reaction (PCR) and this genotypic DST holds promises for significant gains in speed and performance for DST. Genotypic testing used in NTP are: Xpert® MTB/RIF assay, Xpert® MTB/RIF Ultra, Truenat MTB, Genotype MTBDR *plus* Test (1st line LPA), and Genotype MTBDR *sl* Test (2nd line LPA) and Xpert MTB/XDR. In addition, Whole Genome Sequencing (WGS/Next Generation Sequencing (NGS) is also being used in Myanmar for specific purposes.

2.3.1.1 Xpert® MTB/RIF and Xpert MTB/RIF Ultra assay

In 2010, WHO endorsed the Xpert® MTB/RIF assay which is an automated cartridge- based nucleic acid amplification test for simultaneous detection of TB and rifampicin resistance. Xpert MTB/RIF is a fully automated molecular diagnostic test that can detect DNA of MTBC and common mutations associated with rifampicin resistance (*rpoB* gene mutation) directly from sputum specimens within two hours. As per WHO 2020 diagnostic guidelines Xpert MTB/RIF and Xpert MTB/RIF Ultra to be used as an initial priority rapid test for diagnosis of TB/MDR-TB instead of smear microscopy, culture and phenotypic DST. The assay has similar sensitivity, specificity and accuracy as culture on liquid media and can be used from both smear positive and negative specimens. In most settings, particularly where fixed dose combination first line anti-TB drugs are used, resistance to rifampicin is highly associated with resistance to isoniazid. Detection of rifampicin resistance therefore serves as a reliable (although not complete) proxy for MDR-TB in many settings leading to development of MDR-TB. Another significant advantage of using Xpert MTB/RIF is that it can be done in a simple laboratory setting and does not require highly skilled technicians if proper training has been provided. From 2023 onward NTP adopted to use the Ultra cartridges in routine practice.

(a) Recommendations for use of Xpert® MTB/RIF

It is now recommended that in adults and children with signs and symptoms of Pulmonary TB, Xpert MTB/RIF should be used as a primary test to diagnose TB and RR-TB instead of smear microscopy, culture and phenotypic DST (WHO 2020). For diagnosis of PTB in children, with signs and symptoms of TB the ***sputum, gastric aspirates, nasopharyngeal aspirates and stool samples***

should be used for testing with Xpert MTB/RIF rather than microscopy, culture and phenotypic DST. Moreover, similar applies for the ***CSF samples*** testing for adults and children with signs and symptoms of TB Meningitis. Furthermore, it is also recommended that **EP samples (*lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens*)** if available from adults and children with signs and symptoms of EPTB to be tested by Xpert MTB/RIF instead of smear microscopy and Culture. In PLHIV (both adults and children) with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in ***blood***, as a diagnostic test for disseminated TB.

The above mentioned recommendations will be applied at field level as per NTP Xpert testing policy for specified samples, such as sputum , gastric aspirate, lymph node aspirate and CSF.

(b) Recommendations for use Xpert® MTB/RIF Ultra

The Xpert MTB/RIF Ultra assay (hereafter called Xpert Ultra) uses the same GeneXpert® platform as the Xpert MTB/RIF test, with improved sensitivity and reliability of detection of MTBC and RIF resistance. However, the higher sensitivity of Xpert Ultra is accompanied by a slight loss of specificity (i.e. an increase in the number of patients incorrectly identified as having active TB). To address sensitivity, Xpert Ultra uses two multicopy amplification targets (IS6110 and IS1081) and a larger PCR reaction chamber; thus, Xpert Ultra has a lower LOD than Xpert MTB/RIF i.e 16 colony forming units [cfu]/mL and 131 cfu/mL, respectively (WHO 2021).

The Xpert Ultra assay can detect very small numbers of non-viable or non-replicating bacilli, particularly in patients with a history of TB treatment (i.e. completed within the past 5 years). Such non-viable bacteria may also be detected by the other molecular WRDs, though less frequently. The increased sensitivity and loss of specificity are primarily related to the Xpert Ultra "trace" call. The decision pathway should include criteria for interpreting the "MTB detected trace" results, to balance the potential harms of overtreating patients with a false-positive result with the potential benefits of increased numbers of correctly diagnosed TB patients and decreased mortality associated with TB. Overall Xpert Ultra is 5% more sensitive for detection of MTB than Xpert MTB/RIF and 3% less specific than Xpert MTB/RIF. At very low bacteria loads, Xpert Ultra can give a trace result, which is not based on amplification of *rpoB* target and therefore does not give result/information for Rif susceptibility or resistance. **Please be informed that the trace result provides no information on RIF resistance.**

Furthermore, the use of analysis based on melting temperature instead of real-time PCR analysis allows Xpert Ultra to better differentiate silent from resistance-conferring mutations, and minimizes false results on RIF resistance, especially in samples with a low bacterial load. In line with WHO recommendations,

- Xpert Ultra **should** be used in adults with signs and symptoms of TB **without** a prior history of TB or with a **remote** history of TB treatment (> 5 years since end of treatment), instead of smear, culture and phenotypic DST to detect TB and RR-TB . However, Xpert Ultra **may** be used in adults with signs and symptoms of TB and a prior history of TB with an end of treatment within the last five years (WHO 2020).
- In **children** with signs and symptoms of **pulmonary TB**, Xpert Ultra **should** be used as the initial diagnostic test for TB rather than smear microscopy/culture in sputum, nasopharyngeal aspirates, gastric aspirates and stool[4];
- In **adults and children** with signs and symptoms of **TB meningitis**, Xpert Ultra **should** be used in cerebrospinal fluid (CSF) as an initial diagnostic test for TB meningitis rather than smear microscopy/culture;
- In adults and children with signs and symptoms of **extrapulmonary TB**, Xpert Ultra **should** be used for **rifampicin-resistance detection** rather than culture and phenotypic drug susceptibility testing;
- In **adults** with signs and symptoms of **pulmonary TB** who have an Xpert Ultra **trace** positive result on the initial test, **repeated** testing with Ultra may **not** be used;
- In **children** with signs and symptoms of pulmonary TB in settings with pretest probability 5% or more and an Xpert **Ultra negative** result on the first initial test, repeated one Xpert Ultra test (**for a total of two tests**) in sputum and nasopharyngeal aspirate specimens **may** be used.

2.3.1.2 Xpert MTB/XDR testing

Xpert MTB/XDR is a low complexity automated NAATs for detection of resistance to isoniazid and second-line anti-TB agents, endorsed by WHO in early 2021. It has a high diagnostic accuracy in people with microbiologically diagnosed pulmonary TB, overall pooled sensitivity (95% CI) for isoniazid resistance detection was 94.2% (89.3 to 97.0) and specificity was 98.0% (95.2 to 99.2). Overall pooled sensitivity (95% CI) for fluoroquinolone resistance detection was 93.1% (88.0 to 96.1) and specificity was 98.3% (94.5 to99.5). Overall pooled sensitivity (95% CI) for amikacin resistance detection was 89.1% (80.9 to 94.1) and specificity was 99.5% (96.9 to 99.9). Overall sensitivity (95% CI) for ethionamide resistance detection was 96.4% (92.2 to98.3) and specificity was 100.0% (82.5 to 100.0).[5]

Xpert MTB/XDR detects resistance to isoniazid (target genes: *inh*A promoter, *kat*G, *fab*G1, *oxy*R-*ahp*C intergenic region), ethionamide (*inh*A promoter), fluoroquinolones (*gyr*A and *gyr*B), and

[4] WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022

[5] Update on the use of nucleic acid amplification tests to detect TB and drug-resistant TB: rapid communication. Geneva: World Health Organization; 2021.

amikacin (*rrs* promoter) and is positioned as an add-on or "reflex test" in patients with rifampicin resistance detected by Xpert MTB/RIF or Ultra. A key benefit of the Xpert MTB/XDR assay is that it requires the same sample processing steps as Xpert MTB/RIF and Ultra, which have demonstrated robustness in field conditions. Moreover, it also has minimal biosafety requirements, offers rapid turn-around times (results in less than 90 minutes) and can be operated by health personnel with limited training. [6] The limit of detection for Mycobacterium tuberculosis by Xpert MTB/XDR (136 CFU/ml) is comparable to MTB/RIF (131 CFU/ml), but not as low as Ultra (16 CFU/mL).

One module can run up to four Xpert MTB/RIF or Ultra tests, and five Xpert MTB/XDR tests, in a single 8-hour shift. This new tool has been used in Myanmar Since October 2022 and has been recently expanded to all States and Regions.

Table 2.1. Drug related gene targets, codon regions and nucleotide sequences that determine presence of variants associated with drug resistance in the Xpert MTB/XDR assays

Drug	Gene target	Codon regions	Nucleotide
Isoniazid	*inhA* promoter	Not applicable	–1 to –32 intergenic region
	katG	311–319	939–957
	fabG1	199–210	597–630
	oxyR-ahpC intergenic region	Not applicable	–5 to –50 intergenic region (or –47 to –92[a])
Ethionamide	*inhA* promoter	Not applicable	–1 to –32 intergenic region
Fluoroquinolones	*gyrA*	87–95	261–285
	gyrB	531–544 (or 493–505[a])	1596–1632
Amikacin, capreomycin and kanamycin	*rrs*	Not applicable	1396–1417
Amikacin and kanamycin	*eis* promoter	Not applicable	–6 to –42 intergenic region

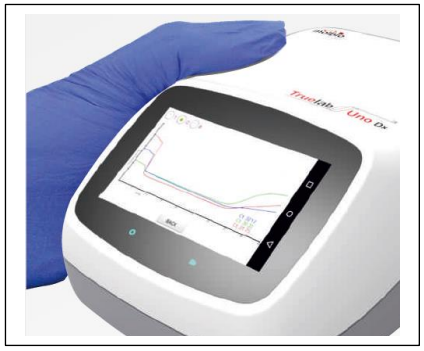
[6] Cao Y, Parmarl H, Gaur R, et al. Xpert MTB/XDR: a ten-color reflex assay suitable for point of care settings to detect isoniazid, fluoroquinolone, and second line injectable drug-resistance directly from Mycobacterium tuberculosis positive sputum. BioRxiv 2020; preprint [https://doi.org/10.1101/2020.09.08.288787].

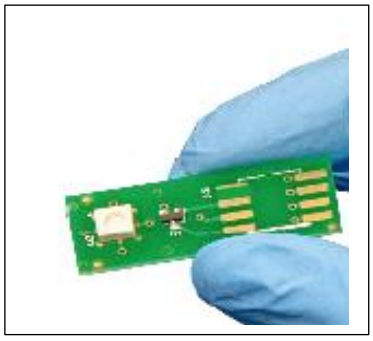
Table 2.2: Sensitivity and specificity of Xpert MTB/XDR, phenotypic DST and sequencing

Drugs	Xpert MTB/XDR		Phenotypic DST		Sequencing	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Isoniazid	94.2	98.0	91.4	99.1	98.8	98.7
Fluoroquinolones	93.1	98.3	93.1	98.5	93.3	100
Amikacin	89.1	99.5	91.9	99.4	96.4	100
Ethionamide	96.4	100.0	64.7	98.3	97.2	100

2.3.1.3 Truenat MTB, MTB Plus and MTB-RIF Dx assays

This recently WHO (2020) recommended molecular rapid assay is for use in peripheral laboratories with minimal infrastructure and trained technicians. The system uses a chip-based real-time micro-PCR for the semiquantitative detection of *Mycobacterium tuberculosis* complex directly from sputum specimens, and report results in less than an hour. The assay uses an automated, battery-operated device to extract, amplify and detect specific genomic DNA loci of TB bacilli.





For Rif-resistant TB detection it is a two-step assay. If the TB assays (Truenat MTB or MTB Plus) result is positive, an aliquot of extracted DNA is tested on Truenat MTB-RIF Dx assay to detect mutations associated with RIF resistance.

WHO recommended this test for:

- In adults and children with signs and symptoms of pulmonary TB, the Truenat MTB or MTB Plus may be used as an initial diagnostic test for TB rather than smear microscopy/culture.

- In adults and children with signs and symptoms of pulmonary TB and a Truenat MTB or MTB Plus positive result, Truenat MTB-RIF Dx may be used as an initial test for rifampicin resistance rather than culture and phenotypic DST:

These recommendations apply to the use of the test with sputum specimens from people living with HIV (PLHIV), based on extrapolation of the data on test performance with smear-negative sputum specimens.

These recommendations apply to the use of the test with sputum specimens from children, based on extrapolation of the data from adults, although the test is expected to be less sensitive in children.

NTP is now planning to conduct operational research for using this tool in hard-to-reach areas of Myanmar and study results will further update and based on NTP policy about expanded use of this tool in Myanmar where indicated.

2.3.1.4 Line Probe Assays - FL-LPA (GenoType MTB DRTBplus) & SL-LPA (GenoType MTBDRsl)

In the LPA control band called TUB band, this zone hybridizes with amplicons generated from all members of MTBC. If the TUB zone is negative the test specimen doesn't contain bacteria belonging to MTBC. The results from these molecular assays are available within three days. However, the results turnaround time might be different while using smear negative samples.

Following are the recommendations for use of FL-LPA and SL-LPA use.

(a) FL-LPA

First-line LPA (FL-LPA) such as GenoType MTBDR*plus* assay allows the detection of resistance to RIF and INH.

WHO in 2020 recommends using FL-LPA in the following situations:

- For smear-positive sputum specimen or a cultured isolate of MTBC, commercial molecular LPAs may be used as the initial test instead of phenotypic culture-based DST to detect resistance to RIF and INH.

- These recommendations apply to the use of FL-LPAs for testing smear-positive sputum specimens (direct testing) and cultured isolates of MTBC (indirect testing), from both pulmonary and extrapulmonary sites.

- Conventional culture-based DST for INH may still be used to evaluate patients when the LPA result does not detect INH resistance. This is particularly important for populations with a high pre-test probability of resistance to INH.

FL-LPA is not recommended for the direct testing of sputum smear-negative specimens for the detection of Mycobacterium tuberculosis complex (MTBC).

As per NTP current testing policy for FL-LPA, priority patients to perform FL-LPA are patients with TI or I result whose 2nd time recheck of mWRDs are still inconclusive; discordant result of RR very low detected new patients; and MTB detected trace "TT".

(b) SL-LPA

Second-line LPA (SL-LPA) such as the GenoType MTBDR*sl* assay allow the detection of resistance to fluoroquinolones and SLIs (Amikacin, Kanamycin, Capreomycin).

WHO in 2020 recommends using SL-LPA in the following situations:

- For patients with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to FQs and Am
- These recommendations apply to the use of SL-LPA for testing sputum specimens, irrespective of the smear status and cultured isolates of MTBC from both pulmonary and extrapulmonary sites.
- Culture-based phenotypic DST may be useful in evaluating patients with negative SL-LPA results, particularly in populations with a high pre-test probability for resistance to FQs or Am.
- SL-LPA tests are also useful for detecting FQ resistance before starting therapy for Hr-TB.

As per NTP policy all RR diagnosed patients are subject to be tested by (Xpert MTB/XDR) or SL-LPA or at baseline to diagnose FQ resistance.

Table 2.3. Performance characteristics of molecular tests for the detection of TB

Performance of molecular WRDs for the detection of MTBC in adults with signs and symptoms being evaluated for pulmonary TB compared with a microbiological reference standard		
Test	**Pooled Sensitivity**	**Pooled Specificity**
Xpert MTB/RIF to detect MTBC	85% (95% CrI: 0.82–0.88)	99% (95% CrI: 0.97–0.98)
Xpert Ultra to detect MTBC	90% (95% CrI: 0.84–0.94)	96% (95% CrI: 0.93–0.98)
Truenat MTB to detect MTBC	73% (95% CI: 0.68–0.78)	98% (95% CI: 0.97- 0.99)
Truenat MTB Plus to detect MTBC	80% (95% CI: 0.75–0.84)	96% (95%CI: 0.95–0.97)

CI: confidence interval; CrI: credible interval

Table 2.4: Performance characteristics of molecular tests for the detection of DR- TB

Performance of molecular WRDs for the detection of drug resistant TB in adults with signs and symptoms being evaluated for pulmonary TB compared with a microbiological reference standard		
Test	**Pooled Sensitivity**	**Pooled Specificity**
FL-LPA for detecting INH resistance	90%	99%
FL-LPA for detecting RIF resistance	97%	99%
SL-LPA for detecting FQ resistance	86%	99%
SL-LPA for detecting Am	87%	99.5%
Xpert MTB/XDR for detecting INH resistance	94.2% [89.3 - 97.0]	98.0% [95.2 - 99.2]
Xpert MTB/XDR for detecting FQ resistance	93.1% [88.0 - 96.1]	98.3% [94.5 - 99.5]
Xpert MTB/XDR for detecting Am resistance	89.1% [80.9 - 94.1]	99.5% [96.9 - 99.9]
Xpert MTB/XDR for detecting Eto resistance	96.4% [92.2 - 98.3]	100% [82.5 - 100]

Low-level resistance and high-level resistance: to apply in clinical practice[7]

Mutations conferring resistance to H and Mfx are stratified into mutations associated with a low-level increase in MIC and high-level increase in MIC depending on their associated MICs distribution. This stratification has important implications for the inclusion of H and Mfx in the treatment regimen since resistance due to mutations associated with low-level increases in MICs for H or Mfx may be overcome by increasing the drug dose.

For Isoniazid:

- ✓ *InhA promoter mutations detected/inferred (in the absence of any katG mutation): associated with low-level increase in MIC, increasing the drug dose (up to 15 mg/kg per day) may be effective:*
- ✓ *katG mutation detected/inferred: associated with high-level increase in MIC, the use of isoniazid even at higher dose is less likely to be effective.*
- ✓ *inhA promoter and katG mutations: associated with high-level increase in MIC, isoniazid cannot be considered as an effective medicine.*

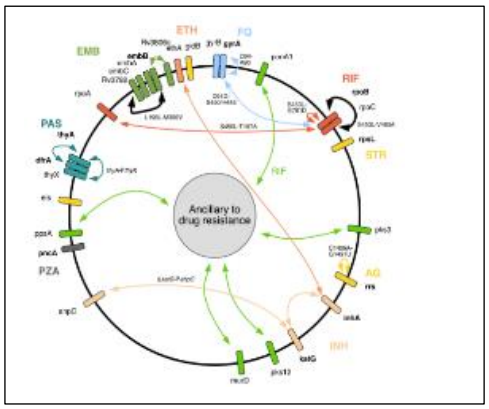
[7] GLI. Line probe assays for drug resistant tuberculosis detection Interpretation and reporting guide for laboratory staff and clinicians.

For Moxifloxacin:

- ✓ *Mutations A90V, S91P, D94A in gyrA, mutations N538D and E540V in gyrB detected or gyrA/gyrB mutations inferred: Mutations associated with a <u>low-level increase in MIC</u> (MIC increases above the critical concentration (CC)[8] but below the clinical breakpoint (CB)[9], <u>high dose Mfx</u> (up to 800 mg daily to adults), is likely to be effective; additional diagnostic action is recommended to perform phenotypic DST for Mfx at CB to exclude resistance. Moxifloxacin could be used at a higher dose and the regimen should be reevaluated based on phenotypic DST results at CB.*

- ✓ *Mutations D94N/D94Y, D94G and D94H in gyrA detected: Mutations associated with a <u>high-level increase in MIC</u> (MIC increases above the CB), Mfx cannot be considered as an effective medicine.*

2.3.1.5 Next-generation Sequencing/ Whole Genome Sequencing



Next-generation sequencing (NGS) or whole genome sequencing (WGS) is a powerful tool with the capacity to improve tuberculosis management and control through the rapid and accurate detection of all clinically relevant mutations, and thereby the rapid diagnosis of drug-resistant TB (DR-TB) in clinical specimens. WGS can provide the near complete genome of Mycobacterium tuberculosis (MTB) in a sample, while targeted NGS can generate MTB sequence data at specific genetic loci of interest.

The use of WGS in epidemiological investigations has allowed for in-depth resolution of transmission events, compared to traditional epidemiological investigations. This is important for the coordination and optimization of local and global TB control measures, especially in early

[8] the lowest concentration of an antibiotic in vitro that will inhibit the growth of 99% of phenotypically wild type strains of bacteria

[9] The concentration of antibiotic used to define whether an infection by a particular bacterial strain/isolate is likely to be treatable in a patient. Typically, these are defined as susceptible or resistant to an antibiotic.

detection of MDR/XDR-TB outbreaks. In addition to guide the clinical decision for DR-TB treatment NGS/WGS could identify strain lineage, resistance mechanisms for TB surveillance and recognize the genetically related strains for the resolution of transmission chains to direct TB control efforts in public health.

2.3.2 Culture and phenotypic DST

All procedures of culture and phenotypic DST for DR-TB samples must be handled in a Class II biological safety cabinets in bio-safety level 3 laboratories. A summary of culture and DST methods is provided in Table 2.5.

Both solid and liquid cultures are used for DR-TB diagnosis and monitoring. But after introducing (and expansion of) Xpert MTB/RIF tests in NTP, cultures are usually used to conduct diagnostic culture and DST for first- or second-line drugs when molecular tests are either not available or inconclusive as well as follow up cultures to monitor the patient's response to treatment.

For culture, pretreatment decontaminating procedure of sputum was done and then treated pellet was inoculated on Lowenstein-Jensen (LJ) media or Middlebrook 7H9 broth bottles according to standard operating procedures. In solid culture, the culture bottles must be incubated at 37 °C and read weekly until colonies are observed. If there is no growth up to six to eight weeks, the result will be given as "culture-negative". In liquid culture the culture bottles are incubated in the Mycobacterium Growth Indicator Tube system (MGIT-960®) and the machine automatically reads the culture bottles every 60 minutes. Positive growth can be detected within a week and if there is no growth after 42 days, culture negative results will come out from the machine.

2.3.2.1 Drug Susceptibility Testing (DST) on solid culture

DST for both first- and second-line anti- TB drugs on solid media (LJ media) can be performed in Yangon and Mandalay BSL-3 laboratories. DST on solid culture media is performed at baseline only for diagnosis of MDR-TB or for confirmation of Xpert MTB/RIF tests during DOTS Plus pilot project and early PMDT period but now no further routine confirmation of solid DST is needed whenever rifampicin resistant is shown by Xpert MTB/RIF test for individual case management. DST results will be obtained in two and a half to three months after the original collection of the sputum as culture is grown first and then DST is performed.

For first-line anti-TB drugs, resistance to isoniazid, rifampicin, streptomycin, and ethambutol are tested. The second line phenotypic DST is performed according to the physician's request and usually tests for levofloxacin, moxifloxacin, and amikacin. For each strain, the number of organisms resistant to each drug concentration must be expressed as a percentage of the number of organisms growing on the drug-free tubes. Resistance is defined when 1% or more growth occurs in drug-containing tubes compared to the drug-free tubes.

2.3.2.2 Liquid culture and liquid DST

Liquid culture and DST are done through the Mycobacterium Growth Indicator Tube system (MGIT-960®). This system uses a liquid medium, Middlebrook 7H9 broth, which has better recovery and faster growth of mycobacteria. The growth supplement and a combination of antimicrobial agents (PANTA) are added to suppress the growth of contaminants. The inoculated tubes are put in MGIT machine which can hold 960 tubes at one time and incubated at 37 °C. The calibrated tubes in the machine evaluate the inoculated tubes for growth detection every 60 minutes. The positive tubes are shown by a flashing red indicator lamp on the screen of the machine drawer. Tubes flagged positive are removed after 24 hours and further tested for confirmation of *M. tuberculosis*. (The tubes can also be visualized manually under ultraviolet light or can be read with the MGIT Tube Reader.) Growth can be detected as early as 4 to 12 days. Negative tubes are shown by a flashing green indicator lamp on the screen of the machine drawer 42 days after inoculation of the tubes. The DST is performed in the same MGIT machine from inoculated liquid culture positive tubes into the drug containing tubes.

The drugs tested for first-line anti-TB drugs by liquid media are isoniazid, rifampicin, streptomycin and ethambutol. The drugs tested for second-line anti-TB drugs by liquid media are Levofloxacin, moxifloxacin, and amikacin. Currently, NTRL Yangon and Mandalay BSL-3 laboratories plan to test bedaquiline, delamanid, linezolid and clofazimine in 2024. Results are mostly available within 3 weeks from the inoculation of *M. tuberculosis* isolates into drug containing MGIT tubes.

2.3.2.3 Identification of M. tuberculosis

Isolated strains of mycobacterium are not always *M. tuberculosis*. As virulence and drug susceptibility patterns vary according to the species of mycobacterium, all positive mycobacterium cultures must be tested to confirm *M. tuberculosis* complex (MTBC). The growth from any positive culture either from solid or liquid is identified by growth rate, colonial morphology, smear microscopy from positive growth and rapid immunochromatographic assay from culture isolates to ratify MTBC. This assay is based on the detection of a specific protein, MPT64, which is secreted specifically by members of MTBC. The results are available within 15 minutes.

2.3.2.4 Nontuberculous mycobacteria (NTM) Detection

Both MTB and NTMs show positivity to the conventional smear acid-fast staining method. Therefore, differential diagnosis of MTB and NTM species is a significant challenge and often

misleading. Thus, the incidence of NTM has been underestimated in many TB-endemic countries. While the identification of NTM by culture, TB reference laboratories are usually using immunochromatographic assay which detects MPT64 antigen, secreted specifically by members of the MTBC. If immunochromatographic assay is negative, then it is reported as NTM.

2.3.3 Smear microscopy

Smear microscopy is a low-cost and essential frontline tool for diagnosis of TB (but not drug-resistant TB). However, with the more advancements in rapid molecular tests availability the role of smear microscopy is being phased out gradually. The newly NTP recommended algorithm (Fig1.1) emphasizes on using CXR and Gene Xpert based algorithm for presumptive TB patients to diagnose TB and RR-TB. The sputum smears are stained using the Ziehl-Neelsen staining method and examined with a bright field binocular microscope and graded according to WHO grading for AFB microscopy. Auramine staining with a fluorescence microscopy is also used instead of bright field microscopy especially in high microscopy workload centers and can increase sensitivity by more than 10%. Microscopy for AFB cannot distinguish viable from non-viable organisms nor differentiate between drug-susceptible and drug-resistant *M. tuberculosis*. Thus, its usefulness in drug-resistant TB treatment monitoring is limited.

The role of smear microscopy is positioned in the DR-TB care for two specific reasons: (i) at the laboratory **to decide if FL-LPA can be done as a direct test** in smear positive or indirect test after culture in smear negative specimen; (ii) for microbiological follow up in regimen of shorter duration to enable **clinical decision on treatment extension in shorter MDR-TB or Hr-TB regimen**.

Table 2.5: Summary of drug susceptibility tests (DST)

	Diagnostic Platform	Test Name	Turnaround Time	Description and comments
Phenotypic DST	Solid Culture and DST	Lowenstein- Jensen	2-8 weeks (for positive culture) 8 weeks (for negative culture)	Egg-based medium, inexpensive. First- and second-line DST can be done.
	Liquid culture and DST	MGIT®	21 days (for positive culture) 42 days (for negative culture)	Present recommended standard for TB culture and test of choice for DST confirmation. Fully automated system exists with MGIT 960. First- and second-line DST can be done.
Genotypic DST	Molecular Testing	Line Probe Assay (LPA)	3 days - direct 21 days-indirect	DNA targets are amplified by PCR and hybridized to immobilize oligonucleotide targets. **Genotype MTB DR*plus* test** identifies MTBC, isoniazid resistance by detecting k*at*G and *inh*A gene mutations and rifampicin resistance by *rpoB* gene mutation. **Genotype MTB DR*sl* test** identifies MTBC, fluoroquinolones resistance by detecting *gyr*A gene and *gyr*B gene mutation, aminoglycosides and cyclic peptides resistance by *rrs* gene and *eis* gene mutation. Can be done directly from smear positive or from liquid or solid culture positive colonies.
		Xpert® MTB/RIF	2 hours	The test uses nested real-time PCR (cartridge-based) to identify MTBC and rifampicin resistance by detecting rpoB gene mutation. Can be done directly from smear-positive or smear-negative specimens.
		Xpert MTB/XDR	90 minutes	Xpert MTB/XDR detects resistance to isoniazid, ethionamide, fluoroquinolones and amikacin.
		Truenat™	1 hour	The test uses nested real-time PCR (chip-based); Truenat is a reflex (two-step) test for rifampicin resistance. Hence, the recommendation for Truenat MTB-RIF Dx is only applicable for those patients with positive Truenat MTB or MTB Plus results.

2.4 Laboratory monitoring of response to therapy with sputum microscopy and culture (follow-up smears and cultures)

Response to therapy is monitored through smears and cultures. A combination of solid and liquid cultures was used before but planned to use only liquid in 2020 and now mainly Liquid CL/DST is being used. Smear examination is done monthly during the whole treatment and culture is done on the same specimen for the months that culture is indicated as per guidelines in treatment monitoring chapter. Monitoring is not done with molecular tests as they will pick up residual fragments of killed bacilli, which can be seen in patients with culture conversion and even in patients who are cured. The chapter on monitoring of DR-TB management provides the monitoring schedule for smears and cultures and information is used to send samples accordingly.

The monthly culture results are of extreme importance to quickly identify the conversion and reversion and to perform DST (Xpert MTB/XDR or LPA and/or phenotypic DST) if one culture is reported positive. This will help to identify failures early and to put them on adequate DST based treatment regimen. Therefore, in addition to FQs DST, DST to Bdq, Lzd, Cfz, Dlm and Z is essential to design effective regimen.

2.5 Infection control and biosafety in the laboratory

Laboratory biosafety is the process of applying a combination of administrative controls, containment principles, safety equipment, good laboratory practices, standard operating procedures, emergency preparedness and facilities to enable laboratory staff to work safely with potentially infectious microorganisms.

Transmission of TB/DR-TB is a recognized risk for laboratory workers. Specimens should be handled in Class 2 Biological Safety Cabinets for all procedures of culture and DST. Xpert MTB/RIF specimens can be processed with the same conditions as smear microscopy alone and do not require special safety cabinets, although if available they can be used. When handling potential DR-TB specimens (including for smear or Xpert MTB/RIF processing), laboratory technicians should use an N-95 respirator and be in a well-ventilated area, with an exhaust fan if adequate window and natural ventilation is not available). For liquid culture and LPA, Biosafety level 3 laboratories are needed. Instructions on safe handling of specimens must be strictly followed. The health status of laboratory workers must be monitored by annual CXR. Laboratory workers who report signs and symptoms suggestive of TB at any time should undergo CXR and Xpert MTB/RIF Ultra testing.

2.6 Quality assurance

To ensure that results of DST are reliable and comparable between different country areas, a system of TB quality assurance (QA) has been developed. As a part of internal quality control, the quality of the staining solutions and prepared media will be controlled for each batch. For QA, susceptibility testing must be performed on the standard H37Rv strain when each new batch of LJ media and drug containing LJ media is prepared for DST. The Supranational Reference Laboratory (SNRL) in Chennai, India assesses proficiency of Culture & DST (both solid & liquid) and LPA annually with specific QA protocols. QA for Xpert MTB/RIF test has started since 2017 in selected sites by the support of JICA and is planned to expand to all sites. Quality assurance of the blood laboratory tests for monitoring adverse effects is also done regularly as per the standards of the specific instrument measuring blood chemistries.

2.7 Surveillance using DST

Drug resistance surveys (DRS) should be done every five years and the strategies of case detection and treatment adjusted according to these results. In addition, ongoing surveillance can be done for the different groups such as failures of initial regimen and retreatment regimen, close contacts, relapse, return after default**.** The fourth DRS using DNA whole genome sequencing was conducted in 2020 and summary data are presented in tables below.

Table 2.6. DR-TB prevalence in new and previously treated patients

Drug resistane pattern	Type of patients	Point prevalence	95% Conficence interval
RR TB	New	3.3%	2.4% - 4.5%
	Previously treated	13.1%	7.8% - 21%
MDR-TB	New	3%	2.1% - 4.1%
	Previously treated	11.8%	6.8% - 19.6%
Any resistance to INH	New	10.2%	8.7% - 12%
	Previously treated	20.8%	14.8% - 28.5%

Source: Fourth Nationwide Anti-TB Drugs Resistance Survey in Myanmar (2020-2021), NTRL.

2.7.1 Prevalence of drug resistant TB in Myanmar

The predictive values of a test vary, depending on the prevalence of TB/ DR-TB in the patient population being tested. NTP considers epidemiology of TB and different forms of DR-TB, the pooled sensitivities and specificities of diagnostic tools, resources available, experiences gained in recent years in choosing the tests to implement in programmatic conditions.

Table 2.7. Drug resistance pattern among bacteriologically confirmed TB cases

Total bacteriological confirmed TB cases	1543	
	Number	Percentage
Streptomycin (S)	167	10.8%
Isoniazid (INH)	167	10.8%
Rifampicin (Rif)	61	3.9%
Ethambutol (ETB)	37	2.4%
Pyrazinamide (Z)	23	1.5%
Amikacin (Am)	2	0.1%
Levofloxacin (Lfx)	29	1.9%
Moxifloxacin (Mfx)	29	1.9%
Ethionamide (Eto)	41	2.7%
Para-aminsalysalic acid (PAS)	0	0%
Cycloserine (Cs)	0	0%
Linezolid (Lzd)	0	0%
Bedaquiline (Bdq)	0	0%
Delamanid (Dlm)	0	0%

Table 2.8. Drug resistance pattern among Rif resistant TB patients (Lower Myanmar Data)

Drug resistant pattern among Rif-resistant TB cases	52	
	Number	Percentage
Isoniazid (INH)	47	90%
Ethambutol (ETB)	31	60%
Pyrazinamide (Z)	16	31%
Amikacin (Am)	1	2%
Levofloxacin (Lfx)	11	21%
Moxifloxacin (Mfx)	11	21%
Ethionamide (Eto)	2	4%

Source: Fourth Nationwide Anti-TB Drugs Resistance Survey in Myanmar (2020-2021), NTRL

Action Points:

- Xpert MTB/RIF and Xpert MTB/RIF Ultra to be used as an initial priority rapid test for diagnosis of TB/MDR-TB instead of smear microscopy, culture and phenotypic DST.
- Xpert Ultra uses two multicopy amplification targets (IS6110 and IS1081) and a larger PCR reaction chamber; thus, Xpert Ultra has a lower LOD than Xpert MTB/RIF i.e 16 colony forming units [cfu]/mL and 131 cfu/mL, respectively
- The increased sensitivity and loss of specificity are primarily related to the Xpert Ultra "trace" call. A clinical approach to be used(CXR and TB S/S) to manage ultra trace results (specially whose TB treatment ended less than 5 years ago)
- In **adults** with signs and symptoms of **pulmonary TB** who have an Xpert Ultra **trace** positive result on the initial test, **repeated** testing with Ultra may **not** be used
- Xpert MTB/XDR should be applied to all RR/MDR TB notified prior to treatment initiation with MDR TB regimens, LPAs and pDST to use as a second option in cases where there is discordance or no results by XDR test.

3. Treatment of DR-TB

In Myanmar, treatment strategies for treatment of MDR/RR-TB are as below:

1. **BPaLM (Bedaquiline, Pretomanid, Linezolid and Moxifloxacin):** A standard regimen with 6 months (26 weeks) of duration. This regimen is to be used as priority regimen among MDR/RR-TB with FQ susceptibility documented or FQ resistance unknown (age 14 years and above) with certain eligibility criteria
2. **9-month all-oral (9-Oral)** of (9-11) months duration as preferred treatment regimen for MDR/RR-TB patients in whom resistance to FQ has been excluded and who are not eligible for BPaLM provided that certain eligibility criteria are met (refer to 9-Oral regimen chapter)
3. **BPaL Regimen** (Bedaquiline, Pretomanid and Linezolid) is applicable for patients with FQ resistance (age 14 years and above) as priority regimen with duration of 6-9 months (26-39 weeks).
4. **Longer Treatment regimens** (minimum 18 months duration) is applicable for-
    a) MDR/RR-TB patient found ineligible for BPaLM, or 9-Oral
    b) Pre-XDR-TB patient found ineligible for BPaL
    c) XDR-TB

    The longer regimen is to be used by choosing at least 4 likely effective drugs from group A-C of WHO grouping of medicines.

Table 3.1: Consideration for selection of treatment regimens for MDR/RR-TB patients

Regimen	Age <14 years	FQ Susceptible	FQ Resistant	XDR-TB	Extensive PTB	EP TB
BPaLM	No	Yes (Unknown FQ susceptible also)	No	No	Yes	All forms of extrapulmonary TB except for TB involving CNS, osteoarticular and disseminated (miliary) TB
BPaL	No	No	Yes	No	Yes	As above
9-Oral	Yes	Yes	No	No	No	Extrapulmonary TB: except for TB involving CNS, osteoarticular and disseminated (miliary) TB, TB pericarditis, TB abdomen, bilateral TB pleural effusion
LTR	Yes	Yes*	Yes **	Yes	Yes	Yes

*if not eligible for BPaLM or 9-Oral ** if not eligible for BPaL

3.1 Patient education and counseling in MDR/RR-TB Management

- Patient education is an essential component of any DR-TB control program and is important for gaining trust in interpersonal communication between patients, their families and medical personnel.
- Provision of emotional & social support to DR-TB patients may increase the likelihood of adherence.
- The organization of patient education should be considered equally with the other components of the DR-TB program (such as detection and diagnostics, drug supply, etc.)
- The patient's knowledge and understanding of his/her role in achieving a successful treatment outcome is an essential component for management of DR-TB.
- Strict DOT or video observed treatment (VOT) is the mainstay of TB/DR TB treatment to increase treatment success rate, cut transmission of TB infection and, reduce morbidity and mortality

Key points for MDR/RR-TB treatment

Followings are strongly recommended before the treatment initiation is considered:

At the time of enrolment on DR-TB treatment, all patients should receive **appropriate counseling** to enable informed and participatory decision-making.

- Ensure that patients are appropriately informed about their **available treatment options** (longer or shorter treatment).
- Ensure **patient-centered approach** to the delivery of care including social and psychological support and any other issue or challenges that may affect treatment adherence.
- Active TB drug safety monitoring and management (**aDSM**) is essential for all patients enrolled on DR-TB treatment including evaluation of history or tendency/risk for adverse drug reactions (ADRs)to second line drugs.
- **Pre-treatment complete Assessment**; investigations to evaluate baseline clinical, radiological, ECG, audiometry(if Am based regimen) and biochemical status, visual assessment, peripheral neuropathy screening , underlying co-morbidity (HIV, DM, liver, renal, cardiac conditions), pregnancy or plan for pregnancy during treatment, contraindications, drug-drug interactions, special situations and need for referral for specialist consultation, history of exposure to second line drugs, contact history, psycho-socio-economic needs, family support for treatment, DOT provider engagement.

3.2 General principles of MDR/RR-TB treatment

The following general principles of MDR/RR-TB should be followed for regimen designing and the objective should be with “no harm practice” keeping in view the effectiveness and safety of the regimen designed.

At the time of enrollment patients should be informed about available options of treatment (longer or shorter) and shared based decisions should be made between doctor and patient for choices of treatment. However, DR-TB physicians have to be vigilant about choosing the right treatment option for patient keeping in view history, co-morbid condition, severity of disease and drug contraindication. Shorter oral regimens (BPaLM,9-Oral, BPaL) are preferred options in eligible patients as they have multiple benefits for the patients and program.

