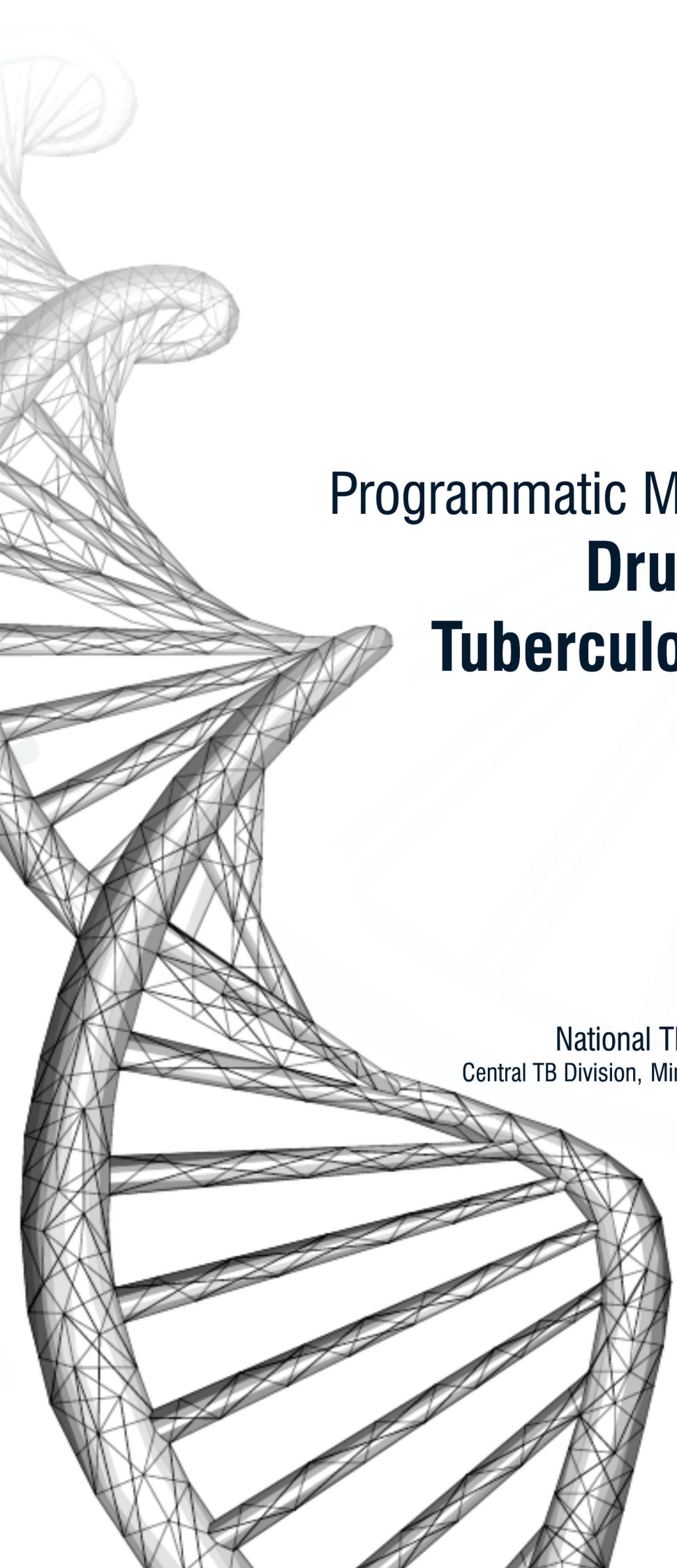
Ministry of Health & Family Welfare
Government of India

World Health Organization
India

Guidelines for Programmatic Management of **Drug Resistant Tuberculosis in India**

March 2021

National TB Elimination Programme
Central TB Division, Ministry of Health & Family Welfare
Government of India, New Delhi



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National TB Elimination Programme
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MESSAGE

डॉ हर्ष वर्धन
Dr Harsh Vardhan
स्वास्थ्य एवं परिवार कल्याण, विज्ञान और प्रौद्योगिकी व पृथ्वी विज्ञान मंत्री, भारत सरकार
Union Minister for Health & Family Welfare, Science & Technology and Earth Sciences Government of India

सत्यमेव जयते

जय विज्ञान जय अनुसंधान

सबका साथ, सबका विकास, सबका विश्वास
Sabka Saath, Sabka Vikas, Sabka Vishwas

MESSAGE

Efforts to end TB in India have intensified through the implementation of the National Strategic Plan (2017-2025) since last 3 years. The national TB Programme was renamed as National Tuberculosis Elimination Programme (NTEP) to establish the resolve to end TB from the country.

During this period, the programme has made tremendous efforts and progress to realize the ambitious goal set by our Hon'ble Prime Minister at the Delhi End TB Summit in March 2018 of ending the TB epidemic by 2025 from the country, five years ahead of SDG goals for 2030. Combating Drug Resistant TB (DRTB) is one of the critical interventions in this endeavour of the government.

As per the Global TB Report 2020, an estimated 3.3% of new cases and 18% of previously treated cases had Multi-Drug/Rifampicin Resistant TB (MDR/RR-TB) in 2019. Overall, there were an estimated 4,65,000 incident cases of MDR/RR-TB in 2019. Nearly 50% of global cases were in India (27%), China (14%) and the Russian Federation (8%). I'm glad to present this evidence based updated guidelines for management of Drug Resistant TB in India with the latest tools, drugs, regimen and efficient systems.

There is a paradigm-shift in the NTEP's overall approach and strategy to further strengthen the foundation of the programme and its last mile reach. For instance, patient-centric support system has been an integral part of NTEP. The programme has established an efficient system of targeted delivery of patient support benefits. Linkages of 'NIKSHAY' and Public Fund Management System (PFMS) has been established to provide Direct Benefit Transfer (DBT). NIKSHAY also expanded the provision of four DBT schemes of the programme:– (a) Nikshay Poshan Yojana (NPY) to patients; (b) Providing incentive to Treatment Supporters; (c) Notification Incentive to Private Providers; and, (d) Transport incentive to Tribal TB patients. DBT transfers under NPY,

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सत्यमेव जयते

one of the fastest ever implemented schemes of Government of India saw over ₹1000 crores being disbursed till 2020 as nutritional support to patients.

Specifically, the engagement of elected representatives is important, especially for a disease like TB that remains surrounded by layers of misinformation, myths and stigma. The programme is closely working with the State/ UTs governments, Members of Parliament and Members of Legislative Assemblies and leveraging the elected representative's tremendous community connect to further spread awareness and dispel myths around TB. Elected representatives can serve as a two-way channel of communication – to sensitize the community about TB and to appraise the health system and the government about the ground realities.

We are committed to addressing the challenge of TB including Drug Resistant TB with innovations and implementation of bold strategies. Under our people's movement "TB Mukt Bharat", I urge all stakeholders – all State/UTs Governments, the development partners, the community, and the civil society at large to come forward and join hands to end TB from the country by 2025.

Harsh

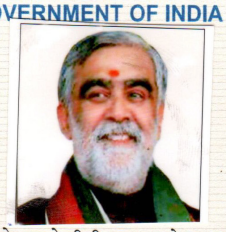
(Dr. Harsh Vardhan)

MESSAGE

राष्ट्रीय स्वास्थ्य मिशन
अश्विनी कुमार चौबे
Ashwini Kumar Choubey

सत्यमेव जयते
सर्वेसन्तु निरामया
स्वच्छ भारत
एक कदम स्वच्छता की ओर

स्वास्थ्य एवं परिवार कल्याण राज्य मंत्री
भारत सरकार
MINISTER OF STATE FOR
HEALTH & FAMILY WELFARE
GOVERNMENT OF INDIA



संदेश

भारत के टीबी उन्मूलन कार्यक्रम में पिछले कुछ वर्षों में काफी प्रगति हुई है और हम वर्ष 2025 के अपने टीबी उन्मूलन के लक्ष्य की ओर बढ़ते हुए अपने माननीय प्रधान मंत्री का उनके नेतृत्व और मार्गदर्शन के लिए आभार व्यक्त करते हैं।

इस वर्ष की शुरुआत में, कोविड-19 महामारी ने देश की स्वास्थ्य प्रणाली पर अभूतपूर्व दबाव डाला। महामारी के प्रति भारत की प्रतिक्रिया का समर्थन करने के लिए एनटीईपी सहित कई स्वास्थ्य कार्यक्रमों को पुनर्निर्मित किया गया। राष्ट्रीय क्षय रोग उन्मूलन कार्यक्रम (एनटीईपी) ने विशेष रूप से संक्रामक रोगों के प्रबंधन में समझ और विशेषज्ञता के कारण एक महत्वपूर्ण भूमिका निभाई।

हम सभी प्रकार की टीबी के लिए गुणवत्तापूर्ण, संवेदनशील निदान और उपचार की सुविधा समाज के हर व्यक्ति तक पहुचाएंगे। ऐसा करने के लिए, हमें कम से कम समय में अधिक से अधिक लोगों तक पहुंचना होगा, और हम यह सभी स्तरों पर समुदाय के प्रभावी नियोजन और सरकार एवं भागीदारों दोनों, व्यक्तियों और एजेंसियों द्वारा उपचारात्मक कार्रवाई के माध्यम से जवाबदेही स्थापित करके करेंगे।

राष्ट्रीय टीबी उन्मूलन कार्यक्रम ने पिछले कई वर्षों में अपने कार्यकलापों और उपचार के क्षेत्र को कई गुना बढ़ाया है। डब्ल्यूएचओ दिशा निर्देश डीआर-टीबी के प्रबंधन के लिए तेजी से बदल रहे हैं। इनके अनुरूप, देश ने जिला स्तर तक डीआर-टीबी के प्रबंधन के लिए विकेंद्रीकृत मॉलिक्यूलर नैदानिक सेवाओं और सुविधाओं का विस्तार किया है। डीआर-टीबी से जुड़ी चुनौतियों को ध्यान में रखते हुए, सभी हितधारकों के लिए कार्यक्रम के साथ निकट समन्वय में काम करना महत्वपूर्ण है। इसमें सभी भागीदारों- सरकार, मरीज, टीबी विजेता, समाज निजी क्षेत्र, मीडिया आदि का योगदान जरूरी है।

इस कार्यक्रम में वर्चुअल बैठकों के माध्यम से टीबी से ठीक हुए लोगों को संवेदनशील बनाने और उन्हें जोड़ने के प्रयासों का विस्तार किया गया तथा देश के दूर-दराज क्षेत्रों से टीबी से ठीक हुए लोग इसमें उत्साह के साथ शामिल हो रहे हैं। नेशनल टीबी फोरम की बैठक में, हमने प्रभावित समुदायों द्वारा सामना की जाने वाली चुनौतियों के साथ-साथ टीबी और कोविड -19 दोनों से जुड़े मुद्दों के समाधान के प्रयासों पर समर्पित टीबी चैंपियंस से इस रोग से ठीक होने की कहानियाँ उनके मुख से सुनी।

मैं व्यक्तिगत रूप से सभी हितधारकों-टीबी विजेता, विकास सहयोगियों, समाज, सिविल सोसायटी, निजी क्षेत्र- से अनुरोध करता हूँ कि इस मुश्किल घड़ी में जब देश दो-दो स्वास्थ्य संकटों से लड़ रहा है, वो आगे आएं और क्षय रोग से संघर्ष में हमारे साथ जुड़ें। हम टीबी मुक्त भारत के अपने लक्ष्य को प्राप्त करने की दिशा में अग्रसर हैं।

टीबी हारेगा। देश जीतेगा।

(अश्विनी कुमार चौबे)

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MESSAGE

राजेश भूषण, आईएएस
सचिव

RAJESH BHUSHAN, IAS
SECRETARY

भारत सरकार
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स्वास्थ्य एवं परिवार कल्याण मंत्रालय
Government of India
Department of Health and Family Welfare
Ministry of Health and Family Welfare

The emergence of drug resistance is a major threat to tuberculosis (TB) care and control in the country. The National Tuberculosis Elimination Programme (NTEP) has developed a National Strategic Plan (NSP) 2017–25 to achieve the milestone of eliminating TB in the country by 2025.

We have made commendable progress by way of scaling-up services for drug-resistant TB across India, yet much more is neededto curb its spread and accelerate the march towards achieving a TB-free country.

The programme has updated the guidelines for Programmatic Management of Drug-resistant TB in India. This now aligns with the WHO End TB Strategy, SDGs and WHO Consolidated Guidelines for Tuberculosis: Module 4 Treatment of Drug-Resistant Tuberculosis 2020 to advance the country to scaling-up universal access to drug susceptibility testing for all diagnosed and notified TB patients and decentralized patient-centric care of drug-resistant TB.

These guidelines will be used for training all health-care workers at various levels for seamless implementation with digital data management and monitoring systems through Nikshay.

Implementing these guidelines will call for greater investments in improving access through the decentralization of specialized service delivery facilities and facilitate efficient information communication, technology (ICT) enabled systems for programmatic management of drug-resistant TB in India.

I would encourage all programme managers, providers, stakeholders, civil society and community members to work together for comprehensive implementation of these guidelines to combat and win over the menace of DR-TB in India.

Place : New Delhi
Date : 19th March 2021

(**RAJESH BHUSHAN**)

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MESSAGE

प्रो.(डॉ.) सुनील कुमार
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स्वास्थ्य सेवा महानिदेशक
DIRECTOR GENERAL OF HEALTH SERVICES

सत्यमेव जयते

भारत सरकार
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स्वास्थ्य सेवा महानिदेशालय
Government of India
Ministry of Health & Family Welfare
Directorate General of Health Services

Message

During last couple of years in India, there has been a paradigm shift in approach to TB elimination. Our Honorable Prime Minister set the vision of End TB in India by 2025 and we all are committed to this. A robust country wide national plan has been developed with a goal of TB Free India. The role of public and private health care facilities, international and national civil society organizations and community engagement have been crucial to attain the End TB 2025 goal and make our country TB Free.

Effective partnerships between TB/DR-TB services and the community may facilitate access by bringing services to people's homes, and reducing the cost of care-seeking for patients and health services as well as the cost of workload for staff. Carefully designed community and/or patient involvement initiatives also facilitate patient and community empowerment. Through the involvement of local communities, education on relevant health issues and stimulation of change in health-related behaviour, communities become increasingly knowledgeable and self-reliant.

Effective community and patient involvement yields positive results, such as improved case-finding and treatment outcomes, raised awareness concerning the nature of the disease and the availability of effective treatment free of charge, or general health promotion. To be successful, community and patient involvement initiatives should be designed and implemented with community members involved as equal partners.

India is one of the first countries to adopt the Communities, Rights and Gender Tools developed by the Stop TB Partnership. This is in line with the programs efforts to engage civil society and affected communities in the TB response through the creation of National, State and District TB Forums and involving TB Champions at various levels.

TB Forums provide a platform to include community as an important stakeholder to improve the quality of TB services and making them patient centric. "TB Champions" is an important strategy in engaging with TB/ DR-TB affected communities. A national level standardized training curriculum has been developed for capacity building of TB survivors.

I am sure community led movement will help the programme in addressing challenges related to DR-TB services as well.

(SUNIL KUMAR)

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MESSAGE

Dr Roderico H. Ofrin, WHO Representative to India

A steady increase in drug-resistant tuberculosis (DR-TB) cases threatens global progress towards the United Nations Sustainable Development Goals (SDGs) to #EndTB. The #EndTB Strategy builds on and significantly expands the scope of global efforts in the context of SDG 3.3 and sets specific indicators, milestones and targets for 2020, 2025, 2030 and 2035.

India bears 27% of the global burden of multi-drug resistant TB (MDR-TB), with an estimated 124,000 people developed the disease in the country in 2019. The COVID-19 pandemic threatens to undo the recent gains that have been made painstakingly to expand case detection and management.

The impact of the pandemic on TB services has been severe, with data collated by WHO from high TB burden countries showing a sharp decline in TB notifications in 2020. Testing for rifampicin resistance was 67% among notified TB patients in India in 2020, which is a 25% decline in its notification as compared to 2019. Although the pandemic is a setback to our efforts to achieve the Sustainable Development Goals, it cannot be allowed to impede our momentum. Instead, we must use the setbacks as motivation to step up efforts by going the extra mile to #EndTB.

India's has reiterated its commitment to End TB by 2025 by launching Jan Andolan, a people's movement. WHO is proud to be associated with the Central TB Division in the Ministry of Health & Family Welfare, Government of India, to ensure early diagnosis and appropriate treatment of various forms of TB and drug-resistant TB reaches everyone who needs them.

The programme has revised its guidelines for Programmatic Management of Drug-Resistant TB (PMDT) to align it with the global evidence and WHO guidelines of 2017 and 2019. The recent Consolidated Guidelines on Tuberculosis: Module 1-4 (2020) have also been incorporated in the key recommendations. These guidelines offer technical and operational guidance to train doctors, care providers and programme managers for early and quality diagnosis and management of DR-TB.

We appreciate the Government of India for developing the ambitious National Strategic Plan (NSP) for the Elimination of Tuberculosis in India (2017-25) that embraces the investments required for the paradigm shift in policy and strategies enshrined in these guidelines. Following a political commitment by the Prime Minister of India, the budget allocation for TB was substantially increased in the NSP.

The PMDT guidelines for India is an important document that requires wide dissemination through various platforms, partners and health professionals, and training of public and private doctors being critical.

WHO is committed to providing the necessary technical guidance and assistance to the Central and State governments to translate these guidelines into quality services for patients. WHO will continue supporting evidence generation through surveillance and research for future refinement of current policies and strategies to ensure alignment with emerging global evidence.

Actions taken today must build on the principles of government stewardship, engagement of civil society, empowering patients, reaching out to the private sector, human rights and equity, and adaptation to the unique context of diverse epidemics and settings. These are the core values of sustainable development, and India has the policy support and the tools to build on the substantial gains made to #EndTB.

MESSAGE

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सत्यमेव जयते

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Nirman Bhavan, New Delhi - 110011

March 22, 2021

MESSAGE

Drug-resistant TB (DR-TB) is one of the major impediments to achieving the National Strategic Plan (NSP) goal of ending TB in India. With India's commitment to end TB by 2025, combating drug resistance TB will be essential to meet this ambitious target.

The time is right to decentralize DR-TB services with an aim to improve access, minimize the number of patient trips and maximize patient satisfaction at health centres. Early diagnosis of drug resistance among all diagnosed TB patients needs to be ensured by providing rapid molecular technology (CBNAAT and LPA) at a more decentralized level with the help of strong specimen collection and transportation system from the first point of contact where the patients choose to seek care. Similarly, treatment of DR-TB services needs to be available at least up to the district level through a team of specialists at district hospitals, medical colleges or through available partnership options backed with patient support systems.

The National Medical Commission had issued a Gazette notification in October 2020 mandating all medical colleges to establish a facility for management of DR-TB by the time of third renewal (admission of fourth batch of MBBS students). Given the availability of expertise commensurate to its strength, the same needs to be tapped for strengthening clinical, adverse drug reactions (ADRs) and co-morbidity management of DR-TB patients across India to improve the quality of care, treatment success and survival of these difficult to treat patients. This will help the programme decentralize the DR-TB services to a large extent. The Central TB Division requested the National Medical Commission to ensure the establishment of DR-TB facility in all medical colleges. The programme has also made provisions to facilitate the establishment of the DR-TB facility in all medical colleges including private medical colleges.

I am very hopeful that these guidelines will play a pivotal role in qualitatively improving the services provided to DR-TB patients in the country. This I believe is a timely intervention to ensure that we witness the end of TB from India.

(Arti Ahuja)

MESSAGE

विकास शील
संयुक्त सचिव
VIKAS SHEEL
Joint Secretary

सत्यमेव जयते

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Message

Noteworthy advances have been made in the diagnosis and treatment of drug-resistant TB under the National TB Elimination Programme. The programme has expanded both the laboratory network as well as rapid molecular diagnostic facilities to cover the entire country. For better management of DR-TB, facilities for the management of DR-TB has been decentralized at the district level. Further, to tap the expertise of clinicians in medical colleges, programme has requested the states to establish facilities to manage DR-TB patients in all the medical colleges.

In line with the global recommendations, programme introduced longer oral regimen containing newer drugs in 2019. This gave programme confidence to implement newer drug containing regimen in programmatic settings and managing the adverse events related to the drugs at decentralized level. It is evident that the injections have their own side effects and adverse events. Hence, the NTEP also targets to replace injections in the shorter MDR-TB regimen with the newer drugs. The evidences have shown that the newer drugs based regimen have 13% higher treatment success rate. The national experts have also recommended introduction of shorter oral regimen in the programme, which is more effective, safer, operationally convenient and more acceptable to patients for the treatment of MDR-TB.

This document gives technical and operational guideline for the implementation of the same. Additionally, this document describes the management of DR-TB patients who are diagnosed with additional resistance during the course of treatment, management of adverse drug reactions, adherence monitoring, importance of counselling of the patient and caregivers etc.

Private sector involvement for TB care has improved in the country in the last few years. A large number of DR-TB patients are also taking care in the private sector. This document also provides guidance to the programme managers for establishing systematic linkages with the private sector through various models for the management of the DR-TB patients seeking care in the private sector.