- Review patient full history of previous treatment, DST results, co-morbid conditions and concomitant drugs in use
- Assessment for underline cardiac disease/ischemic heart disease, peripheral neuropathy, and anemia should be done. Baseline anemia of some degree is likely to be present in chronic TB/MDR-TB patients due to TB disease, mostly iron deficiency anemia, Lzd should be used with caution keeping in view anemia severity grading. Anemia and peripheral neuropathy will be more enhanced in MDR-TB/HIV co-infected patients.
- It is essential that a patient’s MDR/RR-TB strain needs to be tested for susceptibility to medicines planned for inclusion in the regimen at the time of treatment initiation (FQ, Bdq, Lzd, Cfz, Z). Now Xpert MTB/XDR is a useful tool for rapid DST to FQ, H, SLIs and Eto.
- Treatment initiation delays must be avoided preferably within one week in all circumstances as such delays result in further severity of diseases, transmission of strain and lead to lack of trust on health care workers and may increase initial loss to follow up.
- Rapid molecular test should be used as an initial rapid test, in preference to culture and phenotypic DST, to detect resistance to FQs. If DST is readily available for bedaquiline or linezolid, it is highly desirable that this is also carried out at baseline. DST for pretomanid (Pa) is being developed. If resistance to any of the components of regimen are reported later, regimen should be discontinued.
- For some medicines, DST results would present uncertainties (e.g. cycloserine, streptomycin, ethambutol, pyrazinamide). **“Likelihood of effectiveness"** is generally assessed in the programmatic setting on the basis of one or more of the following:
    - (i) DST shows susceptibility in the individual patient
    - (ii) DST shows susceptibility in the presumed source case
    - (iii) no known resistance to another drug which has cross-resistance to the medicine
    - (iv) rare use of the medicine in an area (possibly supported by low drug-resistance levels from surveillance activities)

(v) no previous use of the medicine in a regimen that failed to cure that same patient until recent DST shows susceptibility of the use drug

3.3 Treatment strategies and regimens for MDR/RR-TB treatment

3.3.1: BPaLM (Bedaquiline, Pretomanid, Linezolid and Moxifloxacin)

The 6-month (26 weeks) fixed duration BPaLM regimen is the regimen of choice for patients with MDR/RR-TB with FQ susceptible, absent, or unknown fluoroquinolone resistance. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/ RR-TB, and although it should not delay initiation of the BPaLM regimen. The DST results should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.

BPaLM Inclusion Criteria (same applies to BPaL):

- Adults and adolescents aged 14 years and older regardless of HIV status.
- Patients with MDR/RR-TB(BPaLM) or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB for BPaL).
- No known allergy to any of the BPaLM component drugs.
- Confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving CNS, osteoarticular and disseminated (miliary) TB.
- Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if DST to these medicines shows susceptibility. With resistance to any of bedaquiline, linezolid, delamanid or pretomanid should not use BPaLM.

BPaLM Exclusion Criteria (same applies to BPaL):

- Under 14 years of age
- Confirmed XDR TB patients (MDR/RR-TB that is also resistant to any of FQs, and either Bdq or Lzd or both)
- Pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.
- **If patient has one or more of the following medical conditions.**
  - Baseline QTcF of > 500 ms which cannot be corrected
  - Baseline Grade 3-4 peripheral neuropathy
  - Baseline severe anaemia (Hb < 8.0 g/dl which is un-correctable)
  - Baseline moderate thrombocytopenia (platelet <75000/ mm^3)
  - Baseline moderate neutropenia (neutrophil count <1000/mm^3)

- Baseline ALT/AST > 3 x upper limit of normal

NOTE: In case of possible FQ resistance BPaLM still can be used and modified later to BPaL if FQ resistance is reported. If the result of fluoroquinolone DST is never determined or not done, the BPaLM regimen should be used throughout. BPaLM is given for a duration of 6 months.

Table 3.2: Dosing of medicines for BPaLM regimen

Drug	Dose	Number of Tablets (26 weeks)
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, followed by 200 mg 3 times per week for 24 weeks	200
Pretomanid (200 mg tablet)	200 mg once daily	182
Linezolid (600 mg tablet)	600 mg once daily (adjustable only after 9 weeks)	182
Moxifloxacin (400 mg tablet)	400 mg once daily	182

Note: At this point the Bdq dosage of 400 mg once daily for 2 weeks followed by 200 mg thrice weekly applies, all BPaLM/BPaL medicines best to be taken with meal for best absorption.

The drugs in BPaLM regimen are highly bactericidal and makes it much effective against TB bacteria as following;

- Bedaquiline is a diarylquinoline that blocks adenosine triphosphate (ATP) synthase,
- Pretomanid is a nitroimidazole that inhibits cell wall biosynthesis,
- Linezolid is an oxazolidinone that inhibits protein synthesis
- Moxifloxacin is a fluoroquinolone that inhibits the mycobacterial topoisomerases.

Patients co-infected with HIV and on ART, better not to use efavirenz (EFV) based ART instead priorities dolutegravir (DTG) based regimen, as efavirenz may induce metabolism of Bdq. Likewise, regimens including zidovudine (AZT) should be avoided, if possible, because both zidovudine and linezolid may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity. There should be no dose modifications for bedaquiline, moxifloxacin and pretomanid. Preferably Lzd to be continued at the full dose for the entire duration; however, the dose of linezolid can be reduced to 300 mg or can be discontinued (and restarted when possible) if there is significant toxicity (depending on the severity of specific adverse events or serious adverse events) associated with linezolid, including optic neuritis, peripheral neuropathy or myelosuppression. Lzd dose modification is allowed after 9 weeks of 600 mg both in BPaLM and BPaL regimens.

3.3.2: BPaL (Bedaquiline, Pretomanid and Linezolid) Regimen

Based on NiX TB and ZeNix TB Trial evidence and WHO recommendations, NTP Myanmar has conducted and completed 100 patients enrolment on BPaL as part of global study under operational research conditions in Yangon to produce local evidence. The results from this operational research are very encouraging.

BPaL is applicable to pre-XDR TB patients (a patient who is RR/MDR TB plus resistance to any of FQ). It is best to use the BPaLM regimen until DST for fluoroquinolones is available and if resistance to FQ, the Mfx can be omitted. Individuals who switch from BPaLM to BPaL should consider their treatment start date the same as the date BPaLM was initiated, because the patient remained on treatment with three effective drugs during the entire treatment period.

Inclusion and Exclusion Criteria BPaL

The inclusion and exclusion criteria apply the same as mentioned in the BPaLM section.

Table 3.3*:* Dosing of medicines for BPaL regimen

Drug	Dose	Total number of tablets
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week for 24 weeks afterwards	200 - 278
Pretomanid (200 mg tablet)	200 mg once daily	182 -273
Linezolid (600 mg tablet)	600 mg once daily (adjustable only after 9 weeks)	182 -273

The BPaL regimen is given for a duration of 6-9 months (26 – 39 weeks):

(i)Managing Linezolid dosing in the BPaLM/BPaL regimen

When it comes to Bdq, Pa the toxicity frequency is relatively much lower as compared to Lzd which is more frequent, but toxicity improves after dose reduction or drug interruption (WHO 2022). A toxicodynamic modelling study using Nix-TB data showed lower percentages of patients with severe peripheral neuropathy (median, 5% versus 19%) and severe anaemia (1% versus 15%) in patients using 600 mg compared with 1200 mg linezolid daily (Imperial et al 2022). Nix-TB study data suggested that a decrease in haemoglobin level of 10% or more after 4 weeks of treatment may help to identify those at high risk for severe anaemia (Imperial et al 2022).

- In case of optic neuritis diagnosed at any grade, permanently discontinue linezolid and do not restart until recommended by ophthalmologist.

- If peripheral neuropathy Grade 1- 2, reduce the dose of linezolid to 300 mg per day with a possible drug holiday for 1–2 weeks or 7-10 days before dose reduction; dose reduction and modification of only Lzd is not allowed within 1st 9 weeks of treatment.
- 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 if 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).
- In case of myelosuppression grade 1-2 (if it occurs during 1st 9 weeks of treatment or after 9 weeks of treatment) still whole BPaLM/BPaL regimen to be continued (except in grade 2 neutropenia) with Lzd 600 mg daily. If it is required to temporarily interrupt Lzd during 1st 9 weeks, then only Lzd interruption or dose reduction is not allowed and instead a whole regimen is to be temporarily interrupted and a drug holiday of 7-10 days might be helpful in alleviating toxicity. Monitor closely and if myelosuppression worsens to grade 3 or 4, stop BPaLM/BPaL.
- Reversal from grade 4 to normal may take considerable time and assess patient case-by-case to decide whether to stop BPaLM/BPaL permanently. Reassess CBC after 10 days and if result shows grade 1-2 myelosuppression (except grade 2 neutropenia) then re-introduce whole regimen with 600 mg of Lzd, monitor closely, if it worsens to grade 3-4 again, then stop whole regimen and shift to LTR. During 30 days of treatment, patients can be shifted to Eto based 9-month all-oral (9-Oral) if eligible. There is possibility that grade 3-4 myelosuppression may happen during early weeks of treatment.
- In case of myelosuppression (even of Grade 3 or 4) is often reversible but reversal from grade 3-4 to normal may take considerable or variable time and assess patients case-by-case to decide whether to stop BPaLM/BPaL permanently. However, with a short 7-10 days drug holiday followed by reducing the dose of linezolid to 300 mg per day could be a feasible option; severe anaemia may need to be treated with transfusions or erythropoietin.
- If Lzd is permanently stopped, assess the treatment period -
    - in treatment period less than 18 wks – discontinue BPaLM/BPaL and switch to individualized oral longer treatment regimen
    - in treatment period more than 18 weeks of treatment – omit Lzd and can continue treatment with remaining drugs.

(ii)Modification in BPaLM/BPaL Regimen

Modifications of any component drug of the BPaLM/BPaL regimen because of severe/serious toxicity, consider the following factors.

- Temporary cessation of the full regimen is allowed for suspected drug-related toxicity
- Reintroduction of the full regimen could be considered after a stoppage of no more than 14 days of consecutive treatment interruption or up to a cumulative 4 weeks of non- consecutive treatment interruption.
- In case if moxifloxacin alone is discontinued because of toxicity, the regimen can be continued as the BPaL regimen.
- Where linezolid is to be permanently discontinued (non-manageable toxicity) during the initial 9 consecutive weeks of treatment, the entire regimen should be discontinued; after 9 weeks of treatment Lzd the dose reduction or interruption is allowed
- If linezolid is withheld in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, the regimen can be considered to be completed with the remaining component drugs

(iii)Shifting a patient from BPaLM/BPaL to 9-month all-oral (9-Oral)/LTR

Consider clinical review and switching to an individualized longer regimen should be considered when:

- Consecutive treatment interruption of full regimen more than 2 weeks
- A cumulative of non-consecutive treatment interruption more than 4 weeks of whole regimen
- If only pretomanid or bedaquiline is to be permanently stopped at any point of time
- During 30 days of treatment, patients can be shifted to Eto based 9-month all-oral (9-oral) if eligible.
- If remaining treatment period is more than 8 weeks and Lzd toxicity is not manageable – discontinue BPaLM/BPaL and switch to individualized oral longer treatment regimen

In patients with a high number of missed linezolid dosages – switching to an individualized longer regimen may be considered instead of a BPaL extension

NOTE: Once BPaLM/BPaL is discontinued, the patient is to be declared failure and if response to treatment is adequate at the time of discontinuation the drugs used in the regimen can be considered likely to be effective while constructing LTR.

(iv) Duration of treatment of BPaLM/BPaL

Patients started on BPaLM should be treated for 6 months (26 weeks) given its high bactericidal activity and efficacy with FQ susceptibility. While patients started with BPaL or shifted from BPaLM to BPaL the duration of treatment can be extended to 9 months (39 weeks). The extension of BPaL treatment duration from 6 to 9 months should be considered in the following situations.

1. sputum cultures are positive between months 4 and 6 of treatment **or**

2. Delayed radiological response by 6 months unless there is other indication to stop the treatment

The missed doses up to interruption of one month can be added at the end of treatment in case-by-case situations. Any interruption of longer than 7 days should be made up for by extending the treatment duration (for the number of missed doses).

Table 3.4: Examples of determining treatment duration of BPaL

Month	1	2	3	4	5	6	7	8	9	Comments
CL/Smear Results	CL+ S+	CL+ S-	CL- S-	CL- S-	CL- S-	CL- S-				Evaluate patients clinically/radiologically and give outcomes as cured.
CL/Smear Results	CL+ S+	CL- S-	CL- S-	CL+* S-	S-	S-				DST to Bdq, Pa, Lzd, extend treatment to 9 months and review patients.
CL/Smear Results	CL+ S+	CL+ S-	CL+ S+	CL+* S+	S-	S-				Suspect failure, evaluate patient CXR/Clinically, DST to Bdq, Pa, Lzd.
CL/Smear Results	CL+ S+	CL+ S-	CL- S-	CL- S-	S-	S+				Evaluate patients clinically/radiologically and decide to stop or extend treatment in line with discussions with CME/TWG.

***** In such patients perform DST to Bdq, Pa and Lzd (if one culture (CL) positive by month 4 or beyond)

Note: If a single culture positive is reported by month 4 or beyond (culture conversion was already attained in previous month), BPaL treatment may be extended beyond 6 months while waiting for the result of M 5 and M 6 culture, there should be a strong justification and in line with CME/TWG discussions.

(v) Declaring treatment outcome of failure and cure in BPaLM/BPaL

Treatment failed

A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy [(a)]

a) Reasons for the change include:

- no bacteriological response (*)
- Adverse drug reactions; or

- Evidence of additional drug resistance to medicines in the regimen.

* Persistent culture positive (no conversion) up to 4 months cultures **or** bacteriological reversion after conversion

Cured

A pulmonary DR TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy (6 month for BPaLM and 6- 9 months for BPaL), with 2 consecutive negative culture during last 3 months of treatment (4,5 or 5,6) and no evidence of failure.

Note: Definitions for completed, loss to follow up (LFU), died, not evaluated (NE) apply as of all other regimens.

Action Points

- BPaLM/BPaL can be given to EP TB patients other than TB involving CNS, miliary TB, osteoarticular TB
- BPaLM for 6 months (26 weeks) to be used in FQ susceptible, suspicion of FQ resistance/close contacts of FQ resistant or unknown FQ resistance. Once FQ resistant is reported the Mfx to be discontinued
- BPaL applies to FQ resistant patients and can be extended from 6 to 9 months (from 26 to 39 weeks) if sputum culture is positive between months 4 and 6 or delayed radiological response
- After 9 weeks of treatment with BPaLM/BPaL the Lzd dosage can be reduced if related toxicity develops. However, Lzd can be discontinued permanently (in case of complete intolerance) if remaining duration of the regimen not exceeding 8 weeks, rest of the regimen (BPaLM/BPaL) can be continued
- If either bedaquiline or pretomanid needs to be permanently discontinued, the entire BPaLM/BPaL regimen should also be discontinued
- The missed doses or treatment interruption longer than 7 days up to interruption of one month can be added at the end of treatment in case-by-case situations

3.3.3: 9-month all-oral (9-oral)

WHO has recently updated its recommendation that, in eligible patients with MDR/RR-TB, the 9-month all-oral regimen may be used, and that 2 months of linezolid can be used as an alternative to 4 months of ethionamide within this shorter regimen.The implementation of these two variants of the 9-month all-oral MDR/RR-TB regimen (i.e. including either linezolid for 2 months or ethionamide for 4 months) is expected to provide more flexible and effective treatment options for a wider range of patients requiring treatment for MDR/RR-TB. The 9-oral will be useful for patients who are not eligible for BPaLM. Alternative to Lfx, Mfx can be used in 9-month all-oral (9-oral). The confirmed susceptibility to FQ is crucial while placing MDR/RR-TB patients on 9-month all-oral (9-oral).

The following principles must be observed to implement 9-month all-oral regimens.

Exclusion Criteria

- Patients with documented resistance or suspected ineffectiveness of bedaquiline, clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen)
- Exposure of one or more 2nd line medicine including bedaquiline for more than one month (unless susceptibility is confirmed)
- Patient is known to have a strain resistant to a fluoroquinolone with Xpert MTB/XDR /second line LPA or phenotypic DST
- Patient who has known hypersensitivity to ≥1 drug contained in the shorter regimen
- Patients with extensive (or advanced) tuberculosis (TB) disease: presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography
- Patient with severe extrapulmonary TB: presence of miliary TB/ disseminated TB or TB meningitis, bone TB, TB abdomen, bilateral TB pleural effusion, TB pericarditis
- Patient has AST or ALT >4 times the upper limit of normal
- Patient has a QTcF interval of > 500 ms
- For Lzd containing 9-month all-oral (9-oral), serum haemoglobin below 8 g/dL [if anaemia can be corrected within a week, then can consider using Lzd containing 9-month all-oral (9-oral)], moderate thrombocytopenia (platelet <75000/ mm3), moderate neutropenia (neutrophil count <1000/mm3) at the start of treatment. Likewise, if there is grade 3-4 peripheral neuropathy
- Pregnancy in case of Eto based regimen

3.3.3.1 Composition and Treatment duration of 9-Oral

Following are the two variations of the 9-month all-oral MDR/RR-TB regimens.

9-Oral (Eto variation): 4–6 Bdq (6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E

Initial phase: 4–6 Bdq (6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto

Continuation phase: 5 Lfx/Mfx-Cfz-Z-E

9- Oral (Lzd variation) 4–6 Bdq (6 m)-Lzd (2 m)-Lfx/Mfx-Cfz-Z-E-Hh / 5 Lfx/Mfx-Cfz-Z-E

Initial phase: 4–6 Bdq (6 m)-Lzd(2 m)-Lfx/Mfx-Cfz-Z-E-Hh

Continuation phase: 5 Lfx/Mfx-Cfz-Z-E

Important Practice/Action Points

- The initial phase consists of bedaquiline, levofloxacin, clofazimine, ethambutol, high-dose isoniazid, pyrazinamide and ethionamide given daily (once a day) for 4 to 6 months. The alternative option is Lzd for 2 months instead of Eto. Bedaquiline will be given for 6 months duration (400 mg daily for the first 2 weeks followed by 200 mg three times per week for 22 weeks). Bdq can be extended to 9 months in case-by-case situations, especially where intensive phase is extended from 4 to 6 months, having 4th months sputum positive.
- For body weight 16-30 kg the Bdq dose will be 200 mg tablet daily for 14 days, followed by 100 mg three times/week (M/W/F).
- The continuation of treatment consists of levofloxacin, clofazimine, ethambutol and pyrazinamide (once a day) for 5 months.
- Weight-based dosing of anti-TB drugs are used in 9-month all-oral (Refer to **Annex 1: Weight-based dosing for 9-month all-oral and LTR**)
- Total duration of 9-month all-oral (9-oral) will depend on 4th month smear results and CXR response as follows;

    a) if the smear is negative at month 4 (given that radiological/clinically good response), the initial phase will be only 4 months (Bdq to be continued till end of 6 months), followed by 5 months continuation phase. Then treatment will be 9 months,

    b) if the 4th month smear is positive, the initial phase will be extended for a maximum of 2 months, then total treatment duration will be 11 months. Bdq can be extended up to 9 months. Extension to 12 months treatment is also applicable where CXR lesions are healing relatively slowly,

    c) Failure will be declared at the end of the sixth month for those who have both positive smears at six months and with poor clinical and radiological response to treatment.

months / Drugs in 9-oral	Initial Phase (4-6 months*, Bdq for 6 months)						Continuation Phase (5 months)				
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11
Ethionamide **or** Lzd (2 months)											
Isoniazid high-dose											
Bedaquiline											
Levofloxacin/Moxifloxacin											
Clofazimine											
Pyrazinamide											
Ethambutol											

*Intensive phase extended to 6 months if the month 4 smear is reported positive, CXR healing relatively slowly or as per judgment of treating physician. Bdq can be extended to 9 months in case-by-case situations.

3.3.3.2 Modification of 9-month all-oral (9-oral)

9-month all-oral (9-oral) should be implemented as a standardized package for its composition or duration with a few exceptions, as follows.

- Moxifloxacin may be used instead of levofloxacin, provided close ECG monitoring is feasible
- If, for any reason, a patient is unable to tolerate pyrazinamide or ethambutol within the 9-month regimen, then one (but only one) of these drugs may be dropped during the continuation phase without necessitating a switch to a longer regimen
- If two or more of these drugs are not tolerated within the 9-month regimen, the treatment will have to switch to a longer regimen
- If any of the other drugs within the 9-month regimen (bedaquiline, levofloxacin/moxifloxacin, linezolid/ ethionamide or clofazimine) are stopped early because of toxicity or intolerance then the patient will also have to switch to a new regimen.
- **For Lzd version of 9-month all-oral (9-oral)**, if occasional doses of linezolid are missed during that time, the missed doses can be added on to the end of the 2-month period if the patient is tolerating the drug well.
- If FQ resistance has been definitively ruled out, it may not be strictly necessary to make up the Lzd missed doses.
- The linezolid dose should not be reduced to less than the recommended dose to reduce the severity of adverse effects.
- If the full dose of linezolid (600 mg in adults) is not tolerated for the first full 2 months of treatment (apart from occasionally missed doses, which can be added to the end of

the 2-month period), then the patient must either switch to an ethionamide-containing 9-month regimen (provided resistance to fluoroquinolone is ruled out and the patient is not pregnant) or to an individualized longer regimen without linezolid

- Patients switching to a new regimen due to toxicity or intolerance need to be reported as "treatment failed"

3.3.3.3 Discontinuation of 9-month all-oral (9-oral)

The 9-month all-oral (9-oral) will have to be discontinued in the following situations and such cases should be discussed by using panel base approach:

- The baseline molecular DST (Xpert XDR/second-line LPA) or phenotypic DST came out as resistance to the FQ and/or Bdq or Cfz, Eto after treatment initiation
- Acquired resistance to Bdq, FQ, Lzd, Cfz, Eto during treatment
- Culture reversion
- Patients experience severe/serious toxicity related to 9-month all-oral (9-oral) medicine, which is not manageable.
- When there is a need to permanently discontinue a medicine or more in the 9-month all-oral (9-oral) in line with aDSM protocol, except E or Z (only one) in continuation phase if to be dropped.
- Sputum smears remain positive up to month 6 along with inappropriate treatment response (clinical and/or radiological deterioration together with best judgment of other parameters).
- Pregnancy if during intensive phase of treatment (while patient is on Eto)

3.3.4 Longer treatment regimens (LTR)

The probability of treatment success in MDR/RR-TB patients depend upon patients will and strong adherence to treatment, including severity of disease, resistance patterns and co-morbidities as well as access to health care (e.g., regimens with sufficient effective agents, medications of good quality, attention to adverse events and patient psycho-social support).

MDR/RR-TB patients who cannot benefit from either BPaLM/BPaL or the 9-month all-oral regimen can be opted for the longer MDR-TB regimens. Reasons for not using the shorter regimens may be related to the age of the patients, additional resistance (including fluoroquinolone resistance and other Group A medicines, i.e., XDR-TB), intolerance to key medicines used in shorter regimens, severity of disease, pregnancy, certain types of extrapulmonary TB or other complications needing an individualized approach.

WHO in 2018 convened the GDG (guideline development Group) meeting and assessed the individual contribution of patient outcomes by medicines used in longer MDR TB regimens using primarily the estimates of effects from 2018 individual patient data meta-analysis (IPD

meta- analysis). Following a thorough assessment of relative benefits to harms, recommendations were made for each medicine and classified into three groups:

> **Group A:** fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended, all three to be included in all regimens unless contraindicated;
>
> **Group B:** clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice and at least one to be included as part of standard regimen;
>
> **Group C:** included all other medicines that can be used when a regimen cannot be composed with Group A and B agents.

In general, longer regimen composition is guided by the selection of individual medicines considered to be effective and also by a need to combine sufficient medicines to maximize the likelihood of relapse-free cure without increasing toxicity. The regimens are individualized in line with DST results, baseline contraindications to a drug in regimen, co-morbid condition and concomitant drug in use.

Apart from the ranking by balance of effectiveness and harms, choice is also determined by:

a) preference for composition of agents; the results of drug-susceptibility testing (DST);
b) the reliability of existing DST methods; population drug resistance levels;
c) History of previous use of the medicine in a patient; drug tolerability; and potential drug-drug interactions.

Table below shows the overall approaches for designing longer MDR-TB regimen as opposed to the shorter regimens which are standardized. Based on the WHO 2019 consolidated guideline, the regimen is designed by selecting medicines sequentially going down from group A to group C.

Table 3.5: Grouping of medicines recommended for use in longer treatment regimens[a]

Groups	Steps	Medicines	Abbreviations
A	Include all three medicines in the regimen, if no contraindication	levofloxacin OR moxifloxacin	Lfx Mfx
		bedaquiline [b,c]	Bdq
		linezolid [d]	Lzd
B	Add one or both medicines	clofazimine	Cfz
		cycloserine OR terizidone	Cs Trd
C	Add to complete the regimen, and when medicines from Group A and Group B cannot be used	ethambutol	E
		delamanid [c,e]	Dlm
		pyrazinamide [f]	Z
		imipenem-cilastatin OR meropenem [g]	Ipm-Cln Mpm
		amikacin (OR streptomycin) [h]	Am (S)
		ethionamide [i]OR prothionamide	Eto Pto
		p-aminosalicylic acid [i]	PAS

a. This table is intended to guide the design of longer regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized). Medicines in Group C are ranked by decreasing order of usual preference for use subject to other considerations.
b. Bedaquiline is initially administered once daily for the first 2 weeks with a higher loading dose, followed by a lower maintenance dose three times per week for 22 weeks (total duration of 24 weeks). The use of bedaquiline beyond 6 months still remains as off-label use.
c. Both bedaquiline and delamanid may be used beyond 6 months and concurrently among patients who have limited other treatment options available, and if sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place.
d. Use of Lzd for at least 6 months was shown to increase effectiveness, although toxicity may limit its use.
e. Use of Dlm beyond 6 months should follow best practices in “off-label” use
f. Pyrazinamide(Z) is added in regimen except if there is clinical contraindication for its use and added without DST. In the regimen Z is only counted as an effective agent when DST results confirm susceptibility, if DST shows resistance to Z, then should not be added in the regimen.
g. Every dose of Ipm-Cln and Mpm is administered with oral clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Ipm-Cln or Mpm.
h. Amikacin (Am) and streptomycin (S) are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (S resistance is not detectable with second-line molecular line probe assays and phenotypic DST is

required). Kanamycin (Km) and capreomycin (Cm) are no longer recommended for use in MDR-TB regimens.

i. These agents will be used when no other options of effective drugs are possible to compose a regimen.

3.3.4.1 Composition of longer treatment regimens (LTR)

Stepwise approach is used in constructing the regimens applicable for the country as a principle of DR-TB treatment and regimen construction.

Stepwise approach for regimen construction and treatment

1. If no contraindication to any of group A drugs, preferably all three Group A agents (Lfx/Mfx, Bdq, Lzd) and at least one Group B agents (Cfz or Cs) should be part of regimen
2. If only one or two Group A agents are used, then both Group B agents are to be included in regimen and rest should be chosen from group C to complete the regimen with at least 4 likely effective drugs. The group C agents should be added depending on the confidence in the effectiveness of medicines in this group and the other components of the regimen.
3. Starting treatment with more than four effective agents may also be a practice and this provision is expected to apply to those with additional resistance or suspected resistance to fluoroquinolones or other medicines.
   (a) if 4 drugs from Group A and B are included and there is confidence in all of them, then Group C agents are not needed.
   (b) if 3 drugs Group A and B agents are included and there is confidence in all of them, then at least one Group C agent is added.
   (c) if 2 drugs from Group A and B agents are included and there is confidence in all of them, then at least three Group C agents are added.

   Moxifloxacin, a later-generation fluoroquinolone, may still be effective at a high dose when the fluoroquinolone MIC is below the CB. If the MIC is elevated, then fluoroquinolones are not used.
4. The first six months of treatment consists of at least four second-line agents plus pyrazinamide.
5. The remaining 12 months include the same agents except bedaquiline (Bdq), bringing the total duration to 18 months minimum. However, it is important to remember that during the remaining 12 months of treatment at least one strong bactericidal and sterilizing drug should be part of the regimen.
6. All medicines are given seven days a week, apart from bedaquiline. Bedaquiline is given daily for the first two weeks and three times weekly thereafter.
7. Regimens without an injectable agent (i.e., all oral regimens) are considered not to have an intensive phase.
8. When an injectable has to be used a minimum duration of 6 months with 4 months after culture conversion

9. Bdq use beyond 6 months should be in case-by-case situation keeping in view treatment response and number of effective drugs on board after Bdq is stopped.
10. The use of cardiotoxic drugs (Mfx, Bdq, Dlm and Cfz) in combination should be with caution and with close monitoring. However, recent data shows that combined use of Bdq and Dlm could be safe and QTcF interval with co administration of both drugs is clinically modest (Dooley et al, 2019).
11. The use of Lzd for the whole duration is associated with better treatment outcomes and lower mortality but is expected to cause frequent toxic effects in a significant number of patients. The neurological toxicity is associated with duration, while hematological toxicity/myelosuppression is dose related.
12. If baseline grade 1 to grade 2 anemia (8 - 10.5 g/dl) and baseline peripheral neuropathy of grade 1 and 2 is reported, Lzd 600 mg daily (OD) may be used but with close monitoring to avoid happening of serious adverse effect.
13. Lowering the dose of Lzd from 600 mg daily to 300 mg daily may reduce toxicity but its impact on treatment effectiveness is not known. Therefore, if dose of Lzd is reduced in the initial 6 months of treatment, another effective drug should be added to regimen as case-by-case situations.
14. The addition of pyrazinamide (Z) in the regimen is useful as it has synergistic effects when used in combination with strong bactericidal (FQs, Bdq, Am) and strong sterilizing drugs (Bdq, Cfz). However, if a reliable DST source is confirming resistance, then it should not be used in regimen.
15. Injectable Am should only be used in regimen if there is documented susceptibility to it and appropriate monitoring for hearing loss is available. WHO also recommends to use Am for 18 years of age or above.
16. In cases when there is doubt about the effectiveness of a certain medicine, it may still be included in the regimen, but it should not be considered clean/likely effective to the number of medicines needed in the regimen and clinical judgment is advised to decide if the benefit from its inclusion outweighs any added toxicity or pill burden, for example E, Cs, Eto, PAS.
17. DST to Ethambutol (E) is not routinely recommended because of highly unreliable nature and unreproducible results. For pyrazinamide, WHO recommended high complexity reverse hybridization-based nucleic acid amplification tests (NAATs) may be used on culture isolates for detection of PZA resistance rather than culture-based phenotypic drug susceptibility testing (DST).
18. Panel -based approach is encouraged for management of DR-TB at all levels
    - Basic principle of “never adding a single drug to a failing regimen” should always be applied in treatment of DR-TB.
    - Active drug safety monitoring and management (aDSM) is applicable to all RR-TB patients; therefore, it is imperative to closely monitor patients for side effects of medicines in the regimen.
    - If the long-course regimen fails, treatment options will be very limited. The patient must be further managed according to the support of the technical working group.

3.3.4.2 Dosing and duration of longer treatment regimens (LTR)

Weight-based dosing of anti-TB drugs are used in longer treatment regimen (Refer to **Annex 1: Weight-based Dosing for 9-month all-oral and LTR).** As per new WHO guidelines (2022), for duration of longer regimens, following is recommended.

- A total minimum duration of 18 months
- A treatment duration of 16 months is recommended after culture conversion
- The treatment duration may be modified as per patient's response to treatment
- Prolonging the treatment longer than 18 months may be considered in patients with late converters, extensive disease including pre-XDR and XDR-TB and other risk factors for failure or relapse of treatment.

Table 3.6: Alternatives for MDR/RR-TB patients with contraindications to some drugs in longer treatment regimens [**these are only examples, and it can be highly individualized]

No.	Baseline contraindication	Regimen**	Comments
1	Baseline contraindication to Lzd	18 Bdq (6)-Lfx-Cfz-Cs-Z	1. In patients with peripheral neuropathy at baseline where Lzd/Cs is contraindicated preference may be given to Dlm, Eto, or E. However, in case of severe baseline anemia Cs can be used instead of Lzd 2. Each group C drug is not always an automatic replacement for groups A and B drugs. This should be evaluated clinically as well as likely effectiveness of drugs in the region. If there are doubts, two drugs from group C may be added
2	Baseline contraindication to Bdq	18 Lfx-Lzd-Cfz-Cs-Z	1. Ethambutol (E) with Lzd should be used with close monitoring of optic neuritis 2. Once Bdq is contraindicated for cardiotoxicity Dlm is usually contraindicated (not for Bdq contraindication due to hepatic cause)
3	Baseline contraindication to both Bdq and Lzd	(1)18 Lfx-Cfz-Cs-Dlm (6)- E/Z (2) 6 Am-Lfx-Cfz-Cs- E/Z / 12 Lfz-Cfz-Cs-E/Z	1. Contraindication to Bdq is almost contraindication to Dlm specially for cardiotoxicity (not for Bdq contraindication due to hepatic cause) 2. Use Am only if found susceptible and no baseline contraindication and appropriate monitoring by audiometry in place. 3. If no confidence on E, Z then, Eto can be used instead 4. Intensive and continuation phases are applied once Am is used.

NOTE: Injection Am may be part of MDR/RR- TB treatment where necessary to construct effective regimen and Am to be stopped by 6 months with 4th month negative cultures on board, or to stop early if there is toxicity to it.

It is recommended to review cultures, smears, X-rays and the patient's clinical status, most importantly toxic effect when deciding whether or not to continue an injectable agent longer than the above recommendation.

Early suspension of the injectable agent should be considered when toxicity is reported/detected (See aDSM manual).

Bdq missed doses management

- If a dose of bedaquiline is missed in the maintenance phase but is remembered within that 48-hour dosing period, the dose should be administered as soon as possible
- For example, if bedaquiline is dosed every Monday, Wednesday and Friday, then if the Wednesday dose is missed it can still be taken on Thursday, and then the following dose should be taken on Saturday, with a return to the usual dosing schedule on Monday.
- If bedaquiline is interrupted for less than 2 consecutive weeks during the maintenance phase, no reloading is required.
- If bedaquiline is interrupted for more than 2 weeks (but <8 weeks) during the maintenance phase of dosing, the drug should be reloaded at the higher daily dose for 7 days before resuming the thrice-weekly dosing schedule
- If bedaquiline is interrupted for more than 8 consecutive weeks, then the patient and treatment plan should be reassessed, if all is going well then usually it should be restarted with 400 mg as loading dose for 2 weeks followed by 200 mg thrice weekly

3.3.5 Contraindications and drug-drug Interactions

In line with WHO 2019 guidelines and regrouping of medicine, Bdq and Lzd will be part of standard MDR-TB regimen, while Dlm from group C is an important add on drug and a good choice to replace in cases with toxicities. Therefore, it is important to thoroughly learn about these medicines and their use while constructing the regimen. However, in the best judgement of treating physicians and in line with specialist advice these medicines can be used with precautions.

3.3.5.1 Contraindications and precautions

Table 3.7: Contraindications and precautions with Bdq, Dlm and Lzd

Drug Name	Relative contraindication	Precautions
Bdq, Dlm	History of syncopal episodes, ventricular arrhythmias or severe coronary artery disease Baseline ECG with QTcF > 500 ms (repeated)	Use with caution if QTcF > 450/470 ms in male/female patients. Weekly ECG monitoring and serum electrolyte screening should be performed if Bdq or Dlm is being used despite a cardiac contraindication. Dlm is less cardiotoxic than Bdq (new data has shown that QTcF prolongation with combined use of Bdq and Dlm is clinically modest and safe).
Bdq, Lzd, Dlm	Severe renal Failure	Usually, no dose adjustment is required in mild to moderate renal failure. With precaution in severe renal failure/impairment.
Bdq	Severe hepatic failure	Try not to use if patient has severe liver function impairment. ART should be adjusted if used in HIV cases particularly efavirenz containing regimen should be avoided.
Lzd	Pre-existing mild to moderate peripheral neuropathy (based on Basic Peripheral Neuropathy Screening (BPNS), subjective sensory neuropathy scoring) Severe myelosuppression and anemia, moderate neutropenia	Special precautions when used in combination with Cs, high dose INH and diabetics. In mild to moderate myelosuppression and anemia Lzd can be used with lower doses, 300 mg daily.

It is essential to consider the drug-drug interactions with Bdq, Dlm and Lzd as using in concomitant use of many routinely prescribed drugs may have various level impacts having either decreased or increased absorption, toxicity and adverse events. It may be needed that

patients should be given a card mentioning the name of drugs that should not be prescribed by any GP/doctor while the patient is in ambulatory care in the community. Therefore, treating physicians should review all the medicines patients are taking while enrolling on MDR-TB Treatment.

3.3.5.2 Drug-drug interactions

(a) Drug-drug interactions with bedaquiline

As Bdq is metabolized by cytochrome P450, the following drugs should be avoided to be used with Bdq.

- Strong/moderate inducers of cytochrome P450: These may decrease blood levels of Bdq: efavirenz, rifamycins (rifampicin, rifapentine and rifabutin), phenytoin, carbamazepine, phenobarbital.
- Strong/moderate inhibitors of cytochrome P450: These may increase serum concentration of Bdq: ritonavir-boosted PIs, oral azole antifungals (can be used up to two weeks), itraconazole, fluconazole, macrolide antibiotics other than azithromycin.

(b) Drug-drug interactions with delamanid

Delamanid is metabolized mainly by albumin and to a lesser extent by the CYP3A4 isoenzyme in the liver (cytochrome P450), therefore, it has low potential for drug–drug interactions with CYP3A4 inducers (rifamycins, efavirenz, carbamazapine) or inhibitors (ritonavir-boosted PIs, oral azole antifungals).

(c) Overlapping toxicity with concurrent use

Bedaquiline and delamanid has overlapping cardiotoxicity with concurrent use. Moreover, many other drugs also have additive QT prolongation when used with Bdq and Dlm: anti-TB drugs (fluoroquinolones, clofazimine), (antipsychotic drugs (haloperidol, risperidone, citalopram, escitalopram), many anti-nausea drugs (ondansetrone, granisetron, domperidone, chlorpromazine), methadone, and cardiac drugs that may affect the heart rhythm (amiodarone, beta-blockers, digoxin, quinidine).

Co-administration of delamanid and cycloserine may increase the risk of neuropsychiatric adverse events, especially in children.

(d)Linezolid and concomitant medicines that increase serotonin Levels

- Serotonin re-uptake inhibitors (SSRIs): fluoxetine, paroxetine
- Tricyclic antidepressants: amitriptyline, nortriptyline
- Serotonin 5-HT1 receptor agonists
- MAO inhibitors: phenelzine, isocarboxazid
- Other serotonergic agents: meperidine, bupropion, or buspirone, quetiapine

For more information on drug safety and QT interval prolongation, please visit Woosley et al 2017, CredibleMeds.org

3.3.6 Switching between regimens

There might be an opportunity to switch between the regimens in case-by-case situations and if it is done within 30 days from the start of treatment. For example, if a patient is started on LTR and later mDST confirms susceptibility to FQ, the patient can be switched to 9-month all-oral (9-oral) given that patient meets the eligibility criteria of 9-month all-oral (9-oral) and this change is done within 30 days. Likewise, if a patient is started on BPaLM and Lzd toxicity occurs within 30 days the patient can be switched to Eto based 9-month all-oral (9-oral).

3.4 Treatment of DR-TB in children

MDR-TB in children can either be confirmed (they have clinical TB disease and a sample taken from the child shows MDR-TB) or clinically diagnosed (the child has clinical TB disease and has risk factors for drug resistance).