In light of the available evidences, this document also provides guidance on latent TB management among contacts of DR-TB patients. This will be implemented in a phased manner as per recommendations of the expert group.

(Vikas Sheel)

MESSAGE

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सत्यमेव जयते

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The emergence of resistance to drugs used to treat tuberculosis (TB), particularly multidrug-resistant TB (MDR-TB), has become a significant public health problem in several countries and an obstacle to ending TB. In India, available information from several drug resistance surveillance studies conducted in the past and the recently concluded National Drug Resistance Survey suggest that the proportion of MDR/RR-TB among TB patients is relatively low.

However, this translates into a large absolute number of patients that need to be treated with second-line anti-TB drugs. Specific measures are being taken within the National Tuberculosis Elimination Programme (NTEP) to address the DR-TB challenge through the appropriate strengthening of the health system for effective management of the disease and prevention of transmission of DR-TB.

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

The programme decided to move to case-based- real-time monitoring and reporting of DR-TB cases beginning with the 2018 cohort and will be reporting through Nikshay only. Additionally, the recording formats will be removed in hardcopy and recent developments in Nikshay has given the programme the confidence to move towards paperless recording and reporting with the deadline for the states to move to paperless by October 2021.

Patient support in terms of counselling, linking eligible patients with available services is essential for timely diagnosis and successful treatment of DR-TB patient. Additionally, all the DR-TB patients should also be linked to other support systems for drug safety monitoring and management, nutritional support, vocational rehabilitation and financial protection.

Apart from this, the approaches to active drug safety monitoring, palliative care, management of NTM and airborne infection control are also included in the guidelines. The use of information communication technology (ICT) for adherence monitoring, drug and logistics management (Nikshay-aushadhi) and also for data management and surveillance (Nikshay) is an integral part of these guidelines.

(Dr. Sudarsan Mandal)

TB Mukt Bharat!!

" It's Time To End TB" "TB Harega Desh Jeetega "

Table of Contents

Acknowledgements

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The National Technical Expert Group (NTEG) on Diagnosis and Treatment of TB recommended adoption of the WHO Consolidated Guidelines on Tuberculosis: Module 1-4 (2020) along with the introduction of shorter oral Bedaquiline-containing MDR/RR-TB regimen replacing shorter injection containing regimen for MDR/RR-TB patients, longer oral M/XDR-TB regimen, BPaL regimen in operation research mode and TB preventive treatment for the contacts of MDR-RR/TB & H mono/poly DR-TB patients. Additionally, the experts recommended the adoption of the very recent communication on changes in definition of pre-XDR-TB, XDR-TB and updated definitions on treatment outcomes (2021).

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These guidelines are consistent with the WHO Consolidated Guidelines on Tuberculosis: Module 1-4 (2020), Operational Handbook to WHO Guidelines on PMDT (2020). The technical and operational aspects listed herein are intended to complement the existing NTEP technical and operational guidelines and the National Strategic Plan for Tuberculosis (2017–25): Elimination by 2025 in India. These guidelines will now be implemented across India to gain and document experiences on feasibility, safety monitoring and enhancement in treatment outcomes of DR-TB patients to further guide the country in its refinement as national and global evidence emerges in future.

Abbreviations

AB-PMJAY	Ayushman Bharat – Pradhan Mantri Jan Arogya Yojana
ACF	active case finding
ACH	air change per hour
ADDG	Additional Deputy-Director General
ADR	adverse drug reaction
aDSM	active drug safety monitoring and management
AE	adverse event
AFB	Acid Fast Bacilli
AIC	airborne infection control
AIDS	Acquired Immune Deficiency Syndrome
AIIMS	All India Institute of Medical Sciences
AKI	acute kidney injury
ALT	alanine aminotransferase
Am	Amikacin
AMC	ADR monitoring centre
Amx/Clv	Amoxicillin/clavulanate
ART	anti-retroviral treatment
ARV	anti-retroviral
AST	Aspartate aminotransferase
ATS	American Thoracic Society
Bdq	Bedaquiline
BPaL	Bedaquiline, Pretomanid, Linezolid
BPL	below poverty line
BTS	British Thoracic Society
CAP	Conditional Access Programme
CBNAAT	Cartridge Based Nucleic Acid Amplification Test
C-DAC	Centre for Development of Advanced Computing
C&DST	Culture and Drug Susceptibility Test
Cfz	Clofazimine
CHO	Community Health Officer
CL-HIV	children living with HIV
Clr	Clarithromycin
Cm	Capreomycin
CMO	Chief Medical Officer

CMSS	Central Medical Services Society
CoE	Centre of excellence
CP	continuation phase
Cs	cycloserine
CPT	Co-trimoxazole preventive treatment
CTD	Central TB Division
CUP	Compassionate Use Programme
DAIDS	Division of AIDS
DBT	Direct Beneficiary Transfer
DCGI	Drug Controller General of India
DDG	Deputy-Director General
DDR-TBC	District DR-TB Centre
DDS	district drug store
DG	Director General
DGHS	Directorate General of Health Services
Dlm	Delamanid
DOT	Directly observed treatment
DOTS	Core approach underpinning the Stop TB Srategy for TB control
DRT	Drug-resistance testing
DR-TB	Drug-resistant tuberculosis
DR-TBC	Drug-Resistant Tuberculosis Centre
DSMC	Drug Safety Monitoring Committee
DST	Drug susceptibility testing
DT	Dispersible tablets
DT3C	Difficult-to-Treat TB Clinic
DTO	District TB Officer
DVDMS	Drug vaccine distribution management system
E	Ethambutol
ECG	electrocardiogram
ECHO	Extension of Community Health Care Outcomes
EP-TB	extra-pulmonary tuberculosis
EQA	external quality assurance
Eto	Ethionamide
EU	European Union
FDA	Food and Drug Administration
FEFO	first expiry first out
FL LPA	first line-line probe assay
FQ	Fluoroquinolone
GFATM	Global Fund for AIDS, Tuberculosis & Malaria
Gfx	Gatifloxacin

GLC	Green Light Committee
GMSD	General Medical Stores Depot
GoI	Government of India
GUV	germicidal ultraviolet
H	Isoniazid
HHC	household contact
HEPA	high-efficiency particulate air
HF	health facility
H^h	high dose isoniazid
HoD	Head of department
HRCT	high resolution CT scan
Hr-TB	Isoniazid-resistant TB
ICH	International Conference on Harmonization
ICMR	Indian Council for Medical Research
ICT	Information communication technology
IP	intensive phase
IPAQT	Initiative for promoting affordable & quality TB test
Ipm	Imipenem
IQC	Internal Quality Control
IRIS	Immune Reconstitution Inflammatory Syndrome
IRL	Intermediate reference laboratory
ISO	International Standard Organization
Km	Kanamycin
LC	liquid culture
LFT	liver function test
Lfx	Levofloxacin
LIMS	Lab Information and Management System
L J	Lowenstein Jensen
LPA	Line probe assay
LT	Laboratory technician
LTBI	latent TB infection
LTFU	lost-to-follow-up
Lzd	Linezolid
MAC	Mycobacterium avium complex
MDR-TB	Multi-drug resistant TB
MERM	Medication event reminder monitor device
Mfx	Moxifloxacin
Mfx^h	High dose moxifloxacin
MGIT	Mycobacteria growth indicator tube
MIC	Minimum Inhibitory Concentration

MIS	Management information system
MO	Medical Officer
MoHFW	Ministry of Health and Family Welfare
MOTT	Mycobacterium other than tubercle bacilli
MO-TU	Officer of TB unit (Block Medical Officer)
MoU	memorandum of understanding
Mpm	Meropenem
MR	mono resistance
MSS	monthly stock statement
MTP	medical termination of pregnancy
NAAT	Nucleic Acid Amplification Test
NABL	National accreditation board for laboratories
NDRS	National Drug Resistance Survey
NDR-TBC	Nodal DR-TB Centre
NFM	new funding model
NGO	non-government organization
NGS	Next-Generation Sequencing
NHPS	National health protection scheme
NHM	National Health Mission
NIRT	National Institute for Research in Tuberculosis
NITRD	National Institute for Tuberculosis and Respiratory Diseases
NMC	National Medical Commission
NPY	Nikshay Poshan Yojana
NRL	National reference laboratory
NSP	National strategic plan
NTEG	National Technical Expert Group
NTEP	National Tuberculosis Elimination Programme
NTI	National TB institute
NTM	Non-Tuberculous Mycobacterium
Ofx	Ofloxacin
OPD	out-patient department
PAS	p-aminosalicylic acid
PCR	Polymerase Chain Reaction
Pdx	Pyridoxine
PDR	Poly drug resistance
PFMS	Public Financial Management System
PHA	public health action
PK/PD	Pharmacokinetic/ pharmacodynamics
PLHIV	People living with HIV
PMDT	Programmatic management of drug-resistant tuberculosis

PP	private provider
PQC	product quality compliance
PSM	procurement and supply management
PT	previously treated
PTE	pre-treatment evaluation
Pto	Protionamide
PvPI	Pharmaco-vigilance programme of India
PWUD	people who use drugs
QA	quality assurance
QSE	quality system elements
QTcF	QT prolongation (Fredericia's correction)
R	Rifampicin
RBIPMT	Rajan Babu Institute for Pulmonary Medicine & Tuberculosis
RBRC	Random Blinded Rechecking
RBS	random blood sugar
RNTCP	Revised National Tuberculosis Control Programme
RR-TB	Rifampicin resistant tuberculosis
R&R	recording & reporting
S	Streptomycin
SA	Statistical Assistant
SAE	serious adverse event
SCM	supply chain management
SDG	Sustainable Development Goals
SDS	State drug store
SLD	second-line anti-TB drugs
SLDST	second-line drug susceptibility testing
SLI	second-line injectable
SL-LPA	second-line-line probe assay
SME	supervision, monitoring & evaluation
SMO	Senior Medical Officer
SoP	standard operating procedures
SPC	specimen processing control
STLS	Senior TB Laboratory Supervisor
STO	State TB Officer
STR	standardized treatment regimen
STS	Senior treatment supervisor
TALFU	treatment after lost to follow-up
TAT	turnaround time
TB	Tuberculosis
TDC	TB detection centre

TBHV	TB health visitor
TBI	Tuberculosis infection
TB-IRCU	TB Intensive respiratory care unit
Thz	Thioacetazone
ToR	terms of reference
TPT	Tuberculosis preventive treatment
Trd	Terizidone
TU	TB unit
UDST	Universal Drug Susceptibility Testing
ULN	Upper limit of normal
UPT	Urine pregnancy test
USAID	United States Agency for International Development
USFDA	United States Food & Drug Administration
WCO India	World Health Organization Country Office for India
WHO	World Health Organization
XDR-TB	Extensively-drug resistant TB
Z	Pyrazinamid

Definitions

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

Active case finding (ACF). It is defined programmatically as systematic screening for TB disease through outreach activities outside health facility settings.