Some definitions to consider are:

- **Confirmed MDR/RR-TB**: MDR/RR-TB is diagnosed from the biological specimen of child by mWRDs or culture.
- **Probable MDR/RR-TB:**
    - Symptoms/ signs and/or radiology consistent with TB disease in a child who has been exposed to an adult with infectious MDR/RR-TB (or)
    - Child is not improving after 2-3 months of first-line treatment (with confirmation of treatment adherence and exclusion of likely alternative diagnosis) (or)
    - Close contact with a patient who: died from TB; failed TB treatment or is a TB retreatment case.

Gene Xpert Ultra and culture in liquid media should be prioritized in children and now stool sample testing by Xpert Ultra is recommended as priority among children to diagnose TB/RR TB. All relevant and available tests should be considered; performing multiple tests on one or more samples of a variety of specimen types (stool test and nasopharyngeal aspirates in the absence of sputum sample) significantly increases the diagnostic yield.

Confirmed and clinically diagnosed MDR-TB in children and approach to management

In the absence of bacteriological confirmation where there is high suspicion of MDR TB or Pre-XDR TB (for example close contacts), the initiation of an empirical regimen as of an index patient may be the decision.

- The similar principles of regimen design for adults also apply for children based on the WHO recommended regimen design as per grouping of SLDs. Thus, both 9-month all-oral (9-oral) and LTR can equally be applied to children as of adults.
- The DST cannot be warranted in all younger children and sometimes regimen is empirically constructed in children in the best judgment of treating physician.
- Regimens should consist of at least 4 drugs to which the organism is likely to be effective and susceptible and unnecessary/additional drugs should be avoided to reduce toxicity in children.
- Regimens will need to be designed for each individual patient—taking into account unique resistance patterns and toxicity risks.
- WHO's recommendations expand the age indications for both bedaquiline (as part of shorter and longer regimens) and delamanid (as part of longer regimens) to children of all ages.[10]
- The standardized shorter all-oral bedaquiline-containing regimen may now be used in children of all ages under programmatic conditions. The eligibility criteria for this regimen for children with confirmed MDR/RR-TB are the same as for adolescents and adults.
- The duration of therapy in children should depend upon the site and severity of disease; children with non-severe disease can be treated for 9 to 12 months while children with severe disease will require 12-18 months of therapy depending on their clinical progress.
- For children, **a severe disease** is usually defined by the presence of cavities, or bilateral lung parenchymal disease, or bilateral mediastinal nodes with airway compression on CXR, or extrapulmonary forms of disease other than peripheral lymphadenopathy.
- Treatment of MDR-TB meningitis should be guided by the medicines with good penetration to CNS and use of steroids. Recent studies have shown that Bdq penetrates well into CSF in pulmonary TB patients with presumably intact blood brain barrier (https://pubmed.ncbi.nlm.nih.gov/35257182/ -Upton et al 2022). Overall Bdq, Mfx, Lzd, Mpm, Cs, Eto, Z have good CSF penetration to treat CNS TB.
- In children with fluoroquinolone resistance or in whom there are limited treatment options, extension beyond 6 months and combination of bedaquiline and/or delamanid could be considered on a patient-by-patient basis with careful monitoring.
- Linezolid is a group A drug with good efficacy and well tolerated by children, but its use has been associated with frequent toxicity and related toxicities are duration

[10] WHO Operational Handbook on tuberculosis, module 5. Management of tuberculosis in Children and Adolescent. WHO, 2022

dependent. Therefore, its use for throughout duration cannot be warranted and its monitoring of side effects of neuropathy is challenging in young children. Based on expert opinions, in very young children with no severe disease Lzd can be used for 2 months to avoid unnoticed toxicity (neuropathies).

- Younger children who cannot read can have visual acuity tested using symbol charts. Very young children can have visual tracking assessed. Symptoms of loss of visual acuity may include bumping into things or having difficulty grasping and picking up objects.
- Children of all ages can be assessed for peripheral neuropathy using reflexes and pinprick testing. Symptoms of peripheral neuropathy may include tripping, stumbling, crying, or slapping at the hands/feet.
- In children with HIV and MDR-TB co-morbidity, bedaquiline and efavirenz should be avoided in combination use as efavirenz lowers the concentrations of bedaquiline.
- Ethionamide (if no *Inh*A gene mutation) and high dose INH (if no *kat*G mutation) and PZA are also options to use if documented susceptibility, PAS can also be used if no other effective option is left.
- The child friendly formulations and weight-based dosing of the second-line drugs should be used. If few medications are not available in child friendly formulations/dosages, then daily dosing will be approximate: tablets may be cut into fragments and crushed, capsules may be opened, and the content fractioned. Small discrepancies will even out over time. The drugs may be mixed with small amounts of liquid or soft food, particularly sweet jam.
- The children with MDR TB to be treated with close consultation of pediatrician expert in MDR TB management

3.5 Treatment of MDR/RR-TB with additional resistance and non-responders (failure) to DR-TB treatment

3.5.1 Treatment principles for the management of DR-TB with additional resistance and failures

The diagnosis of additional resistance on top of MDR-TB may present at baseline or may be revealed after MDR-TB treatment has started.

1. It is imperative that all diagnosed MDR-RR TB should be placed on DST and the current availability of rapid molecular DST (Xpert MTB/XDR and LPAs) make the DST results to be known quickly.
2. BPaL being shorter and effective regimen should be used as priority regimen for eligible patients.

3. As per revised definition of XDR-TB, it is crucial to send sample for DST to Bdq and Lzd to perform phenotypic DST.
4. The DST result to FQ should be known as soon as possible and regimen to be adjusted accordingly.
5. However, if there are delays in result, treatment initiation with the best empirical regimen should not be delayed.
6. Designing longer regimen for MDR-TB patients with additional resistance follows the same principle as without additional resistance.
7. The basic principle of having at least 4 effective drugs on board in the beginning and at least 3 drugs to be continued when Bdq or Dlm is stopped after 6 months.
8. With the emergence of new drugs, repurposed drugs and analytical results of currently used SLDs it seems that using large numbers of drugs is probably no longer required.
9. Individualized longer regimen designed based on resistance/tolerance/prior use of drugs from group A, B and C to have at least 4 effective drugs in initial and 3 in later phase.
10. The duration of treatment also applies the same as minimum 18 months and can be extended based on the patient's response to treatment.

3.5.2 Suggested regimens for use in Pre-XDR-TB and XDR-TB

Table 3.8: Regimens for pre-XDR and XDR-TB

NOTE: The following are the **baseline regimens(examples)** for RR/MDR TB with additional resistance (pre-XDR-TB and XDR-TB), please construct regimens based on DST results, previous exposure of drugs and contraindications to a drug.

DR-TB Type		Baseline regimens	Remarks/comments
1	Baseline FQ resistance with no or less than 30 days exposure to Bdq, Lzd	BPaL Regimen (bedaquiline, pretomanid, linezolid for 6-9 months)	1.Follow the set eligibility criteria 2. If DST to Bdq and Lzd shows susceptibility then despite previous more than 1 month exposure BPaL can be used
2	For patients with fluoroquinolones resistance and not eligible for BPaL (Pre-XDR TB)	(1) 18 Bdq (12)-Lzd-Cfz-Cs-Z (2) 18 Bdq (12)-Dlm (6)-Lzd-Cfz-Cs (3) 18 Bdq-Am (6)-Cfz-Cs-Eto-E	1.If lzd is contraindicated at baseline then use Dlm instead or Am (if susceptible with close monitoring) 2.Bdq can be extended to 12 months or throughout treatment duration in case-by-case situation 3. Once Bdq is stopped and mutation for Mfx^{h} suggest its use then please add Mfx high dose in regimen

			4. Dlm is very expensive and its availability for all FQ resistant patients may not be guaranteed
3	For Patients with FQ resistance plus resistance to Bdq or Lzd (XDR TB)	If Lzd resistance/contraindication 18 Bdq-Cfz-Cs-Dlm (6)-E/Z-Mfx^{h}* If Bdq Resistance, 6 Am-Lzd-Cs-Dlm-Eto-Z / 12 Lzd-Cs-Eto-Z If resistant to both Bdq and Lzd, 6 Am-Cfz-Cs-Dlm-Eto-Z / 12 Cfz-Cs-Dlm-Eto-Z	1.If no confidence on E, Z then choose Eto, PAS in regimen 2.Where possibility to use Mfx^{h}*, please add but avoid using together with Bdq/Dlm Cfz is added if susceptibility is confirmed

3.5.3 Treatment regimens for MDR/RR-TB failures

Approaching person-centered care for re-treat MDR/RR-TB is essential, which includes provision of proper counselling and assessing barriers for the anti-TB treatment, vigilant monitoring of side effects and early management, integrated care for comorbid diseases, proper treatment and referral for comorbidities, nutritional assessment to provide therapeutic foods and ration, and enhance DOT provision.

Table 3.9: Treatment regimens for MDR/RR-TB failures

Failed regimen	Regimen**	Comments
Failure of all 9-month all-oral (OSSTR) #	(1) 18 Lzd-Dlm (6)-Cfz-Cs (2) 6 Ipm/Cln-Amx/clv-Lzd-Dlm-Cs-PAS-Z /12 Am (6)-Lzd-Cs-PAS-Z	1. Send samples for requesting DST to Bdq, Lzd, Cfz, Dlm/Pa drugs and adjust the regimen once the pDST result in hand 2.If FQ and Eto is confirmed to be susceptible by rapid diagnostic tests, then those should be part of regimen while waiting for the pDST result. 3. Injection (Ipm/Am) can also be part of regimen, if susceptible and appropriate audiometry in place, especially when Lzd cannot be used 4. Bdq can still be part of regimen, with close monitoring of QTcF when concurrent using of Bdq and Dlm 5. Dlm may be extended beyond 6 months after evaluation of patient response and remaining drugs in the regimen 6. In case of Lzd variant failure, evaluate its usage in the new regimen
Failed by MDR-TB all oral longer treatment or recurrence of MDR-TB	6 Ipm/Cln-Amx/clv-Dlm-E-Eto-Cs-PAS-(Lfx/Mfx*)/12 Amk(6)-Dlm(6)-Eto-Cs-PAS-(Lfx/Mfx^{h}*)	1. DST to FLD and SLDs should guide further modification where necessary 2. Use Am if documented susceptibility to it, design regimen based on previous exposure to SLDs and likely effective drugs. 4. Ipm/Cln may be used as required, but avoid two injections at one time 3.If susceptible to FQ, high dose Lfx or Mfx can be used, if resistance to FQ then FQ can

		be used in line with level of resistance reported (Mfx^{h} only) 4.Extending use of Dlm for whole duration is a possibility if there is no other option 5. If Cs was used as a part of previous failing regimen, then do not use
Failed by BPaLM/BPaL Regimen#	12 Ipm/Cln (6)-Amx/Clv (6)-Cfz-Cs-Eto-Z/E-Dlm (6) / 6 Am-Cfz-Cs-Eto-Z/E	DST guided Regimen Mfx^{h} can be part of regimen per criteria Dlm has cross resistance with Pretomanid

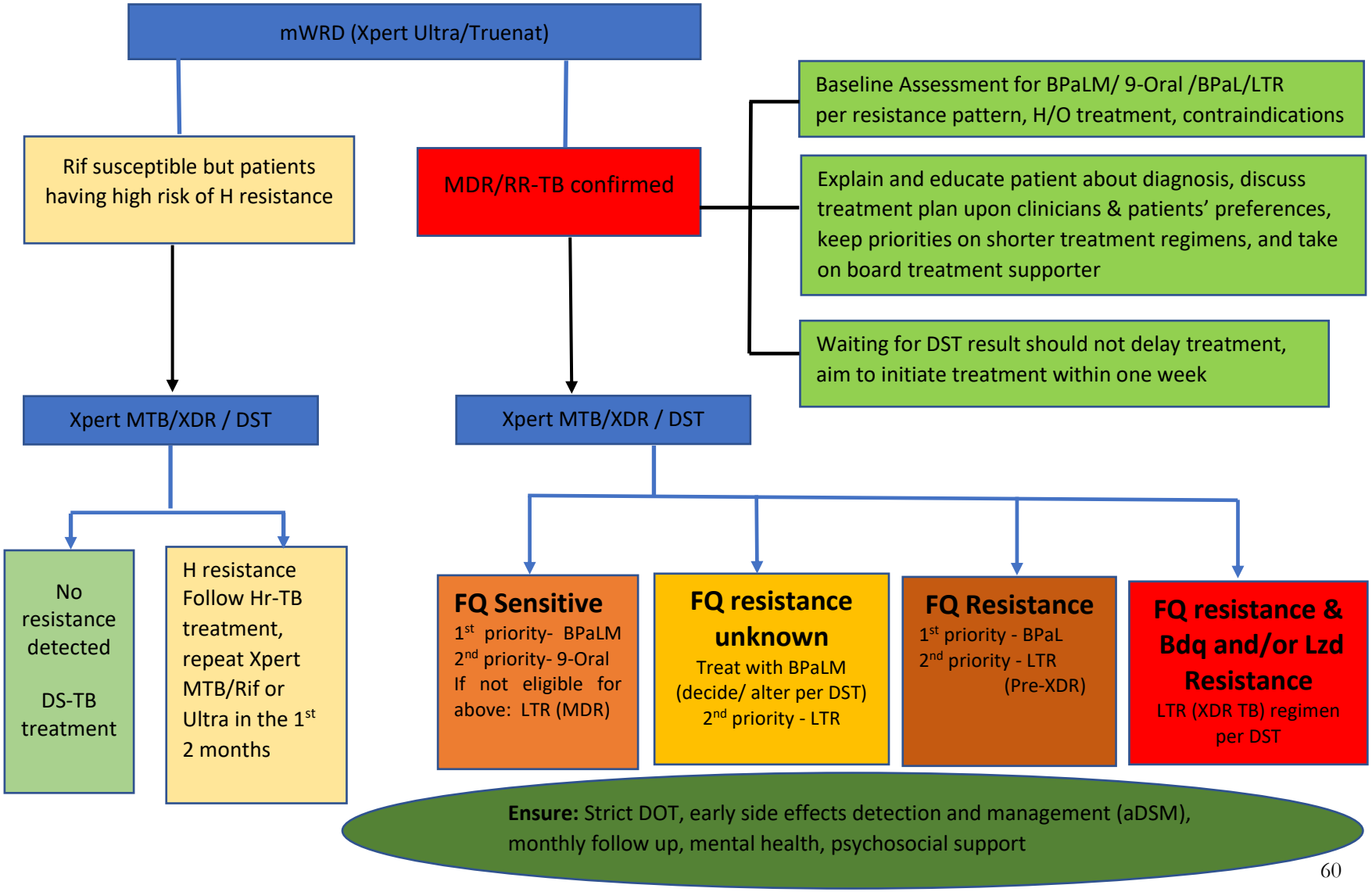
***These are the examples of regimen construction, while in practice, design regimen based on DST results, previous exposure to SLDs and contraindications to a drug*

 # If failure in 9-month all-oral (9-oral) or BPaLM/BPaL is due to Adverse drug reaction (ADR) and patient is responding well to treatment, then drugs used can be considered as likely effective while designing the regimen

Action Points

- 9-month all-oral (9-Oral) is the 2nd priority once patient is not eligible for BPaLM
- LTR generally of individualized nature is to be used once none of the shorter regimens can be used, particularly contraindication to any of the drugs in shorter regimens, failure of shorter regimens and XDR-TB.
- In LTR for FQ resistant patients, Bdq to be used for at least 12 months
- Injection amikacin is to be used with strict monitoring when there is no other option is left to treat effectively and is susceptible
- The regimen construction should follow the same principle for MDR/RR, pre XDR, XDR TB and failures of having at least 4-5 likely effective drugs in the regimen
- Children are eligible for 9-Oral and if need to treat with LTR majority of children with non- severe disease can be treated with 9-12 months of duration and with severe disease from 12-18 months depending upon treatment response
- Never add a single drug in failing regimen
- aDSM applies to all regimens and SAEs to be reported per NTP protocols
- In TB/DR TB with diabetes make all efforts to control hyperglycemia preferably with insulin therapy

Figure 3.1 DR-TB treatment algorithm



3.6 Treatment of NTM and MDR/RR-TB co-infection

The family of non-tuberculous mycobacteria (NTM) consists of about 170 species of mycobacteria. However, pulmonary diseases in humans are mostly caused by species of *M. avium complex* (MAC), *M. kansasii*, and *M. abscessus* (Johnson et al, 2014). Human infections due to NTM are primarily acquired from the environment, although the precise mode of transmission remains unclear. Treatment of NTM diseases follows specific guidelines, based on the nature of infecting bacteria, and requires species identification. Unlike TB, the treatment for NTM disease takes at least 18 months, with 12 months sputum-negative period.

The prevalence of pulmonary NTM diseases increased from 1.3 to 7.9 cases/100,000 population in Asia, most of which were due to MAC and *M. abscessus*. Diagnostic of NTM while patients are on TB or MDR TB treatment is challenging, specially to differentiate between MTB and NTM. However, solid or liquid including MGIT but with p-nitro benzoic acid test (PNB) and LPAs are the routine tools to differentiate between MTB and NTM. Before embarking on the treatment of NTM while a patient is on MDR TB treatment, it is necessary to confirm NTM growth at least 2 to 3 cultures isolate as one culture with NTM can be an environmental contamination. Culture may be repeated with another sputum sample earlier than 30 days apart to confirm NTM and to offer treatment. One of the vital biochemical tests used routinely in clinical laboratories to discriminate MTB from NTM is the p-nitro benzoic acid test (PNB). In the PNB inhibition test, while the growth of MTB is inhibited, NTMs grow on culture medium containing PNB, as they are resistant to PNB. Few commercially available tests, for example EZplex MTBC/NTM kit and VereMTB detection kit, were also evaluated and shown to be useful for detecting NTM species directly from a sputum sample. The sensitivity and specificity of this method were 98.8%-100% for NTM.

3.6.1 Species wise NTM suggested treatment

Pulmonary NTM disease is predominantly caused by five of the NTM species (MAC, *M. abscessus*, *M. kansasii*, *M. xenopi*, and *M. malmoense*), with a different incidence of each of the strains, worldwide.

1. MAC (*M. avium* complex): During MDR TB Treatment most of the SLDs included will cover NTM-MAC treatment and requires adding ethambutol 15 mg/kg/day and azithromycin 500 mg OD, rifampin 600 mg administered daily or three times per week
2. *M. abscessus*: In addition to MDR TB treatment just add azithromycin 500 mg OD
3. *M. Kansassi* : Rifampin 10 mg/kg/day; ethambutol 15 g/kg/day; isoniazid 5 mg/kg/day in addition to MDR TB Treatment
4. *M. malmoense* and *M. xenopi*: In addition to MDR-TB treatment, add isoniazid, rifabutin or rifampin, ethambutol, and azithromycin

3.6.2 Duration of NTM treatment

Usually, during MDR TB treatment, the NTM treatment may last 12-18 months with 12 months after negative culture for NTM (smear may also be considered if negative). However, if NTM is detected by end of TB/MDR TB treatment then stop MDR TB treatment and continue only NTM treatment with azithromycin and other drugs as stated above. Moreover, these guidelines are also recommending injection amikacin for 3 months, but in MDR TB treatment we have already enough drugs to cover which are Lzd, FQs and Am to be used where there is no other choice with caution.

4. Monitoring and outcome of DR-TB treatment

4.1 Follow up schedules

Patients will have to come to the MDR-TB center by the end of second week (W2) and fourth week (W4) in the first month and then, every month from the second month onward. This is to monitor treatment response and adverse drug actions, and to ensure adherence. Thereafter, follow up will be monthly or more often as per decision of treating physician.

4.2 Monitoring by follow up sputum smear and culture

Box 4.1. Treatment monitoring by smear microscopy and culture (liquid) for BPaLM/BPaL

Tests	Timeframe (months)									
	0	1	2	3	4	5	6	7*	8*	9*
Smear	√	√	√	√	√	√	√	√	√	√
Liquid Culture	√	√	√	√	√	√	√	√	√	√

Note: * smear and culture of 7,8,9 will be applied if BPaL treatment is extended beyond 6 months

Box 4.2. Treatment monitoring by smear microscopy and culture (liquid) for 9-month all-oral (9-oral)

Tests	**Timeframe (months)**											
	Initial Phase (IP)							**Continuation Phase (CP)**				
	0	1	2	3	4	5	6	7	8	9	10*	11*
Smear	√	√	√	√	√	√	√	√	√	√	√	√
Liquid Culture			√	√	√		√		√	√	√	√

Note: * Smear and culture for month 10 and 11 would be applicable for patients on 9-month all-oral (9-Oral) with total duration of treatment for 11 months.

Box 4.3 Treatment monitoring by smear microscopy and culture (liquid) for all longer treatment regimens

Tests	Timeframe (months)																			
	0	1	2*	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Smear	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Liquid Culture			√	√	√		√		√				√		√		√		**	**	**

Note: * to perform at month 2, so that treatment can be stopped by month 18, given that there is 16 months of treatment after culture conversion. Moreover, minimum treatment duration is 18 months and may last up to 20 months or more as per treatment response.
** if required.

If there is one culture positive or 2 consecutive smears positive during treatment at any time (after smear/culture conversion) then follow the monthly culture schedule for that patient.

4.3 Monitoring by clinical evaluation, ECG and biochemistry tests for DR-TB regimens

This includes body weight and height (children), temperature, review of sputum smear and culture results, monitoring of symptoms, monitoring of QTc, evaluation of any possible side effects by clinical signs and symptoms as well as by laboratory monitoring for timely and appropriate management. CXR must be taken 6 monthly to evaluate the radiological improvement and documentation.

Table 4.1: Monitoring follow up and testing schedule for BPaLM/BPaL/9-month all-oral (9-oral)/LTR

Flowing schedule applies to all regimens per their treatment duration

	Follow up months																			
Monitoring	BL	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
ECG[1]	X	XX	X	X	X	X	X														
CBP[2]	X	XX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual assessment [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral Neuropathy[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum creatinine [4]	X																				
Serum electrolytes [5]	X	X	X	X	X	X	X														
Serum Uric Acid	X																				
LFT including Liver enzymes [6]	X	X	X	X	X	X	X														
Blood Sugar Test [7]	X																				
TSH [8]	X			X			X														
HIV Tests [9]	X																				
HBs Ag [9]	X																				
HCV antibody [9]	X																				
Pregnancy Test [9]	X																				
Serum Albumin [10]																					
CXR	X						X						X						X		

1. BL, 2 times testing in the first month & then monthly and as long as BDQ is part of treatment regimen
2. BL, 2 times testing in the first month & then monthly and as long as Lzd is part of treatment regimen
3. BL thorough screening and examination, monthly verbal screening and if positive to proceed to thorough examination
4. BL, and monthly for patients with preexisting renal insufficiency and also if indicated
5. BL, and then monthly and as long as BDQ is part of treatment regimen
6. BL, monthly for 6 M and after 6 M as indicated for patients at risk for hepatitis and MDR-TB/HIV patients
7. BL and monthly for DM patients
8. If Eto is one of the drugs in the regimen
9. BL and to repeat when there is indication
10. If necessary (eg, Dlm is one of the drugs in the regimen)

Note: The following tests should only be done when further investigation is required to evaluate a patient's underlying condition – T3, T4, serum amylase, retic count, iron study, HbA1C, serum lactate, PT, INR, USG abdomen.

Table 4.2: Normal ranges for blood monitoring tests (note that values can vary by method and instrument)

Sr. No.	Blood tests	Reference range		Reference range (SI units)	
1	Hb			M 13.5 - 17.5	g/dl
				F 12.0 - 15.5	g/dl
	WBC			4.00 – 11.00	10^3/µL
	Platelet count			150 - 400	10^3/µL
2	Serum albumin	3.4 - 5.4	g/dL		
3	Serum Creatinine	0.6–1.6	mg/dl	M 60 – 106	µmol/L
		0.4- 1.6	mg/dl	F 40 – 106	µmol/L
4	Serum Potassium			3.6 – 5.0	mmol/L
	Serum Magnesium			0.7 - 1.05	mmol/L
	Serum Calcium			2.15 - 2.55	mmol/L
5	Serum Uric Acid	3.5 - 7	mg/dl	M 240 – 530	µmol/L
				F 150 – 450	µmol/L
6	Random blood sugar	80 - 180	mg/dl		
	Fasting blood sugar	70 - 110	mg/dl		
7	Total Bilirubin	up to 1.0	mg/dl	<17	µmol/L
	Direct Bilirubin			0-3	µmol/L
	Indirect Bilirubin			3.0 - 14	µmol/L
8	Alk. Phosphatase			M 40 – 129	U/L
				F 35 – 104	U/L
9	ASAT/SGOT			M ≤ 40	U/L
				F ≤ 32	U/L
10	ALAT/SGPT			M ≤ 41	U/L
				F ≤ 33	U/L
11	TSH			0.27 - 4.2	mIU/L
	T3 (Free)			4 - 8.3	pmol/L
	T4 (Free)			10.6 – 19.4	pmol/L

4.4 Post-treatment follow-up

After completion of treatment, patients will be informed of the risk of recurrent TB and advised to return for clinical assessment. Patients will also be advised to return for sputum smear examinations and cultures to continue to monitor them at 6 and 12 months after completion of treatment to ensure sustained cure. A single sputum specimen for smear and culture will be collected at each follow-up visit. Chest X-ray may be done as required.

4.5 Treatment outcomes for DR-TB patients

Following are the updated Definitions to be used to document treatment outcome and these definitions apply to both DS and DR TB (WHO 2022).

(a)Treatment failed

A patient whose treatment regimen needed to be terminated or permanently changed [(a)] to a new regimen or treatment strategy.

(b)Cured

A pulmonary DR TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy[(b)], with evidence of bacteriological response [(c)] and no evidence of failure[(d)].

(c)Treatment completed

A patient who completed treatment as recommended by the national policy, whose outcome does not meet the above definition for cure or treatment failure.

(d)Died

A patient who died[(e)] before starting treatment or during treatment.

(e)Lost to follow-up

A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

(f)Not evaluated

A patient for whom no treatment outcome was assigned[(f)]

Treatment success: The sum of cured and treatment completed.

[a)] Reasons for the change include:

- No clinical response and/or no bacteriological response[c]
- Adverse drug reactions; or
- Evidence of additional drug resistance to medicines in the regimen.

[b)] National policy for treatment duration**:** The treatment duration policy applies differently to different regimens used in Myanmar. For **BPaLM**: The total Duration of treatment is 6 months, for **BPaL** treatment duration is 6-9 months and 9-12 months for **9-month all-oral (9-oral).** While for **LTR** the minimum duration is 18 months with 16 months post culture conversion (see notes below).

[c)]Bacteriological response**:** This refers to bacteriological conversion with no reversion. Bacteriological conversion describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures at least 30 days apart are negative. Bacteriological reversion describes a situation where at least two consecutive cultures at least 30 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

[d)]No evidence of failure: Applies to all DR TB patients on treatment while being assessed for end of treatment that there is adequate clinical and radiological response to treatment per given treatment duration of the regimen and no suspicion of clinical or radiological deterioration.

[e)] Patient died for any reason.

[f)] This includes cases "transferred out" to another treatment unit and those whose treatment outcome is unknown; however, it excludes those lost to follow-up.

Notes: MDR/RR-TB, Pre-XDR TB, XDR-TB patient who has converted to negative (see conversion definition) and received minimum 18 months of treatment with at least 16 months (for LTR) after culture conversion and at least 2 consecutive cultures are negative after 12 months of treatment (for example 12,14 or 14,16 or 16,18 culture are negative) are to be declared as cure. While 2 consecutive negative cultures equally apply to BPaLM/BPaL/9-month all-oral (9-oral) in order to declare cure as per treatment duration policy. If there is one culture positive (without clinical and radiological deterioration) by end of treatment it should be followed by 2 negative cultures and switch to monthly cultures.

5. Treatment of rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB)

In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is to be given for a duration of 6 months. However, as no REZ FDC is available, the suitable option is to use HREZ FDC with Lfx, and a weight band dosing scheme is recommended.

The implementation to this recommendation requires that the (H)REZ-Lfx regimen is administered only in patients in whom resistance to isoniazid is confirmed and resistance to rifampicin has been excluded. Preferably, testing for resistance to fluoroquinolones possibly prior to treatment initiation with Xpert MTB-XDR or SL-LPA is desirable among such patients. It is also important to test for resistance to pyrazinamide (after NTP has adopted Genoscholar PZA-TB II (Nipro)) and later treatment adjusted, while DST for E is not useful on treatment. Empirical treatment of Hr-TB is not recommended.

5.1 Scenarios and action required for Hr-TB patient management

Practically following scenarios (and actions required) will be encountered.

5.1.1 Hr-TB and FQ susceptibility is confirmed before TB treatment is started

- Treatment with the 6 (H)RZE-Lfx is started immediately.
- If the isoniazid resistance is strongly presumed (e.g., close contacts of a confirmed Hr-TB source case), but results of drug susceptibility testing are still pending the (H)RZE-Lfx regimen may be introduced. When drug susceptibility test results (at baseline) eventually came out as susceptibility to isoniazid, then levofloxacin is stopped, and the patient continues treatment in order to complete a 2HRZE/4HR regimen.

5.1.2 Hr-TB is confirmed after the start of treatment with 2HRZE/4HR regimen

- This applies to patients who developed isoniazid resistance while on first-line treatment, at this point rapid molecular testing for rifampicin and FQ resistance must be done (or repeated).
- Once rifampicin resistance is excluded, a full 6-month course of (H)RZE-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this.
- If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB treatment regimen keeping in view the previous exposure of drugs in Hr-TB treatment.

5.2 Treatment principles for Hr-TB

Following should be considered for Hr-TB management;

1. It is imperative to perform Xpert MTB/RIF and Xpert MTB/XDR or SL-LPA in all probable mono, poly,Hr-TB patients, before enrolling them on treatment, this excludes those with Rif resistance, as such patients require full MDR-TB treatment.
2. Always rule out FQ resistance and send quality specimen for DST (Xpert MTB/XDR or SL-LPA) to exclude FQ resistance while enrolling patient on mono and poly DR-TB treatment regimen.
3. If the patient is new and H resistance is reported during IR treatment, the regimen 6(H)RZE,Lfx may suffice and extension beyond 6 months may be considered case-by -case. If Lfx cannot be added in Hr-TB treatment due to various reasons then treating with 6HRZE is also an option.
4. Patients who are failures of IR or retreatment regimens with H resistance, or where additional resistance is suspected(E or specially to Z) or where Lfx cannot be used , for such patients individualized regimen should be designed in consultation with experts. This is because for such patients, still WHO has not provided clear guidance and risk is that such patients with only RZE, Lfx based regimen may be at high risk of under treatment and higher risk of development of resistance to Lfx. Moreover, DST to Z & E might not be available and DST to E is of unreliable nature. Likewise, there is also a chance that Xpert and FL-LPA may not detect Rif resistance if resistance is happening outside of rpoB gene or heteroresistance. Therefore, both Xpert and LPA may miss RIF resistance, particularly heteroresistance with mutations that cause fitness loss and this may be more encountered with pDST(Van Deun et al 2020). Thus, Whole Genome Sequencing (WGS) could be the best solution. The poor treatment outcomes and amplification of resistance to FQ in Hr-TB treatment is because of missed rifampicin resistance(Van Deun et al 2020). Therefore, a stronger regimen at baseline should be designed with at least three to four likely effective drugs on board. Therefore, Lzd, Cs, Eto may be considered for such cases (WHO 2018). Bdq, Dlm are not recommended in Hr-TB treatment and Mfx^{h} can be considered in Hr-TB treatment when low level FQ resistance is reported, though plasma peak concentration and exposure to Mfx decreases significantly when used with Rifampicin. Also, with Mfx^{h} the QTcF interval risk is highly increased.
5. The basic principle to treat mono and poly DR-TB (Rif susceptible) is to have at least 3 to 4 likely effective drugs on board. It is the decision of the physician keeping in view previous history of TB medicine exposure in failed regimen/ previous treatment outcome, DST patterns to treat with Hr-TB or to place patients on full MDR TB treatment as proxy of MDR TB and this should be considered case-by-case.

6. Assess and address adherence issues in patients who failed DS-TB regimens, because in those who either do not take drugs or miss the doses repeatedly, none of the treatment can be helpful.
7. Treatment prolongation up to 9 months may be considered for patients with extensive cavitary disease or in patients slow to convert to negative smear/culture.
8. Likewise, it is essential to always repeat Xpert MTB/RIF or Xpert ultra at month 1, 2 of Hr-TB treatment or if smear is reported positive after negative smear. If rifampicin resistance is found, switch to MDR-TB treatment keeping in view previous exposure of drugs.
9. These recommendations also apply to children and HIV patients
10. For monitoring purposes, it should be followed as a DS-TB regimen.
11. Principle of never adding a single drug to a failing regimen is the whole through for all TB treatment.

5.3 Examples of treatment regimens for mono and poly-resistant DR-TB

Table 5.1 Examples of regimens for mono and poly-resistant DR-TB other than RR-TB*

Background History /resistance pattern	Regimen	Comments
INH resistance in new patients (including contact of Hr-TB patient)	(H)RZE,Lfx for 6 months If Lfx can not be used then 6(H)RZE is also an option	Rule out and exclude FQ resistance by Xpert MTB/XDR / SL-LPA/pDST
INH resistance among patients who are IR failure/retreatment cases	6-9 RZE,Lfx,Lzd**	If Lzd cannot be given then choice could be Cs/Eto
Resistance to H&Z	6-9 RZE,Lfx, Lzd**	Same as above
Resistance to H & Lfx (+/- Z)	6-9 RZE,Lzd,Cs,Eto**	Assess case-by-case and design regimen If need arises to treat with multiple SLDs in Hr-TB treatment, then consider treating with MDR TB oral longer regimen as proxy of MDR TB

***Assuming that rifampicin is susceptible in these cases.

** If SLDs other than levofloxacin are needed in Hr-TB treatment, the regimen to be discussed in CME with expert members.

Note : All are empirical treatment unless DST for all FLDs are unknown.

5.4 Dosage for Hr-TB

5.4.1 Weight-based dosing for adult Hr-TB

Weight band (in Kg)	HRZE (75/150/400/275)	Levofloxacin 250 mg
30-39#	2-3 tablets	Apply dose of levofloxacin in second-line TB medicine weight-based dosing table
40-54	3 tablets	
55-70	4 tablets	
>70**	Number of FDCs adjusted to dose	

The patient with the body weight of 30 – 39 kilogram can take 3 tablets of 4FDC

Note: ** patients > 70 kgs may receive weight-based dosing of individual drug

5.4.2 Weight-based dosing for paediatric Hr-TB

Weight band (in Kg)	Paediatric HRZ (50/75/150)	Ethambutol 100 mg	Levofloxacin 100 mg
4-7	1 tablet	1 tablet	Apply dose of levofloxacin in second-line TB medicine weight-based dosing table
8-11	2 tablets	2 tablets	
12-15	3 tablets	3 tablets	
16-24	4 tablets	4 tablets	

Note: In children weighing 25 kg or more the adult schedule shown in the previous section is followed.

If levofloxacin 100 mg dispersible tablet is not available, the 250mg tablet can be used with 6(H)REZ in children aged 0-14 years, based on a slightly different weight band from the above:

Weight	Levofloxacin 250mg
5 - 6 kg	Apply dose of levofloxacin in second-line TB medicine weight-based dosing table
7 - 9 kg	
10 – 15 kg	
16 – 23 kg	
24 – 30 kg	
31 kg +	

5.5 Follow up monitoring of Hr-TB patients

1. In large treatment, monitoring applies the same to DS -TB. However monthly smear may be necessary practice to closely monitor these patients for treatment response and to detect early failures , baseline and monthly LFT, visual checks if complaint of blurred vision, peripheral neuropathy assessment at baseline and monthly, blood CP at baseline and monthly to monitor myelosuppression for Lzd included regimen, ECG may not be required as Lfx has low cardiotoxicity profile until unless there is an underline risk or electrolytes imbalance.
2. Repeat Xpert MTB/Rif for at least 2 times (M1 and M2) to see if Rif resistance has developed.
3. Culture routinely not to be performed until necessary or DST is required.
4. Hr-TB patients to be registered in SLD register for drug consumption from second line agents, but should not be enumerated in MDR/RR-TB cohort.
5. Monitor separately for Hr-TB detection, testing and treatment coverage, outcomes from other DS-TB and MDR/RR-TB patients.
6. Generally, with 6–9 month duration of Hr-TB treatment, the outcome definitions of DS-TB are applied.
7. aDSM in terms of reporting does not apply to Hr/polydrug resistant TB patients.
8. Post outcome follow up at month 6 and 12.

6. Adjuvant therapies, interventions, care and support for DR-TB patients

6.1 Pyridoxine

Several side effects related to the nervous system can be prevented by the daily administration of pyridoxine. Pyridoxine (vitamin B6) should be given to all TB patients who receive second-line therapy. The usual dosage is 50 mg per day in children and 100 mg per day in adults. If cycloserine is part of the treatment regimen, the recommended dose is 50 mg for every 250 mg of Cs and if Lzd and or H^h is part of the regimen then 100-200 mg of pyridoxine should be part of the regimen.

Table 6.1. Daily dosing of pyridoxine according to daily administration of cycloserine prescribed

Daily dose of cycloserine	Daily dose of pyridoxine
250mg	50mg
500mg	100mg
750mg	150mg
1000mg	200mg

6.2 Use of steroids in TB/DR-TB

Steroids are useful in cases of TB meningitis and TB pericarditis, and also for children with miliary TB or obstruction of the bronchi as a result of mediastinal TB adenitis. Their use may also be considered in cases with severe respiratory insufficiency. The usual dosage is prednisone 1 mg/kg/day, to be tapered over 6–8 weeks to arrive at a maintenance dose of 5mg/day. Steroids will also be given if a severe paradoxical reaction (IRIS) occurs, especially in patients with TB/HIV co-infection.

Corticosteroids are immunosuppressive and therefore can weaken the body's response to fight TB; hence, they should only be used if clearly indicated and if the patient is on an adequate effective regimen. If corticosteroids are used in an inadequate regimen, this could accelerate the patient's deterioration. Oral treatment can be given, but when a more immediate response is needed injectable corticosteroids are often used initially.

6.3 Role of Surgery

When some cases of MDR/XDR-TB are virtually untreatable with all available drugs or risk having serious sequelae, surgery may be an effective adjunct to chemotherapy. If the lung lesions are not extensive, partial lung resection (lobectomy or wedge resection) for patients with MDR/pre-XDR/XDR-TB is only to be considered when good surgical facilities, staffed by trained and experienced surgeons, and excellent postoperative care are available.

- The role of pulmonary surgery is re-evaluated as a way to reduce the amount of lung tissue with intractable pathology and to reduce bacterial load and thus may improve prognosis.
- In patients with MDR/RR-TB patients with resistance to additional medicines, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended DR-TB regimen.
- The surgery should be performed under stringent infection control measures (given that infectious material and aerosols are generated in large quantities during surgery).
- The relative benefit of the surgery is expected only when patient has no other associated factors for poor prognosis.
- It may be considered an adjunct to chemotherapy and appears to be beneficial for improved outcomes. It is not indicated in patients with extensive bilateral disease.
- Minimum two months of effective therapy should be given prior to surgery and ideally after culture conversion, resection surgery should take place to decrease the bacterial infection in the surrounding lung tissue.
- Resection surgery should be timed to give the patient the best possible chance of cure with the least risk of harm. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower (e.g., when the disease is still localized to one lung or one lung lobe).
- Even with successful resection, the total duration of treatment and the duration of treatment after culture conversion should be guided by as described in chapter 3.

6.4 Social and enablers support for MDR/RR-TB patients

All registered MDR-TB patients receive monthly social support. The support for DR-TB patients are as follows which may change in future in line with NTP and GF policy.

DR-TB support package

- Transportation allowance for follow up clinic visits (in cash)
- Nutrition support (in cash)
- DOT provision either by a BHS or a volunteer

- Treatment adherence support and referral
- Infection control measure
- Side effect monitoring, referral, and psychological support
- Awareness raising & contact tracing

Other supports by NTP

- Laboratory investigation cost support (baseline investigations as well as follow up investigations)
- Nutrition therapy for DR-TB patients with BMI <16
- Pre -treatment transportation allowance which may be variably applicable to Regions and States

6.5 Treatment, care and support for patients with DR-TB treatment failure

MDR-TB treatment often consists of a treatment cycle; if no response is seen, reassessment of the regimen and treatment plan as well as formulation of a new plan of action are necessary. Suspension of drug therapy is recommended in cases where the treating physicians in a panel-based approach are confident that all the prescribed drugs have been ingested/exhausted and there is no possibility of using other drugs or carrying out surgery. Please refer to the definition of failure in the relevant section.

6.6 Approaches to suspending treatment

There are at least three important considerations in suspending anti-TB therapy and changing it to palliative/end-of-life care: (i) *the patient's quality of life*: the drugs used in MDR-TB treatment have significant adverse effects, and continuing them while the treatment is failing may cause additional unnecessary suffering; (ii) *the public health interest*: continuing a treatment that is failing can amplify resistance in the patient's strain, and will result in a waste of resources; (iii) *the model of care available* to provide palliative care *and* proper TB infection control to patients who have no effective treatment alternatives, while remaining a source of TB infection.

WHO defines palliative care as an “approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (WHO 2012)

The appropriate palliative care is the right of the patient and should be integrated as core part of TB/MDR-TB care, treatment, support and DOT. Following measures should be followed and ensured while patients are on palliative care after end of treatment (WHO 2014). The palliative care remains the responsibility of NTP as the patient remains the source of infection.

- **Relief from dyspnea.** Oxygen may be used to alleviate shortness of breath in some cases. The cause of dyspnoea is to be further investigated and treated accordingly.

- **Relief from pain and other symptoms.** Paracetamol, or codeine with paracetamol, gives relief from moderate pain. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable.

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

- **Nutritional support.** Small and frequent meals are often best for a person at the end of life.

- **Regular medical visits.** When MDR-TB treatment stops, regular visits by health-care providers and the support team should be continued to address medical needs. It needs to ensure that infection control practices are being followed.

- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued as needed.

- **Hospitalization, hospice care or nursing home care.** Having a patient die at home can be difficult for the family. Home-based care should be offered to patients and families who want to keep the patient at home, whenever appropriate infection control practices can be followed.

- **Provide psychosocial support.** It aims to assist patients and the family in the planning of decisions related with the end of life, and provide emotional support, especially in settings in which strong stigma is attached to the disease.

7. Treatment of MDR/RR-TB in special situation

7.1 MDR/RR-TB in women of child-bearing age and pregnancy

Most second-line drugs can be toxic for the fetus. Before starting any second-line treatment, all women of childbearing age should have a pregnancy test. If the test is negative, contraception must be recommended. The use of oral contraceptives is not contraindicated during MDR-TB treatment, but several second-line drugs may cause vomiting. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and therefore of decreased efficacy. The contraceptive should be taken at a time when vomiting as a result of the anti-TB medications is least likely to occur. Patients who vomit at any time directly after, or within the first two hours after taking the contraceptive tablet, should use a barrier method of contraception until they have been able to take the contraceptive tablets without vomiting for a full month.

- Pregnancy is not a contraindication for treatment of active drug-resistant TB, but DR-TB poses great risk to the lives of both the mother & fetus.
- The risks and benefits of treatment should be carefully considered, with the primary goal to protect the health of the mother and child, both before and after birth.
- Most pregnant patients should be started on treatment as soon as the diagnosis is made.
- It is better to start treatment with safer options.
- Counselling should be done in line with relevant family, religious, cultural and social dynamics.
- Despite limited data on safety and long-term use of fluoroquinolones, cycloserine in pregnancy, they are considered the drug of choice for MDR-TB treatment during pregnancy. Clofazimine has been used extensively in leprotic pregnant patients and use of it in pregnant DR-TB patients so far has not reported serious consequences. Similarly, bedaquiline has been used in pregnant women in South Africa with no apparent AEs and recently in 2020 WHO also recommended the use of Bdq in pregnancy.
- There are limited data on use of linezolid in human pregnancy but no reports of increased malformation or other direct or indirect harmful effects on the human fetus. So, linezolid may be used with caution if it is necessary for an effective regimen.
- The safety profile of para-aminosalicylic acid (PAS) is unknown; however, it is used during pregnancy. There is limited information on its use while breastfeeding (a proportion goes into human milk).
- Treat with three or four oral second-line anti-TB drugs including Bdq, which are likely to be highly effective plus pyrazinamide and regimen should be reinforced with other drugs as needed immediately postpartum. *(WHO 2022)*

- Ethionamide should be avoided as it can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.
- Amikacin and Streptomycin are usually contra-indicated during pregnancy.
- In pregnancy, **longer regimens are to be individualized** to include components with an established safety profile.
- The termination of pregnancy should be the last choice of action if it would carry a significant risk to her life. The decision will be heavily influenced by religion and culture.
- Total duration is the same as for non-pregnant women.
- The child should receive Bacillus Calmette–Guérin (BCG) vaccination at birth as per national policy.

Box 7.1 Treatment regimen for MDR/RR-TB in pregnancy

1.	9-month all-oral (Lzd variation) 4–6 Bdq (6 m)-Lzd (2 m)-Lfx/Mfx-Cfz-Z-E-Hh / 5 Lfx/Mfx-Cfz-Z-E	1. Cfz is relatively safe in pregnancy based on experience in human use in leprosy patients and now developing experience in MDR-TB. Recent WHO 2022 Guidelines also suggest Lzd use in pregnancy specially in 9-month all-oral (9-Oral) for 2 months instead of Eto. 2. FDA classifies Bdq in safety class B in pregnancy, in south Africa Bdq in pregnancy has shown safety.
2.	18 Bdq (6), Lzd, Lfx, Cfz, Z	

7.2 MDR/RR-TB in breastfeeding woman

Breastfeeding is no contra-indication for MDR-TB treatment as anti TB drugs excretion through breast milk is in very low concentration that is not harmful for neonate, but the benefit of breastfeeding has to be weighed against the risk of exposure to MDR-TB infection to the infant and infection prevention control should be in place, for example, breastfeeding should be in open place and wearing surgical mask by mother. Infant formula can only be considered a valid alternative to breastfeeding if all required resources are available and appropriate training has been provided. If the infection prevention can be maintained through personal protection like a mask to the mother and good environmental control, then breast feeding is preferred. If not, the option is to keep the baby away from the mother as long as she is contagious, and to collect the mother's milk using a breast pump and bottle-feed the baby until it is safe to reunite mother and child.

7.3 MDR/RR-TB and HIV co-infection

The treatment of DR-TB in PLHIV is not different from the treatment in HIV-negative people. If the TB/HIV patient is already on ART, it is to be continued. If not yet on ART, it must be prescribed according to the recommendations of the National AIDS Program (NAP) and started treatment rapidly regardless of CD4 count, as soon as the patient is seen to tolerate the MDR-TB treatment, possibly within 8 weeks. All TB/HIV patients must receive cotrimoxazole preventive therapy (CPT). All patients co-infected with HIV and MDR/RR-TB must be managed at the DR-TB Centre.

The DR-TB therapy in PLHIV is complicated by:

- cumulated drug toxicities
- drug-drug interaction
- other co-infections exacerbating drug toxicity
- malabsorption of drugs leading to treatment failure
- paradoxical worsening of TB symptoms when ART is started (Immune Reconstitution Inflammatory Syndrome or IRIS: see National HIV/AIDS Guidelines).

The risk of adverse drug reactions in PLHIV treated with second-line TB drugs increases with the degree of immunosuppression. ART and anti-TB drugs have potential overlapping or additive toxicities and the identification of the source of adverse effects is difficult. It is often impossible to link side effects to a single drug. Using agents with shared adverse effect profiles is not the preferred option but often, the benefit of the drugs outweighs the risk. Increased monitoring of adverse effects is recommended rather than disallowing a certain combination.

The main overlapping toxicities between the second-line drugs and the anti-retroviral drugs commonly used when treating TB/HIV co-infected patients (TDF, 3TC and EFV) are shown in table 7. 1.

Table 7.1. Potentially overlapping adverse effects between ART drugs and second-line drugs to treat PLHIV with MDR-TB

ART drug	Second-line drug	Adverse effect
EFV	Lfx, Mfx, Dlm, Am, Cs, Mpm Bdq, Eto/ Pto, H, Pa	CNS toxicity Depression
EFV, AZT	Cs, Bdq	Headache
Many ART drugs	Z, H, Pa, Bdq, Eto/Pto, PAS	Hepatotoxicity
AZT	Lzd	Bone marrow suppression
AZT, 3TC	Lzd	Lactic acidosis
All ART drugs	Eto, PAS	Abdominal pain
Most ART drugs	Eto, PAS, Bdq, Dlm, H, E, Z	Nausea, vomiting
Most ART drugs	Most Second-line drugs	Skin rash
Most ART drugs	Bdq, Dlm, Mfx, Cfz	Prolongation of QT interval

Concomitant use of bedaquiline with efavirenz (EFV) is not recommended due to possible decreasing serum concentration of bedaquiline. EFV should be replaced by dolutegravir (DTG) if available and MDR/RR-TB regimen should be preferred with Bdq. Protease Inhibitors (PIs) can be used with Bdq but should be administered with extreme caution because boosted protease inhibitors can increase bedaquiline exposure. Zidovudine (AZT) and Lzd concomitant use should also be avoided, if possible. But if there is no option apart from concomitant use of zidovudine (AZT) and Lzd, it should be used with caution. Please see more information in the table below.

Table 7.2: Possible drug-drug interactions between antiretrovirals and the new TB drugs (adopted from End TB guidelines 2018)

	Drugs	Instructions
ARVs to avoid with Bdq	Efavirenz (EFV) (Using EFV with Bdq will result in low serum level of Bdq)	Substitute integrase inhibitors instead of EFV. Allow a 5-day washout of EFV if possible, substitute dolutegravir (DTG) on day 1 and then start MDR regimen 5 days later. If a patient is critically ill with MDR-TB, no washout period is necessary.
	Ritonavir containing protease inhibitors (PIs) (Using ritonavir with Bdq will result in high levels of Bdq)	If possible, use an ARV regimen with no PI. One possible solution is to substitute the PI with an integrase inhibitor (INSTIs), e.g. dolutegravir (DTG) or raltegravir (RAL). If a ritonavir-containing PI must be used, check ECG every two weeks to detect early on bedaquiline-related adverse drug reactions (e.g., QT interval prolongation).
ARVs to avoid with Dlm	None	Dlm has very little drug-drug interactions with ARVs and no extra drug monitoring or regimen adjustment is needed.
ARVs to avoid with Lzd	Zidovudine (AZT)	Concomitant use of Lzd and AZT should also be avoided, if possible, because of the increased risk of myelosuppression.

Patients receiving ART and MDR-TB treatment must be closely monitored. Daily DOT is obligatory, because the large pill burden and the many side effects may compromise treatment adherence. Whenever adverse effects occur, they must be treated without delay. At the same time, it is important to be alert for signs and symptoms of malabsorption: diarrhoea, abnormal stools, poor nutritional status, evidence of vitamin deficiencies, weight loss, etc. Diarrhoea should be treated aggressively as it may lead to decreased drug

absorption and impair correct treatment.

7.4 Patients with extra-pulmonary DR-TB and DR-TB meningitis

Patients with extrapulmonary (EP) MDR/RR-TB can be initiated in BPaLM or 9-month all-oral (9-oral) except those with severe form of EPTB (TB meningitis, bone TB, miliary or disseminated TB, TB pericarditis) and PLHIV with EPTB.

Patients with severe EP MDR/RR-TB should not be treated with the 9-month all-oral because several of the drugs in this regimen penetrate poorly into bone and soft tissues and the CSF. Therefore, it is imperative to design appropriate regimens having sufficient drugs which can cross the blood brain barrier.

The example of effective regimen for CNS TB/TB meningitis could be:

18 Bdq (6), Mfx, Lzd, Cs, Z **(**Ipm-Cln/Mpm can be prioritized too)

Following table should be followed while designing an effective regimen to treat DR TB meningitis.

Table 7.3: TB Drugs with different level of penetration in CSF

CNS penetration	Medication	Remark
Good	Moxifloxacin	Good penetration in animals
	Levofloxacin	65% of serum concentrations
	Ipm/Cln, Mpm	Excellent
	Linezolid	Animal studies showed CSF levels at 30% of serum levels: widely used in humans with excellent results
	Cycloserine	CSF levels similar to serum levels
	Ethionamide	CSF levels similar to serum levels, but higher end dosing (20 mg/Kg), recommended in children
	Pyrazinamide	CSF levels similar to serum levels
Poor penetration, except in the presence of meningeal inflammation	Amikacin	Poor penetration except in the presence of meningeal inflammation
	Isoniazid	20% of serum concentrations except in the presence of meningeal inflammation
	PAS	Poor penetration except in the presence of meningeal inflammation
Poor penetration	Ethambutol	Poor penetration
Limited data available	Bedaquiline	Recent data suggests good penetration into CSF
	Delamanid	Limited human data but good CSF penetration in mice: studies ongoing
	Clofazimine	Limited data available

Some forms of EP, when treated, may show a paradoxical worsening. This is quite common in patients co-infected with TB and HIV (Immune Reconstitution Inflammatory Syndrome or IRIS: see National HIV/AIDS Guidelines). In certain types of EP, if IRIS occurs, adjuvant steroid therapy may be helpful.

7.5 MDR/RR-TB patients with hepatitis

Many anti-TB medications have the potential to cause hepatotoxicity, and their use must be carefully contemplated in the setting of severe liver dysfunction. Possible anti-TB drugs that can cause hepatotoxicity are Z, H, PAS, Eto/Pto, Bdq, Cfz and Clavulanic acid. Fortunately, the most important second-line anti-tuberculosis drugs used for treatment of drug-resistant disease do not affect the liver. Among the first-line drugs, Z is the most hepatotoxic, followed by H. Among the second-line drugs, Eto and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with fluoroquinolones. Lfx is less hepatotoxic than Mfx.

Hepatitis itself is not a contraindication to start DR-TB treatment unless liver enzymes are raised to unacceptable levels i.e 5-fold increase in liver enzyme. Patients with a history of liver disease can receive the usual anti-TB drug regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carriage, recent history of acute hepatitis or excessive alcohol consumption. In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Treatment of drug-resistant TB in the setting of liver failure is complicated and depends on the degree of liver damage. A long-course regimen with at least 4 non-hepatotoxic drugs is required. However, as per the newly WHO recommended regimen, the drugs from group A and B are safe to use, but Cfz has some lower degree of hepatotoxicity.

If a patient with acute hepatitis requires MDR-TB treatment, it may not be possible to refer to the treatment until the acute episode has resolved and liver enzymes become normal. Treatment with due considerations for drugs may have to be given. Viral hepatitis should be treated if medically indicated and treatment can be given during drug-resistant TB treatment.

Some Key messages for hepatotoxicity;

- Mild elevation of liver enzymes, especially at baseline, may be related to TB rather than an adverse effect of treatment
- Rule out viral hepatitis and alcoholic hepatitis

- ALT-AST Levels indicate degree of liver inflammation and liver cell damage - ALT is more specific for liver injury
- If ALT, AST levels are reported >5 times above the normal limit, stop all drugs including anti TB medicine, check liver enzymes weekly. In 9-month all-oral (9-oral) if Z is causing liver toxicity, then it can be stopped/interrupted during the continuation phase if safe to do so.
- Reintroduce drugs once liver enzymes return to normal with Least hepatotoxic 1st every 3-4 days, monitor LFTs
- If Z or Cfz or H^h is likely to be an offending drug, stop 9-month all-oral (9-Oral) permanently and switch to a safer regimen. Similarly, in longer regimens if Z is likely to be an offending drug, stop Z permanently and introduce a safer drug instead.

For more information, please refer to aDSM chapter and side effects management

7.6 DR-TB patients with nephrotoxicity (renal failure)

In DR-TB patients with renal insufficiency, the dosing of the second-line drugs is to be adjusted that are cleared by the kidneys if the creatinine clearance is <30ml/minute. The general strategy is to increase the interval between dosing rather than to decrease the dose: see table below.

To calculate the creatinine clearance following is detailed guidance.

Normal values for creatinine are

Women: 45-90 µmol/L (about 0.5 to 1.0 mg/dl)
Men: 60-110 µmol/L (about 0.7 to 1.2 mg/dl)

Estimation of GFR (Creatinine clearance) (Cockcroft-Gault method)

$$\text{Estimated GFR} = \frac{\text{Weight (kg)} \times (140 - \text{age}) \times (\text{constant})}{\text{Serum creatinine (µmol/litre)}}$$

The constant = 1.04 for women and 1.23 for men

If creatinine is reported in conventional units (mg/dl) from the laboratory, one can convert it to a SI Unit (µmol/L) by multiplying by 88.4. (For example, creatinine = 1.2 mg/dl is equivalent to (88.4 x 1.2) = 106.1 µmol/L.)

Normal values for creatinine clearance (CrCL)

Women: 88 to 128 ml/minute
Men: 97 to 137 ml/minute

Example (calculation with serum creatinine in µmol/litre)
A woman with 50 kg, 46 years, serum creatinine = 212 µmol/litre

$$\textbf{CrCl} = \frac{50\ \text{Kg} \times (140 - 46) \times 1.04}{212\ \mu\text{mol/litre}} = \frac{4888}{212} = 23.1\ \text{ml/min}$$

CrCl is < 30 ml/minute, therefore, adjust each drug as required according to the table **(7.4).**

Note: Check with a calculator for creatinine clearance; https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation

Overweight and obese patients

For overweight (BMI > 25) or obese (BMI > 30) patients, use the **ideal body weight (IBW)** rather than the actual body weight to avoid overestimation of the CrCl.

The IBW is calculated using the patient's height

IBW women (kg) = 45.4 + 0.89 (height in cm – 152.4)
IBW men (kg) = 49.9 + 0.89 (height in cm – 152.4)

Example:
A woman, weight 70 kg, height 160 cm (BMI = 27.3, i.e., overweight)
IBW for this overweight woman = 45.4 + 0.89 (160 – 152.4)

= 45.4 + 0.89 (7.6) = 45.4 + 6.76 = 52.2 kg

NOTE: check with a calculator for adjusted body weight; https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight

Table 7.4: Dosing recommendations of anti-TB drugs in adult patients with creatinine clearance <30 ml/min

Drug	Change in frequency?	Recommended dose and frequency
Isoniazid (H)	No change	300 mg once daily, or 900 mg 3 times/week
Rifampicin (R)	No change	600 mg once daily, or 600 mg 3 times/week
Pyrazinamide (Z)	**Yes**	**25– 35 mg/kg/dose 3 times/week (not daily)**
Ethambutol (E)	**Yes**	**15–25 mg/kg/dose 3 times/week (not daily)**
Levofloxacin (Lfx)	**Yes**	**750 –1000 mg/dose 3 times/week (not daily)**
Moxifloxacin (Mfx)	No change	400 mg daily
Cycloserine (Cs)	**Yes**	**500 mg/dose 3 times/week**
Ethionamide (Eto)	No change	15–20 mg/kg/day (can be in divided doses)
Para-aminosalicylate	No change	4 gm/dose twice daily
Linezolid (Lzd)	No change	600 mg daily
Clofazimine (Cfz)	No change	100 mg daily
Amikacin (Am)	**Yes**	**12–15 mg/kg/dose 2–3 times/week**
Imipenem/cilastatin	**Yes**	For creatinine clearance of 20–40 mL/min →750 mg every 12 hours For creatinine clearance <20 mL/min → 500 mg every 12 hours
Meropenem	**Yes**	For creatinine clearance 20-40 ml/min →750 mg every 12 hours. For creatinine clearance of <20/min → 500 mg every 12 hours
Bedaquiline (Bdq) and Delaminid (Dlm)	No change with mild to moderate renal dysfunction but use with caution in severe renal disease	

NOTE: Avoid sodium salt formulations of PAS in patients with severe renal disease (risk of excessive sodium load).

7.7 MDR/RR-TB patient with diabetes

The diagnosis of DM is made using the following thresholds and cut-off points based on whether the person investigated is symptomatic (for example, polyuria, polydipsia, unexplained weight loss) or asymptomatic.

- If **symptomatic**, then a single fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl), a post-prandial plasma glucose ≥11.1 mmol/l (≥200 mg/dl) or HbA1c≥6.5% (≥48 mmol/mol) will suffice for diagnosis. A random blood glucose≥11.1 mmol/l (≥200 mg/dl) in persons with clear symptoms of DM is also diagnostic.
- If **asymptomatic**, then it is advisable to obtain a fasting plasma glucose≥7.0 mmol/l (≥126 mg/dl), a post-prandial plasma glucose ≥11.1 mmol/l(≥200 mg/dl) or HbA1c ≥6.5% (≥48 mmol/mol) on two separate occasions.

Outcomes for patients who have both TB and diabetes are poorer than for TB patients without diabetes. Diabetes must be managed closely throughout the treatment of drug-resistant TB. **If the patient is on oral hypoglycaemic agents, he/she may need to be switched to insulin for the duration of the MDR-TB treatment if the diabetic control is unsatisfactory.** None of the anti-TB drugs are contraindicated.

Patients with diabetes and MDR-TB may be at increased risk of adverse events since many of the anti-TB drugs have side effects that place diabetic patients at special risk. Patients with long-standing diabetes may have underlying renal impairment that can be worsened by the second-line injectable drugs. Neuropathy is a common complication of diabetes and also can be worsened by several drugs used to treat MDR-TB such as high-dose INH, cycloserine, linezolid and the fluoroquinolones. Some preliminary evidence suggests that improving glycaemic control can lead to better TB treatment outcomes and reduced risk of relapse and recurrence.

Patients with diabetes may have decreased gastric motility (gastroparesis) and may be at increased risk of nausea and vomiting with medications like ethionamide or other MDR-TB drugs. Gastroparesis should be treated ideally with domperidone (caution with QT prolonging drugs), but metoclopramide is also effective. For peripheral neuropathy treatment in diabetic the choice could be pregabalin. For blood pressure management choice should be ACE inhibitors or alternatively, calcium channel blockers, with ACE inhibitors. Routine monitoring of creatinine, eGFR is necessary and do not prescribe ACE inhibitors in renal failure.

7.8 MDR/RR-TB patients with mental health problem

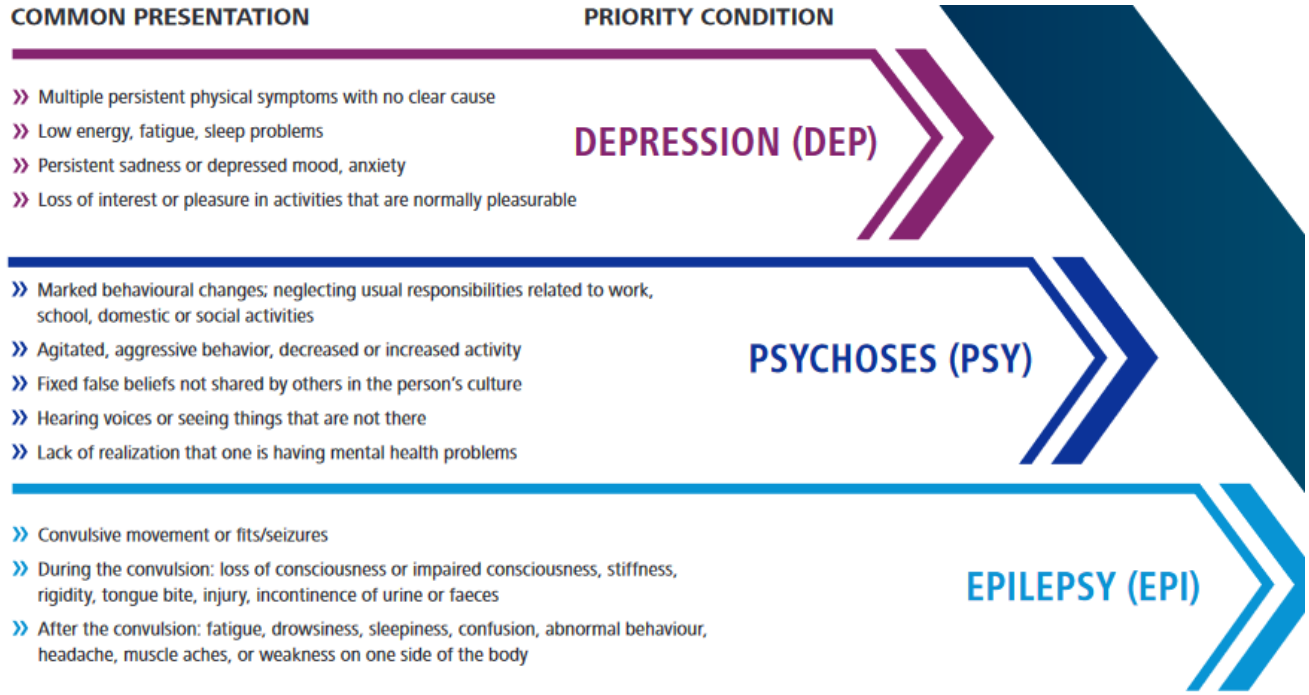
Currently NTPs globally are not addressing mental health problems in TB/MDR-TB, while End TB strategy explicitly mentions MDR/RR-TB and mental health integration. Chronic diseases like DR-TB is itself a matter of psychological disturbance leading to stressful situations and some level of depression.

A systematic review and meta-analysis findings (Alena et al 2018) concluded that, mental health and social functioning are compromised in a significant proportion of MDR-TB patients, a finding confirmed by the poor health-related quality of life reported. Thus, there is a substantial need for integrating mental health services, social protection, and social support into the clinical and programmatic management of MDR-TB.

This section may only cover some basic and fundamentals of mzzental health problems and their management in the context of MDR-TB. Please always assess for serious thoughts and acts of self-harm, alcohol and substance use and withdrawal. Recent thoughts or acts of self-harm are red flags and refer to specialists. It is also important to assess status by using Patient Health Questionnaire-9 (PHQ-9). The management of most common presentations (depression, anxiety, psychosis, and epilepsy) should be amenable to care-providers due to

overlapping toxicity of Bdq, Dlm and Lzd with 1st and 2nd line agents to treat depression, anxiety, psychosis and epilepsy.

Figure 7.1: Overview of priority mental health conditions in DR-TB (WHO, mhGAP guideline 2016)



The drugs should be avoided to be used with Bdq & Dlm are citalopram, amitriptyline, phenytoin, carbamazepine, phenobarbital, and antipsychotic drugs (haloperidol, risperidone).

Moreover, following should be avoided with Lzd. Linezolid and concomitant medicines that increase serotonin levels and may cause **serotonin syndrome**:

- Serotonin re-uptake inhibitors (SSRIs): citalopram, escitalopram, sertraline, fluoxetine, paroxetine
- Tricyclic antidepressants: amitriptyline, nortriptyline
- Serotonin 5-HT1 receptor agonists
- MAO inhibitors: phenelzine, isocarboxazid
- Other serotonergic agents: meperidine, bupropion, or buspirone, quetiapine

It is important to remember that before prescribing antidepressants, it is important to manage with non-pharmacological measures first particularly in mild to moderate depression where there is no red flag.

Keeping in view the above the choices and options of agents to be used for management of depression remain limited. As per NHS, UK guidelines 2018, in MDR-TB patients, **citalopram** (start with low doses, 10-20 mg) may only be used when Mfx^{h}/Bdq/Dlm are not on board or no risk of arrhythmia, including **contraindication for elderly patients**. Baseline ECG is necessary to start with citalopram. In MDR-TB patients on Mfx^{h}/Bdq/Dlm the drug of choice

to treat depression could be sertraline (50-100 mg tablet), even it is appropriate in renal impairment, but if Lzd is on board then sertraline cannot be used due to risk of serotonin syndrome. Moreover, if **Lzd/Dlm/Bdq is on board then Mirtazapine 15, 30 or 45 mg tablet** (a noradrenergic and specific serotonergic antidepressant – NaSSa) **is the drug of choice**, this is also useful in elderly and with GI trouble or at risk of GI bleeding. However there still is a risk for serotonin syndrome and therefore monitoring is essential during treatment with Lzd and mirtazapine.

8. Active TB drug-safety monitoring and management (aDSM)

TB patients who are treated with second-line anti-TB drugs are more likely to have toxic reactions than patients with first-line drugs, making pharmacovigilance becomes important in programmatic management of drug-resistant TB (PMDT) to monitor patient safety. aDSM is a public health surveillance activity designed to inform the management of TB patient safety measures.

8.1 Objectives of aDSM

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

8.2 Definitions

1. **Active drug-safety monitoring and management (aDSM):** is the active and systematic clinical and laboratory assessment of patients on treatment with (a) new anti-TB drugs, such as Bdq and Dlm; (b) new DR-TB regimens, such as BPaLM/BPaL,the shorter (or 9-month) MDR-TB regimen; or (c) XDR-TB regimens on new/repurposed drugs, in order to detect, manage and report suspected or confirmed drug toxicities.
2. **Adverse event (AE):** any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.
3. **Adverse drug reaction (ADR):** a response* to a TB medicine that is noxious and unintended, and which occurs at doses normally used in humans. * Response: a *causal relationship* between a medicine and an adverse event is at least a reasonable possibility.
4. **Serious adverse event (SAE):** an AE which leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly. The definition includes SAEs that do not immediately result in one of these outcomes but may require an intervention to prevent it from happening. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event.
5. **AE of special interest:** AE documented to have occurred during clinical trials and for which the monitoring program is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the TB treatment.
6. **AE of clinical significance**: AE that (a) is serious (SAE); (b) is of special interest; (c) leads to a discontinuation or change in the treatment; or (d) is judged as otherwise clinically significant by the clinician.

7. **Adverse event leading to treatment discontinuation or change in drug dosage** is an event that leads a clinician to stop, interrupt temporarily or change the dosage of one or more drugs, regardless of its seriousness, severity or causal relationship to the TB treatment.
8. **Causal relationship** is a relationship between an exposure (A) and an event (B) in which A precedes and causes B. This may refer to the causal association between an exposure to a TB medicine and the occurrence of an adverse reaction.
9. **Causality assessment**: the evaluation of the likelihood that a TB medicine was the causative agent of an observed adverse reaction.
10. **Signal**: reported information on a possible causal relationship between an adverse event and a TB medicine, the relationship being unknown or incompletely documented previously or representing a new aspect of a known association. Signal detection has not been a practice in Myanmar so far but may be the future practice.

8.3 What to monitor for aDSM

This national guideline adopts DR-TB treatment regimens recommended by WHO and as "new and repurposed drugs" are now part of standard regimen, therefore, aDSM is applicable across the board to all MDR/RR-TB, Pre-XDR and XDR patients. Adverse events (AEs) and adverse drug reactions (ADRs) may occur during treatment of DR-TB with various severity grading. Often, AEs or ADRs are the reasons for treatment irregularities or inadequate therapy. Timely recognition and proper management of AEs or ADRs will help avoid these.

All health workers dealing with DR-TB must be able to **recognize** SAE, AEs and ADRs to be graded for severity and seriousness, know how to **manage or refer** according to their level of the health care system and **record and report** of SAE in a timely manner. Myanmar NTP has adopted the core package of aDSM which means only **serious** AEs/ADRs are reported although all detected AEs need to be managed. When AEs and ADRs are identified, they are to be graded for **seriousness** and **severity**.

Seriousness is defined by the outcome of an adverse event. A serious adverse event (SAE) is one that leads to any of the outcomes mentioned in SAE definition. Possible explanation of SAE cases are DR TB patients under any SLD regimens whose adverse events result to one of the following outcomes:

1. Death (severity grading 5)
2. Life-threatening (Adverse event of severity grading 4 is always SAE)
3. Hospitalization due to adverse event
   (Remark: hospitalization for treatment initiation or managing co-morbid disease is not included for reporting, however, these cases need to report when SAE occur during hospitalization after treatment initiation or hospitalization extended to manage SAE)
4. Permanent disability (such as some cases of ototoxicity, optic neuritis, grade 4 neuropathies)

5. Significant disability (such as peripheral neuropathy with incapacitating e.g., cannot wear slipper, patient is not able to feel shoes wearing, all cases of optic neuritis)
6. Other medically serious (doctor decide to do intervention to prevent death or life-threatening event such as IV infusion for vomiting, managing for grade 2 QT prolongation with chest symptoms, etc)
7. Congenital anomaly (pregnancy is not SAE, pregnant woman under SLD should follow up after giving birth to assess the occurrence of SAE)

Note: (1) Stopping the suspected drug or reducing the dose of the suspected drug which is causing toxicity is not always SAE until unless any of the above conditions are met.

(2) all death cases related to AEs to be reported with as much relevant information as possible on the cause of death

Severity is defined by the impact on the patient's ability to function. It is graded on a scale of 1 to 5, as shown below:

Table 8.1: General definitions on severity grading of adverse events

Grading of adverse events		
Grade 1	Mild	Small or transient inconvenience that does not limit normal daily activity. No need for medical intervention or corrective treatment.
Grade 2	Moderate	Partial limitation of normal daily activity. In some, but not all cases, medical intervention or corrective treatment is necessary. No need to discontinue the treatment.
Grade 3	Severe	Limitation of normal daily activity. Medical intervention and corrective treatment, often requiring hospitalization, are necessary. The responsible drug may have to be stopped temporarily, until the symptoms have disappeared.
Grade 4	Life threatening	Very severe limitation of normal daily activity. Medical intervention and corrective treatment, requiring hospitalization, are necessary. The responsible drug may have to be stopped indefinitely.
Grade 5	Death	Death related to adverse event

Box 8.1: aDSM Package

Package	Level of monitoring and reporting
Core	All SAEs
Intermediate	All SAEs as well as AEs of special interest
Advanced	All SAEs, AEs of special interest, AEs leads to a discontinuation or change in the treatment, or is otherwise judged as being clinically significant by the clinician

Myanmar NTP has adopted the **Core Package of aDSM** that serious AEs/ADRs are necessary to report while all detected AEs need to be managed.

8.4 Important elements of aDSM

There are three fundamental elements of aDSM to achieve the above objectives:

1. **Active and systematic clinical and laboratory assessment** during treatment to detect drug toxicity and AEs. There are ways to help health providers do this step.
   a. **Observe and listen** to patients. The detection of AEs is primarily dependent upon reporting from patients, family members, nurses, doctors, counsellors, etc. At every DOT encounter, health workers should **ask** the patient and family members about clinical symptoms of common AEs including nausea, vomiting, peripheral neuropathy, skin rash, psychiatric disturbance (headache, anxiety, depression, irritability, behavior change), hearing loss, jaundice, vestibular toxicity (vertigo, ataxia, hearing loss), and symptoms of electrolyte wasting (muscle cramping, palpitations). All healthcare professionals involved must be trained on adverse event screening.

   b. Perform routine clinical assessments as well as specific and thorough clinical assessment as necessary such as visual assessment (visual acuity and color vision), assessment of PN (BPNS, evaluation of vibration perception, deep tendon reflexes); assessment for treatment adherence and tolerance, for mental health status, and review of case management for co-morbidity and co-infection. If there is indication, patients are referred to consult with the psychiatrist, ophthalmologist, HIV specialist, etc. Clinical follow-up with the MDR-TB physician for all patients is at a minimum of 2 weeks after the start of MDR-TB treatment, then monthly until the treatment completion. More frequent visits are required for some patients such as uncontrolled DM, patients with underlying disease(s).

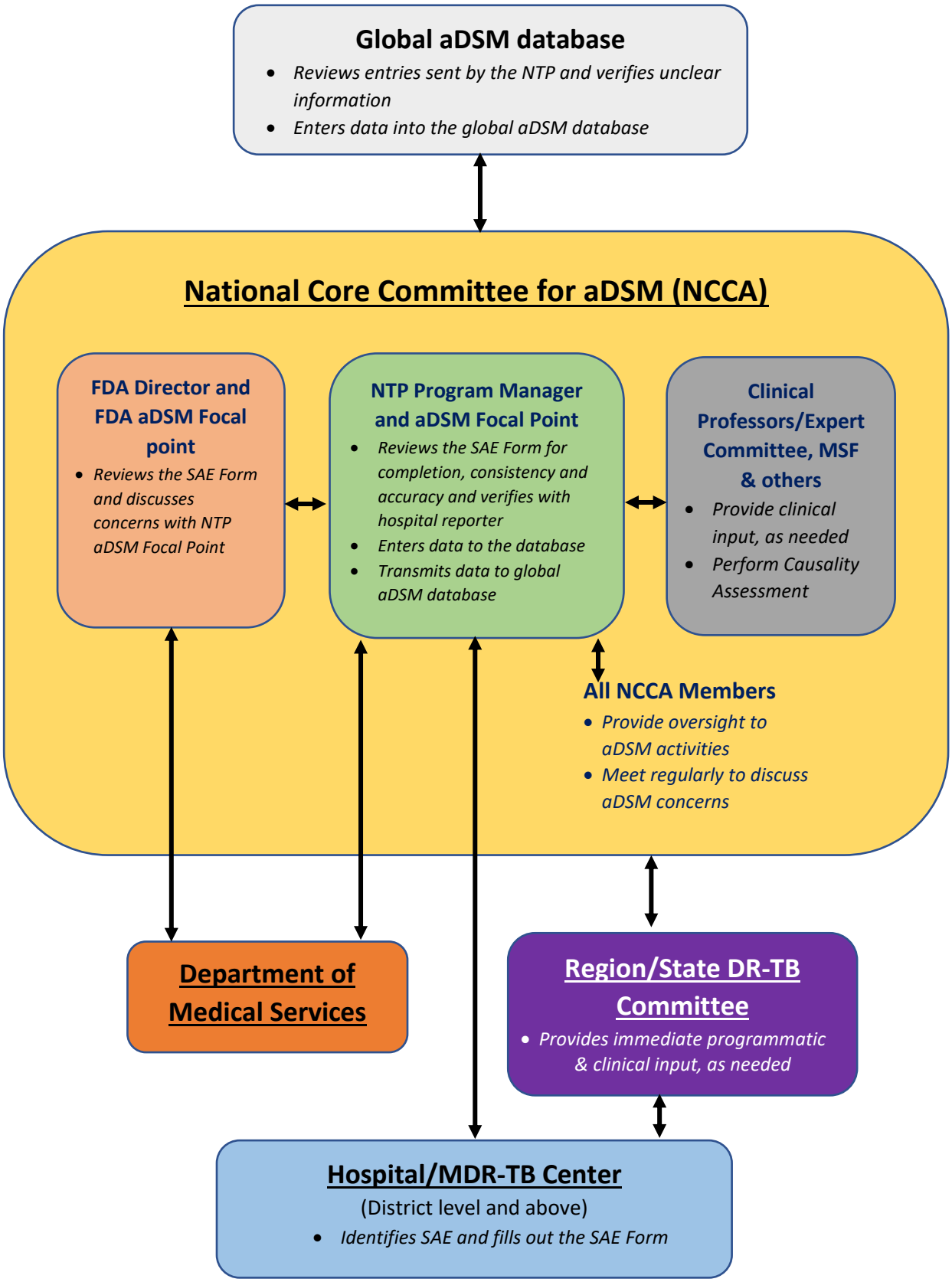
   c. Schedule regular laboratory screening (see tables 4.1), even if the patient has no specific complaints, e.g., creatinine, ECG, liver function tests, etc. Regular laboratory monitoring detects occult adverse effects. Laboratory tests and procedures related to treatment should be available and accessible to patients, free of charge.