Adult. For programmatic purpose in India, an adult is a person over 19 years of age.

At-risk group. Is any group of people in whom the prevalence or incidence of TB is significantly higher than in the general population.

Bacteriologically confirmed TB. TB diagnosed in a biological specimen by smear microscopy, culture or a WHO-endorsed rapid molecular test and adopted by NTEP such as Xpert MTB/RIF®/Truenat®.

Child. For programmatic purpose in India, a child is a person up to and including 18 years of age. [This includes adolescents aged 10–18 years].

Contact. Is any individual who was exposed to a person with active TB disease.

Contact investigation. Is a systematic process for identifying previously undiagnosed people with TB disease and TB infection among the contacts of an index TB patient and/or other comparable settings where transmission occurs. [Contact investigation consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB treatment (for people with confirmed TB) or TB preventive treatment (for those without TB disease)].

Close contact. This is a person who is not in the household but shares an enclosed space, such as at a social gathering, workplace or facility, for extended periods during the day with the index TB patient during the three months before commencement of the current TB treatment episode. This group will be included for all interventions as applicable for household contacts in these guidelines.

Drug susceptibility testing. DST refers to in-vitro testing using either of the phenotypic methods to determine susceptibility.

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

Extensively drug resistant TB (XDR-TB). TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone (levofloxacin or moxifloxacin) and at least one additional Group A drug (presently to either Bedaquiline or linezolid [or both])(1).

Extent or severity of disease. In patients older than 18 years, this is usually defined by the presence of cavities or bilateral disease on chest radiography or smear positivity.

In children under 18 years, severe disease is usually defined by the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression). In children, the occurrence of advanced malnutrition (defined by syndrome or by metrics) or advanced immunosuppression or positive tuberculosis (TB) bacteriology (smear, NAAT, culture) may also be considered when determining disease severity.

High TB transmission setting. This is a setting with a high frequency of individuals with undetected or undiagnosed TB disease, or where infectious TB patients are present and there is a high risk of TB transmission. [TB patients are most infectious when they are untreated or inadequately treated. Transmission will be increased by aerosol-generating procedures and by the presence of susceptible individuals. These settings with health-care workers, prisoners, miners, slum dwellers, tribals, migrant labourers etc. could be mapped out as part of the vulnerability mapping exercise done for and prioritized by states for specific TPT interventions guided by differential TB epidemiology in the respective state].

Household contact (HHC). Is a person who shared the same enclosed living space as the index TB patient for one or more nights or for frequent or extended daytime periods during the three months before the start of current TB treatment. [For simplicity, close contacts may be considered inclusive in this term throughout the guidelines].

Index patient of TB. This is the initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. [An index TB patient is the person on whom a contact investigation is centered but is not necessarily the source].

Infant. Is a child under one year (12 months) of age.

Isoniazid-resistant TB (Hr-TB). A TB patient, whose biological specimen is resistance to isoniazid and susceptibility to rifampicin has been confirmed.

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

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

People who use drugs. PWUD are those who engage in the harmful or hazardous use of psychoactive substances, which could have a negative impact on the user's health, social life, resources and legal situation.

Presumptive TB. This refers to a person with any of the symptoms or signs suggestive of TB. [Diagnosis of TB is difficult in certain key groups of the presumptive TB patients like extra- pulmonary, PLHIV, children, smear -ve /NA with x-ray suggestive of TB, other vulnerable groups as defined in TOG-2016 and DR-TB contacts, hence, NAAT is offered upfront for diagnosis of TB among these presumptive TB patients.]

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

Pre-extensively drug resistant TB (Pre-XDR-TB). TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone.(1)

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

Programmatic management of TB preventive treatment. PMTPT includes all coordinated activities by public and private health caregivers and the community aimed at scaling-up TB preventive treatment to people who need it.

Rifampicin resistant TB (RR-TB). A TB patient, whose biological specimen is resistant to R, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R, in the form of mono-resistance, poly-resistance, MDR or XDR.

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

Systematic screening for TB disease. Is a systematic identification of people with presumed TB disease, in a predetermined target population, using tests, examinations or other procedures that can be applied rapidly. [Among those screened positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments, which together have high accuracy.]

Tuberculosis (TB). Is the disease that occurs in someone infected with M. tuberculosis. [It is characterized by signs or symptoms of TB disease, or both, and is distinct from TB infection, which occurs without signs or symptoms of TB. In this document, it is commonly referred to as “active” TB or TB “disease” to distinguish it from TB infection.]

Tuberculosis infection (TBI). Is a state of persistent immune response to stimulation by M. tuberculosis antigens with no evidence of clinically manifest TB disease. [There is no gold standard test for direct identification of M. tuberculosis infection in humans. Most infected people have no signs or symptoms of TB but are at risk for developing TB disease. TB infection is also known as “latent TB infection” (LTBI), although this term is being discarded given that infection cannot always be considered latent.]

Tuberculosis preventive treatment (TPT). Treatment offered to individuals who are considered to be at risk of developing TB disease, in order to reduce that risk. [Also referred to as treatment of TB infection.]

Universal DST. Refers to universal access to rapid DST for at least rifampicin, and further DST for at least fluoroquinolones among all TB patients with rifampicin resistance (preferably before initiation of treatment to maximum within 15 days of diagnosis) (2).

Underweight. In adults and adolescents, underweight usually refers to a body mass index <18.5 kg/m2 and in children < 10 years to a weight-for-age < –2 z-scores.

CHAPTER 1

BACKGROUND AND FRAMEWORK FOR EFFECTIVE IMPLEMENTATION OF DRUG-RESISTANT TUBERCULOSIS SERVICES

Learning objectives

In this chapter, we will learn about:

- Global and national magnitude of drug resistant tuberculosis (DR-TB) problem.
- Status of DR-TB services and treatment outcomes in India.
- National strategic plan 2017-25 (pertaining to DR-TB).
- Causes and prevention of DR-TB.
- Broad overview of the updated strategies and activities for implementation of DR-TB services.

Programmatic management of drug resistant TB (PMDT) is complex and requires a perfect blend of clinical and programmatic interventions. India has gathered experience of nearly two decades in planning and implementation diagnosis and clinical management of DR-TB.

1.1. Global and national magnitude of DR-TB problem

- Recent global estimates indicate that about a half million new cases of rifampicin resistant TB (RR-TB) occurred in 2019 with 78% of them having confirmed MDR-TB (3).
- Estimated number of MDR/RR-TB cases in India is 124 000 (9.1/lakh population) (3).
- The first national anti-tuberculosis drug resistance survey (NDRS) revealed that 28% of TB patients were resistant to any drugs (22% among new and 36.82% among previously treated) and 6.19% had MDR-TB (2.84% among new and 11.62% among previously treated [PT]) (4).
- Further, any Isoniazid (H) resistance (16% in all with 11.6% in new and 25% in PT) being driver for RR-TB.

1.2. Status of drug-resistant TB services in India

- PMDT services were rolled out in 2007 and complete geographic coverage achieved by 2013 *(5)*.
- Services were expanded in terms of eligibility for testing RR to all diagnosed TB patients (2017).
- Massive expansion undertaken of diagnostic network of C&DST (81), CBNAAT (1268), Truenat (1879) and LPA (FL-67, SL-57) laboratories, availability of new drugs (Bedaquiline [Bdq], delamanid [Dlm]) and decentralized treatment services by creation of nodal (173) and district (620) DR-TB centers (N/DDR-TBC).

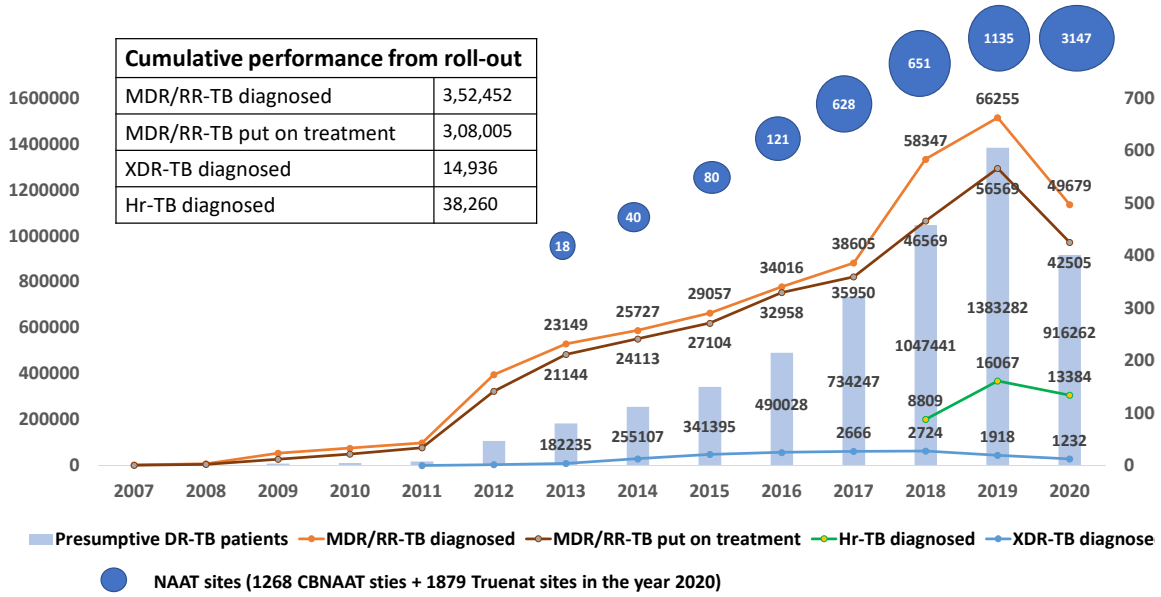


Figure 1.1 Expansion of PMDT services in India and performance since roll out

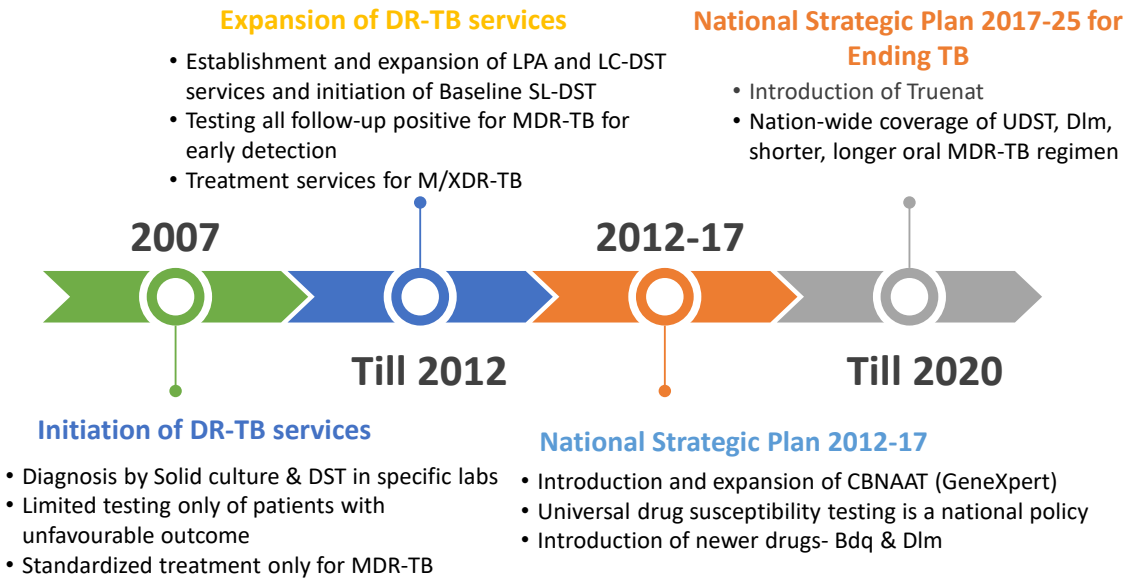


Figure 1.2 Milestones in evolution of PMDT in India

- Improved drug logistic management facilitated expansion of services **(Figure 1.1 and 1.2).**
- Till 2020 December, 96 913 patients were put on shorter MDR-TB regimen with injectable second-line drugs (SLD).
- Success rate of patients treated with this shorter MDR-TB regimen with injectable in 2018 was 60%. Preliminary success rates were reported up to 57% in 2019 **(Figure 1.3).**
- Male gender, age above 60 years, pulmonary disease, HIV positivity, delay in initiation of treatment (> 15 days), resistance to additional drugs were some of the important reasons for unfavourable treatment outcomes of shorter MDR-TB regimen.

Figure 1.3: Treatment success rate of M/XDR-TB patients on different regimens

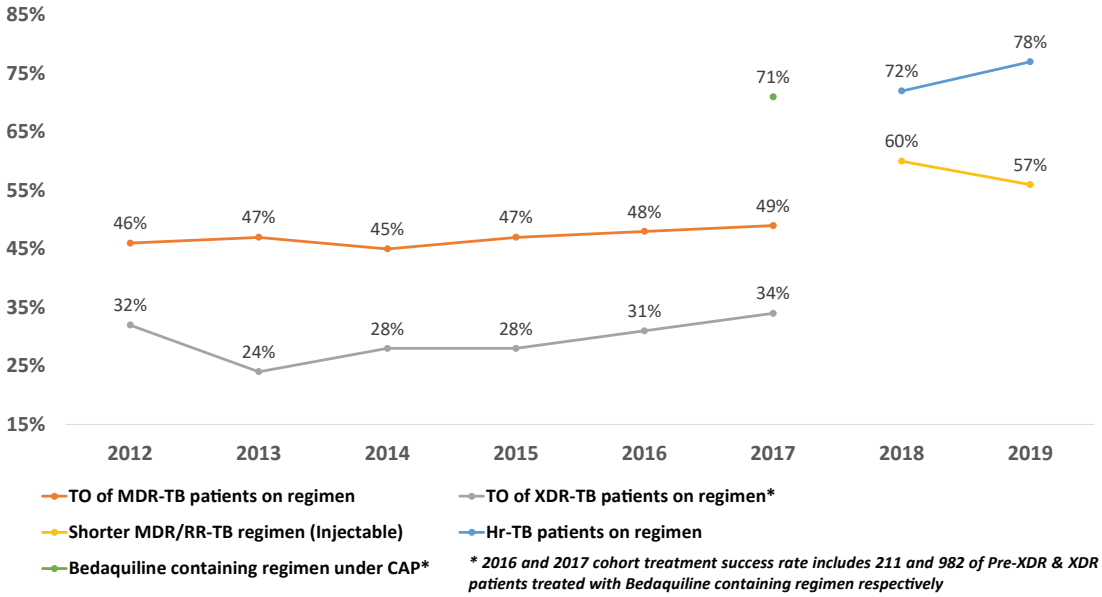


Figure 1.3 Treatment success rate of M/XDR-TB patients on different regimens

- Average success rate of conventional regimen of MDR-TB from 2014 to 2017 was 49% *(5) (6)(7).*

Till 2020, as many as 22 729 and 652 patients were put on Bdq and Dlm containing regimen respectively. Success rate of patients (extensively drug resistant [XDR] & MDR/RR-TB with additional resistance to fluroquinolones (FQ) or injectable (SLDs) treated under Bdq conditional access programme (Bdq-Cap) was 71% (2016–17 cohort).

- Average success rate of conventional XDR-TB patients put on treatment (without Bdq) from 2016 to 2018 is 29%. This increased to 34% in 2017 *(2) (3) (4).*
- Success rate of 78% is reported for H mono/poly DR-TB regimen registered in 2019 *(6).* Female gender, younger age (18-35 years) and extra-pulmonary TB (EP-TB) have been significantly associated with favourable treatment outcomes of H mono/poly DR-TB.

National Strategic Plan 2017–25

In order to expedite the interventions for achieving sustainable development targets by 2025, Central TB Division (CTD), GoI has prepared National Strategic Plan (NSP) 2017–25. Management of DR-TB is a vital component in all strategic areas of prevent, detect, treat & build.

Prevent. Ensuring airborne infection control at facility, household and community level and access to effective TB preventive treatment (TPT) and programmatic management of TPT is part of the strategy to prevent DR-TB. Guidelines of TPT for contacts of MDR-TB enumerated in this guideline are part of the NSP 2017–25.

Detect. Undertaking early identification of presumptive TB & diagnosis by highly sensitive diagnostic tools for TB & DR-TB are components of strategies to detect DR-TB.

Treat. The strategic area of treatment includes expanded treatment and management of DR-TB in line with guidelines of shorter oral Bedaquiline-containing MDR/RR-TB regimen.

Build. Ensuring adequate funding, human resources, community engagement, use of ICT for treatment support, promoting TB research, strengthening drug logistic management are some of the important components of NSP to build systems for PMDT. The PMDT 2020 guidelines follow the principles enumerated in NSP 2017–25 which are in line with the direction for Ending TB in India by 2025.

1.3. Causes of drug resistance

- From bacteriological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli.
- In clinical settings, an inadequate or poorly administered treatment regimen allows drug resistant mutants to become the dominant strain.
- Clinical characteristics of patients have also been recognized where appropriately administered drugs have not achieved necessary drug levels to deal with all population of mycobacteria.
- From a programmatic perspective, weak TB services lead to delay in detection and effective treatment of drug resistance.

1.4. Prevention of drug resistance

- Drug resistance cannot be addressed by mere diagnosis and treatment of DR-TB.
- Basic TB diagnostic and treatment services should receive priority.
- Systems for early detection and treatment of DR-TB should be integrated into existing TB services and the general health system.
- Health-care facilities and congregate settings should be provided with proper infection control measures.
- Transmission should be prevented by addressing non-specific determinants like access to care, comorbidities and awareness.

1.5. TB preventive treatment

There is an exclusive chapter that describes the eligibility criteria, regimen, monitoring & operational aspects of implementation of preventive treatment for contacts of MDR-TB and the same is included in this guideline. This policy has major impact implication in preventing transmission of DR-TB in the community.

1.6. Improved case finding

- Universal drug susceptibility testing (UDST) is to be provided for rapid detection of R and further detection of FQ among RR-TB.
- Diagnostic algorithm provides an opportunity for upfront NAAT testing for certain types of presumptive TB (such as PLHIV, presumptive EP-TB cases, presumptive pediatric TB, contacts, smear-ve X-ray suggestive of TB and other vulnerable groups).
- Expansion of NAAT provides opportunity of upfront NAAT for all presumptive TB.
- Additional DST technologies in the development pipeline including Xpert XDR cartridges for CBNAAT will be made available as they are endorsed for use by WHO/GoI.

1.7. Treatment of DR-TB

- Patients with drug resistant TB are managed with the support of a nation-wide network of DR-TB centres, NTEP staff, general health system staff, community volunteers and the private health facilities.
- Treatment follows a pre-treatment evaluation to identify potential risk factors.
- The DST results, history of previous treatment and adverse reaction to drugs are taken into account to further guide the selection of the regimen.
- Treatment may be initiated in the ward or on an out-patient basis depending on the clinical conditions, access to services and patient preferences.

1.8. Newer treatment regimen

- NTEP provides simplified regimen for various types of DR-TB including shorter oral Bedaquiline-containing MDR/RR-TB regimen and longer oral M/XDR-TB regimen based on DST/DRT results with scope in difficult patients to extend Bdq beyond 6 months, combined use of Bdq and Dlm and Bdq use in pregnancy.
- As the fully oral regimens get scaled up nationwide, the current shorter MDR-TB regimen with injectable SLDs will be phased out.
- Injectable SLDs will be available for use under PMDT to substitute oral SLDs based on DST and ADR.
- Guidance is also provided for using Bdq for children above 5 years and Dlm for children above 6 years.
- Use of BPaL regimen consisting of Bdq, pretomanid (Pa) & linezolid (Lzd) are ongoing in select group of patients on a research mode.

1.9. Sustaining and improving the quality of DR-TB care

- PMDT ensures decentralized management of DR-TB patients.
- Availability of in-patient care, drugs and mentoring/guidance have been ensured for N/DDR-TBC.
- All treatment regimen including shorter oral Bedaquiline-containing MDR/RR-TB regimen and longer oral M/XDR-TB regimen are to be initiated from DDR-TBC, preferably ambulatory.
- H mono/poly DR-TB treatment to be initiated at HF level.
- To further improve the quality of care offered by the DR-TB centres, difficult-to-treat TB clinics (DT3C) are established at state and national levels.

1.10. Patient-centric care

- Successful treatment and care can only result when patients' preferences, values and needs are satisfactorily addressed along with clinical care.
- The diagnosis of DR-TB should be early, accurate and affordable and the treatment is to be delivered in a manner that is easily accessible, affordable and acceptable to the patients.
- Confidentiality and dignity of patient should be protected.
- Prevention, management and mitigation of stigma and discrimination are essential elements of a patient centric care.

1.11. Customized treatment supervision & patient support

- Direct observation of treatment (DOT) including family DOT remains the pillar for treatment support.
- With development of information communication technology and ready insight offered by artificial intelligence (AI), real-time monitoring of treatment adherence without affecting confidentiality of patients can be ensured *(7).*
- Medication Event Reminder Monitor (MERM) is an ICT enabled treatment adherence mechanism.
- The adherence calendar will be linked to Nikshay. Provision of dashboards in Nikshay enabling real-time customized access to DR-TB data enables efficient and effective monitoring of DR-TB services.