2. **Management of AEs in a timely manner**: Early detection of signs and symptoms is key to proper management of AEs that significantly impacts patient well-being, overall treatment acceptance, and adherence. Management includes measures taken to alleviate the signs and symptoms of adverse reactions with careful individual case review. Level of AE management will be ranged: (a) reassurance, if AE is minor; (b)

lowering the dose of the offending drug; (c) stopping the drug; (d) drug replacement; (e) providing ancillary medications; and (f) other interventions (surgery, transfusion, psychological support, etc.). Ancillary medicines should be available and accessible to patients, free of charge.

3. **Recording and reporting**: All AEs must be recorded properly using aDSM R&R forms (patient's booklet and patient's card) and all Serious Adverse Events (SAEs) must be reported using reporting tools as per NTP aDSM protocols by filling google form using link:*https://docs.google.com/forms/d/e/1FAIpQLSciutzbctv_h0dXbvRTX_9STpjr1X2IqhRlEGLhWtsS7h9s0g/viewform?usp=pp_url.* The reporting must be done in **24 to 48** hours of occurrence of any serious AEs/ADRs. Recording and reporting of AEs/ADRs are equally important as clinical monitoring and management of the AEs/ADRs.

Figure 8.1: Reporting flow for SAE



8.5 Management of AEs or ADRs

Management of AEs and ADRs are equally crucial as monitoring and reporting. For a number of drugs, the toxicity is dose dependent. Reducing the dosage may be an effective method of managing these adverse effects. *But attention! The reduced dose must still be effective!* If the serum level of the drug is too low, it will compromise the treatment regimen lowering the dose by more than one weight class (according to dosages table) for the long-course regimens) should be avoided. Serious adverse events would be avoidable by systematic aDSM implementation and dose reduction or replacement with an appropriately effective drug.

Particular attention needs to be paid to the side effects of linezolid; a potent but toxic drug used as a part of standard regimen. Monitoring the adverse drug reactions of Lzd requires specific investigations.

Table 8.2: Severity grading scales and suggested action for common AEs (adopted from End TB Guidelines 2018, updated per WHO 2022 Guidelines)

Severity grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening
1. Peripheral neuropathy Possible anti-TB drug causes: Lzd, H, Cs, Lfx, Mfx, Am; Possible other causes: d4T(stavudine), ddI (didanosine)				
Paresthesia (Burning, tingling, etc.)	Mild discomfort; non-narcotic analgesia; and/or BPNS (Brief Peripheral Neuropathy Screen) subjective sensory neuropathy score 1-3 on any side.	Moderate discomfort: non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/ or BPNS subjective sensory neuropathy score 7-10 on any side.	Incapacitating; or not responsive to narcotic analgesia
Action	- Stop Lzd and Cs, reduce the dose of linezolid to *300 mg per day with a possible drug holiday for 7 to 10 days before dose reduction. - Reconsider adding Cs if symptoms improve. - Provide symptomatic relief *In BPaLM/BPaL/9-Oral, Lzd dose reduction during the first 9 weeks of treatment is not recommended, after interruption of Lzd, only restarting with 600 mg OD is recommended if it is safe. For detailed information, please refer to BPaLM/BPaL section/ guideline.	Same as Grade 1	Stop Cs and Lzd. If symptoms improve, consider restarting Cs. Do not reintroduce Lzd until condition reverses back to grade 1, then can start with *Lzd 300 mg. Provide symptomatic relief	Same as Grade 3.

2. Myelosuppression (anemia, thrombocytopenia, or neutropenia) Possible anti-TB drug causes: Lzd, Mpm, H, Pa; Possible other causes: AZT (zidovudine), cotrimoxazole				
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL
Platelets decreased	75,000 – 99,999/mm³	50,000 – 74,999 /mm³	20,000 – 49,999/mm³	< 20,000 /mm³
Absolute neutrophil count low	1500 - 1000/mm3	999 - 750/mm3	749 - 500/mm3	<500/mm3
Action	- Monitor carefully and consider reduction of dose of Lzd* (300mg daily). - Drug holiday for 7-10 days before dose reduction possibly may help in reducing myelosuppression. *In BPaLM/BPaL/9-Oral, Lzd dose reduction during the first 9 weeks of treatment is not recommended, after interruption of Lzd, only restarting with 600mg OD is recommended if it is safe. For detailed information, please refer to BPaLM/BPaL section/ guideline.	-Monitor carefully, perform CBC weekly and consider reduction of dose of Lzd* (300mg daily), in case of Grade 2 neutropenia, stop Lzd immediately. - Restart at reduced dose once toxicity has decreased to Grade 1. In case of Grade 2 anemia, consider erythropoietin (EPO). - Drug holiday for 7-10 days before dose reduction possibly may help in reducing myelosuppression.	- Stop Lzd immediately. In case of Grade 3 anemia, consider EPO. Restart at reduced dose* once toxicity has decreased to Grade 1. - Drug holiday for 7-10 days before dose reduction possibly may help in reducing myelosuppression.	- Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose* once toxicity has decreased to Grade 1. - Drug holiday for 7-10 days before dose reduction possibly may help in reducing myelosuppression.

3. Prolonged QT interval Possible anti-TB drug causes: Cfz, Bdq, Mfx, Dlm, Pa and Lfx (a mild QT prolonging drug). Possible other causes: drugs, e.g., erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, antipsychotics (haloperidol, chlorpromazine and risperidone), many anti-nausea drugs (ondansetron, domperidone), methadone, and some anti-retrovirals; genetic causes such as long QT syndrome; hypothyroidism				
Prolonged QTcF	QTcF 450 – 480 ms	QTcF 481 – 500 ms	QTcF ≥ 501 ms without signs/ symptoms of serious arrhythmia.	QTcF≥ 501 ms or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms
Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.
4. Optic nerve disorder (optic neuropathy) - Possible anti-TB drug causes: Lzd, E; Possible other causes: ddI (didanosine)				
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40[6/12] or better)	Limiting vision in the affected eye (worse than 20/40[6/12] but better than 20/200[6/60])	Blindness (20/200[6/60] or worse) in the affected eye
Action	Stop Lzd immediately if there are any suspicions of optic neuritis and refer for specialist opinion. Do not restart it, if the patient is diagnosed as optic neuritis.	Stop Lzd immediately if there are any suspicions of optic neuritis and refer for specialist opinion. Do not restart it, if the patient is diagnosed as optic neuritis.	Stop Lzd immediately if there are any suspicions of optic neuritis and refer for specialist opinion. Do not restart it, if the patient is diagnosed as optic neuritis.	Stop Lzd immediately if there are any suspicions of optic neuritis and refer for specialist opinion. Do not restart it, if the patient is diagnosed as optic neuritis.

5. Hepatitis - Possible anti-TB drug causes: Z, H, Pa, Bdq, Eto/Pto, Trd/Cs, PAS. Possible causes: alcohol, some herbal medicine, viral hepatitis				
ALT (SGPT)	1.1 – 3.0 x upper limit of normal (ULN)	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST (SGOT)	1.1 – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Bilirubin	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Action	- Continue treatment regimen. - Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	- Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation. - Stop all drugs, including anti- TB drugs if the patient is symptomatic (fatigue, nausea, vomiting, liver tenderness)	- Stop all drugs, including anti-TB drugs; measure LFTs weekly. - Treatment may be reintroduced after toxicity is resolved (liver enzymes returned to Grade 1).	- Stop all drugs, including anti-TB drugs; measure LFTs weekly. - Treatment may be reintroduced after toxicity is resolved (liver enzymes returned to Grade 1).
6.Acute kidney injury - Possible anti-TB drug causes: Am. Possible ART causes: Tenofovir (TDF)- rare Note: (inj: Am) are to be used only when there is no effective option left to treat given that Am is susceptible and sufficient monitoring is present				
Acute kidney Injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0mg/dL; hospitalization indicated	Life-threatening consequences: dialysis indicated
Action	- Consider stopping injection Am until creatinine has returned to baseline. - Consider restarting the injectable at lower frequency (e.g., MWF).	- Stop injection Am until creatinine has returned to baseline. - Consider restarting the injectable at lower frequency (e.g., MWF) or **substitute with a non-nephro-toxic drug.**	- Stop injection Am until creatinine has returned to baseline. - Consider restarting the injectable at lower frequency (e.g.MWF) or **substitute with a non-nephrotoxic drug.**	- Stop injection Am until creatinine has returned to baseline. - Consider restarting the injectable at lower frequency (e.g.MWF) or **substitute with a non- nephrotoxic drug.**

7. Hypokalemia and hypomagnesemia: Possible anti-TB drug causes: Am, S. Possible ART causes: TDF (rare)				
Hypokalemia	3.4 - 3.0 mmol/L	2.9 - 2.5 mmol/L	2.4 - 2.0 mmol/L or intensive replacement therapy or hospitalization required	< 2.0 mmol/L or abnormal potassium *with* paresis, ileus or life -threatening arrhythmia
Action	- Continue injecting Am. - Start oral potassium replacement therapy. - Check serum magnesium and replace it if necessary.	- Continue injecting Am. - Start aggressive oral potassium replacement therapy. - Check serum magnesium and replace it if necessary.	- Continue injecting Am. - Start IV potassium replacement therapy in addition to oral. - Replace magnesium and other electrolytes as necessary.	- Stop injecting Am temporarily. - Start IV potassium replacement therapy in addition to oral. - Replace Mg^{2+} and other electrolytes as necessary.
Hypo-Mg^{++}	0.70-0.60 mmol/L	0.59-0.45 mmol/L	0.44-0.30 mmol/L	<0.30 mmol/L
Action	Start oral magnesium replacement therapy.	Start aggressive oral magnesium replacement therapy.	Start IV magnesium replacement in addition to oral. Replace other electrolytes as necessary.	Start IV magnesium replacement in addition to oral. Replace other electrolytes as necessary.
8. Hypothyroidism: Possible anti-TB drug causes: Eto/Pto, PAS. Possible ART causes: d4T				
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting iADL (instrumental activities of daily living) *	Severe symptoms; limiting self-care ADL* hospitalization indicated	Life-threatening consequences: urgent intervention indicated
Action	Continue anti-TB drugs.	Continue anti-TB drugs. Start thyroxine.	Continue anti-TB drugs. Start thyroxine.	Stop all anti-TB drugs. Start thyroxine.

**https://www.payingforseniorcare.com/longtermcare/activities-of-daily-living.html#tit*

9. Hearing loss Possible anti-TB drug causes: S,Am. Possible other causes: none. Note: (inj(Am) are to be used only when there is no effective option left to treat given that Inj is susceptible and sufficient monitoring is present				
Hearing loss	- **Adults** enrolled on a monitoring Program (on 1,2,3,4,6 and 8 kHz audiogram): threshold shift of **15 - 25 dB** averaged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a grade 1 threshold shift. - **Pediatric** enrolled on a monitoring Program (on 1,2,3,4,6 and 8 kHz audiogram): threshold shift **>20 dB** at **8kHz** in at least one ear.	- **Adult** enrolled in monitoring program (on 1,2,3,4,6 and 8 kHz audiogram): threshold shift of **>25 dB** averaged at **2** contiguous test frequencies in at least one ear. - Adult not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. - **Pediatric** (on1,2,3,4,6 and 8 kHz audiogram): threshold shift **>20 dB** at **4 kHz** and above in at least one ear.	- **Adult** enrolled in monitoring program (on 1,2,3,4,6 and 8kHz audiogram): threshold shift of **>25 dB** averaged at **3** contiguous test frequencies in at least one ear; therapeutic intervention indicated. - Adult Not enrolled in monitoring program: hearing loss with hearing aid or intervention indicated; limiting self- care ADL. - **Pediatric** (on a 1, 2, 3, 4, 6 and 8kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids: Threshold shift **>20dB** at **3kHz** and above in at least one ear; additional speech-language related services indicated.	- **Adults**: profound bilateral hearing loss (Threshold **>80dB** HL at **2kHz** and above); non-serviceable hearing -**Pediatric**: audiologic indication for cochlear implant and additional speech-language related services indicated.

Action	Consider **suspension** of injection, replace with safer drug.	**Consider replacing injectable agent with a non- ototoxic TB drug.**	The injectable should be stopped and **replaced with a non-ototoxic TB drug.**	The injectable should be stopped and **replaced with a non-ototoxic TB drug.**

Table 8.3: WHO classification grading scale for hearing loss

40dB Slight/Mild	41-60 dB Moderate*	61-80 dB Severe	Over 81 dB Profound
Difficulty in hearing and understanding soft speech, speech from a distance, or speech against a background of noise	Difficulty in hearing regular speech, even at close distance.	May only hear very loud speech or loud sounds in the environment, such as a fire truck siren or a door slamming. Most conversation speech is not heard.	May perceive loud sounds as vibrations

Note: In the case of moderate hearing loss, the range for *children is 31-60 dB.

8.6 Causality sssessment of serious adverse event (SAEs)

For all SAEs, the *first level Causality Assessment* can be done at the DR-TB treatments centers/TB hospitals by the treating doctor using the below Adverse Event Causality Assessment definitions and flowchart: This will be helpful in recognizing the most relevant drugs to adverse event and then stopping the drug early to further reduce the progression of SAEs. However, later all reported SAEs are presented and discussed in the National core committee for aDSM (NCCA) in Myanmar and causality assessment is done and reported.

CAUSALITY ASSESSMENT

Causality assessment (CA) is an integral part of clinical management. In TB, evaluating the likelihood that a TB medicine was the causative agent of an observed adverse reaction forms part of clinical evaluation. While the details of the systematic method of conducting CA may not be familiar to the practitioner, the overall approach is not too different from the clinical practice followed when evaluating any patient on treatment.[11]

CA involves making an attribution or describing the ***relationship*** between the AE and an exposure by a physician or any other health care professional with the right expertise which forms part of clinical monitoring and management. This determination must be recorded both in the patient's medical record as well as in a case report form. For aDSM, CA should be made either at the country level or Region/State level, if resource and capacity has been built, by consulting the relevant data sources close to where the event occurred. Attributing a relationship requires a systematic process and is one of the main reasons why data are collected in aDSM. CA once done attributes a ***level of certainty*** between the event and the exposure, ranging from certain to unrelated.

CA is conducted by the Clinical professors of the NCCA, who also comprise the National DR-TB Expert Committee, with the participation of other designated members. CA should be conducted using a systematic tool provided later in this section, involving inputs from the panel of experts beyond the treating physician. The steps in doing CA are as follows:

- The hospital site will provide all details to the NTP aDSM Focal Point (within 24-72 hours from SAE detection) in the NTP SAE Form (google form), including the following key data elements:
    a) medical history (including concomitant disease),
    b) other risk factors (social factors, alcohol use, substance abuse, etc.),
    c) details of drugs taken, names, doses, routes,
    d) start and stop dates and indications for use,
    e) description of adverse event, including clinical description, baseline, monthly and ad hoc laboratory results, and date of onset / end and

[11] aDSM training package (training slides prepared by KNCV Tuberculosis Foundation, Management Sciences for Health (SIAPS), Médecins sans Frontières, World Health Organization https://who-umc.org/education-and-training/self-paced-online-courses/

f) evolution of event, severity, seriousness, and outcome.

- The NTP aDSM Focal Point collects all reported SAE cases in excel (National aDSM database) from NTP SAE google form regularly, as well as informs the reported SAE cases as necessary to the clinical Professors and all who are involved in CA, and other NCCA members
- The NTP aDSM Focal Point schedules a CA meeting quarterly or as necessary
- Prior to the meeting, each member of the CA team will individually review the SAE cases guided by the WHO-Uppsala Monitoring Centre (UMC) Causality Algorithm or the Naranjo ADR probability scale.
- During the CA meeting, the individual CAs will be considered until a **NCCA Causality Consensus** is arrived.

The goal for CA is to decrease inter-individual differences in the assessment of a given event, classify the likelihood of a relationship between the drug and the event, and improve scientific evaluation.

The table below summarizes the steps and timelines for SAE reporting in Myanmar.

Table 8.4: Summary of steps and timelines for SAE reporting, Myanmar

STEP	Event description	Action taken	Responsible party	Forms sent to	Time frame
STEP 1	SAE event detected	SAE Form filled out and submitted	Medical Officer (TB Hospital/DR TBC) who firstly detect SAE	NTP aDSM Focal Point via NTP SAE google form	Within **24 -72 hours** of SAE detection
STEP 2	SAE Report Form received at the national level	SAE Form completed with all details, upon verification with the hospital/MDR-TB Centre reporter; meeting for CA scheduled	NTP aDSM Focal Point	Clinical Professors and all members of the NCCA including FDA, and to the Department of Medical Services	Within **72 hours** of SAE detection for initial reporting, then follow-up
STEP 3	SAE entry to National Database	All entries of SAE Form entered to National aDSM Database	NTP aDSM Focal Point	National aDSM Database	Download/backup the updated National aDSM database from google form regularly
STEP 4	Clinical Professors' meeting and causality consensus at Central level	Meeting conducted for CA, and Causality consensus made	NCCA Clinical Professors and other designated partners	NTP	During quaterly meeting or as necessary

STEP 5	CA report completed	Feedback to the NTP and the hospital	NTP aDSM Focal Point	WHO Global aDSM database aDSM-database@who.int	Quarterly

Table 8.5: The WHO-UMC classification system for causality assessment

Causality term	Definition	Assessment criteria*
Certain	**Clearly caused by the exposure** *There is **clear** evidence to suggest a causal relationship and other possible contributing factors can be ruled out.*	• Event or laboratory test abnormality, with ***plausible time*** relationship to drug intake • ***Cannot*** be explained by disease or other drugs • Response to withdrawal ***plausible (pharmacologically, pathologically)*** • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge ***satisfactory***, if necessary
Probable/Likely	**Likely to be related to the exposure** *There is evidence to suggest a **likely** causal relationship and the influence of other factors is unlikely.*	• Event or laboratory test abnormality, ***with reasonable time*** relationship to drug intake • ***Unlikely*** to be attributed to disease or other drugs • Response to withdrawal ***clinically reasonable*** • Re-challenge ***not required***
Possible	**May be related to the exposure** *There is **some** evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).*	• Event or laboratory test abnormality, with ***reasonable time*** relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear

Causality term	Definition	Assessment criteria*
Unlikely	**<u>Doubtfully related</u> to the exposure** *There is **little** evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study regimen). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).*	• Event or laboratory test abnormality, ***with a time to drug intake that makes a relationship improbable*** (but not impossible) • Disease or other drugs provide ***plausible explanations***

8.7 Expansion of aDSM implementation, role of aDSM focal point (Region/State) and quarterly SAE report

- All MDR/RR-TB patients in PMDT will be under aDSM, while reporting will be only for serious adverse events, along with nation-wide oral regimen expansion
- All assigned medical doctors of the DR-TB centers will be coordinating with concerned TB/ general hospitals to follow up SAE
- The SAE from regions and states will be reported to NTP (central) aDSM focal point, and to the aDSM focal point of the concerned region/state.
- Region/ state DR-TB committees will perform causality assessment of the reported SAE after receiving a proper capacity building training from NCCA
- After causality assessment meeting of Region/ State DR-TB committees, aDSM focal point of the concerned region/state will submit the Region/ state SAE database to NTP aDSM focal point.
- The NTP Focal Point should be entered/ reviewed/ updated regularly to the National SAE Database (possible/probable /certain in causal relationship) in a format linked with the Global aDSM Database sharing the same key variables to facilitate data transmission and contribution of the data from the country to the Global Database.
- Region/ State TBC will submit SAE reports quarterly/annually. (Please see Chapter 11: Quarterly report of SAE)

8.8 Management of adverse events

Timely detection and proper management of adverse events are important, moderate adverse events which have negative effects on quality of life may lead to treatment adherence problems while severe ones can lead to life-threatening conditions.

Table 8.6: Adverse events, suspected agents, and management strategies*

Adverse effect	Suspected agent	Suggested management	Comments
Rash, allergic reaction and anaphylaxis	Any drug	1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis, manage with standard emergency protocols. 2. Eliminate other potential causes of allergic skin reaction (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include: • Antihistamines, • Hydrocortisone cream for localized rash, • Prednisone in a low dose of 10 to 20 mg per day for short course can be tried if other measures are not helpful, • Phototoxicity may respond to sunscreens, but these can also cause rash,	1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Hot flashes, itching, palpitations can be caused with isoniazid and tyramine-containing foods (e.g., cheese and red wine). If this occurs advise patients to avoid foods that precipitate the reaction. Antihistamines can be used. Avoid some antihistamines (H1 receptor antagonist e.g., diphenhydramine) as they associate with QT prolongation. 3. Hives (urticaria) can be caused by any drug. To identify the drug, introduce the drugs one at a time. In the case of hives a desensitization attempt can be made; methods are described elsewhere.

		• Dry skin may cause itching (especially in diabetics); liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine, • Topical benzoyl peroxide for acneiform rashes. 4. Once rash resolves, reintroduce remaining drugs one at a time, with the most likely culprit last. Consider not re-introducing in the challenge any drug that is highly likely to be the culprit. This may necessitate changing the regimen.	4. A non-serious acneiform papular rash is reported in MDR/RR-TB regimens containing novel and repurposed drugs particularly in adolescents. 5. Any drug that resulted in anaphylaxis or Steven-Johnson syndrome should never be reintroduced to the patient, not even as a challenge.
Nausea and vomiting	Eto, Pto, PAS, Amx/ Clv, Bdq, Lfx/Mfx, Mpm, H, E, Z, Cfz, Dlm, imp/cln, Pa, Lzd, S	1. Assess for danger signs including dehydration, electrolyte disturbances and other causes (e.g; hepatitis, pancreatitis, increased intracranial pressure, pregnancy, and gastroenteritis); initiate rehydration therapy if indicated and correct any electrolyte disturbances. If blood is in the vomit, check haemoglobin and treat possible bleeding ulcers. 2. Initiate stepwise approach to nausea and vomiting. Phase 1: Adjust medications and conditions without lowering overall dose: • Give the Eto/Pto at night • Give Eto or PAS twice daily. • Give a light snack (biscuits, bread, rice, tea) before the medications. • Give PAS 2 hours after other anti-TB drugs Phase 2: Start antiemetic(s):	1. Nausea and vomiting is common in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at least in the initial period and patient should be advised about this side effect. 2. Creatinine and electrolytes should be checked if vomiting is severe. Give IV fluids and replace electrolytes as needed. 3. Another strategy is to stop a responsible medicine for two or three days and then add it back, gradually increasing the dose (advise the patient the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated).

		• Metoclopramide 10 mg 30 minutes before anti-TB medications. • Ondansetron 8 mg 30 minutes before the anti-TB drugs and again 8 hours after. Ondansetron can either be used on its own or with metoclopramide (If ondansetron is not available, promethazine can be used). For refractory nausea, 24 mg 30 minutes before the dose can be tried. Phase 3: Decrease dose of the suspected drug by one weight class if this can be done without compromising regimen. Rarely, it is necessary to suspend the drug completely.	4. Odansetron (not recommended with QT Interval prolonging drugs) is serotonin 5-HT3 receptor antagonist and has strong anti-emetic properties. It is on the WHO essential drug list. Trying different antiemetics, even if from the same class, may be helpful for some patients. 5. For patients particularly anxious about the nausea (and who have "anticipatory nausea and vomiting"), a small dose of an anti-anxiety medicine (5 mg of diazepam) 30 minutes prior to the anti-TB drugs can help. 6. Antihistamines (e.g; promethazine) may be useful for nausea associated with CNS or vestibular toxicity.
Diarrhoea and/or flatulence	PAS, Eto/Pto, Mpm. Amx/Clv, Lzd, Lfx, Mfx, Pa, S	1. Encourage patients to tolerate some degree of loose stool and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhoea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours. 4. Check serum electrolytes (especially potassium) and dehydration status if diarrhea is severe. In children with	1.Fever and diarrhoea and/or blood in the stools indicate the diarrhoea may be secondary one other than a simple adverse effect of the anti-TB drugs: • Pseudo-membranous colitis (fever, bloody diarrhoea, intense abdominal pain and increased white blood cells) related to broad-spectrum antibiotics (e.g, FQs) is a serious and even life-threatening condition.

		acute diarrhoea, supplement zinc (20 mg per day) for 10–14 days to improve water and electrolyte absorption.	• Parasites and common water-borne pathogens in the area should be looked for in the patient and treated. • Lactose intolerance, especially if a patient has been exposed to new foods in a hospital not normally part of their diet. 2. Loperamide can be used in children over 2 years old.
Hepatitis	Z, H, R, Pa, Bdq, Pto/Eto, PAS, Alcohol, Hepatitis A, B, C virus	1. If enzymes are either more than five times the upper limit of normal regardless of symptoms or more than three times with symptoms (nausea, vomiting, fatigue, malaise, pruritus, fever, right upper quadrant pain, tender liver and jaundice), stop all drugs, and wait until < 3 times to reintroduce. Reintroduction is started with three of the non-hepatotoxic medications (e.g; fluoroquinolone, linezolid and clofazimine). 2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol-induced hepatitis being the two most common causes) and treat any identified. 3. Consider suspending most likely agents permanently. Reintroduce remaining drugs one at a time, with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely culprit is not essential, consider not re-introducing it.	1. Hepatocellular drug-induced liver injury with jaundice (and raised total bilirubin levels) indicates a serious reaction (Hy's law) and presents a high risk for acute liver failure. 2. History of previous drug-related hepatitis should be carefully analyzed to determine most likely causative agent(s); these drugs should be avoided in future regimens. 3. Viral serology should be done to rule out other etiologies of hepatitis if available, especially to hepatitis A, B, and C virus. 4. Alcohol use should be investigated, and address alcoholism if found. 5. Generally, hepatitis due to medications resolves upon discontinuation of suspected drugs.

			6. Do not rechallenge with Z following a drug-induced liver injury. 7. In complex hepatotoxic patients, consult a hepatologist for expert opinion.
Hypothyroidism	Eto/Pto, PAS	1.Exclude other causes (e.g., lithium, amiodarone, previous radioiodine therapy, pregnancy-associated thyroid dysfunction and Hashimoto's disease). 2.If TSH > 5 IU/ml and decreased free T4 or clinical hypothyroidism, thyroxine supplementation may be considered. 3.If TSH > 10 IU/ml, start levothyroxine in the following manner: • Young healthy adults can be started on 75 to 100 mcg daily • Older patients should begin treatment with 50 mcg daily • Patients with significant cardiovascular disease should start at 25 mcg daily. Thyroxine should be taken in the early morning 30 minutes before breakfast. Most adults will require 100 to 150 mcg of thyroxine/levothyroxine daily.	1. Hypothyroidsm may be an independent cause of QT prolongation 2. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, depression, and inability to concentrate. 3. Do not start treatment unless TSH is above 1.5 to 2.0 times upper normal limit. 5. The combination of ethionamide/prothionamide with PAS is more frequently associated with hypothyroidism, but it is completely reversible upon discontinuation of these drugs.

		4. Monitor TSH every 1 to 2 months and increase dose by 12.5–25 mcg until TSH normalizes. Adjust dose more slowly in the elderly and patients with cardiac conditions.	
Arthritis and arthralgias	Z, Bdq, Lfx/Mfx, H	1. Initiate therapy with non-steroidal anti-inflammatory drugs twice daily or ibuprofen 400–800 mg three times a day). 2. Lower dose of suspected agent (most commonly pyrazinamide) if this can be done without compromising regimen. 3. Discontinue suspected agents, if this can be done without compromising regimen.	1. Symptoms of drug-induced arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgias, although it may be helpful if gout is confirmed. 3. If acute swelling, redness, and warmth are present in a joint, consider aspiration for diagnosis (gout, infection, autoimmune disease, etc).
Electrolyte disturbances (Hypokalemia and hypomagnesae-mia)	Am, S	1. Check potassium. If potassium is low, also check magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalemia). 2. Check renal functions and other cause of electrolyte imbalance (e.g vomiting, diabetes and use of insulin, use of diuretics) 3. Replace electrolytes as needed (refer to Annex 5: Management of Electrolyte Disturbances). Dose oral electrolytes apart from FQ (either two hours before or four hours after) as they can interfere with FQ absorption.	1.Mild hypokalemia are often asymptomatic, clinical symptoms may not be present until moderate and severe cases. 2.Hypokalaemia, hypomagnesaemia and hypocalcaemia are attributable causes of QT interval prolongation, so closer ECG monitoring is required until levels are corrected. 3.Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhea. Good source of dietary

		4. Severe hypokalaemia (<2.5 mmol/L) should be hospitalized for IV replacement and cardiac monitoring.	potassium: bananas, oranges, tomatoes, and grapefruit juice should be encouraged. 4. Amiloride 5–10 mg per day or spironolactone 25 mg per day may decrease potassium and magnesium wasting and is useful in refractory cases.
Nephrotoxicity (Renal toxicity)	Am, Possible ART: TDF	1. Discontinue suspected agent. 2. Consider other contributing etiologies (NSAIDs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated. 3. Follow creatinine (and electrolytes) closely, every 1 to 2 weeks. 5. Consider changing injectable agent to a safer and effective drug i.e Bdq, Lzd, Dlm. 5. In patients with creatinine clearance <30 ml/min, adjust renally excreted TB medications for renal dose (Table 7.4).	1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. 2. An example of how to calculate a creatinine clearance based on the serum creatinine (Refer to section 7.6) 3. Renal impairment may be permanent.
Ototoxicity (hearing loss and tinnitus, vertigo)	S, Am	1. Document hearing loss and compare with baseline audiometry if available. (Some degree of hearing loss occurs with most patients, starting with high-frequency loss). **If early symptoms of hearing loss are seen, then discontinue the injectable agent and replace with another suitable drug** (Bdq, Lzd, Dlm) if this can be done without compromising the regimen.	1. Am is the last resort to treat if there is no other suitable option left and baseline audiometry is essential with proven Am susceptibility.

		2. Check renal function as nephrotoxicity is associated with AE due to injectable drugs, and a reduced creatinine clearance with increased drug exposure may exacerbate ototoxicity. 3. Vestibular symptoms (e.g., dizziness and nausea) may improve with antihistamines such as meclizine or dimenhydrinate.	2. Hearing loss may be reversible with early Am discontinuation or permanent (often permanent) if continued despite toxicity.
Myelosuppression (anemia, thrombocytopenia, or neutropenia)	Lzd, Mpm, H, Pa Possible other causes: AZT, cotrimoxazole, TB itself, iron deficiency, GI bleeding	1. Do not initiate or continue Lzd when serum haemoglobin <8 g/dL, neutrophils <0.75 x 10^9/L or platelets <50 x 10^9/L (severity grading 3 & 4), hospitalization and blood transfusion may be required. When treatment is initiated, Lzd may be full dose if haematological parameters improve with blood transfusion. 2. Investigate other causes: - anaemia (e.g. TB and other chronic diseases, nutritional deficiencies, pregnancy and blood loss), - neutropenia (HIV and other viral infections, leukaemia and lymphoma) - thrombocytopenia (pregnancy, other drugs and autoimmune disorders), and manage appropriately. 3. In mild to moderate anemia/myelosuppression, continue close monitoring and consider dose reduction of Lzd to 300 mg daily. In severe and life-threatening situations (grade 3-4), stop Lzd immediately.	1. Lzd associated myelosuppression is very common, approximately 18-21% of patients taking linezolid may experience anemia/ myelosuppression. If the patient has thrombocytopenia or neutropenia, this is more likely to be due to linezolid 2.Lzd associated Myelosupression is dose related and may occur in few days after start of treatment. 3. Many chronic TB/DR TB patients may have iron deficiency anemia at baseline due to inflammatory process and production of hepcidin and influencing iron hemostasis. 4. Monitor full blood count regularly. 5. Mpm and H can cause haemolytic anaemia in rare cases.

		4. A drug holiday of 7-14 days may alleviate toxicity. 5. Transfuse/hemotransfusion, consider erythropoietin with specialist advice. 6. Restart Lzd at reduced doses once severity has become to grade 1 or 2. 7. If necessary, stop Lzd and consider another safer drug.	6. Concomitant use of zidovudine and linezolid should be avoided because of the increased risk of myelosuppression.
Peripheral neuropathy	Lzd, H, Cs/Trd Lfx/Mfx, Am	1.Manage risk factors such as nutrition deficiency, diabetes. 2. Prophylaxis dose of pyridoxine (B6) 50 mg in adults (25 mg in children) should be given, but not to increase pyridoxine beyond 100 mg because it can paradoxically worsen symptoms. 3.For Grade 1-2 PN, reduce the dose of linezolid to 300 mg per day with a possible drug holiday for 7 to 10 days before dose reduction. 4. Consider whether the dose of cycloserine can be reduced without compromising the regimen. 5. Initiate symptomatic medical therapy: • NSAIDs or acetaminophen may help alleviating symptoms. • Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime; the dose may be increased to a maximum of 150 mg). Do not use with QT prolonging drugs. Avoid using Lzd and amitriptyline together because of risk of serotonergic syndrome.	1.Nutritional status is important to see as low BMI puts at high risk of PN with use of Lzd, Cs. 2.Lzd associated peripheral neuropathy may be a result of disrupted mitochondrial function in neurons. 3. Patients with co-morbid disease (e.g., diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 4. Neuropathy may be irreversible, but many patients experience improvement when offending agents are suspended. A drug holiday of 7-14 days may alleviate toxicity. 5. However, the neuropathy associated with linezolid is common after prolonged use and often permanent (for this reason suspension of this agent

		• Carbamazepine at 100–400 mg twice daily can be tried. Carbamazepine is a strong inducer of CYP3A4 and should not be used with bedaquiline or delamanid. • Either gabapentin 100-300 mg daily at night/100 mg TID or pregabalin 25-50 mg TID is a good therapy, and many clinical trials support its use. 6. Rarely, medication may be discontinued for non-remitting symptoms. This may necessitate a change in regimen if a standardized regimen is used.	should be considered when painful neuropathy develops).
Depression	Socioeconomic circumstances, chronic disease, Trd/Cs, Dlm, Lfx, Mfx, Eto	1. Assess and address underlying socioeconomic issues. 2. Assess patients for co-existing substance abuse and refer to treatment if appropriate. 3. Initiate individual counselling (or group counselling if the patient is smear- and culture-negative). 4. When depression is more significant, initiate antidepressant therapy (sertraline or mirtazapine), preferably to consult for expert opinion. 5.In DR-TB patients on Mfx^h, Bdq, Dlm, the drug of choice to treat depression could be sertraline (50-100 mg), if **Lzd** is on board, **sertraline** cannot be used due to risk of **serotonin syndrome**.	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine if possible.

		6.Mirtazapine has relatively lower risk of serotonin syndrome, so it is a preferred antidepressant for patients with linezolid. 7. Lower dose of suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine to 500 mg daily is a common strategy to reduce depressive symptoms.). 8. Discontinue suspected agents if this can be done without compromising regimen.	4.Question the patient regarding suicidal ideation any time if the depression is judged to be more than mild. 5.Two antidepressants should not be given concomitantly due to risk of serotonin syndrome. 6. It is important to be aware that antidepressants usually take 2-4 weeks to get its therapeutic effects.
Suicidal ideation	Trd/Cs, Dlm Lfx, Mfx	1. Hospitalize the patient and put under 24- hour surveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation. 4. Initiate antidepressant therapy.	1. Keep the patient in the hospital until risk of suicide has passed. 2. If no improvement occurs after holding cycloserine, hold Dlm, Lfx, Mfx.
Psychotic Symptoms (Hallucinations, delusions, and odd behaviors)	Dlm, Trd/ Cs, H Lfx, Mfx	1. Withhold suspected agent for a short period of time (1–4 weeks) in severe cases. The most likely drug is cycloserine followed by high-dose isoniazid. 2. If bdq/dlm are on board, olanzapine 5-20 mg or aripiprazole 5-10 mg is preferred because of relatively lower risk of QT prolongation compared to haloperidol. 3. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others.	1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy (and discontinue upon completion of MDR-TB therapy). 2. Previous history of psychiatric disease is not a contraindication to the use of cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment.

		4. Increase pyridoxine to maximum daily dose (100 mg per day). 5. Lower dose of suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising regimen. 6. Discontinue suspected agent if this can be done without compromising regimen. 7. Once all symptoms resolve and patient is off cycloserine, anti-psychotic therapy can be tapered. If cycloserine is continued at a lower dose, anti-psychotic therapy may need to be continued and any attempts at tapering should be done with a psychiatrist trained in the adverse effects of second-line anti-TB drugs.	3. Some patients will tolerate cycloserine with an antipsychotic drug, but this should be done in consultation with a psychiatrist as these patients will need special observation and this should only be done when there is no other alternative. 4. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent. 5. Always check creatinine in patients with new-onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.
Seizures	Cs, H, Mpm, Ipm/cln, FQs, Lzd,	1. Hold suspected drugs pending resolution of seizures and exclude other causes. 2. Increase pyridoxine to maximum daily dose (100 mg per day). 3. Check renal function and serum electrolytes. 4. Anticonvulsant therapy (e.g., sodium valproate) may be needed to control seizures. 5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is essential	1. Phenytoin and carbamazepine are strong CYP3A4 inducers and should not be used with Bdq. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled. 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy. 4. Always check creatinine in patients with new-onset seizures. A decrease in renal function can

		to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.	result in high blood levels of cycloserine, adjusting the dose of cycloserine is needed to control the seizures.
Optic neuropathy	Lzd, E	1. Symptoms of optic neuritis includes slowly progressive painless bilateral simultaneous symmetric visual loss and colour fading / dullness. 2. Stop Lzd/ ethambutol and refer patient to an ophthalmologist. 3. Only consider reintroducing Lzd if other MDR/RR-TB treatment options are severely limited and optic neuritis has been definitively ruled out.	1. The most common drug responsible is Lzd, ethambutol. Combination of E and Lzd enhances the risk. (Patient receiving E and Lzd must be counseled to recognize early symptoms of optic neuritis) 2. Usually reverses with cessation of ethambutol, Lzd 3. Improve blood sugar control in diabetic patients
Metallic Taste	Eto/Pto, H, FQs	1. Consider other causes (diabetes, zinc deficiency) and drugs (metformin, lithium, phenytoin) leading to metallic taste 2. Sucking hard candy or chewing gum can be helpful. 3. Reassure the patient to tolerate this side effect.	1. Normal taste returns when treatment is stopped.
Gynecomastia	Eto/Pto, H	1. Breast enlargement can be a troublesome side-effect of Eto/Pto therapy, especially for male patients. Consider other causes (obesity, older age, puberty in boys, recreational substances and other drugs) 2. Reassure the patients that changes in breast will return to normal following treatment stopped	1.Other drugs that can cause gynaecomastia include spironolactone, cimetidine, ketoconazole, risperidone, omeprazole and efavirenz.