POINTS TO REMEMBER

- ✓ Estimated number of MDR/RR-TB cases in India is 124 000 (9.1/lakh population). The first NDRS revealed that 28% of TB patients were resistant to any drugs (22% among new and 36.82% among previously treated) and 6.19% had MDR-TB (2.84% among new and 11.62% among PT).
- ✓ PMDT services were rolled-out in 2007 and complete geographic coverage achieved by 2013. Massive expansion of diagnostic network of laboratories, availability of new drugs, shorter regimen, decentralized treatment services, improved drug logistics management facilitated expansion of services.
- ✓ In recent years, treatment success rates with Bdq containing regimen, shorter MDR-TB regimen with injectables and H mono/poly DR-TB regimen have improved compared to the prior longer M/XDR-TB regimen (DST guided regimen).
- ✓ In order to expedite the interventions for achieving sustainable development targets by 2025, CTD, GoI has prepared NSP 2017–25 through Prevent-Detect-Treat-Build strategies.
- ✓ To further improve access, treatment success and quality of care of DR-TB patients, a number of new interventions are introduced through these updated guidelines for patient centric care including DR-TB treatment centres at every medical college, DT3Cs, updated algorithms with patient turnaround timelines, shorter oral Bedaquiline-containing MDR/RR-TB regimen, longer oral M/XDR-TB regimen with limited scope extending Bdq, combined use with Dlm, Bdq in pregnancy and children from 5 years and above, BPaL in research mode, preventive treatment for contacts of DR-TB patients private sector engagement, simplified supply chain management, transition to Nikshay-based digital recording, reporting and monitoring systems.

CHAPTER 2

STRUCTURE & RESPONSIBILITIES

Learning objectives

In this chapter, we will learn about:

- Establishments under NTEP for providing DR-TB services.
- Decentralized DR-TB management through N/DDR-TBC.
- Role of various stakeholders including private sector in management of DR-TB and mechanism for collaboration between public and private sector.
- Mechanism under NTEP for capacity building/ mentoring the health staff.
- Institutionalization of 'Difficult-to-Treat-TB clinic' at national and state level.

2.1. Cascade of DR-TB services and functions of stakeholders

With service expansion of rapid molecular testing (Nucleic Acid Amplification Test [NAAT]) in all presumptive TB patients for early detection of TB and DR-TB as well as decentralized management of DR-TB patients and treatment adherence, the role of monitoring all stakeholders, especially general health system staff is of critical importance. Flow diagram in **Figure 2.1** presents specific functions of various stakeholders in the DR-TB service cascade.

Presumptive TB/ DR-TB is identified by the health facility doctor during passive screening or by health staff/ community volunteer during active case finding (ACF). Quality in screening and identification of presumptive TB/DR-TB is crucial. Prompt referral and sample collection is an important step after identification of presumptive TB/ DR-TB. Capacity building with respect to the processes of collection, storage and transport of specimen are equally important. Availability of logistics in adequate quantity and appropriate quality is to be ensured for 50 ml conical tube, sample packaging material, referral slip and TB bacteriology request form. Timely and correct testing of sample by the laboratory technician (LT) and prompt recording of results in Nikshay is also critical. Conveying results to patients by NTEP supervisor/HF staff to patients along with initial counselling goes a long way in prompt initiation of treatment.

Referrals should be made promptly by the CHO at HWC/ STS/ TBHV to the health facility or N/DDR-TBC for pre-treatment evaluation and treatment initiation. Provision of treatment enablers/incentives like disbursement of travel expenses and benefits of Nikshay Poshan Yojana is to be ensured. Availability of facility of free pre-treatment evaluation and initiation of treatment is mandatory. Referral linkages for further domiciliary treatment is to be ensured by health facility doctor, N/DDR-TBC, senior DR-TB TB-HIV supervisor, STS, TBHV, CHO and general health staff. Identification of suitable treatment supporter by CHO/ STS/ TBHV is underlined. Periodic follow-up of clinical/ bacteriological examination is to be managed.

Implementation of activities at various levels and coordination amongst providers can ensure quality service delivery.

2.2. Coordination

In view of the involvement of a diverse set of activities in the DR-TB care cascade, coordination of activities at all levels is critical. Coordination needs to include the contribution of all key stakeholders, organizations and external partners, as outlined below:

2.2.1. Central TB division

The Central TB Division (CTD) is the central coordinating body for activities described in the framework. The responsibility of CTD extends to commitment of necessary resources, particularly towards a strong central management team, ensures all elements are in place, from the procurement of second-line anti-TB drugs to appropriate implementation and monitoring of PMDT services. As needed, partnerships with all relevant health-care providers needs to be built. The CTD is supported by National Technical Expert Groups, comprising members from national institutions such as the National Institute for Research in Tuberculosis (NIRT), National Institute for Tuberculosis and Respiratory Diseases (NITRD) and the National Tuberculosis Institute (NTI); eminent faculties from medical colleges and the WHO *(8).*

2.2.2 Local health system

DR-TB activities will be tailored to fit into the respective state and district level infrastructure. The exact organizational structure of PMDT services may vary between different settings and depending on how local health-care is provided. Transfer between hospitals to outpatient settings or between treatment centres requires great care, planning and effective communication. Given the type of care required in the treatment of DR-TB, a team of health workers including physicians, nurses and social workers (wherever available) should be used. Resources of private sector will be utilized in mutually beneficial terms. Various mechanisms like TB forums/co-morbidity committees/ PMDT committees may need to include the DR-TB component for review and action.

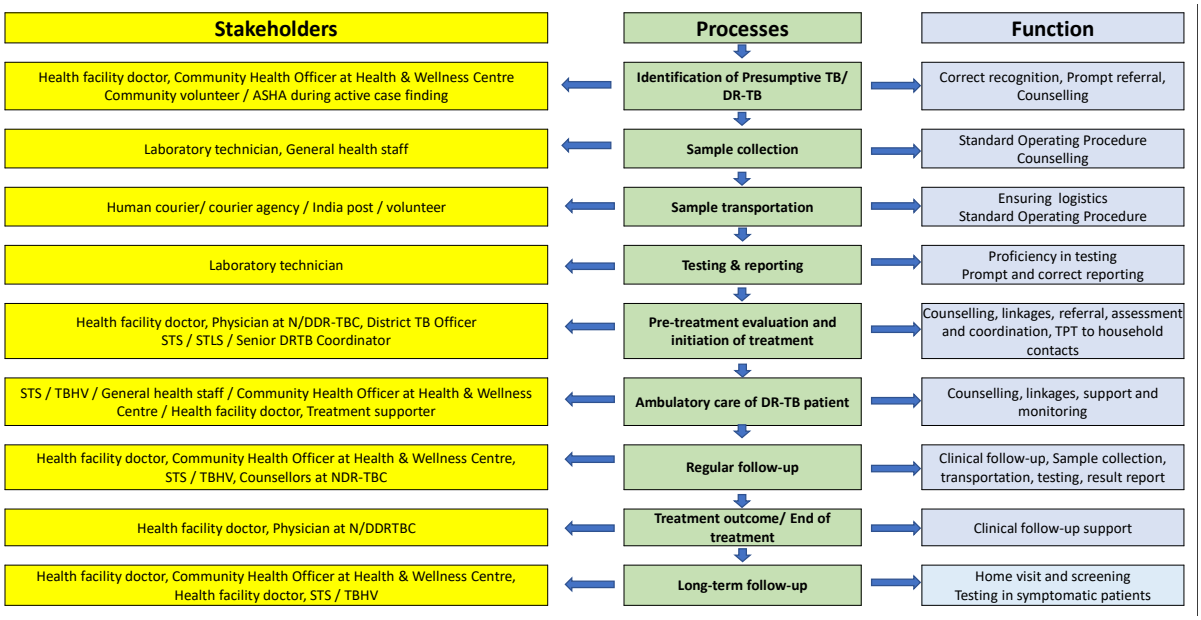


Figure 2.1 Cascade of DR-TB services and functions of various stakeholders

2.2.3. Community-level

Community involvement and communication with community leaders can greatly facilitate implementation of PMDT and may respond to behavioural, social aspects of drug-resistant tuberculosis. Community education, involvement and organization around TB issues can encourage a feeling of community ownership of TB programmes and reduce stigma. In some circumstances, communities can help address the patient's interim needs including provision of treatment support, food and/or housing, vocational support etc. Services from cured TB patients as TB champions is well recommended.

2.3. Mechanism for effective service delivery through the public health system

Involvement of general health staff- DR-TB management had been challenging in view of clinical complexity and diverse programme management requirements. Involvement of general health staff that includes the auxiliary nurse midwife (ANM), multi-purpose worker (MPW), LT, pharmacist, HF doctor, Block Medical Officer [MO-TU], CHO etc) is extremely important. The organizational structure and ToRs are depicted in **Table 2.1** and roles of various levels under PMDT highlighted in **Figure 2.2.**

Table 2.1: Organizational structure and terms of reference (ToR)

Level	Organizational structure	ToRs
National-level	Central TB Division (CTD), MoHFW, GOI	Providing resources/ devising policies/ issuing guidelines Monitoring and evaluation
	National Technical Expert Group	Reviewing evidence Recommendation in guidelines
State-level	State TB Cell, Health Department	Providing resources, implementing guidelines, monitoring and evaluation
	State PMDT Committee	Planning implementation as per guideline Review the progress in implementation Feedback/suggestion to NTEG
District-level	Chief Medical Officer/ Chief District Health Officer District TB 0fficer	Implementing guidelines Monitoring and evaluation Demonstration of best practices
	District TB Forum	Facilitate and monitor involvement of communities
	District Co-morbidity Committee	Review and rectify TB-comorbidity components with regard to HIV, diabetes, addiction and other review coordination with other health programmes like Rashtriya Bal Swasthya Karyakram (RBSK), Rashtriya Kishor Swasthya Karyakram (RKSK), Reproductive Maternal Newborn Child plus Adolescent Health (RMNCH+A) etc.
Block-level/ Ward-level	Block Medical Officer STS / STLS / TBHV	Implementation of guidelines Monitoring and evaluation Feedback
Health facility-level	Health facility doctor, MPHS, MPHW, ASHA	Implementation and review

Level	Organizational structure	ToRs
Health & Wellness Centre, Sub-centre	Community Health Officer	TB screening and community intervention Coordination amongst various health programmes for TB related activities
Community	ASHA PRI Anganwadi workers (AWW) Other volunteers Community leaders	Implementation Community engagement through Panchayati Raj Institutions (PRI) Village Health and Nutrition Day (VHND) Community meetings Peer educators/TB champions/adolescent groups Anganwadi sessions