QT prolongation	Cfz, Bdq, Mfx, Dlm Pa, Lfx	1.Ask drug history and history of cardiac symptoms. 2.Check serum electrolytes and TSH. 3. Repeat ECG after patient's rest and calculate QTcF interval manually. 4. For any patient found to have > 500 ms **or** QTcF ≥ 450 ms (M)/ ≥ 470 ms (F) but ≤ 500 ms with signs/symptoms (palpitations, tachycardia, lightheadedness, fainting, syncope, chest pain, loss of consciousness) should cause concern. (Please refer NTP's *Guidance on QTc measurement for Monitoring and Management of Patients on QT-prolonging Agents* and annex 3 for detailed managment*)*	1.The QT interval is a physiological parameter that fluctuates throughout the day. Emotion, hunger, anxiety, exercise, endocrine and metabolic disturbances, and exogenous substances affects the QT interval. 2.Concomittant use of QT-prolonging drugs and presence of other factors (electrolyte and thyroid disturbances) increase risk of prolonged QTc. 3.Patients with prolonged QTc (substantially with QTcF >500 ms) are at risk of developing cardiac arrhythmias such as TdP, which can lead to sudden death.

*Adapted from WHO operational handbook on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update. Web Annexes and endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. Version 4.0; January 2018

9. Storage & supply Chain management of Medicines at field level

Receiving: Before the shipment, it needs to make sure that there is enough space for the coming medicines. On receiving the medicines, the followings must be checked:

1) Quantity
2) Quality
3) Expiry Date

Quantity: the quantity of physical count must be matched with the quantity on the delivery notes. When it is not possible to count every box, a random check can be done.

Quality: The bottles must not be opened, the color of the medicines must not be changed, the strips must not be torn. Every damage or quality issue must be recorded and reported with photo evidence. The disqualified medicines must not be used and kept separately with clear marking.

Expiry date : There must be enough shelf-life at the time of receiving. The expired or nearly expired medicines must be recorded and reported. Never use expired medicines.

After receiving, the medicines must be put away to the respective areas, recorded in the stock book and electronic system (if any). When putting the medicines in the store, the following general rules must be followed:

- Arrange products to facilitate the first-to-expire, first-out (FEFO) procedure
- Ensure the expiry date is easily visible
- At least 10 cm (4 inches) off the floor
- At least 30 cm (1 foot) away from the walls and other stacks
- No more than 2.5 m (8 feet) high
- Follow the manufacturer or shipper's directions and follow labels for storage conditions
- Place liquid products on the lower shelves or on bottom of stacks
- Store products that require cold storage in appropriate temperature-controlled place (eg. Refrigerator, cold box etc.)
- Store high security/high value products in appropriate security area (e.g., Iron cage or cabinet with lock)
- Separate damaged or expired products from the usable stock and clearly marked not to dispense
- Arrange cartons with arrows point up

- Always store flammables in their original container and separate from other products
- Always store corrosive substances away from other products especially flammables
- The temperature of the storeroom must be monitored with thermometer and temperature records
- The temperature of the storeroom must be maintained with air conditioner or ventilation so it is not more than 30 degree C
- Eating in the store must not be allowed
- The store and its surrounding must be kept clean

Fire Protection:

- Fire protection is very important for medical stores. The following measures must be taken:
- Make standard fire extinguishers available in the storeroom and always check to ensure that pressures are maintained, and the extinguisher is ready for use
- All staff must be trained to use fire extinguishers
- Strictly prohibit smoking in the store
- Conduct fire drills for personnel every 6 months
- Clearly mark emergency exits and check regularly to be sure they are not blocked or inaccessible
- Display fire precaution signs in appropriate places in the storage facility (especially locations where flammables are stored)

Stock count:

- Physical inventory count must be done from time to time (monthly, quarterly or yearly).
- If the results of the physical inventory differ from the balance on the stock/bin card, update the balance by adding or subtracting the excess or missing quantities.
- Dispose of damaged or expired products found during the physical inventory.
- For either of the above, identify, document, and correct the cause of the problem.

10. Information system and data management for DR-TB

10.1 Objectives and concept

The aim of the PMDT information system is

A. to monitor trends of drug resistances (Rifampicin among all notified TB patients and Fluroquinolones among all notified MDR/RR-TB patients) at national and sub-national levels
B. to improve the efficiency and effectiveness of PMDT. The achievements will be monitored against set targets and activities planned in TB NSP (2021-2025) and Global Fund workplan (2024-2026).

All steps of information system are to be done properly, because

1) captured data will be used to promote quality of care,
2) analyzed information is an invaluable tool for program management and planning
3) it provides a useful base for evaluation.

10.2 Monitoring and evaluation processes

Three sessions play a key role in monitoring and evaluation of PMDT.

1 The indicators and targets
2 Data collection, recording and reporting
3 Review and annual evaluation

10.2.1 The indicators and targets

Table 10.1: The indicators and targets

Standard indicators (NSP 2021-2025)		2019 (baseline)	2021	2022	2023	2024	2025
Prevalence of MDR/RR-TB among new TB patients		4.9%	4.9%	4.9%	4.9%	4.9%	4.9%
Number of MDR/RR-TB patients notified		3205	5121	5437	5598	4864	4638
Percentage of MDR/RR-TB patients that began second-line treatment		90%	93%	94%	95%	95%	95%
Percentage of confirmed MDR/RR-TB patients tested for resistance to second-line drugs[12]		66%	68%	70%	>70%	>70%	>70%
TSR of MDR/RR-TB patients		80%	80%	81%	82%	82%	82%

[12] Budget and logistics have been planned to expand second line DST to all diagnosed MDR/RR-TB patients nation-wide (100% coverage) starting from mid-2021 with the Global Fund.

Percentage of MDR/RR-TB patients started on treatment who were lost to follow-up during the first 6 months of treatment		2.6%	<3%	<3%	<3%	<3%	<3%
Indicators and targets committed to GF and linked with annual procurement and budget		2019	2021	2022	2023	2024	2025
Total number of MDR/RR-TB with or without additional resistances (MDR-TB/pre-XDR-TB/XDR-TB)		2891	3319	3751	4255	3636	3700
Proportion of MDR/RR-TB patients on (18-20-month regimens)			*40%*	*15%*	*10%*	32%	32%
Proportion of MDR/RR-TB patients on (9-11-month regimen: 9-month all-oral (9-oral))			**60%**	**85%**	**90%**	68%	68%

10.2.2 Data collection, recording and reporting

To this end, the NTP is responsible for supplying the standardized recording and reporting forms and register books (table 10.2) to the health facilities within the NTP's network. NTP will provide required trainings for recording and reporting of PMDT to the assigned staff of those health facilities. All data are to be filled out by assigned staff and will be verified by M&E focal in the region/ state TB office.

Table 10.2: The standardized data collection forms, registers and reporting forms of PMDT

SN.	DR-TB form/ register number	Recording and reporting forms	Where to be kept	Responsible person to fill and update information in the form
1.	TB-05 TB-05b	Request for examination of biological specimen for TB Report form for Genotypic-DST	All townships/ All TB clinics and PPM hospitals NTRL/Regional level Labs	TB coordinator/ focal staff/Lab in-charge Lab officer/ Microbiologist
2.	TB-04	Lab. register for sputum microscopy and Xpert MTB/RIF ULTRA	All townships/ TB Laboratory of PPM hospitals	Lab Technician
	TB-04b	Xpert MTB/XDR Testing Register	TB Laboratory of S/R TBC	
3.	06	Notified DR-TB register	R/S, District, Township TBC and INGO clinic	TB team leader/ coordinator
4.	14	Patient's informed consent for treatment	All townships	MO or TB Team leader or TB coordinator
5.	03	DR-TB patient's identity booklet	Patient	MO at MDR-TB Center
		Carbon copy of proforma forms of 03	MDR-TB center	
6.	01	DR-TB Treatment Card	MDR-TB center	MO at MDR-TB Center
			township[13]	Team leader/TB coordinator
7.	02	DR-TB Treatment register	MDR-TB center	MO at MDR-TBC
			township	Team leader/TB coordinator
8.	12	Register for missed dose tracing	All townships	TB Team leader/coordinator
9.	13	Directly observed treatment Card[14]	All townships	TB Team leader or TB coordinator
			With assigned HCW	Assigned HCW (BHSP or trained volunteer)
10.	15	DR-TB referral form	MDR TB center	MO or TB Team leader or TB coordinator
11.	11	Quarterly and annual report on culture and DST	Culture and DST Laboratories	Lab officers/ microbiologist
12.	06b	Quarterly report for cumulative DR-TB notification	MDR-TB center	MO at MDR-TBC
			All townships	TB Team leader or TB coordinator
13.	07	Quarterly report on DR-TB case registration	MDR-TB center	MO in charge/ TB Team leader or TB coordinator
14.	08	6-month progress assessment report of DR-TB cases		
15.	10b	Report of treatment outcomes of DR-TB cases on shorter regimens		
	10	Report of treatment outcome of DR-TB cases		
16.	16	Quarterly second line Drug Report	All townships	TB Team leader or TB coordinator
17.		Quarterly report of SAE	DR-TBC /TB Hospital	MO at DR-TBC/TB Hospital

[13] A shorter version of DR-TB 01 (4 pages) is to be kept and updated by TBC at township level in stead of keeping 6 pages 01 that will be kept only in MDR-TB centers.
[14] This card will also be used for VOT.

(1) TB-05: Request for examination of biological specimen for TB

The person who requests tests for diagnosis of TB/DR-TB needs to fill all data including his or her contact number to prevent initial loss. When RR-TB is diagnosed at an Xpert facility, it is the **responsibility of the Lab personal** (i) to prepare an duplicate (by fill-in a new TB-05 or make an copy) of TB-05 with RR-TB result (ii) to request second line DST[15] on it (iii) to send the request form along with the same specimen or a new specimen to a health facility with Xpert MTB/XDR platform or to the related Culture and DST TB laboratory (iv) to trace, receive and provide second line DST results to medical doctor/ team leader of the MDR-TB center.

If **specific/additional drug susceptibility tests** are required for the effective regimen construction of some exceptional cases, the medical doctor needs to mention required specific test(s) (genotypic/ phenotypic or both) and specific drugs (first line/ second line) in TB 05 **precisely**. It is advisable to consult with a senior microbiologist before specimens are submitted. If the medical doctor needs to know exact mutations (low or high resistance), s/he may request the results to be provided in TB 05b.

TB-05b will be used by culture and DST Labs to provide information about the resistant conferring mutation resulting from Line probe assay or Xpert-MTB/XDR assay.

(2) TB-04: Lab. register for sputum microscopy and Xpert MTB/RIF ULTRA, TB-04b: Xpert MTB/XDR Testing Register

These registers are to be filled in by the respective laboratory person, to be counterchecked with DR-TB 06 by TB coordinator and team leader in order to validate the notification data.

(3) DR-TB 06: Notified DR-TB register

This register is kept in the R/S, District, Township HC and INGO clinic; data are filled and regularly updated by the MO at MDR-TB Center, TMO/Township TB Coordinator and the INGO staff, respectively. The data are to be updated regularly to produce a cumulative report of DR-TB 06b. The information about all notified DR/RR-TB patients (**including** patients[16] notified as DR-TB but **without laboratory confirmation**) must be entered in this register, then patients will be counselled for early treatment initiation. (refer to counseling guidelines)

Proper recording of the dates for notification of DR-TB and dates for DR-TB treatment initiation must be done to monitor the improvement in "time to treatment initiation".

(4) DR-TB form 14: Patient's informed consent for MDR-TB treatment

This form formalizes the contract between the patient and the MDR-TB Center to encourage compliance with treatment and to educate about patients' responsibilities. This form must be

[15] Basically, Lab in charge of the Xpert facilities will request genotypic SL DST either by Xpert MTB/XDR or SL LPA, unless the medical doctor in charge specifically requests additional drug susceptibility tests.
16 Example cases are probable and possible paediatric MDR-TB patients, refractory severe EP cases like bone TB, failure of Hr-TB treatment whose DST result does not show RR-TB .

read aloud to the patient by the counselor at the MDR-TB Center or TB Hospital after the three adherence counseling sessions have been successfully conducted. The concerned MO of the MDR-TB Center or the hospital must read and explain the content of the consent form to the patient. The form must be signed by (1) MO of the MDR-TB Center/ TB Hospital, (2) patient or parent/ guardian of the child and (3) DOT Provider before starting the treatment.

When a patient who was initiated DR-TB treatment in the hospital is discharged, the assigned staff or medical social worker will contact the concerned Region/State TB office to inform about patient's information and for the continuation of treatment under care of the related MDR-TB center and township health department. A copy of consent form along with a filled referral form (DR-TB 15) must be sent with the patients to the new MDR-TB center.

(5) DR-TB Form 03: MDR-TB Patient Identity Booklet

This booklet contains all the essential information related to the DR-TB patient, such as the name and address, medical and social history relevant for current treatment, key educational message for the patient to follow and for self-monitoring, data for treatment monitoring (smear and culture results), and patient's proforma form to assist attending clinician for aDSM (to actively search for any adverse reaction, to practice timely appropriate case management and for standardized and systematic recording). A carbon copy of filled proforma form of each follow up visit will be taken out from 03 and will be attached to the patient's file kept in the MDR-TB center.

Patients are informed to take this booklet whenever they visit a health facility for any health problem. Since all necessary information is summarized in a patient's booklet, these will help health care providers of outside NTP network to give appropriate medical care to DR-TB patients.

(6) DR-TB Form 01: MDR-TB Treatment Card

When a patient is registered for MDR-TB treatment, an MDR-TB treatment card must be filled in by the MO in-charge at the MDR-TB Center. The card must be filled in completely and to be updated regularly till treatment completion since it is the primary source of information for the DR-TB register.

The original 6 pages DR-TB treatment card must be kept at the MDR-TB Center and a shorter version of duplicate card (4 or 2 pages) must be given to the Township TBC or the I/NGO clinic, who will be responsible for case holding and monitoring of drugs side effects at community level.

The DR-TB treatment card contains the following information:

Page (1)

- Basic demographic information: name, age, sex, address, etc.
- Registration number: this is a new unique identification number for each patient. The

NTP will use serial number for each MDR-TB Center

- Date of registration
- Type of patient
- Previous anti-TB treatment episodes and outcomes
- Information about co-morbidities and co-infections
- Concomitant medications
- Drug susceptibility tests done, and their results
- The regimen at treatment initiation

Page (2 and 3) to record data at baseline and of each follow up visits

- Sputum smear and culture results
- Biochemistry results
- CXR results
- ECG monitoring
- Visual acuity and color vision monitoring
- Monitoring for peripheral neuropathy
- Monitoring by audiometry

Page (4) to record and/ or monitoring of

- Duration for drug dispensing and next appointment
- Body weight

Page (5)

- DR-TB regimen (date of treatment started, dosage (mg), frequency of dose, dosage adjustment, and cessation of drugs), any serious adverse event happened or not.
- Record any remark and decision by the DR-TB Committee for DR-TB Management.

Page (6)

- For additional comments and to record management of mental health problems
- Treatment outcome categories and date
- To record patients' clinical information at each post treatment, follow up visits

(7) DR-TB Form 02: DR-TB Register

MDR-TB patient information from DR-TB 01 must be recorded in the MDR-TB Register (DR-TB 02) that is kept at the MDR-TB Center, TB Hospitals and township health department/ TBC. This register **must be updated regularly** for below information.

- Monthly sputum smear and scheduled culture results
- Regimen change and associated date
- Drug susceptibility results
- CPT/ART information whenever relevant

The DR-TB Register contains the following information:

- Serial No.
- Patient name, sex, age, date of birth, address, contact number and registration group

- DR-TB registration number, date of treatment initiation, name of DR-TB regimen given
- Date of DST and results (for first line drugs and second line drugs)
- "Not Lab confirmed case" column - if patient is treatment initiated due to clinical decision and/or based on (contact) history and in the absence of confirmed DST result
- Date of smear and culture examinations and results
- Treatment outcome and date
- HIV status, and related data if positive (CPT, ART)
- DM and other co-morbidity data
- Data about post treatment follow up
- Comments: (1) in comment (2) information related to side-effects, non-adherence, retrieval action taken, etc. should be recorded in this section

Note: The following data are to be reported by region and state TBC to central M&E on annual basis in order to report to the Global TB Program. As such, proper filling and regular updating of DR-TB 02 is of importance.

i. Number and proportion (denominator: total patients for treatment initiation) of second line DST performed
ii. Number and proportion (denominator: those tested for SL DST and results available) of cases with FQ resistance
iii. Number of patient treatment initiated who are not confirmed by Laboratory tests (eg, probable and possible paediatric MDR-TB patients or adult EPTB case started for DR-TB based on clinical evaluation and decision)

(8) MDR-TB Form 12: Register for Missed Dose Tracing

This register is kept at the R/S TBC, TB Hospital, District and township HC for each MDR-TB patient and it must be filled in any time a patient absconds and one or more treatment dose(s) are missed. Once the patient is traced, the MO in-charge at the MDR-TBC, hospital or the TPHO or TB Coordinator at township level must specify the number of missed dose(s), the reasons for missing treatment. The decision taken is recorded and signed in the register in agreement with the patient.

(9) MDR-TB Form 13: List of Directly Observed Treatment

This form is used to record daily about a patient's drug intake per doctors' prescription, by ticking the appropriate box of month and day after witnessing the intake of medicines by DOT/ VOT. This form is kept with the DOT-provider/ the MDR-TB patient and filled in by the DOT Provider BHS or the assigned Volunteer. The form has then to be reviewed by the DOT Supervisor who will copy the drug intake records into the MDR-TB Treatment Card in township TBC. The same form must be used during the hospitalization to document regular taking of medicines.

(10) DR-TB Form 15: DR-TB Referral Form

This form should be used by any health-care provider who refers/ transfers an MDR-TB patient to another health facility for the management of special medical condition(s) (OR) to another MDR-TB center for the continuation of treatment. This form will be used also when a patient is referred to hospital and when the patient is discharged and is sent back to MDR-TB center. All required information is to be filled properly such as characteristics of patient, disease classification, registration group, treatment regimen and date of initiation, co-infections and co-morbidities, results of sputum smear, culture and DST, reason for referral, and the date up to which medicines are supplied to the patient.

(11) DR-TB 11: Quarterly and annual report for culture and DST by culture and DST laboratories

The numbers of samples processed for cultures (solid/ liquid), the numbers of drug susceptibility tests performed (genotypic and phenotypic) and results of cultures and DST are collectively reported in DR-TB form 11.

The report should be submitted to the M & E team in central NPT according to the PMDT quarterly report timelines knowing that not all results are available by that time. The information about numbers of tests performed “by quarter” and “by culture and DST labs” are valuable inputs for program management.

The comprehensive quarterly reports inclusive of DST results should be available by the end of the following quarter. The analytical data are to be presented in regular and ad hoc National Expert DR-TB committee meetings.

(12) DR-TB 06b: Cumulative Quarterly Report on MDR-TB, pre-XDR TB and XDR-TB Notification

This report is prepared by the focal person of the MDR-TB centers by extracting data from DR-TB 06. There are six variables in DR-TB 06b segregated for male/female and <15 years and ≥ 15 years.

a) Total notified MDR-TB cases
b) Died before started Treatment
c) Refused
d) Initial loss
e) Patients started on SL treatment with any type of regimen
f) Waiting for treatment

DR-TB 06b for XDR-TB notification are reported by region/state TBC in collaboration and through effective communication channels with TB specialty hospitals.

Note:

1) The patient in "c", "d" and "f" may convert to "e" after the quarterly reporting period. That's why annual cumulative report should be submitted to central M&E unit of NTP in annual basis

(eg, number of patients who were notified and waiting for treatment in quarter 1 of 2024 and who receive treatment in quarter 2 of 2024 must be reported by moving those number from variable “f” to “e”.)

2) In case of a notified case as DR-TB but without laboratory confirmation, i.e, if patient is initiated treatment due to clinical decision and/or based on (contact) history and in the absence of confirmed DST result, such kinds of cases must be entered and mentioned total no. of cases in the remark session.

(13) DR-TB Form 07: Quarterly Report on DR-TB Case Registration

(to be completed at the end of reporting quarter)

This report is completed with data from the township DR-TB Register kept at MDR-TB Centers and Township TBC. This quarterly report records the number of DR-TB patients who were registered, and treatment initiated in the MDR-TB programme of NTP during the reporting quarter.

The data are to be reported by registration group and type of regimen; segregated by sex (male/female), age (<15 year and ≥ 15 years) and HIV status (Positive, Negative and Unknown). numbers of patients recorded and reported are inclusive of those treatment initiated without Laboratory confirmation, such as probable and possible paediatric DR-TB cases. This report is completed quarterly for the previous quarter by the MO in-charge at MDR-TB Center and (township health departments when feasible) or MDR-TB clinic of an I/NGO. The report must be submitted on a regular basis directly to the R/S TBC to be verified, compiled and sent to the central M&E unit of NTP.

(14) DR-TB Form 08: 6-Month Interim progress assessment report to MDR-TB patients, pre-XDR-TB patients and XDR-TB patients

(to be completed 9 months after treatment initiation)

This interim progress report evaluates status of a cohort (a group of patients who were registered and treatment initiated in the same quarter) 6-9 months after MDR-TB treatment initiation, to know program efficacy and quality of care without waiting the final outcomes which will be available only two years after treatment initiation for those put on 18-month longer regimens. The report is prepared by data extraction from the DR-TB Register kept at the MDR-TB Centers and/or township health departments. Concerned MO or TB- Coordinator is responsible for the timely and regular submission of the report to the R/S TBC to be verified, compiled and sent to the central M&E unit of NTP.

The information such as number and proportion of culture converted, died, lost to follow up are of invaluable inputs for program monitoring and management and planning and therefore, **data analysis of 08 has to be done regularly not only at central level but also at region and state levels.**

(15) MDR-TB Form 10 and 10b STR: Report of Treatment Outcomes of MDR-TB Cases; pre-XDR-TB and XDR-TB Form 10

This report shows the final treatment outcomes for patients in the MDR-TB Programme who were registered, and treatment initiated in the same quarter or year. The data in the report highlights overall achievement of the PMDT as well as highlights a specific center/ region/ state who needs attention or requires more support. The annual reports on final treatment outcomes should be completed 24 months after the treatment initiation. However, the final outcomes of patients put on 6 months or 9-11-month Shorter Treatment Regimen(s) are to be reported using DR-TB 10b (variables are same as DR-TB 10) to the central M&E unit as this information is essential for program management and planning during transition years.

The treatment outcome report (quarter/annual) is completed after thorough updating and extraction of data from MDR-TB Register kept at District/MDR-TB center and township TBC. The MO in-charge at MDR-TB Center or Township TB Coordinator is responsible for the timely and regular submission of the report to the R/S TBO to be verified, compiled and sent to the central M&E unit of NTP.

(16) MDR-TB Form 16: Quarterly Drug Report Form

This form is to be reported the current drug stock at the Central TB Drug Store, the R/S TBC, MDR-TB Centre/Decentralized Townships, TB Hospital ward and the I/NGO clinic. This report should be completed on a quarterly basis and sent to the R/S TBO and NTP Central Office. More information on the use of this form can be found in the chapter on Management of Second-line Anti-TB Drugs of 2017 guidelines.

17 MDR-TB Form 17: Quarterly Report of SAE

This form is for reporting SAE cases quarterly by the R/S TBC and MDR-TB Centers to NTP Central Office and aDSM focal person. SAE cases which are reported through google form of SAE report form (National Tuberculosis Programme) are primary record of this report.

Computerized system

At present, data entry, data extraction for reporting and compilation is carried out manually at township and R/S levels. At the same time, the electronic recording and reporting system/ the case-based system “OpenMRS” for recording of MDR-TB patients’ information and auto-reporting for scheduled time frame has been set up in all MDR-TB centers. Since those parallel systems cause extra-burden for the health workforce, omitting paper-based system would be considered at least partially when OpenMRS becomes stable and more user friendly.

Reporting of PMDT activities

All reports belong to groups of patients who were notified or started treatment in the same quarter or in the same year for the quarterly reports and annual reports, respectively. The

reporting schedules are prepared in figure 10.1 to generate reports for the same cohort by each and every reporting unit (townships/district/region and state TBCs).

(1) Figure 10.1 Reporting schedule for monitoring of the MDR-TB programme

	Annual 2023					Annual 2024					Annual 2025	
Reporting (dued month)	Apr-23	Jul-23	Oct-23	Jan-24	Apr-24	Jul-24	Oct-24	Jan-25	Apr-25	Jul-25	Oct-25	Jan-26
enrolled cohorts												
Q1 2021	Form 10											
Q2 2021		Form 10										
Q3 2021			Form 10									
Q4 2021				Form 10								
Q1 2022					Form 10							
Q2 2022	Form 08					Form 10						
Q3 2022		Form 08					Form 10					
Q4 2022			Form 08					Form 10				
Q1 2023	Form 07 and 6 b			Form 08					Form 10			
Q2 2023		Form 07 and 6 b			Form 08					Form 10		
Q3 2023			Form 07 and 6 b			Form 08					Form 10	
Q4 2023				Form 07 and 6 b			Form 08					Form 10
Q1 2024					Form 07 and 6 b			Form 08				
Q2 2024						Form 07 and 6 b			Form 08			
Q3 2024							Form 07 and 6 b			Form 08		
Q4 2024								Form 07 and 6 b			Form 08	
Q1 2025									Form 07 and 6 b			Form 08
Q2 2025										Form 07 and 6 b		
Q3 2025											Form 07 and 6 b	
Q4 2025												Form 07 and 6 b

Quarterly reports

There are three quarterly reports for DR-TB (DR-TB06b, DR-TB 07, DR-TB 08); one quarterly reports for treatment outcomes of DR-TB (DR-TB 10), to be submitted to central M&E unit of NTP from region and state TBC after data verification and validation. Examples of quarterly reports to be generated **by the end of January 2026** are as below.

SN.	Quarterly reports of PMDT	For patients notified/ started treatment in
1.	DR-TB 06b (MDR-TB+pre-XD-TB+XDR-TB+Mono/poly resistant TB)	October-December 2025 (Q4 2025)
2.	DR-TB 07 (MDR-TB+pre-XD-TB+XDR-TB+Mono/poly resistant TB)	October-December 2025 (Q4 2025)
3.	DR-TB 08 (MDR-TB+pre-XD-TB+XDR-TB)	January-March 2025 (Q1 2025)
4.	DR-TB 10 (MDR-TB+pre-XD-TB+XDR-TB)	October-December 2023 (Q4 2023)

Annual reports of 2025

SN.	**Annual reports of PMDT for the year 2025**	
1.	DR-TB 06b (MDR-TB+pre-XD-TB+XDR-TB+Mono/poly resistant TB)	January to December 2025 (cumulative report for the same year)

2.	DR-TB 07 (MDR-TB+pre-XD-TB+XDR-TB+Mono/poly resistant TB)	January to December 2025
3.	DR-TB 10 (MDR-TB+pre-XD-TB+XDR-TB)	January to December 2023
4.	DR-TB 10b	January to December 2024

10.2.3 Supervision

Supervision is the observation of health workers in their workplace, performed on a regular basis, with the aim of developing their knowledge, perfecting their skills, solving problems, correcting errors, improving attitudes towards their work and increasing staff motivation. Ultimate aim is to improve efficiency in their job. Supervision should be educative, supportive and corrective, not punitive.

Internal supervision

- The quality of DR-TB management is ensured through regular internal supervision at all levels. The NTP has set up the following annual targets for on-site specific supervision for DR-TB management:
- At least one supervisory visit per year to Regions/States implementing DR-TB management, by the National Expert DR-TB Committee
- At least one supervisory visit per year to Regions/States implementing DR-TB management, by central NTP staff including central NTP microbiologist as well as WHO
- At least one joint supervisory visit per year to townships implementing DR-TB management activities, by central NTP Level / Region/State Level and WHO
- At least one joint supervisory visit to the TB reference laboratories, by the National Health Laboratory with NTP and WHO
- At least one joint supervision to DR-TB sites jointly implemented with NGOs and other partners.
- In addition, DR-TB management will be routinely supervised as part of the general annual supervision scheme of TB control activities, as follows:
- Two supervisory visits per year to districts and townships by Region/State-level staff
- Four supervisory visits per year to townships by district-level staff
- Four supervisory visits per month to DR-TB patients' home by Health Assistants, Lady Health Visitor and Public Health Supervisor.
- Four visits per year by the central level NTP to ensure anti-TB drug management supervision to Regions/States
- Four visits per year by Region/State level to ensure anti-TB drug management supervision to District/Townships standardized supervision checklists are available for all levels for basic TB control activities.

In addition, a checklist has been developed for townships managing MDR-TB. The supervisory teams should develop a report during the visit and provide it to the TB staff responsible for immediate action. The main recommendations should be discussed and, if possible, agreed upon during the visit. The report should be short and should include actions taken since the last visit, main achievements and constraints observed during the visit, recommendations and

proposed next steps before the next visit to overcome problems and improve programme performance. Supervisory visit plans are developed every year and refined during the development of the NTP quarterly activity work plans at central and Region/State level.

External supervision technical assistance plans by external experts are to be managed by the NTP and WHO. WHO ensures annual missions as follows:

- Technical assistance on MDR-TB and XDR-TB clinical and programmatic aspects
- Supervision and technical support from the SNRL for support to DR-TB and XDR-TB diagnosis
- Annual the regional green light committee (rGLC) mission for PMDT management
- Mission by the Global Drug Facility to monitor progress on first- and second-line anti-TB drug management.

Ad hoc missions are to be organized based on needs to cover specific aspects of DR-TB control, including data management, infection control, diagnosis, etc. Every three years, the NTP and WHO organize external comprehensive reviews of TB control efforts in Myanmar. In these review missions, DR-TB experts are always included

10.2.4 Review and annual evaluation

- Every year, the regional green light committee mission comes to Myanmar, conducts monitoring visits to selected sites, discusses with key implementers, gives relevant trainings upon request by NTP and debriefs to the national expert DR-TB committee members.
- National expert DR-TB committee, organizes ad-hoc and quarterly meetings, oversees PMDT and gives not only technical support but also suggestions for improvement especially for implementation of new drugs and regimens.
- Annual evaluation for PMDT is done to monitor the achievement against target sets (NSP and GF); to discuss challenges and solution.

10.3 Roles of the MDR-TB centers and related health facilities in M&E aspect of PMDT

MDR-TB centers[17]

The district level health facilities and some prioritized townships are functioning as MDR-TB centers who have following capacities and responsibilities (DR-TB forms).

1. Diagnose MDR-TB (by Xpert MTB/RIF assay at its site); diagnose additional resistances (by Xpert MTB/XDR platform at its site or/ and by specimen transportation to NTRL/ culture and DST Labs (TB-05)
2. Initiate MDR-TB treatment (DR-TB 03, 01, 02) and refer to township (Form 15)

[17] By 2021, clinics of some INGOs (MSF-OCA and SMRU) are also functioning as MDR-TB centers and report to related state TBC.

3. Perform or arrange for laboratory investigations (for baseline and follow up visits)
4. Do clinical assessments for treatment monitoring (in collaboration with District/TS hospitals)
5. Manage adverse effects of second line drug
6. Report PMDT activities according to National Guidelines (06b, 07, 08 and form 10) to region/state TBC.

Township Health Departments / MDR-TB clinics of I/NGOs

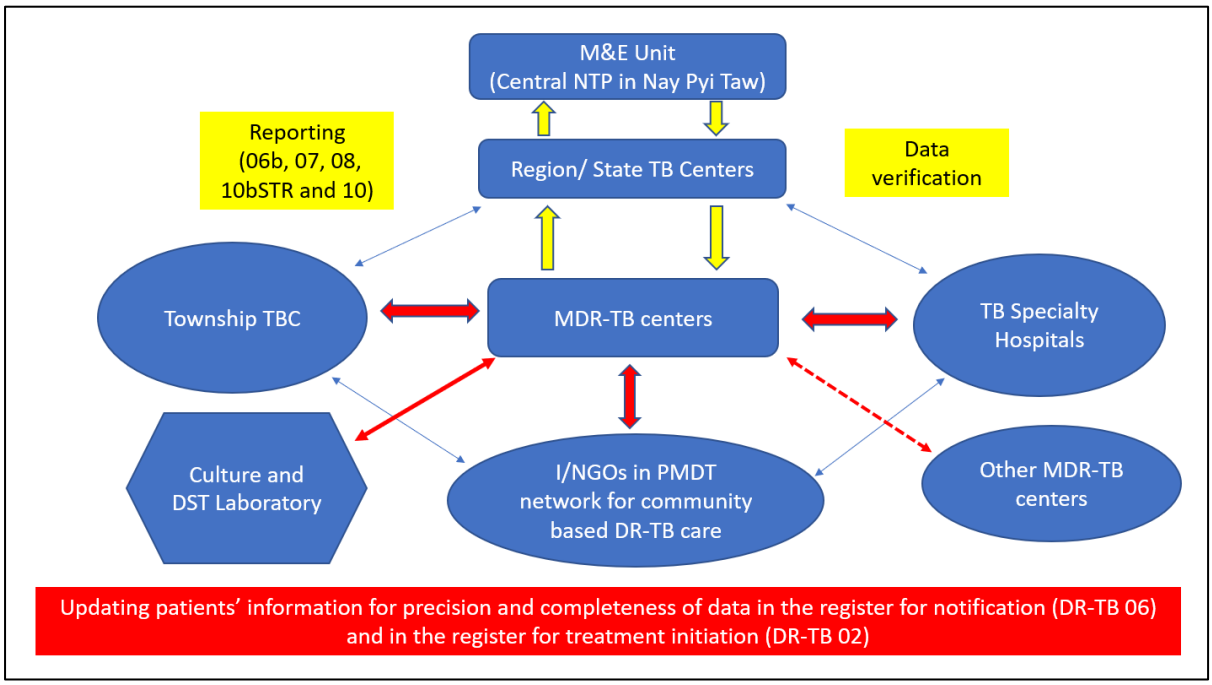
1. Execute case finding of MDR-TB by strictly following national guidelines and NTP's policy
2. Send specimen (sputum or EP specimens) together with properly filled in TB-05 to Xpert site to test with X pert MTB/RIF assay
3. If Xpert result (and/ or) other DST result showed Rif resistance (RR), filled in the Notified DR-TB Register (DR-TB 06)
4. Counsel and refer (DR-TB 15) patient to MDR-TB center for prompt treatment initiation.
5. Patients referred back from MDR TB center with (Treatment Card 01, Consent form 14 and referral form 15), are recorded in the township MDR-TB register (DR-TB 02) by TB Coordinator and the consent form is signed between patient and DOT/ VOT provider (BHS/volunteer).
6. Conduct initial home visit and contact tracing activities per national guidelines.
7. Take responsibility for case holding and proper DOT/ VOT (DR-TB 12 & 13) for MDR-TB treatment, ensure monthly follow up smear to be done at respective township.
8. Monitor the drug adverse effect. Treat for minor A/E and refer to the MDR-TB Center for major adverse effects.

TB specialty hospitals[18]

1. Receive all referred MDR-TB patients and provide in-patients DR-TB care and general medical care (record in the DR-TB 01, 03 and 02 of hospital if patient stays for several months)
2. Communicate with related region/ state TBC and MDR-TB centers for (a) registration in a patient's home township and MDR-TB centers (b) to inform about progress of management (c) to provide information before a patient is discharged.
3. Discharge patients and send DR-TB forms (copy of 01 and form 15) along with the patient/ care takers.

[18] TB specialty hospitals perform recording in patient's treatment card DR-TB 01. However, reporting (of notification, treatment initiation and treatment outcomes) for those initiated, followed up in hospitals will be by related region/ state TBC.

Figure 10.2: Diagram of data updating and reporting for PMDT



All MDR/RR-TB patients who did not enrolled in the MDR-TB programme of NTP and received treatment at their own cost in a private-for-profit facility but are reported through mandatory notification must be recorded and reported to the central M&E unit of NTP by the R/S TBO, who will use the same recording and reporting system described above.

10.4 Forms, registers and reports used in PMDT

TB-05 Request for examination of biological specimen for TB

Request for examination of biological specimen for TB (TB – 05)

Referred/ Treatment unit: _____ Date of request: _____

Patient's name: _____

Age (years): _____ Date of birth: _____ Sex: ☐ Male ☐ Female

Patient's address: _____

_____ Telephone: _____

Previously treated for TB:	☐ Yes	☐ No	☐ Unknown
if Yes: Took full course?	☐ Yes	☐ No	☐ Unknown
DM status:	☐ Yes	☐ No	☐ Unknown
HIV Status:	☐ Positive	☐ Negative	☐ Unknown

Reason for examination: _____

☐ Diagnosis Presumptive TB Reg. / OPD No._____ TB No._____

☐ Follow-up Township TB No/MDR-TB No._____ Month of treatment_____

Specimen type: ☐ Sputum ☐ Gastric Aspirate ☐ CSF ☐ Other (specify):_____

Test(s) requested:

☐ Microscopy ☐ Xpert MTB/RIF Ultra

☐ Xpert MTB/XDR : Pt's Type ☐RR ☐ Non-converter ☐ Other

☐ Line probe assay (FL) ☐ Line probe assay (SL)

☐ Other molecular tests ……

☐ Culture ☐ DST ……

Date of Specimen Collected ……

Requested by Signature: _____

Name: _____

Designation: _____

Contact phone no. : _____

Microscopy results (to be completed in laboratory) ☐ FM ☐ ZN

Date of specimen received	Laboratory serial number(s)	Specimen type	Visual appearance (blood-stained, mucopurulent or saliva)	Result (tick one)				
				Negative	Scanty	+	++	+++

Examined by Signature: _____

Name: _____

Designation: _____

Date of result: _____

X-pert MTB/RIF Ultra test result (to be completed in the laboratory)

X-pert Lab No : _____

N	I	T	RR	TI	TT

N = No MTB, **I** = Invalid / Error/ No result, **T** = MTB detected, **RR** = Rif resistant, **TI** = MTB (+) Rif resistance indeterminate, **TT**= MTB detected (Trace)

X-pert MTB/XDR test result (to be completed in the laboratory if test is performed)

X-pert Lab No: _____

N	I	H	Fq	Am	Km	Cm	Eto

N = No MTB, **I** = Invalid / Error/ No result

If MTB detected, to fill results in Block

S = Resistance not detected; **R** = Resistance detected; **LR** = Low resistance detected; **TI** = Resistance indeterminate

Examined by Signature: _____

Name: _____

Designation: _____

Date of result: _____

Culture results (to *be completed in the laboratory*)

Media Used	Date of Specimen Received	Laboratory Serial no	Results *(tick one)*						
			Negative	scanty	+	++	+++	NTM	Contaminated
L-J									
MGIT									

Examined by Signature: _____

Name: _____

Designation: _____

Date of result: _____

Drug susceptibility test (DST) results (to be completed in the laboratory)

Date sample received	Method [a]	Laboratory serial number(s)	**Results** [b] (mark for each drug)														
			H	R	Z	E	S	Eto	Ini	Fq	Bdq	Lzd	Cfz	Dlm	Pa	PAS	Cs

[a] Specify: solid DST; liquid DST; direct LPA; indirect LPA; WGS

[b] Results codes: **R** = Resistant; **S** = Susceptible; **C** = Contaminated; **NA** = Not applicable; — = Not done

Signature of Microbiologist: _____

Name: _____

Designation: _____

Date of result: _____

DR-TB 05b Report for DST results by line probe assay and/ or Xpert MTB/XDR

Genotypic DST (Line Probe Assay/ Xpert MTB-XDR) Report

Date of Specimen received ..... Patient's ID (DR-TB code) .....