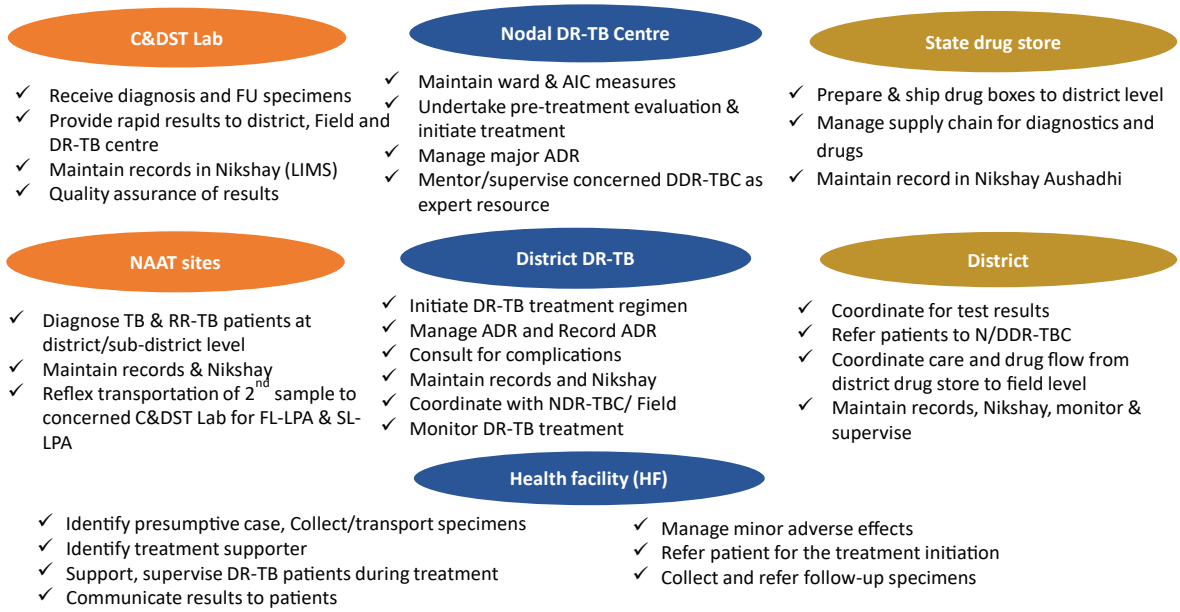


Figure 2.2 PMDT structure and roles

2.4. Decentralized management of DR-TB

Decentralized DR-TB diagnosis and treatment is crucial to ensure early diagnosis and prompt treatment of DR-TB patients.

- NTEP has established a network of NAAT sites at least at district level. States/districts may procure additional NAAT machines as per need from their resources. N/DDR-TBC have been initiated at district level.
- C&DST labs are established by under NHM or external aid support.
- States may procure diagnostic services like NAAT, LPA, liquid C&DST from the private sector as per their need and Guidance Document on Partnerships 2019. The resources for these may be budgeted in NHM PIP, where required.
- N/DDR-TBC can be established in the public sector where appropriate facilities are available. The DR-TB centre can also be established in the private sector on mutually agreeable terms & conditions based on the Guidance Document on Partnerships 2019.

2.4.1. Process of establishing nodal and district DR-TB centres

NDR-TBC is established to manage all forms of DR-TB, including the complex form of DR-TB. The nodal DR-TB centre is established as per need and is generally in a tertiary care setting where expertise and facilities for management of DR-TB are available. The nodal DR-TB centre can initiate all types of treatment regimen of DR-TB.

DDR-TBC can be established at district or sub-district level. It may be established in institutes like medical colleges, district hospitals, TB hospitals and private or corporate institutes, Trust hospitals or other sector hospitals with the availability of required clinical expertise. There should be at least one DDR-TBC available in all the districts. However, more than one DDR-TBC can be established to improve access and preference of patients to seek care. DDR-TBC can be established on outpatient department (OPD) basis as well. DDR-TBC can initiate H mono/poly DR-TB, shorter oral Bedaquiline-containing MDR/RR-TB regimen or longer oral M/XDR-TB regimen provided the centre does have expertise for the same. Checklist to guide preparation of DDR-TBC to be able to initiate newer drug containing regimen is enclosed as **Annexure 1**. CTD should be informed above upgradation of any institute as DR-TBC. Requirements for infrastructure and HR may be proposed in annual PIP.

2.4.1.1. N/DDR-TBC Committee

N/DDR-TBC Committee is a clinical committee where the Dean/ Principal/ Director is chairperson and Head of the Department (HoD) or a senior faculty member from the department of Pulmonary Medicine/ General Medicine is the nodal officer. HoDs or senior faculty members of other specialties are members. Clinical function of these committees must be adequately supported by the administrative or management committees of the institution in which the STO/ State representative or District representative is an ex-officio member. Composition and ToR of N/DDR-TBC committee are detailed in **Annexure 2.**

Whenever any child with any form of DR-TB needs to be admitted for pre-treatment evaluation and management, the child may be managed in the DR-TB wards. In addition, all DR-TBCs must proactively engage available pediatricians (in-house/ honorary) in the DR-TBC committee for the management of pediatric DR-TB patients.

2.4.1.2. Mandatory establishment of DR-TB centres in all medical colleges

National Medical Commission (NMC) issued a Gazette notification in October 2020 mandating all medical colleges to establish a facility for management of DR-TB by the time of 3rd renewal (admission of 4th batch of MBBS students) *(9)*. In view of availability of expertise in medical colleges, there is a felt need to leverage on their strength to improve clinical, adverse drug reactions (ADRs) and comorbidity management of DR-TB patients across India for enhancing quality of care, treatment success and survival of these difficult to treat patients.

Table 2.2: Provisions under NTEP for establishing DR-TB facilities in medical colleges

Establishment	Provisions under NTEP for DR-TB facilities in medical colleges
Infrastructure development	Normative amount as per "Norms and basis of costing" for NTEP. Unit cost for initial establishment/ refurbishment/ upgradation/ maintenance of civil work to be carried out as per rates prescribed by PWD or cell/division/corporation/wing for infrastructure development
Human resource	All medical colleges have the provision of MO-medical college (1); TBHV (1); LT for TB detection centre (TDC) (1)

Establishment	Provisions under NTEP for DR-TB facilities in medical colleges
Diagnosis (referral/ linkages)	Provision of linkages and consumables required for specimen collection and transportation to offer the tests as per the integrated DR-TB algorithm
Capacity building	Training to build capacity of service providers on NTEP guidelines on management of DR-TB and Nikshay Refresher trainings can be organized as per requirement
Drugs and logistics	Supply of diagnostic logistics- sputum cups, 50 ml conical tubes, sample packaging materials, cartridges/chips if NAAT available etc Stock of FL and SL drugs including drugs for prophylaxis Support for ancillary drugs by linkages with General Health System
Patient support	Identification of convenient treatment supporter for the patients to ensure treatment adherence at field level. Incentives under NPY to patients notified/ initiated on treatment
Support for recording and reporting	Provision of recording and reporting formats and registers and access to Nikshay
Financial support	Provision of timely payments to the service provider, if any identified as per the partnership options

Private and NGO hospitals are considered to serve as N/DDR-TBC at places where there is a need in the form of additional workload, non-availability of appropriate public facility, preference of patients in area etc. Terms and conditions for establishing that centre may be arrived at local level as per prevailing market rates in concurrence of state/ district health society of National Health Mission (NHM). Expertise of private health-care provider/ specialist can also be availed for DR-TBCs established in the public health facility as per need and mutually agreeable terms & conditions. Details about mechanism of engagement in the private sector for establishment of DR-TBC can be referred to in the Guidance Document of Partnerships 2019.

2.4.1.3. Requirements from institution for establishing N/DDR-TBC

- It should preferably be a tertiary/secondary care institute.
- All investigations under pre-treatment evaluation (PTE) & other PMDT services should be provided free of cost to the patient. If not available in the public sector, the service may be procured from private sector under NHM.
- Separate wards for male and female patients (including children) should be available with at least 10 beds in each for NDR-TBC while at least 2 beds in each for DDR-TBC (if indoor facility is being established).
- An outpatient clinic and a separated well-ventilated waiting area in an open-air and shaded area to be made available as per the Airborne Infection Control (AIC) guidelines.
- Administrative, environmental and personal protective measures for airborne infection control to be in placed in all indoor and outdoor facilities.
- N/DDR-TBC committee to be formally established with required set of experts as per **Annexure 2.**
- Relevant specialties like physician (nodal officer), psychiatrist, dermatologist, ENT specialist, nutritionist, anesthesiologist or palliative/end-of-life-care specialist, pediatrician, cardiologist/physician and gynecologist etc. to be made available and supported by the NDR-TBC committee. This can be regular or through honorary visits mainly to provide

specialist consultations. Services of specialists if not available in the public facility may be hired from the private sector under partnership options.

- Availability of oxygen and ventilators for patients needing critical care support.
- All experts at DR-TB centre must be trained in the latest PMDT guidelines.
- Ancillary drugs to be provided for management of ADRs as per N/DDR-TBC committee`s advice at no cost to patients.
- Doctors, nursing and support staff should be available from the institute.
- Records and reports to be maintained for PMDT.
- Nikshay entries to be done on real-time basis with regular electronic updates; and
- Financial requirements to be availed through institute/ state budgets or under NHM.

2.4.1.4. Provision under NTEP

- Existing MO-DTC (second MO of DTC) or MO-medical college will provide support to the physician in-charge serving as nodal officer of the DDR-TBC.
- Remuneration of Senior Medical Officer (SMO), Statistical Assistant (SA) and counsellor may be made available for NDR-TBC provided it is approved in the PIP.
- Senior DR-TB TB-HIV supervisor to maintain all records and reports including Nikshay entry and coordination with all health facilities and TB unit staff for DDR-TBC while SA of NDR-TBC to maintain the same NDR-TBC.
- Training concerned staff and monitoring of real-time recording and reporting in Nikshay and providing computer/ internet facility and Nikshay login ID for the institute.
- Ensuring availability of logistics, including 12 lead automated ECG machines as per specifications given in **Annexure 3** and drugs.