Date of result ..... Laboratory Serial no .....

Test performed ☐ LPA FL ☐ LPA SL ☐ Xpert MTB/XDR

Line Probe Assay Report (First Line LPA)/ Xpert MTB/XDR Assay Report

Drug	Gene	Mutation	Interpretation
Rif	*rpoB*		
H	*katG*		
	fabG1[1]		
	oxyR- ahpC[1]		
	inhA		
Eto	*inhA*		

[1] (INH) resistance-associated mutations detected by Xpert MTB/XDR

Line Probe Assay Report (Second Line LPA)/ Xpert MTB/XDR Assay Report

Drug	Gene	Mutation	Interpretation
Lfx	*gyrA*		
	gyrB		
Mfx	*gyrA*		
	gyrB		
SLI	*rrs*		
	eis[2]		

[2] In case of rrs mutations only or mutations in both rrs and eis, resistance to SLI drugs is predicted In case of *eis* mutation c-14t only: amikacin is effective.

[2]In case of both WT1 and WT of *rrs* developed, and one of the WT of *eis* did not develop Amikacin is likely effective.

Signature of Microbiologist: _____

Name: _____

Designation: _____

Laboratory register for smear microscopy and Xpert MTB/RIF ULTRA (TB-04)

Laboratory register for smear microscopy and X-pert MTB/RIF ULTRA (TB - 04)

Lab Sr. No.	Date	Patient's name	Sex M/F	Age	Patient's Address Phone No.	Referred/ Treatment unit	OPD No. (or) TB No. (or) DR-TB No.	HIV status (Pos/ Neg/ Unk)	DM status (Y/N/ Unk)	Previously treated for TB (Y/N/Unk)	Examination type		Examination results			Remarks
				D.O. B							Dx	F/U (Mth)	Smear microscopy		Xpert MTB/RIF Ultra result	
													Spot	Home	Lab. No	

Xpert MTB/XDR Testing Register (TB-04b)

Xpert MTB/XDR Testing Register (TB-04b)										
Sr No.	Date	Patient's Name	Xpert MTB/RIF Ultra Lab No.	Xpert MTB/RIF Ultra Result	Xpert MTB/XDR Lab No.	Sex	Age	Address and Ph no.	Referred treatment unit	OPD No/ TB No/DR-TB Reg No.

Xpert MTB/XDR Testing Register (TB-04b)

HIV status (Pos/Neg/Unk)	Previously treated for TB (Y/N/Unk)	Type of patient (RR/ non-converter/ other)	Xpert MTB/XDR										Remark
			MTB detected (Yes/No)	INH (S, R, LR, TI)	FQ (S, R, LR, TI)	Am (S, R, TI)	Km (S, R, TI)	Cm (S, R, TI)	Eto (S, R, TI)	Error	Invalid	No result	

DR-TB 06 Township DR-TB notification register

Notified DR TB register NATIONAL TUBERCULOSIS PROGRAM (DR-TB FORM 06)

Sr. No	Name	Sex	Address & Phone No.	OPD No./ Tsp.TB No.	Type of patient	X-pert MTB/RIF Ultra lab No.	X-pert MTB/ RIF Ultra Result	Culture lab No.	Culture Result	DST (liquid DST/ LPA/WGS/ Xpert MTB-/XDR) lab No.	DST results for (Liquid DST/LPA/ WGS/ Xpert MTB/XDR) (S=susceptible, R=resistant, LR=Low resistant, C=contaminated, NA=not available)														
Date	Nationality (N/NN)	Age				Result Date		Result Date		Result Date	H	R	Z	E	S	Eto	Inj	Fq	Bdq	Lzd	Cfz	Dlm	Pa	PAS	Cs

Died before started DR-Treatment (Date)	Refused (Date)	Initial loss (Date)	DR-TB treatment started date	DR-TB Reg. No.	Type of DR-TB (mono/poly/MDR/RR, PreXDR/XDR)	Name of treatment center	Remarks

DR-TB 14: Informed consent form

Informed consent form | National TB Program | DR-TB form 14

ကတိဝန်ခံချက်

ကျွန်တော်/ကျွန်မ.....သည်ယခု စမ်းသပ်စစ်ဆေးတွေ့ရှိသော ဆေးယဉ်ပါးတီဘီရောဂါကုသရန်အတွက် (၉လမှ၁၁လ/၁၈လ) ကုထုံးဖြင့် ဆေးကုသမှု ကာလတစ်လျှောက်လုံး နေ့စဉ်မှန်မှန် တစ်ရက်မပျက်ဆေးသောက်ပါမည်ဟု ဝန်ခံကတိပြုပါသည်။ ဆရာဝန်/ဆရာမများ၏ လမ်းညွှန်မှုအတိုင်း စနစ်တကျ ကုသမှုခံယူလျှင် ရောဂါဝေဒနာများသက်သာပျောက်ကင်းလာပါမည်။ ဆေးကုသစဉ်အတွင်း လိုအပ်လျှင် ဆေးရုံ/တီဘီရောဂါအထူးကုဆေးရုံ (အောင်ဆန်း/ပုသိမ်ကြီး) တက်၍ ကုသမှုခံယူရမည်ကို သိရှိနားလည်ပါသည်။ ထို့အပြင် ဖြစ်ပေါ်လာတတ်သောဘေးထွက် ဆိုးကျိုးများကို သိရှိပြီးဖြစ်၍ လိုအပ်လျှင် အခြားသင့်တော်သော တီဘီဆေးများ/ကုထုံးများဖြင့် ပြောင်းလဲကုသမှုခံယူရန် နှင့် ဆရာဝန်/ဆရာမများ ၏ လမ်းညွှန်မှု အတိုင်း တိတိကျကျ လိုက်နာရန်လိုအပ်ကြောင်း သိရှိသဘောတူပါသည်။ ဤကဲ့သို့ ဆေးကုသမှုကို စနစ်တကျမခံယူလျှင် /ဆေးမှန်မှန်မသောက်လျှင် မိမိတွင် ကုသရန်ခက်ခဲသော ဆင့်ကဲ ဆေးယဉ်ပါးမှုများ ဖြစ်ပေါ် ပြီး ကျန်းမာရေး ပိုမို ထိခိုက်လာစေမည့်အပြင် ထိုဆေးယဉ်ပါးပိုးသည် မိမိနှင့် အတူနေ မိသားစု၊ မိတ်ဆွေနှင့် လုပ်ဖော်ကိုင်ဖက် များကိုပါ ကူးစက်စေနိုင်မည်ကို သိရှိပါသည်။ ဆေးမှန်မှန်သောက်ရန် ပျက်ကွက်လျှင် ဆေးကုထုံးအသစ်ဖြင့် အစမှ ပြန်၍ ဆေးကုသမှုခံယူရမည်ကိုလည်း သိရှိပါသည်။ ဆေးယဉ်ပါးတီဘီကု ဆေးဝါးများသည် ကိုယ်ဝန်ဆောင်စဉ် သောက်သုံးလျှင် သန္ဓေသား ပေါ်တွင် ထိခိုက်မှုများ ရှိနိုင်သည်ကို သိရှိပါသည်။ လူနာ၏ ကိုယ်ရေးအချက်မှ အပ ကုသမှုဆိုင်ရာ အချက်အလက်များကို ဆေးပညာတိုးတက်ရေး လုပ်ငန်းစဉ်များတွင် အသုံးပြုခြင်းကိုလည်း လက်ခံသဘောတူပါသည်။

နေ့စွဲ..... အသက်..... အမည်..... .လက်မှတ်.....

နေရပ်လိပ်စာ နှင့် ဖုန်း

.....

MS/DMO/TMO

ကျွန်ုပ်.....သည် ဆေးယဉ် တီဘီရောဂါကုသရန်အတွက် (၉လမှ ၁၁လ / ၁၈လ) ကုထုံးဖြင့်သတ်မှတ်ထားသည့်အတိုင်း ဆေးထိုး၊ ဆေးသောက် မှန်ကန်ရန် အရေးကြီးပုံ၊ အခက်အခဲများရှိနိုင်ပုံကို ရှင်းပြပြီး ဖြစ်ပါသည်။

(လူနာ) ..... အား ဆေးကုသမှုပြီးဆုံး ပျောက်ကင်းသည်အထိ အားပေး ကူညီသွားမည်ဖြစ်ပါသည်။

နေ့စွဲ.....အမည်.....လက်မှတ်..... ရာထူး.....

.....

DOT-PLUS PROVIDER

ကျွန်ုပ်..... .သည် လူနာ.....ဆေးကုသမှုပြီးဆုံးသည် အထိ (၉လ မှ ၁၁လ/ ၁၈လ) လုံးလုံးတာဝန်ယူတိုက်ကျွေးပါမည်။ လူနာမှဆေးသောက်ရန် ပျက်ကွက်မှုရှိသည်နှင့် တပြိုင်နက် ပျက်ကွက်ခြင်း၏ အကြောင်းအရင်းကိုစုံစမ်း၍ အတတ်နိုင်ဆုံး ဖြေရှင်းပေးပြီး၊ဆေးဆက်သောက်စေပါမည်။ မိမိမှ မဖြေရှင်းနိုင်သည်များကို TMO ထံတွင် တင်ပြ ဆွေးနွေးကူညီဖြေရှင်းစေပြီး ဆေးဆက်သောက်ခိုင်းမည် ဖြစ်ပါသည်။

နေ့စွဲ.....အမည်.....လက်မှတ်..... ရာထူး.....

DR-TB 03: OPD booklet with proforma patient's information

Proforma Patient's information

Name of Patient: ..... **DR TB Reg No.** ..... **date of visit** .....

Chief complaint during the visit

1		4	
2		5	
3		6	

Clinical Findings: BW_____Kg, BP_____mmHg, PR_____/min, SPO2_____%, QTcF_____ms, FBS/2HPP_____

Drug side effect

- ☐ Abdominal pain
- ☐ Allopecia
- ☐ Anxiety
- ☐ Arthralgias/arthritis
- ☐ Change in skin colour/texture
- ☐ Depression
- ☐ Dermatitis
- ☐ Diarrhoea and/or Flatulence
- ☐ Dizziness
- ☐ Flushing/itching reaction
- ☐ Gastritis
- ☐ Gout/Elevated Uric acid
- ☐ Gynaecomastia
- ☐ Headache
- ☐ Hypersensitivity
- ☐ Hypothyroidism
- ☐ Jaundice
- ☐ Lactic Acidosis
- ☐ Loss of Appetite
- ☐ Myalgia
- ☐ Superficial Fungal Infetion/thrush
- ☐ Nausea/Vomitting
- ☐ Photosensitivity
- ☐ Psychotic symptom
- ☐ Seizures
- ☐ Sleep disturbances
- ☐ Suicidal ideation
- ☐ Tendonitis and/or tendon
- ☐ Vestibular toxicity (Tinnitus & vertigo)
- ☐ Visual Disturbance
- ☐ Other

Please circle the severity grading for the following Adverse Events

☐ Anemia/Red cell aplasia	1	2	3	4
☐ Electrolyte disturbance	1	2	3	4
☐ Elevated liver enzymes	1	2	3	4
☐ Hearing loss	1	2	3	4
☐ Leukopenia/neutropenia	1	2	3	4
☐ Optic Neuritis	1	2	3	4
☐ Peripheral neuropathy	1	2	3	4
☐ QT prolongation (.....ms)	1	2	3	4
☐ Renal insufficiency/toxicity (est.GFR = ...ml/min)	1	2	3	4
☐ Thrombocytopenia	1	2	3	4

Management of Side Effects

Other Treament

	Name of Drug	Strength/unit, Quantity, Frequency, Duration (days)
1		
2		
3		
4		
5		

Investigations

Other Information

.....ရက်တွင်ရိုးရိုးသလိပ်စစ်ပါ။ .....ရက်တွင်ပိုးမွှေးသလိပ်ပို့ပါ။ .....ရက်တွင်ပြန်ပြပါရန်။

Medical Officer: name & signature

DR-TB 01: DR-TB Treatment Card

DR-TB Treatment Card

Transfer-in ◻

Name: ……

Sex: ◻ M ◻ F Nationality: ◻ N ◻ NN

Age: …… Date of birth ……/……/……..

Father/ Mother's name: ……

NRC number: ……

Occupation: ……

Initial weight (kg): …… Height (cm): …… BMI:……

Site: ◻ Pulmonary ◻ Extra-pulmonary ◻ Both

If extra-pulmonary, specify site: ……

Address: ……

……

Phone number: ……

DR-TB initiation center: ……

DC site/center: ……

Name & phone no. of DOT provider: ……

Name of phone no. of DOT supervisor: ……

No	Type of patient
1	New
2	Non-converter ◻ IR ◻ RR
3	Treatment after lost to follow up ◻ IR ◻ RR
4	Treatment after failure of treatment ◻ IR ◻ RR
5	Relapse ◻ IR ◻ RR
6	Treatment after DR-TB regimen 1.1 ini: STR 1.2 ini:LTR ◻ LFU ◻ Failure ◻ Relapse 2.1 OSSTR 2.2 OLTR 2.3 BPaL/M ◻ LFU ◻ Failure ◻ Relapse 3. LTR (MDR/preXDR/XDR)/other ◻ LFU ◻ Failure ◻ Relapse 4. Mono/Poly DR TB regimen ◻ LFU ◻ Failure ◻ Relapse
7	Others 1. Unknown regimen/ outcome of previously treated TB 2. Patient who does not fit in registration group 1 to 6)

DR-TB registration number: _____

Date of registration: _____/_____/_____

Previously tuberculosis treatment episodes			
Previous Township TB number	Start date (if unknown, put year)	Regimen (in drug abbreviations)	outcome

HIV information
HIV testing done: ◻ Y ◻ N ◻ unknown
Date of test……/……/…… Result: ……
Started on ART: ◻ Y ◻ N Date: ……/……/……
Started on CPT: ◻ Y ◻ N Date: ……/……/……

Relevant Drug History	
Diseases	Concomitant Medicines (Drugs taken regularly)
HIV	
Hepatitis	
DM	
Hypertension	
Others	

Co-morbidities & Co-infections	Others
Hepatitis B ◻ Y ◻ N	Pregnancy ◻ Y ◻ N
Hepatitis C ◻ Y ◻ N	Contraception ◻ Y ◻ N
Diabetes mellitus ◻ Y ◻ N	Smoking ◻ C ◻ P ◻ N
COPD ◻ Y ◻ N	Alcohol ◻ C ◻ P ◻ N
Heart Disease ◻ Y ◻ N	
Hypertension ◻ Y ◻ N	
Mental Health problem ◻ Y ◻ N	

Numbers of House Hold members	< 5 year =	≥ 5 year =

Date of result	Lab No.	Xpert MTB/RIF Ultra Result

Not lab confirmed ◻

Lab. No	Type of DST (Xpert MTB-XDR/ Liquid DST/ LPA/ WGS)	Date	S=susceptible, R=resistant, LR=low resistant, C=contaminated, NA=not available														
			H	R	Z	E	S	Eto	Ini (_)	Fq	Bdq	Lzd	Cfz	Dlm	Pa	PAS	Cs

DR-TB Treatment Regimen
◻ 6 (Bdq, Lzd, Pa, Mfx) **BPaLM**
9-month all oral regimen
◻ 4-6 (BDQ (6) Lfx Eto Hh Cfz E Z)/ 5 (Lfx Cfz E Z)
◻ 4-6 (BDQ (6) Lfx Lzd (2) Hh Cfz E Z)/ 5 (Lfx Cfz E Z)
◻ 6-9 (Bdq, Lzd, Pa) **BPaL**
◻ LTR (MDR/preXDR/XDR) ……
◻ Mono/Poly DR TB other than RR TB……

Month	Smear microscopy			Sputum Culture			Date	Cr	Electrolytes			LFT				CP			Bl. Sugar	Uric Acid	TSH	Other
	Date	Lab.No	Grade	Date	Lab.No	Grade			K+	Mg+	Ca+	T.bili	ALP	AST	ALT	Hb	N'phil	Plt				

Date of Xray _____

Date of Xray _____

Date of Xray _____

Date of Xray _____

	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	Month 13	Month 14	Month 15	Month 16	Month 17
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Visual Acuity	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/	L-20/ R–20/
Ishihara Test	**Nl/Abn** L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -
ECG	**QTcF =**																	
Peripheral Neuropathy (Subjective Symptoms) Scoring 1------10	**Pain** L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -
	Burning Sensation L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -
	Numbness L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -	L - R -
Ankle Reflexes																		
Vibration Perception (Sec)	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –
Audiometry	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –	L – R –									

Vibration Perception:
0 = felt >10 sec (Normal)
1 = felt 6-10 sec (Mild loss)
2 = felt <5 sec (Moderate loss)
3 = not felt (Severe loss)
8 = Unable to/ did not access

Ankle Reflex:
Normal/ Hypo/ Hyper

No	mm-yy	Drug Taking Days																														Weight (kg)
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
1																																	
2																																	
3																																	
4																																	
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Mark in the boxes: ✓ **= Directly observed** **X = not supervised** **Ø = drugs not taken**

DR-TB REGIMEN (date of treatment started, dosage(mg), frequency of dose, dosage adjustment, and cessation of drugs)

Date	Regimen	H	Z	E	S/Am	FQ ( )	Eto	Cs	Lzd	Cfz	Bdq	Dlm	PAS	Imp/ Mpm	Amx/ Clv	Pa		Comments SAE (Y/N)

od = once a day bd = 12 hourly, morning and evening dose Regimen = LTR, OSSTR, OLTR/Individualized MDR, Individualized Regimen (Pre-XDR), BPaLM, BPaL.

DR-TB Committee/ Panel Discussion and Decision

Date	Issues and Discussion	Decision

COMMENTS

Management of Mental Health Problems

Outcome (Circle one)	Date
Cured	
Completed	
Failed	
Died	
Lost to follow up	
Not Evaluated	
Moved to preXDR/ XDR	

6th month Follow up after completion of treatment				
Date	Smear	Culture	CXR	Clinical
12th month Follow up after completion of treatment				
Date	Smear	Culture	CXR	Clinical
18th month Follow up after completion of treatment				
Date	Smear	Culture	CXR	Clinical
24th month Follow up after completion of treatment				
Date	Smear	Culture	CXR	Clinical

DR-TB 02 Treatment register

No	DR-TB registration number	Date of treatment initiation	[a]Type of DR-TB regimen	Name (in full)	Sex (M/F)	Age Date of birth	Address & phone number	Nationality (N/NN)	Transfer in (T)	[b]Type of pateint

Type of Disease (P/EP)	BMI at Tx initiation	TB/HIV activities				Smoking (current/ past/never)	Co-morbidities		[c]Xpert MTB/RIF & Ultra result	DST (liquid DST/ LPA/WGS/ Xpert MTB-/XDR)	[d]Result of drug susceptibility testing (DST) (S=susceptible, R=resistant, LR=low resistant, C=contaminated, NA=not available)														
		HIV test done (Y/N/Unk)	HIV test result	on CPT (Y/N/Unk)	on ART (Y/N/Unk)		DM (Y/N/Unk)	Hepatitis (B/C)	Date & Lab No.		H	R	Z	E	S	Eto	Inj	Fq	Bdq	Lzd	Cfz	Dlm	Pa	PAS	Cs
			test Date	Start date	Start date					Date & Lab No.															

Not Lab confirmed (Y/N)	Month 0		Month 1		Month 2		Month 3		Month 4		Month 5		Month 6		Month 7		Month 8		Month 9		Month 10		Month 11		Month 12		Month 13		Month 14		Month 15	
	[e]S	[f]C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
	Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date	

Month 16		Month 17		Month 18		Month 19		Month 20		Month 21		Month 22		Month 23		Month 24		[g]Treatment outcome	6-Month post treatment		12-Month post treatment		18-Month post treatment		24-Month post treatment		Remarks
S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C		S	C	S	C	S	C	S	C	
Date		Date		Date		Date		Date		Date		Date		Date		Date		Date	Date		Date		Date		Date		

DR-TB 12 Register for missed dose tracing

REGISTER FOR MISSED DOSE TRACING NATIONAL TUBERCULOSIS PROGRAMME (DR-TB FORM 12)

Patient name _____

MDR-TB reg. no. _____

Dates of treatment interruption	Number of doses (-)	Reasons (according to patient)	Conclusion and decision	Date of meeting	MO/TMO signature	Patient signature
from…/…. to…/….						
from…/…. to…/….						
from…/…. to…/….						
from…/…. to…/….						
from…/…. to…/….						
from…/…. to…/….						
from…/…. to…/….						
from…/…. to…/….						
from…/…. to…/….						
from…/…. to…/….						

DR-TB 13: Directly observed treatment card

NATIONAL TUBERCULOSIS PROGRAMME
DIRECTLY OBSERVED TREATMENT CARD **(DR-TB FORM 13)**

Patient name________________________ | MDR-TB register no.__________________ Treatment started date.:________________

month_____ year____

#	drugs	dose/form	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

month_____ year____

#	drugs	dose/form	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

month_____ year____

#	drugs	dose/form	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

DR-TB 15: Referral Form

NATIONAL TUBERCULOSIS PROGRAMME

DR-TB Referral Form (FORM 15)

(Fill in duplicate. Send one copy to the respective facility receiving the patient, and keep the duplicate copy on file.)
Name and address of referring health facility _____
Name of health facility to which the patient is being transferred _____
Name of patient _____ Age _____ Sex M☐ F☐
Complete address (existing add)/ address belonged to receiving MDR center)
_____

Disease classification
☐ Pulmonary
☐ Extra-pulmonary (Site _____)
☐ Both

No	Registration group
1	New
2	Non-converter ◻ IR ◻ RR
3	Treatment after lost to follow up ◻ IR ◻ RR
4	Treatment after failure of treatment◻ IR ◻ RR
5	Relapse ◻ IR ◻ RR
6	Treatment after DR-TB regimen 1.1 SSTR 1.2 LTR ◻ LFU ◻ Failure ◻ Relapse 2.1 OSSTR 2.2 OLTR ◻ LFU ◻ Failure ◻ Relapse 3. Individualized/ other regimen ◻ LFU ◻ Failure ◻ Relapse
7	Others 1. Unknown regimen/ outcome of previously treated TB 2. Patient who does not fit in registration group 1 to 6)

Important co-infection and co-morbidities

Sputum, culture and DST details
Baseline (Date .....)

TB Lab Tests	Date	Result
Sputum smear		
Xpert MTB/RIF		
LPA (first line)		
LPA (second line)		

Most recent follow up Month (____)
Date .....

TB Lab Tests	Date	Result
Sputum smear		
Xpert MTB/RIF		
LPA (first line)		
LPA (second line)		

Details of MDR-TB patient
MDR-TB reg no. _____
Name of MDR TB center _____
Date of MDR-TB treatment initiation_____
DR-TB Regimen _____
Supply of medicines given to patient up to (date)
.....

Reason for referral
☐ Psychosis ☐ Liver problem
☐ Depression ☐ Renal problem
☐ Seizures ☐ change of residence
☐ Other _____

Date of referral for MDR-TB treatment _____
Referred for ☐In-door treatment ☐Ambulatory treatment ☐Transfer

Remarks _____
_____

Name _____ Contact phone no and email_____

Signature _____ Designation _____

Reminder for the health facility where the patient is being referred to: please send an e-mail to the referring unit, informing the referring doctor of the date that the above-mentioned patient reported at the receiving health facility.

DR-TB 11 Quarterly/ annual culture and DST report by Culture and DST Laboratories

Quarterly/Annual Report for Culture and Drug Susceptibility Tests by Culture and DST Laboratories

Culture and DST Laboratory: NTRL/ MDL-PTG/ TGG/ MLM/…….

Date of report completion……/……/……..

Samples received/ processed during quarter ……..of year……..

Table 1: Number of samples tested with MTBDR*plus* (First line LPA)

Sensitive	Resistance			NTM (TUB neg)	Result not available/others	Total LPA tests done
	HR[a]	R	H[b]			

a. ( ) had isolated InhA mutation; ( ) had isolated KatG; ( ) had mutations to both.

b. ( ) had isolated InhA mutation; ( ) had isolated KatG; ( ) had mutations to both.

Table 2.1 Number of RR-TB samples tested with MTBDR*sl* (Second line LPA)

Resistant to FQ not detected	RR-TB with additional resistances			Result not available/others	Total LPA tests done
	Res. to SLI	Res. to FQ[c]	Res. To both SLI and FQ[d]		

c. ( ) had low resistance; ( ) had high resistance.

d. ( ) had low resistance; ( ) had high resistance.

Table 2.2 Number of "non RR-TB/ Hr TB" samples tested with MTBDR*sl* (Second line LPA)

Resistant to FQ not detected	Res. to SLI	Res. to FQ[e]	Res. To both SLI and FQ[f]	Result not available/others	Total LPA tests done

e. ( ) had low resistance; ( ) had high resistance.

f. ( ) had low resistance; ( ) had high resistance.

Table 3.1 Number of RR-TB samples tested with Xpert MTB/XDR

	Resistant to FQ not detected	RR-TB with additional resistances			Result not available/ others	Total tests done
		Res. to SLI	Res. to FQ	Res. To both SLI and FQ		
Resistance to H not detected						
InhA mutation detected (not to *Kat G*)						
KatG mutation detected (not to *InhA*)						
Both *KatG* and *InhA* mutation detected						
Other mutations to H (not to *KatG* and *InhA*) detected						
Total samples						

Table 3.2 Number of "non RR-TB/ Hr TB" samples tested with Xpert MTB/XDR

	Resistant to FQ not detected	Res. to SLI	Res. to FQ	Res. To both SLI and FQ	Result not available/ others	Total tests done
Resistance to H not detected						
InhA mutation detected (not to *Kat G*)						
KatG mutation detected (not to *InhA*)						
Both *KatG* and *InhA* mutation detected						
Other mutations to H (not to *KatG* and *InhA*) detected						
Total samples						

Table 1. Solid and liquid cultures

Types of cultures	Number of culture samples								Total culture
	For diagnosis				For follow-up "PMDT"				
	Culture (+) ve	Culture (-) ve	NTM	Contaminated/others	Culture (+) ve	Culture (-) ve	NTM	Contaminated/others	
Solid Culture									
Liquid Culture									

Table 5. First-line Phenotypic DST

Number of DST samples														Total DST
Solid culture							Liquid culture							
Drug-sensitive TB	Mono-resistance	Mono-resistance	Mono-resistance	Mono-resistance	MDR-TB	Poly-resistance other than MDR-TB	Drug-sensitive TB	Mono-resistance	Mono-resistance	Mono-resistance	Mono-resistance	MDR-TB	Poly-resistance other than MDR-TB	

Table 6. Second-line Phenotypic DST (for Cfz, Lzd, Bdq, Dlm and Pa)

Number of DST samples						Total DST
No resistance to SLD of table 6	Res. To Cfz	Res. To Lzd	Res. To Bdq	Res. To Dlm	Res. To Pa	

Remark:……
……
……

Prepared by Signature …… Name ……. Title …… Contact no ……..	Verified by Signature …… Name …… Title …… Contact no ……..

DR-TB 06b: Quarterly Report on DR-TB Notification

NATIONAL TUBERCULOSIS PROGRAMME

Quarterly Report on DR-TB Notification **(DR-TB FORM 06-b)**

DR-TB Township:

Patients registered in **notified DR-TB register at quarter.....of year.....**

Report submission date: ..... /..... /.....

		Total notified cases (a)		Died before started Treatment		Refused (c)		Initial Loss (d)		Started on DR-TB treatment		Waiting for treatment (f)	
		M	F	M	F	M	F	M	F	M	F	M	F
RR/MDR-TB	<15												
	≥15												
preXDR-TB	<15												
	≥15												
XDR-TB	<15												
	≥15												
Total	<15	0	0	0	0	0	0	0	0	0	0	0	0
	≥15	0	0	0	0	0	0	0	0	0	0	0	0
Grand Total		0	0	0	0	0	0	0	0	0	0	0	0

Hr-TB	<15												
	≥15												
Other resistance	<15												
	≥15												
Total	<15	0	0	0	0	0	0	0	0	0	0	0	0
	≥15	0	0	0	0	0	0	0	0	0	0	0	0
Grand Total		0	0	0	0	0	0	0	0	0	0	0	0

Remark:.....

Note: It will be always "a=b+c+d+e+f". The patient in column (e) may not be the same with cumulative number of "total RR/MDR-TB patients started on MDR-TB 07 report of the same reporting period because 07 may include back log patients

The patient in column "c", "d" and "f" may convert to coulumn "e" after quarterly reporting period. That's why annual cumulative report should be submitted at the end of the year.

In case of notified as DR-TB **but without laboratory confirmation**, such kind of cases must be entered and mentioned total no. of cases in remark session.

Reported by:

Signature .....
Name .....
Designation .....

Checked by:

Name .....
Signature .....
Designation .....

DR-TB 07: Quarterly report on DR-TB case registration

NATIONAL TUBERCULOSIS PROGRAMME
Quarterly Report on DR-TB Case Registration

DR-TB initiation center: **(DR-TB FORM 07)**

Patients registered in **DR-TB Treatment Register during quarter……..of year……..**

Report submission date: ..... /..... /.....

	New		Previously treated patients										Other		Total	
	1. New		2. Non Converter (IR,RR)		3. Treatment after LFU (IR,RR)		4. Treatment after failure of treatment (IR,RR)		5. Relapse (IR,RR)		6. Treatment after DR-TB treatment					
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
MDR-TB															0	0
Pre-XDR-TB															0	0
XDR-TB															0	0
Total	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hr-TB															0	0
Other resistance															0	0
Total	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Total no. of MDR/RR-TB, PreXDR and XDR -TB	<15	≥15	Total
Pulmonary DR-TB (Lab Confirmed)			0
Pulmonary DR-TB (not Lab Confirmed)			0
Extra-Pulmonary DR-TB (Lab Confirmed)			0
Extra-Pulmonary DR-TB (not Lab Confirmed)			0
Total	0	0	0

Type of regimen	<15		≥15		Total
	M	F	M	F	
BPaLM					0
BPaL					0
9-month all oral					0
LTR (MDR)					0
LTR (Pre-XDR)					0
LTR (XDR)					0
Total	0	0	0	0	0
Hr-TB					0
Other resistance					0
Total	0	0	0	0	0

HIV status (only for MDR/RR-TB, PreXDR and XDR -TB) Postive.....Negative..... Unknown.....

Transfer in: (M) ....., (F)

Remark : .....

.....

Reported by:

Signature .....

Name .....

Designation .....

Checked by:

Signature .....

Name .....

Designation .....

DR-TB 08: 6-months Interim Progress Assessment Report of MDR-TB, pre-XDR-TB and XDR-TB cases

NATIONAL TUBERCULOSIS PROGRAMME
6-months Progress Assessment Report of DR-TB cases
(To be filled out 9 months after treatment initiation)

DR-TB initiation center: **(DR-TB FORM 08)**

Patients registered in **DR-TB Treatment Register during quarter ……..of year……..**

Report submission date: …… /……. /……

DR-TB cases	Number started on treatment in the quarter	Smear and culture results at 6-months of treatment (results of patients still on treatment)									No longer on treatment				
		Culture negative			Culture positive			Culture unknown			Died	Lost to follow-up	Failed	Not evaluated	moved to preXDR/XDR
		smear negative	smear positive	smear unknown	smear negative	smear positive	smear unknown	smear negative	smear positive	smear unknown					
MDR-TB															
Pre-XDR-TB															
XDR-TB															
Total	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Transfer in: (M)…… , (F)……..
Remark:

Reported by:
Signature ……..
Name ……..
Designation ……

Checked by:
Signature ……
Name ……..
Designation ……

MDR-TB form 10: Report of treatment outcomes of DR-TB cases

NATIONAL TUBERCULOSIS PROGRAMME
Report of Treatment Outcomes of DR-TB cases
(To be filled in 24 months after treatment initiation)

DR-TB initiation center: ……..…….. (DR-TB FORM 10)

Patients registered in DR-TB Treatment Register during quarter ……..of year……..

Report submission date: …… /…… /……

Type of regimen	Total Registered	Cured	Completed	Failed	Lost to follow-up	Died	Not evaluated	Moved to preXDR/XDR
BPaLM								
BPaL								
OSSTR/ 9-month all oral								
OLTR/LTR (MDR)								
LTR (Pre-XDR)								
LTR (XDR)								
Total		0	0	0	0	0	0	0

Disaggregation	Total Registered	Cured	Completed	Failed	Lost to follow-up	Died	Not evaluated	Moved to preXDR/XDR
HIV positive								
<15 yrs								
Female								

Transfer in: (M) ……, (F) ……..

Remark: ……

Reported by:

Signature ……

Name ……

Designation ……

Checked by:

Signature ……

Name ……

Designation ……

XDR-TB DR-TB form 10b: Report of treatment outcomes of DR-TB cases on shorter regimens

NATIONAL TUBERCULOSIS PROGRAMME

Report of Treatment Outcomes of DR-TB cases on shorter regimens

(To be filled in 12 months after treatment initiation)

DR-TB initiation center: ……..…….. (DR-TB FORM 10b)

Patients registered in DR-TB Treatment Register during quarter ……..of year……

Report submission date: ……. /…… /……

Type of regimen	Total Registered	Cured	Completed	Failed	Lost to follow-up	Died	Not evaluated	Moved to MDR/ preXDR/XDR
BPaLM								
BPaL								
OSSTR/ 9-month all oral								
Total	0	0	0	0	0	0	0	0

Hr-TB								
Other Resistance								
Total	0	0	0	0	0	0	0	0

Transfer in: (M) ……, (F) ……..

Remark: ……

Reported by:

Signature ……..……

Name ……..……

Checked by:

Signature ……..……

Name ……..……

Quarterly Report on Serious Adverse Event (SAE)

NATIONAL TUBERCULOSIS PROGRAMME
Quarterly Report on Serious Adverse Event (SAE)

Region/State:

Reporting period: **quarter……..of year……..**

Report submission date: …… /……. /……

No. of DR-TB Centers during the reporting period	
No. of DR-TB Centers with at least one SAE reported during the reporting period	
No. of DR-TB Centers with no SAE occurence during the reporting period	
No. of SAE during the reporting period	

Reported by:

Signature ……..

Name ……..

Designation ……

Checked by:

……

……..

……

11. Annexes

11.1 Annex 1: Weight-based dosing second-line TB medicines for 9-month all-oral (9-Oral) and longer treatment regimens (LTR)[a]

Table 11.1: Weight-based dosing of second-line TB medicines (adults and children)

Group A Medicines	Formulation (tablets diluted in 10 ml of water)	Weight bands (Kg)											Comments
		3-<5	5-<7	7-<10	10<16	16-<24	24 -<30	30-<36	36-<46	46-<56	56-<70	≥70	
Levofloxacin	100 mg tab (dt)	0.5 dt	1	1.5	2	3	-	-	-	-	-	-	
	250 mg tab (25 mg/ml)	2ml[b]	5 ml (0.5 tab) [b]		1	1.5	2	3	3	4	4	4	Max: dose 1500mg
	500 mg tab	-	-	-	-	-	1	1.5	1.5	2	2	2	
Moxifloxacin	100 mg tab	0.5	0.8	1.5	2	3	4	4	4	-	-	-	
	400 mg tab (40 mg/ml) Standard dose	1ml[b]	2ml[b]	3ml[b]	5ml (0.5 tab) [b]	7.5 ml (0.75 tab) [b]	1	1	1	1	1	1	
	400 mg tab High dose[c]	-	-	-	-	-	-	1	1.5	1.5 or 2	2	2	
Linezolid	150 mg tab (dt) (15 mg/ml)	2.5 ml[b]	5 ml (0.5 tab)	1 tab	1 tab	1.5 tabs[e]	2 tabs	2 tabs	3 Tabs	-	-	-	
	600 mg tab (60mg/ml) [b]	-	1.25 ml[b]	2.5 ml[b]	2.5 ml[b]	5 ml[b,e]	5 ml[b,e]	5 ml (0.5 tab)[b]	7.5 ml (0.75 tab)[b]	-	-	-	If adult tablet is crushed to dissolve
	600 mg tab	-	-	-	-	-	-	0.5	1	1	1	1	

Group A Medicine	Formulation	Weight bands (Kg)										Comments
		3-<5	5-<7	7-<10	10<16	16-<24	24 -<30	30-<36	36-<46	46-<56	56-<70	≥70	
Bedaquiline	20 mg tab (dt)	0-<3 months 1.5 OD 2weeks, then 0.5 OD (M, W, F) for 22 weeks ≥ 3 months 3 OD 2weeks, then 1 OD (M, W, F) for 22 weeks		0-<3 months 1.5 OD 2weeks, then 0.5 OD (M, W, F) 3 - <6 months 3 OD 2weeks, then 1 OD (M, W, F) ≥6 months 4 OD 2weeks, then 2 OD (M, W, F)	3 - <6 months 3 OD 2weeks, then 1 OD (M, W, F) ≥6 months 6 OD 2weeks, then 3 OD (M, W, F)	10 OD 2weeks, then 5 OD (M, W, F)							For dispersible tablet
	100 mg tab (10mg/ml) [d]	0-<3 months 3ml[b] OD 2weeks, then 1 ml[b] OD (M, W, F) for 22 weeks ≥ 3 months 6 ml[b] OD 2weeks, then 2 ml[b] (M, W, F) for 22 weeks		0-<3 months 3 ml[b] OD 2weeks, then 1 ml[b] OD (M, W, F) 3 - <6 months 6 ml[b] OD 2weeks, then 2 ml[b] OD (M, W, F) ≥6 months 8 ml OD 2weeks, then 4 ml OD (M, W, F)	3 - <6 months 6 ml[b] OD 2weeks, then 2 ml[b] OD (M, W, F) ≥6 months 12 ml[b] OD 2weeks, then 6 ml[b] OD (M, W, F)	2 OD 2weeks, then 1 OD (M, W, F)							If adult tablet is crushed to dissolve
	100 mg tab	-				2 OD 2weeks, then 1 OD (M, W, F)		4 OD 2weeks, then 2 OD (M, W, F)					For adults, standardized dosage 400 mg for 2 weeks, and then 200 mg daily

Group B Medicine	Formulation (tab diluted in 10 ml of water)	Weight bands (Kg)										Comments
		3-<5	**5-<7**	**7-<10**	**10<16**	**16-<24**	**24 -<30**	**30-<36**	**36-<46**	**46-<56**	**56-<70**	**≥70 kg**	
Clofazimine	50 mg cap or tab[f]	1 M/F	1 M/W/F		1	1	2	2	2	2	2	-	For children <24 kg, the use of the 50 mg tab is preferred
	100 mg cap or tab[f]	-	1 M/F		1 M/W/F		1	1	1	1	1	1	
Cycloserine or terizidone	125 mg cap (12.5 mg/ml)	2ml[b,g]	4 ml[b]	1	2	3	4	4	4	-	-	-	
	250 mg cap (25 mg/ml)	1 ml[b,g]	2 ml[b]	5 ml[b]	1	2	2	2	2	2	3	3	
Group C Medicine	**Formulation (tab diluted in 10 ml of water)**	**Weight bands (Kg)**										**Comments**
		3-<5	**5-<7**	**7-<10**	**10<16**	**16-<24**	**24 -<30**	**30-<36**	**36-<46**	**46-<56**	**56-<70**	**≥70 kg**	
Ethambutol	100 mg tab (dispersible) 10 mg/ml	5 ml (0.5 tab)	1	2	3	4	-	-	-	-	-	–	
	400 mg (40 mg/ml)	1.5ml[b]	3 ml[b]	4 ml[b]	6 ml[b]	1	1.5	2	2	3	3	4	
Delamanid	25 mg tab (dispersible)	1 OD	<3 months – 1 OD **≥ 3months – 1 BD**		1 BD	2 morning 1 evening		2 BD		-			
	50 mg tab[h] (5 mg/ml)	5 ml OD[b] (0.5 tab)	<3months – 5ml OD[b] **≥ 3months – 5 ml BD[b]**		**5 ml[b] (0.5 tab) BD**	10 ml[b] (1 tab) morning 5 ml (0.5 tab) evening		1 BD		2 BD			For adults, to apply the standardized dosage of 200 mg (50 mg 2 BD)
Pyrazinamide	150 mg tab (dt) (15 mg/ml)	5 ml (0.5tab)	1	2	3	5	-	-	-	-	-	-	
	500 mg tab (50 mg/ml)	2 ml[b]	5 ml[b]	5 ml[b]	1	1.5	1.5	2	2	2.5	3	4	

Group C Medicine	Formulation	Weight bands (Kg)										Comments
		3-<5	**5-<7**	**7-<10**	**10<16**	**16-<24**	**24 -<30**	**30-<36**	**36-<46**	**46-<56**	**56-<70**	**≥70 kg**	
Imipenem-cilastatin	500 mg + 500 mg powder for injection, vial (10 mL)	Not used in patients aged < 15 years (use meropenem)						2 vials (1 Gm + 1Gm) BD					To be used with clavulanic acid.
Meropenem	1 g powder for injection, vial (20 mL)	1 ml tid	2 ml tid	4 ml tid	6 ml tid	9 ml tid	11 ml tid	1 vial tid or 2 vials BD					To be used with clavulanic acid.
Amikacin	500 mg/2 mL solution for injection, ampoule	Not recommended in children and adolescents below 18 years of age, but if it is used as salvage therapy, calculate according to dilution used[i]						500 mg	750 mg	750-1000 mg	1 Gm	1 Gm	Recommended only in adults aged >18 years. Adult over 59 years of age, the dose will be reduced to 10 mg/kg (max-750mg)
Ethionamide	125 mg dt (12.5 mg/mL)	3ml	7 ml	1	2	3	4	4	4	-	-	-	Ramping at 1st two week, then once daily dose
	250 mg (25mg/mL)	-	3 ml[b]	5 ml[b] (0.5 tab)	1	2	2	2	2	3	3	4	
Para-aminosalicylic acid (PAS)	PAS sodium salt (equivalent to 4 g PAS)	0.3 g BD	0.75gBD	1 gm BD	2 gm BD	3 gm BD	3.5 BD	4 gm BD				4-6 gm BD	Usually given in divided doses.

Other Medicines	Formulation (tab diluted in 10 ml of water)	Weight bands											Comments
		3-<5	5-<7	7-<10	10<16	16- <24	24 - <30	30-<36	36-<46	46-<56	56-<70	≥70 kg	
Isoniazid[j] (high dose)	100 mg tab (dt) (10 mg/ml)	5 ml 0.5 tab	1	1.5	2	3	4	4	4.5	-	-	-	100 mg isoniazid tablet can facilitate the administration of certain dosages. Pyridoxine is given with isoniazid in patients at risk (e.g. those with HIV or malnutrition)
	300 mg					1	1.5	1.5	1.5	2	2	2	
Clavulanic acid[j]	125 mg clavulanic acid as Amx/clv 500/125 mg (50/12.5mg/ml)	1.5 ml tid	2 ml tid	3 ml tid	5 ml tid	8 ml tid	1 bd or tid						Only to be used with carbapenems
Pretomanid		-	-	-	-	-	-	1	1	1	1	1	Currently only use as part of BPaLM/BPaL regimens

bd: two times a day; cap: capsule; dt: dispersible tablet; g: gram; GDG: Guideline Development Group; kg: kilogram; mg: milligram; mL: millilitre; M/F: Monday and Friday; M/W/F: Monday, Wednesday and Friday; od: once daily; tab: tablet; tid: three times a day.

[a]Dosing guidance is based on currently available data and may be revised once additional data are available. Dosages were established by the GDGs for the WHO guidelines on DR-TB treatment (2018 and 2020 updates), the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and the expert consultation on dosing convened by WHO in October 2021, following the GDG meeting on child and adolescent TB in June 2021.

Doses for children and young adolescents weighing <46 kg were revised according to Annex 6 of the 2022 WHO operational handbook on tuberculosis – Module 5: Management of tuberculosis in children and adolescents. They are based on the most recent reviews and best practices in the treatment of (paediatric) MDR/RR-TB. For certain medicines the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling and maturation. Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here to achieve blood concentrations similar to target levels in an average adult patient. The guidance for the 3–<5 kg weight band and for bedaquiline and delamanid is based on currently available data and may be revised when new data become available.

[b] Dissolving of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide. This avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred).

[c] The higher dose may be used except when there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has low-level drug resistance

[d] Bedaquiline adult tablets (100 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole. Vigorous stirring/shaking is needed prior to administering the 100 mg tablet crushed and suspended in water.

[e] When using the 600 mg tab and the 150 mg dt to dose children weighing 16 to <24 kg, the dose in mg/kg will exceed 10–12 mg/kg and clinicians may opt to administer 1.5 dt or 4 mL of the 600 mg tab dispersed in 10 mL water.

[f] Clofazimine tablets are technically not dispersible, but they do slowly (this takes approximately 5 minutes) dissolve in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred prior to administration. The 100 mg soft gel capsule is difficult to swallow for young children and therefore countries are strongly encouraged to make the 50 mg tablet formulation available.

[g] In children weighing 3 to <7 kg doses are lower than previously recommended. This is because of relatively high exposures associated with risk of neuropsychiatric adverse events, which is especially concerning when co-administering cycloserine with delamanid.

[h] Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole

[i] Amikacin and streptomycin may be used in adults aged 18 years or more, in situations where an effective regimen cannot otherwise be designed using oral agents, when susceptibility is demonstrated and when adequate measures are in place to monitor for adverse events. Given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school, the use of injectable agents in children should be exceptional and limited to salvage therapy, and the treatment needs to be provided under strict monitoring to ensure early detection of ototoxicity. If used, the weight-based daily dose for amikacin is 15–20 mg/kg and for streptomycin it is 20–40 mg/kg for children aged 2 years and older. To determine the dosing for infants and children aged below 2 years, a paediatric DR-TB expert should be consulted, and a lower mg/kg dose used to compensate for immature clearance. Co-administration with lidocaine is advised to reduce pain at the injection site.

[j] These medicines are only recommended as a companion agent (amoxicillin/clavulanic acid) or are not included in Groups A, B and C, because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (isoniazid).

Specific comments on dosing children with medicines used in second line MDR-TB regimens:

• For dosing of premature and low birth weight infants weighing <3 kg, advice should be sought from a paediatric DR-TB expert.

• For dosing of infants weighing 3 to <5 kg, a paediatric DR-TB expert should be consulted whenever possible.

• The use of child-friendly, dispersible tablets in infants and young children is preferred over manipulating adult tablets or administering or manipulating capsules. Where applicable, the dosing provided is based on dissolving the dispersible formulation in 10 mL of water and administering the number of mL (aliquots). The number of mL in the table reflects the dose to provide. The dissolved solution should be used immediately and the remainder of the 10 mL should be discarded.

• For some weight bands, dosing is indicated with both child-friendly, dispersible formulations and adult formulations. If adult formulations are used, the table provides the dose using aliquots in mL and tablet fractions where applicable (if the fraction is 0.5 or more). Aliquots refer to the volume to administer after crushing and dissolving the tablet in 10 mL of water

11.2 Annex2: Sputum collection and Transportation

(a) Instruction for sputum collection

Good sputum means sputum containing purulent or mucopurulent particles. Two sputum specimens (one spot and one early morning) must be taken. One of them must be early morning specimen.

Place to collect the sample

- Sputum collection place must be away from other people, in open air
- No one should be standing in front of the patient during collection

Collection procedure

- Rinse the mouth with water before producing sputum
- Take two deep breaths, holding the breath for a few seconds after each inhalation
- and then exhaling slowly
- Breath a third time and then forcefully blow the air out
- Hold the container close to the lip and spit into it gently after a productive cough
- Tightly close the lid of the container

After sputum collection

- Ask the patient to wash the hands with soap and water.

(b)Packing and transportation

Packaging of specimens/culture

The culture bottles must be wrapped separately with tissue paper or other absorbent materials (to prevent breakage) and then placed in plastic boxes.

Transportation of specimen/culture

The plastic bags/culture bottles containing specimens must be placed in a transport box (fibreboard box) containing absorbent materials – tissues or cotton wool – between, above and below the containers to prevent leakage during transportation.

During transportation if the weather is hot (temperature above 37 °C) the transport boxes must be sent with a cold chain. Copies of questionnaire and requisition forms must be sent along with the specimens. It is important to write down the name and signature of the sender/receiver in the dispatch book.

If the specimen transport is going to be longer than 3 days, cetylpyridinium chloride (CPC) or cetylpyridinium bromide (CPB) is required. Specimens with CPC cannot be used with liquid culture and cannot be refrigerated (they will crystalize and ruin the specimen). CPC can be used with Xpert MTB/RIF instruments.

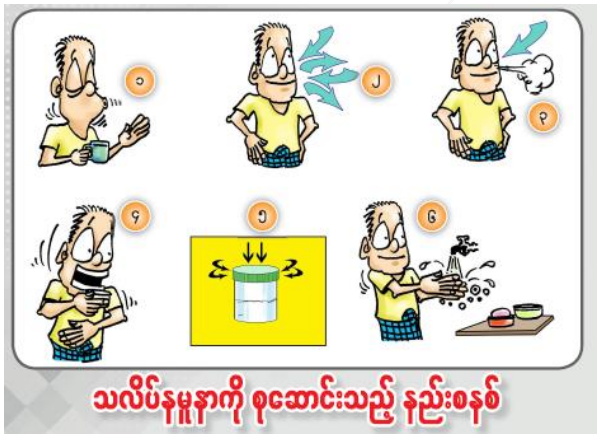
Cold Chain Method for transport (preferred method for short transport times, less than 3 days, as MGIT can be used with the same specimen for confirmation)

- At township TB workers will collect sputum from all DR TB suspects/patients.
- Refrigerate at +4-+8 °C until transport.
- Put the sputum container in the cold box to maintain the cold chain and send it to a laboratory facility with Xpert MTB/RIF and or culture/DST.

CPC Method for transport (preferred for long transport times, longer than 3 days. MGIT cannot be used in a specimen with CPC)

- Falcon tubes containing 5ml of CPC sol. will be made available at the townships.
- At township TB workers will collect sputum from all DR TB suspects/ patients.
- About 5 ml sputum will be transferred to the CPC-containing falcon tube, and the tube then closed tightly.
- Sputum samples in the falcon tube will be sent to the nearest facility with Xpert MTB/RIF.
- DST results will be sent to the periphery in vice-versa via e-mail to the Outpatient DR-TB Team and to the UHC that sent the results.

Figure 11.1: Illustration for collection of a good quality sputum sample



(၁) သလိပ်မထွေးမီ ပါးစပ်ကို ရေနှင့် ပလုတ်ကျင်းရပါမည်။

(၂) ပထမအကြိမ်နှင့် ဒုတိယအကြိမ်တွင် အသက်ပြင်းပြင်းရှူသွင်းပြီး၊ စက္ကန့်အနည်းငယ် အသက်အောင့်ထား၍ ဖြည်းဖြည်းချင်း ရှူထုတ်ရပါမည်။

(၃) တတိယ အကြိမ်ထပ်ရှူသွင်းပြီး၊ ပြင်းပြင်း ရှူထုတ်ရပါမည်။

(၄) သလိပ်ခွက်ကို နှုတ်ခမ်းနား ကပ်ထားပြီး ရင်ခေါင်းထဲမှ သလိပ်အတုံးအခဲကို ဟပ်၍ ဖြည်းဖြည်းထွေးထုတ်ပါ။

(၅) သလိပ်ခွက်၏ အဖုံးကို သေသေချာချာ ရစ်၍ ပိတ်ပါ။

(၆) သလိပ်နမူနာကို စုဆောင်းပြီးသည့်အခါ၊ လူနာက ရေနှင့် ဆပ်ပြာတို့ဖြင့် လက်ဆေးရန် ဖြစ်သည်။

11.3 Annex 3: Prolongation of QTc interval and measuring of QTcF

Common causes of QT prolongation

- TB drugs causing QT prolongation: Cfz, Bdq, Mfx, Dlm, Pa, Lfx
- Many other drugs: e.g., erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, Antipsychotics (all have some risk including haloperidol, chlorpromazine, and risperidone), Many anti-nausea drugs (ondansetron/granisetron, domperidone), methadone, some antiretrovirals.
- Other causes: hypothyroidism, hypothermia, myocardial ischemia, increased ICP, and electrolyte imbalance
- Genetic causes such as congenital long QT syndrome

<table>
<tr><th>QTcF</th><th>Male</th><th>Female</th><th>Action Required</th></tr>
<tr><td>Normal</td><td><430</td><td><450</td><td>ECG monitoring as routine schedules</td></tr>
<tr><td rowspan="2">Prolonged</td><td>≥450</td><td>≥470</td><td rowspan="2">• Repeat ECG and confirm the prolongation
• Electrolyte testing
• More frequent ECG monitoring</td></tr>
<tr><td colspan="2">An increase of greater than 60 ms from baseline</td></tr>
<tr><td>Dangerous</td><td colspan="2">≥500</td><td>Stop the use of QT prolonging drugs</td></tr>
</table>

A value of greater than 450/470 ms is considered prolonged in male/female patients. If a male/female patient taking SL medicine (s) like bedaquiline, delamanid, high dose Mfx, clofazimine has a QTcF value of greater than 450/470 ms (or an increase of greater than 60 ms from baseline) on his or her ECG, electrolyte testing and more frequent ECG monitoring should be performed. A QTcF interval of more than 500 ms is considered dangerous and is the reason to stop the use of QT prolonging drugs in the regimen.

Borderline QTcF

If the QTcF interval remains above normal value but still below 500 ms (and the patient is stable and electrolyte values are within normal limits) repeat weekly ECGs to confirm that QTcF interval is stable.

Dangerous QTcF

Any patient found to have a QTc value greater than 500ms should be managed carefully.

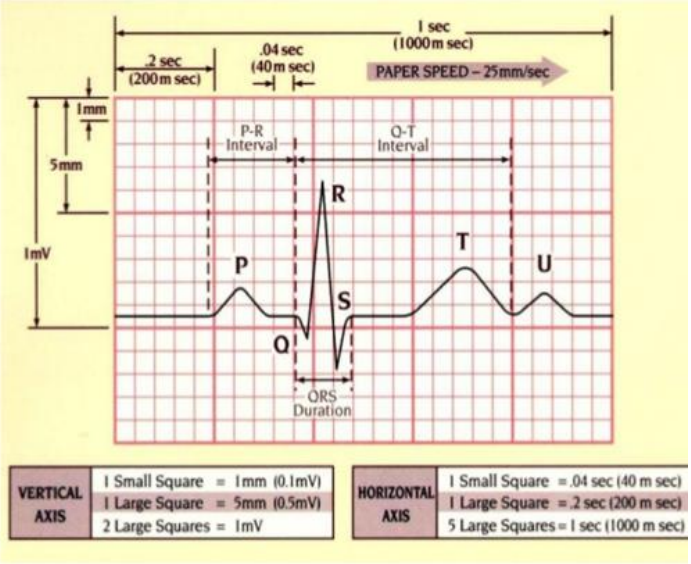
- ✓ Repeat ECG and confirm the prolongation.
- ✓ Discontinue Bdq / Dlm/Mfx^{h}/Cfz for QTc value greater than 500ms.
- ✓ Check potassium, ionized calcium and magnesium levels. Electrolyte levels should be maintained in the normal range in any patients with an elevated QT interval.

- ✓ If low K+ is detected, urgent management needed with replacement and frequent repeat K+ test (daily or multiple times a day) to document K+ is improving.
- ✓ If K+ is low, always check Mg++ and Ca++, and compensate as needed.
- ✓ If unable to check, consider oral empiric replacement doses of Mg++ and Ca++.
- ✓ It is suggested to maintain potassium levels of more than 4 mEq/l and magnesium levels of more than 1.8 mg/dl.
- ✓ Withhold offending drugs until the electrolytes have normalized.
- ✓ ART is not stopped unless the patient is severely unstable.
- ✓ Check a TSH and treat any hypothyroidism found.
- ✓ Assess and avoid other drugs that increase the QT interval.
- ✓ Monitor the patient's renal and hepatic function and adjust the dose of fluoroquinolones if impairment is present.
- ✓ Monitor ECGs at least weekly to confirm that the QTcF interval has returned to baseline.
- ✓ If cardiac symptoms appear (tachycardia, syncope, palpitations, weakness or dizziness), obtain an ECG to check the QT interval and rule out an arrhythmia.

Note: The information below is about QTcF measurement and for management please see the relevant information in chapter 8 (aDSM).

What Pathologies can ECG detect?

- **Arrhythmias**
- **MI, IHD**
- **Cardiac Hypertrophy**
- **Electrolyte Disturbances(hypo-Hyperkalemia/calcemia**
- **Drug Toxicities, QT Interval- Digoxin, Bdq, Lzd, Mfx-Cfz etc**



What is QT Interval and measuring QTc (Ref: E. Burns 2017)

- QT Interval is the time measurement from the start of Q wave to the end of T wave
- It tells us the time taken for ventricular depolarization and ventricular repolarization- means ventricular contraction to relaxation
- QT interval is inversely proportional to heart rate; QT shortens at faster heart rate and QT lengthens at slower heart rate
- Abnormally prolonged QT wave is associated with sudden arrhythmias and leading to Torsade de pointes (Tdp**)**

Measuring QTc: Standardization

- The QT interval should be measured in long lead II, V5, V6
- Several successive beats should be measured with the maximum interval taken
- Large U waves (more than 1 mm) that are fuse to the T wave should be included in measurement
- Small U waves and those which are separate from T should be excluded
- The maximum slope intercept method is used to define the end of T wave

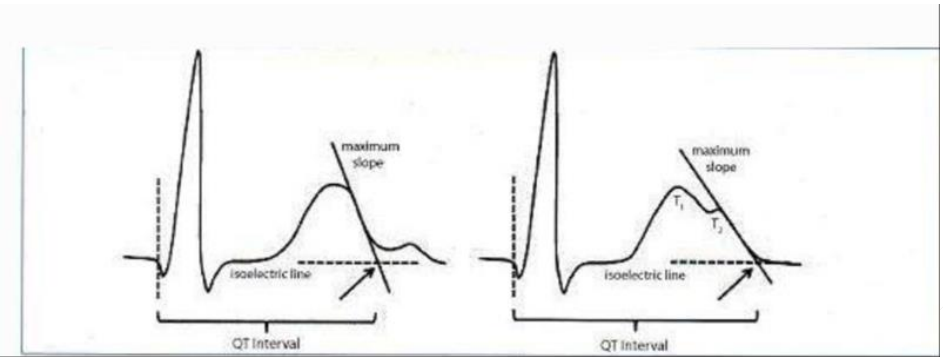


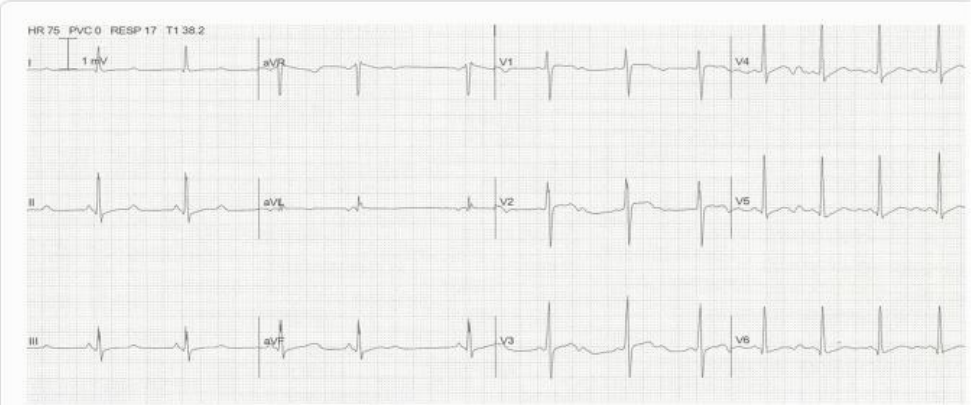
Fig: maximum slope down of T wave

Corrected QT– is called QTc

- With irregular rhythms (such as Atrial Fibrillation) always note the general (average) ventricular rate (QRS's per 6-sec. strip ✕ 10)

Prolonged QTC in Hypoklaemia-Example

Ref: E. Burns 2017



Apparent QTc 500ms – prominent U waves in precordial leads (hypokalaemia (K+ 1.9))

Rule of Thumb: Always remember

1. Use triplets method quickly to estimate heart rate, one larger square is 300, 2 LSs = 150, 3LSs=100,4 LSs=75,5LSs =60 all per minute
2. The normal QT interval is between 7-11 small squares
3. The normal QT is less than half of the preceding RR interval

QTcF Nomogram

How to use the QTcF Nomogram

1. Identify the patient's HR or RR interval on the top of the table.
2. Identify the measured QT (uncorrected) interval on the left of the table.
3. Find the corresponding calculated QTcF in the cell below the HR (or RR) and to the right of the QT interval.

QTcF Nomogram

Heart rate (beats per minute)	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
R-R interval (sec)	1.33	1.20	1.09	1.00	0.92	0.86	0.80	0.75	0.71	0.67	0.63	0.60	0.57	0.55	0.52	0.50	0.48	0.46	0.44	0.43	0.41	0.40
QT interval (msec) 300	273	282	291	300	308	316	323	330	337	343	350	356	362	367	373	378	383	388	393	398	403	407
310	282	292	301	310	318	326	334	341	348	355	361	368	374	379	385	391	396	401	406	411	416	421
320	291	301	311	320	329	337	345	352	359	366	373	379	386	392	397	403	409	414	419	424	429	434
330	300	311	321	330	339	347	355	363	371	378	385	391	398	404	410	416	421	427	432	438	443	448
340	309	320	330	340	349	358	366	374	382	389	396	403	410	416	422	428	434	440	446	451	456	461
350	318	329	340	350	359	368	377	385	393	401	408	415	422	428	435	441	447	453	459	464	470	475
360	327	339	350	360	370	379	388	396	404	412	420	427	434	441	447	454	460	466	472	477	483	489
370	336	348	359	370	380	390	399	407	416	424	431	439	446	453	460	466	473	479	485	491	497	502
380	345	358	369	380	390	400	409	418	427	435	443	451	458	465	472	479	485	492	498	504	510	516
390	354	367	379	390	401	411	420	429	438	446	455	462	470	477	484	491	498	505	511	517	523	529
400	363	376	389	400	411	421	431	440	449	458	466	474	482	490	497	504	511	518	524	531	537	543
410	373	386	398	410	421	432	442	451	460	469	478	486	494	502	509	517	524	531	537	544	550	556
420	382	395	408	420	431	442	452	462	472	481	490	498	506	514	522	529	536	543	550	557	564	570
430	391	405	418	430	442	453	463	473	483	492	501	510	518	526	534	542	549	556	563	570	577	584
440	400	414	427	440	452	463	474	484	494	504	513	522	530	539	547	554	562	569	577	584	590	597
450	409	423	437	450	462	474	485	495	505	515	524	534	542	551	559	567	575	582	590	597	604	611
460	418	433	447	460	472	484	496	506	517	527	536	545	554	563	571	580	588	595	603	610	617	624
470	427	442	457	470	483	495	506	517	528	538	548	557	566	575	584	592	600	608	616	623	631	638
480	436	452	466	480	493	505	517	528	539	549	559	569	578	587	596	605	613	621	629	637	644	651
490	445	461	476	490	503	516	528	539	550	561	571	581	590	600	609	617	626	634	642	650	658	665
500	454	471	486	500	514	526	539	550	562	572	583	593	603	612	621	630	639	647	655	663	671	679
510	463	480	495	510	524	537	549	561	573	584	594	605	615	624	634	643	651	660	668	676	684	692
520	472	489	505	520	534	547	560	572	584	595	606	617	627	636	646	655	664	673	681	690	698	706
530	482	499	515	530	544	558	571	583	595	607	618	628	639	649	658	668	677	686	694	703	711	719
540	491	508	525	540	555	568	582	594	606	618	629	640	651	661	671	680	690	699	708	716	725	733
550	500	518	534	550	565	579	592	605	618	630	641	652	663	673	683	693	702	712	721	729	738	746
560	509	527	544	560	575	590	603	616	629	641	653	664	675	685	696	706	715	725	734	743	751	760
570	518	536	554	570	585	600	614	627	640	652	664	676	687	698	708	718	728	738	747	756	765	774
580	527	546	563	580	596	611	625	638	651	664	676	688	699	710	720	731	741	751	760	769	778	787
590	536	555	573	590	606	621	636	649	663	675	688	700	711	722	733	743	754	763	773	783	792	801
600	545	565	583	600	616	632	646	660	674	687	699	711	723	734	745	756	766	776	786	796	805	814

11.4 Annex 4. Clinical examination of peripheral neuropathy

Note: Please use this with relevant chapter of aDSM to follow grading and management

It is characterized by a decline and damage of nerve function leading to loss of sensation, ulceration and subsequent amputation. There is a common misconception that diabetic neuropathy is a phenomenon limited largely to the lower limbs, which is not really true. About 40% of patients with neuropathy have upper limb involvement in addition and the associated symptoms could be positive with that of pain, paresthesias and dysesthesias, typically glove and stocking distribution.

There is probability that in some TB, HIV, diabetic patients there is some level of pre-existing peripheral neuropathy and use of toxic drugs may further exacerbate the situation leading to grade 1 or grade 2 of PN, which limits the use of such toxic drugs (for example Lzd, Cs, high dose INH)

Table; Distal symmetrical Polyneuropathy, small fiber and large fiber neuropathy (Source: ***A Practical guide to DM,7th edition,*** **© 2016, Jaypee Brothers Medical Publishers**

	Small fiber neuropathy	*Large fiber neuropathy*
Fiber	C-fiber type	Delta type (Aδ)
Sensory loss	0 to + (Warm thermal perception) Pinprick hypoesthesia Light touch sensation ↓↓ Monofilament testing—1 and 10 g)	0 to +++ (touch, vibration perception)—checked with biothesiometer and tuning fork (128 Hz) ↓ position sense and muscle strength ↓ sharp-dull and two-point discrimination.
Prominent symptoms	Hyperalgesia-superficial pain (+ to +++) Constant burning Allodynia—↓ sweating → dryness Severe hyperesthesia Shock-like sensations Hypoalgesia—late	Deep-seated, dull aching pain (+ to +++) Sensory ataxia → falls → minor trauma/ fractures → ulcers/amputation

ACTG Brief Peripheral Neuropathy Screening Tool (Source: NIAID Adult AIDS Clinical Trials Group)

Following are the step wise approaches to detect peripheral neuropathy in patients. Please remember that this assessment is subjective and may lead to wrong scoring if not properly carried out. Therefore, it is imperative that doctors/nurses/health care workers should be appropriately trained to carry out below assessments.

1: Elicit Subjective Symptoms

Ask the subject to rate the severity of each symptom listed in Question 1 on a scale of 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb). If a symptom has been present in the past, but not since the last visit, enter "00 - Currently Absent." If the symptom has never been present, enter "11 - Always Been Normal."

Always Been Normal	Currently Absent	Mild ⟷ Severe									
11	00	01	02	03	04	05	06	07	08	09	10

Symptoms	R	L
a. Pain, aching, or burning in feet, legs		
b."Pins and needles" in feet, legs		
c. Numbness (lack of feeling) in feet, legs		

2. Grade Subjective Symptoms

Use the single highest severity score from Question 1 above to obtain a subjective sensory neuropathy score. If all severity scores are "00" or "11," the subjective sensory neuropathy score will equal "0."

Subjective Sensory Neuropathy Score	Severity grade
11 or 00	0
01 - 03	1
04 - 06	2
07 - 10	3

R	L

3. Evaluate Perception of Vibration

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject's wrist or hand to be sure that he/she can recognize the vibration or "buzzing" quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe.

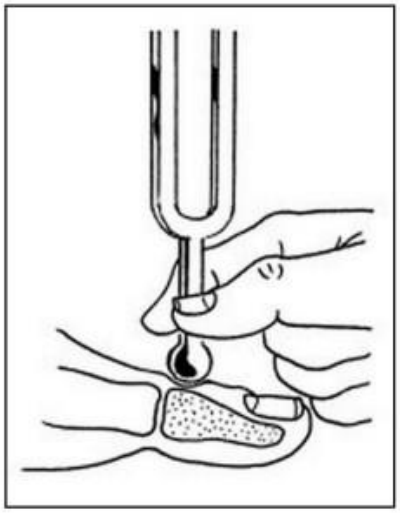
Vibration perception

a. Great toe DIP joint perception of vibration in seconds
b. Vibration perception score

0 = felt >10 seconds (normal)
1 = felt 6-10 seconds (mild loss)
2 = felt <5 seconds (moderate loss)
3 = not felt (severe loss)

R	L

Picture: Adopted from, End TB Guidelines 2018



4. Evaluate Deep Tendon Reflexes

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject's ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon is struck. Use reinforcement by having the subject clench his/her fist before classifying the reflex as absent.

Ankle Reflexes Score

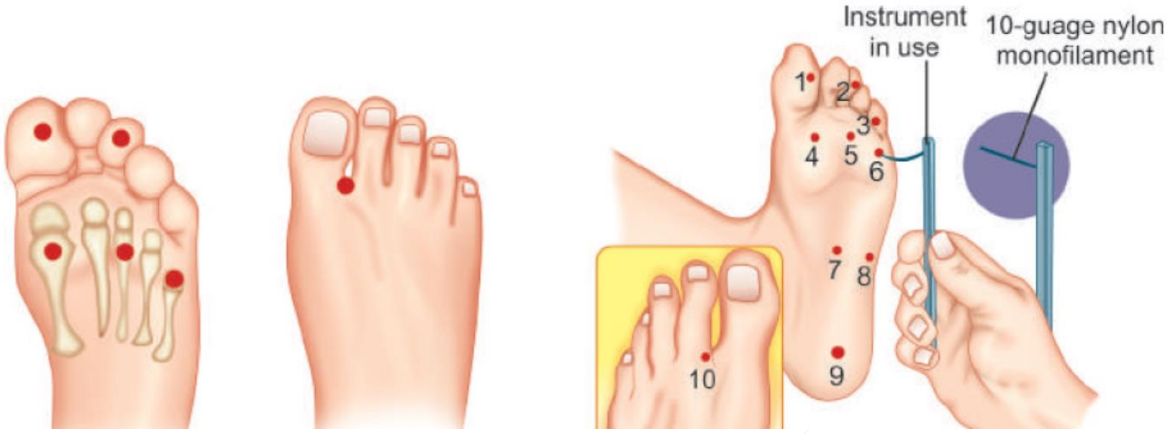
0 = absent
1 = hypoactive
2 = normal deep tendon reflexes
3 = hyperactive
4 = clonus

R	L

Nylon Monofilament Test (Source: a practical guide to DM, 7th edition)

The Semmes-Weinstein monofilament: The standard American Diabetes Association (ADA) criteria will mention that it is only necessary to do a 2 g and a 10 g monofilament testing. In leprosy or TB, up to 300 g may be utilized.

a



11.5 Annex 5: Management of electrolyte disturbances

Although often asymptomatic, low serum potassium and magnesium may present as fatigue, myalgias, cramps, paraesthesias, lower extremity weakness, behaviour or mood changes, somnolence, and confusion. More severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias. The magnitude of total body depletion of potassium (K+) and magnesium (Mg++) may be far lower than that which is reflected in serum levels.

Warning: Coadministration of oral divalent or trivalent cation-containing compounds (i.e. Mg++ and Ca++) with oral fluoroquinolones may impair fluoroquinolone absorption. They must be dosed at least 2 hours before and three hours after the fluoroquinolone.

Hypokalaemia (defined as a serum potassium less than 3.5 mEq/L) and **hypomagnesaemia** (defined as a serum magnesium less than 1.8 mEq/L) are common in patients receiving MDR-TB therapy and are caused by the following:

- Direct renal tubular effect of aminoglycosides and capreomycin
- Vomiting and diarrhoea.

Once hypomagnesaemia or hypokalaemia is diagnosed:

- Underlying causes such as vomiting and diarrhoea should be treated.
- Arrhythmogenic medications (such as digoxin, tricyclic anti-depressants) should be discontinued if possible.
- An electrocardiogram should be performed in patients with significant electrolyte disturbances; if the QT segment is prolonged, any drugs contributing to QT prolongation— including certain fluoroquinolones, haloperidol, fluconazole, and cisapride— should be held.

Treatment of hypokalaemia and hypomagnesaemia:

- Should be administered orally if electrolyte disturbance is not severe (it is safer to give electrolytes, especially potassium, orally than intravenous).
- Intravenous treatment is required for patients with gastrointestinal disorders or when the potassium deficiency is severe and life-threatening.
- If severe, hold the injectable agent until potassium is in a safe range.
- Replacement may be needed during the whole time during the use of the aminoglycoside or capreomycin.
- The electrolyte abnormalities will correct after suspension of the injectable in the intensive phase. If electrolyte abnormalities do not correct once the injectable is suspended, suspect another aetiology.
- Hypokalaemia will be refractory to treatment unless hypomagnesaemia is also treated (it is acceptable to screen electrolyte disturbances with a serum potassium. If low obtain a serum magnesium and calcium. (If unable to screen for magnesium, empiric magnesium replacement with the potassium replacement is often essential, since potassium wasting will continue in hypomagnesaemic states).

- Normal renal function should be confirmed prior to instituting repletion, although even patients with renal failure should receive repletion in smaller doses.
- In cases of refractory electrolyte abnormalities, amiloride or spironolactone may be used to decrease potassium and magnesium wasting in the renal tubules (amiloride 5-10 mg once daily or spironolactone 25 mg once daily).
- Frequent potassium monitoring must be used when potassium-sparing diuretics are given in conjunction with potassium supplements, as hyperkalaemia may result. Continue with potassium and magnesium supplements, but often can use lesser quantities.

The following are general recommendations for electrolyte replacement. Optimal replacement schedules have not been determined and individual programmes may vary:

Potassium

Oral Supplementation

- Occasional gastric intolerance.
- May dilute KCl tablets in water or take them as pills.
- May split dose and give two or three times per day.
- Supplement diet with banana, orange/tomato/grapefruit juice.

IV Supplementation

- May produce burning at the infusion site.
- Should NOT exceed more than 20 meq/h of KCl.
- Normal preparation is 40 meq in 1 litre of NaCl 0.9%, maximum preparation is 60 meq/L.

Table 1. Frequency and replacement table for potassium

Potassium Level (mmol/L)	Quantity of KCl	When to do next control (sooner if pt has vomiting or diarrhoea)
4.0 or more	None	Monthly
3.7 – 4.0	None	Monthly
3.4 – 3.6	20 - 40 meq	Monthly
3.0 – 3.3	60 meq	Two weeks
2.7 – 2.9	80 meq	One week
2.4 – 2.6	80-120 meq	1-2 days
2.0 – 2.3	60 meq IV and 80 meq PO	Every 6 to 24 hr
<2.0	60 meq IV and 100 meq PO	Every 6 hrs with aggressive IV replacement. Consider holding injectable until >2.

Notes on dosing potassium: The dosage of potassium supplements is usually expressed as mEq of potassium. Forty mEq of potassium is provided by approximately the following quantities:

- 3.9 g of potassium acetate

- 4.0 g of potassium bicarbonate
- 3.0 g of potassium chloride
- 4.3 g of potassium citrate
- 9.4 g of potassium gluconate

The acetate, bicarbonate, chloride, citrate, and gluconate salts of potassium can all be administered orally. Potassium chloride and potassium acetate may be administered by IV infusion. Intravenous vials often come with a percentage of potassium. For example, a 10 ml vial of 10% potassium chloride is 1 gram of potassium chloride and would be 13.3 mEq of potassium.

Magnesium

Oral Supplementation

- Magnesium citrate
- Magnesium lactate
- Magnesium glycinate
- Magnesium gluconate
- Magnesium chloride
- Magnesium oxide

Different preparations have different amounts of elemental magnesium. Recommended types include magnesium citrate, magnesium gluconate and magnesium lactate, all of which are more easily absorbed into the body than other forms. While magnesium oxide is probably the most common form given for replacement because of its low cost, Mg oxide does not have high bioavailability (i.e. the body does not absorb Mg oxide that well).

For example, magnesium chloride, lactate, citrate and glycinate each have around the bioavailability 4 times greater than the oxide form. Magnesium citrate is probably the best in terms of absorption. (Patients with hypomagnesaemia will benefit from Mg oxide, so if other formulas are not affordable Mg oxide can be used. Other forms (chloride, lactate, citrate or glycinate) in tablet form are preferable. Quantities greater than 2000 mg are often more easily given IV or IM.

IV Supplementation

- Maximum concentration: 5 g or 40 meq $MgSO_4$ in 1 liter of NaCl 0.9% or Dextrose 5%.
- Do not exceed 150 mg per minute.
- If not emergency:2 g in 100 ml administered over 1–2 hours
- 4 g in 250 ml administered over 2–4 hours

Intramuscular Supplementation

- 1 g (or up to 250 mg/kg) of $MgSO_4$ without dilution IM every 6 hours.
- No advantage over IV magnesium.

- Indicated if supplementation cannot be received PO or IV.
- Potassium sparing diuretics may also help with magnesium wasting.

Table 2. Frequency and replacement table for magnesium

Magnesium level (mEq/L)	Quantity of Mg (Total daily dose)	When to do next control
2.0 or more	None	Monthly
1.5 – 1.9	1000 mg – 1200 mg	Monthly
1.0 – 1.4	2000 mg (consider IM)	1–2 week
<1.0	3000 mg – 6000 mg (give IV or IM)	1–6 days

Calcium

- Symptomatic hypocalcaemia should be treated on an emergency basis with 2 grams of calcium gluconate (180 mg elemental calcium or 20 ml 10% calcium gluconate) IV over 10 minutes, followed by infusion of 6 grams calcium gluconate in 500 ml D5W over 4–6 hrs. The IV infusion should be tapered. The initial oral dose during the transition from IV to oral therapy is 1–2 g elemental calcium three times a day.
- For long-term therapy the typical dose is 0.5–1.0 g PO three times a day.
- Hypomagnesaemia must be treated if present.
- Total serum calcium levels need to be adjusted for low albumin (if the laboratory tests for serum ionized levels of calcium, these do not need to be adjusted). The total serum calcium can be corrected by adding 0.8 mg/dl for every 1 g/dl decrease of serum albumin below 4 g/dl. By doing this calculation one can determine if true hypocalcaemia is present:

Corrected calcium = 0.8 (4.0 – measured albumin) + reported calcium

Table 3. Frequency and replacement table for calcium

Calcium level (total calcium adjusted for low albumin)	**Dose of Calcium**	**When to do next control**
>8.5 mg/dl (>4.2 meq/L)	None	
7.5 – 8.4	500 mg three times a day	Monthly
7.0 – 7.4	1000 mg three times a day	1–2 weeks
<7.0	Consider IV and taper to 1000 mg three times a day	1–4 days

Repeat warning: Always give any electrolyte replacement a few hours apart from the fluoroquinolones and the cations Mg++, and Ca++ can combine with the anions of the fluoroquinolones and decrease absorption.

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