2.4.1.5. Functions of the N/DDR-TBC

The package of services at these N/DDR-TBCs includes:

- **Pre-treatment evaluation (PTE).** All investigations (detailed in the relevant section) would be done at no cost to patients. If there are some investigations which are not available within the public sector, then adequate linkages will be established with the private laboratories with proper memorandum of understanding (MoU) mechanism as per options available under Guidance Document on Partnerships 2019.
- **Providing counselling to patient and family members.** Counsellor/staff at N/DDR-TBC will provide counselling and health education which is an essential part of the social support to the DR-TB patient and her/his family members about the disease; necessity of taking regular and adequate treatment; possible adverse events and mechanisms of TB transmission; prevention and mitigation of stigma and discrimination; nutritional counselling and assistance to avail social support and social protection schemes.
- **Treatment initiation of DR-TB patients.** Treatment initiation based on results of quality ensured rapid molecular testing with NAAT or LPA will be done by N/DDR-TBC committee. Treatment of the patient can be initiated by the nodal person of N/DDR-TBC with timely post facto referral/ approval of other committee members after pretreatment evaluation of the patient is completed. Treatment regimen change if required may be done by N/DDR-TBC.
- **Follow-up monitoring.** N/DDR-TBC committee would ensure timely follow-up for all DR-TB patients initiated on treatment as per the follow-up schedule for clinical, biochemical and culture including audiometry, mental health monitoring and electrocardiogram (ECG)

monitoring for QTC interval as applicable (details of follow-up schedule are given in relevant sections).

- **Management and monitoring of adverse drug events.** N/DDR-TBC staff in supervision of nodal officer will observe, monitor, manage and document all the adverse events routinely and the doctor will report them as per the aDSM framework. If required, the patients may be referred to the NDR-TBC for the management of the serious ADRs after providing initial management.
- **Recording and reporting.** Records of individual activity will be entered by staff of corresponding facility in Nikshay. Overall responsibility of ensuring completion of real-time updating of Nikshay lies with the District TB officer (DTO). Private facilities enrolled under partnership options (lab, DR-TB centre etc.) are expected to complete recording/ reporting as per guidelines. Cost of recording/ reporting if any, may be built by private facilities in costing of services under partnership options.
- **Airborne infection control measures.** These would be implemented as per Guidelines on AIC in health-care and other settings. During routine household visits, patient and family members will be advised on measures needed for infection control by the concerned health staff **(Annexure 4).**
- **Nutritional assessment.** Nutritional assessment will be undertaken for all patients and the corresponding nutritional advice and support will be provided, according to guidelines for nutritional assessment and support for TB patients in India.
- **Mental health.** Assessment of mental health is essential in all patients at the time of diagnosis and regular monitoring of all patients.
- **Pediatric patients.** Facilities for managing DR-TB among children of all ages must be integrated with N/DDR-TBC. Engagement with a pediatrician is highly desirable.
- **TB intensive respiratory care unit (TB-IRCU).** Availability/linkage of TB IRCU care needs to be ensured in NDR-TBC. Resources required for the same may be proposed through annual PIP. Equipment like ventilators, systems like central oxygen etc. may either be made available from local institutions/ state budgets or under NHM.
- **Palliative care.** Palliative/ end-of-life care with priority for patients with M/XDR-TB patients with poor prognosis will be provided. In addition, guidance will be shared by NDR-TBC to the DDR-TBC and concerned health staff for palliative care at community level.

2.5. Centre of Excellence (CoE)

In order to enhance quality of PMDT services, NTEP intends to upgrade some of the existing NDR-TBC established in premier institutes as CoE. The CoEs apart from providing high-end clinical services may work for providing guidance and mentoring to institutions with a view to offer standards of excellence across every state. Some of the high-end clinical services envisaged under CoE are surgical interventions, palliative care, pulmonary rehabilitation etc. Necessary additional support for infrastructure upgradation/equipment/ human resources for provision of these services may be provided by NTEP through PIP mechanisms. In order to fulfil the unmet need of qualified expert clinicians in the field of DR-TB, CoEs are encouraged to institute certificate/ diploma courses for medical professionals in TB care. Guidance on curriculum, enrolment, assessment etc. would be provided by NTEP. The CoEs are also expected to support programmatic components like operational research, monitoring and evaluation, analytical excellence, social determinants, advocacy strategies etc.

NTEP has established few pediatric CoEs to cater to the needs of pediatric TB patients. Necessary requirements for pediatric CoE in terms of diagnostics, treatment, capacity building and research are envisioned to be made available through pediatric CoE. All NDR-TBCs are expected to be upgraded as CoEs in due course of time.

2.6. DR-TB services for patients seeking care in the private sector

NTEP recognizes the fact that significant number of patients are seeking health services from the large private/other sector, with unknown quality of diagnosis and treatment and huge costs involved. Reaching out to these patients is equally important, especially to deliver essential public health services to prevent the spread of disease and emergence of drug-resistance, to support TB patients on treatment and address comorbidities to ensure successful treatment outcomes. Patients seeking care in private/other sectors are equally eligible for diagnostics, drugs and all supportive services offered to patients seeking care in the public sector.

A strong and sustainable partnership between NTEP and providers is necessary to establish linkages to ensure availability of all services for any DR-TB patient irrespective of where the patient chooses to seek care. One of the options for such linkages available within NTEP currently is the Guidance Document on Partnership 2019 *(10)*. The Guideline provides options for purchasing services for diagnosis, specimen transportation, DR-TBCs and treatment support to all type of TB patients. It also provides an opportunity of constructing option as per felt need.

Involvement of professional associations and corporate hospitals/chain hospitals either based on Guidance document of partnerships/PM-JAY/corporate social responsibility (CSR) etc. is recommended to ensure participation of private sector commensurate to need. Further details are included in **Chapter 7**.

2.7. Ayushman Bharat - Pradhan Mantri Jan Arogya Yojana (AB-PMJAY)

AB-PMJAY is a flagship scheme of the GoI to achieve universal health coverage. AB-PMJAY is the largest health assurance scheme in the world which aims at providing a health cover of Rs. 5 lakhs per family per year for secondary and tertiary care hospitalization to over 10.74 crores poor and vulnerable families. Linking eligible DR-TB patients who require indoor care with PM-JAY is important to ensure free indoor care to admitted DR-TB patients in public sector/ private sector. Recognizing hospitals empanelled in PM-JAY as DR-TB centre can be game changer for DR-TB patients who may need hospitalization. Effort to link DR-TB care to health assurance scheme of PM-JAY will go long way in ensuring zero catastrophic cost to DR-TB patients. States may need to establish coordination mechanism for the same. (http://pmjay.gov.in)

2.8. Difficult-to- Treat TB Clinic (DT3C)

In view of clinical/ programmatic complexity associated with DR-TB management, handholding and mentoring of DDR-TBC in effective management of DR-TB cases is extremely important. Decentralization of treatment services can be ensured only if DDR-TBCs are equipped and supported to deal with nuances of DR-TB patient management. DT3C is an initiative to support DR-TBCs in appropriate patient management. It is functional at national level by collaboration of NITRD-CTD-NTF and expected to be established at state level or NDR-TBC level (in larger states). Experts involving various specialty are included in team as mentors. Information/

query regarding the patient is shared in standardized format by DDR-TBC beforehand to facilitate discussions through state nodal officer.

National level DT3C clinic is established which mentors state DT3C experts. This three-tier structure is intended to improve quality of DR-TB care. All states should have at least one (more than one in larger states) DT3C established **(Annexure 5).** Expenses for establishing/ running DT3C clinic if any may be proposed through annual PIP.

2.9. Capacity building

In view of complexity of clinical and programme management components and involvement of various stakeholders in PMDT, strong training plan at levels for all cadre of staff is imperative.

- All the national officers, state programme officers and doctors/ faculties of N/DDR-TBCs are expected to undergo national level training. (duration- 3-5 days training).
- All district officers, MO-DTC or MO-TU, Senior DR-TB TB-HIV supervisor, STS/STLS/TBHV are expected to undergo state level training (duration- 2-3 days training).
- All the HF doctors, CHO at HWC, general health staff, MPHS & MPHW are expected to undergo district level training (duration- 2-3 days on job training).
- Training should also imparted to ASHA (duration 1 day).
- Level of training and duration may be revised by state as per local situations and need.
- Opportunity of Swasth e-gurukul (platform for online training) may be utilized to train the staff. Refresher training of all cadre of staff is expected every 2 years or whenever guidelines are updated.

POINTS TO REMEMBER

- ✓ Involvement of CHO at HWC and general health staff as well as all the stakeholders for implementation and supervision is crucial for effective DR-TB care.
- ✓ Coordination amongst all health-care providers is crucial to provide various clinical and allied services to patients.
- ✓ Decentralized management of DR-TB in the form of availability of NAAT for diagnosis and DR-TBC for treatment in each district is crucial for provision of early and prompt services.
- ✓ All patients attending public or private health facility should receive diagnosis and management services free of cost. Linking indoor DR-TB care with PM-JAY provides an opportunity for free care to DR-TB patients.
- ✓ Private sector facilities may be involved for all services (diagnosis, treatment etc.) on mutually agreeable terms under PPP model. Guidance document on Partnerships 2019 can be referred.

CHAPTER 3

DR-TB CASE FINDING

Learning objectives

In this chapter, we will learn about:

- Various methods for DST, test result interpretation and the integrated algorithm of DR-TB.
- Process of specimen collection and transportation to C&DST laboratories.
- Laboratory information management system, quality assurance certification processes.
- Infection prevention and control (IPC) and biomedical waste management.
- Involvement of private laboratories through Promoting Affordable and Quality TB Tests (IPAQT).
- Diagnosis of DR-TB in children.

The vision of NTEP is to provide early diagnosis to all persons with any form of DR-TB through universal access to drug susceptibility testing. Rapid identification of DR-TB is achieved by using a combination of NAAT (CBNAAT/ Truenat), first- and second-line LPA and liquid C&DST for specific drugs, using a step-wise approach elaborated in integrated DR-TB diagnostic algorithm described in this chapter. DST is divided into phenotypic tests that observe growth or metabolic inhibition in anti-TB drug-free and drug-containing media and molecular tests that detect mutations in genes associated with drug resistance. The case finding efforts are supported with quality assured and certified C&DST labs that are equipped with information management systems for real-time reporting of results to the field. Quality assured services are also provided through certified laboratories in the private sector. This chapter also describes the standard processes of sample collection and transportation that simplify field operations and augment the accuracy of test results under programmatic conditions.

Further reading: Diagnosis and management of NTM is provided in Annexure 6.

3.1. Detection of drug resistance/susceptibility

There are two methods available to determine drug resistance/susceptibility:

1. Rapid molecular diagnostic method for **Drug Resistance Testing (DRT)**. These are genotypic tests that detect specific genetic mutations that are associated with drug resistance. Respiratory specimen, non-respiratory specimen and culture isolates can be subjected to DRT; and

2. Growth based **Drug Susceptibility Testing (DST)**. These are phenotypic tests wherein bacilli are grown and subsequently tested for drug susceptibility using various drug containing and drug-free media.

3.1.1. Rapid molecular drug resistance testing (genotypic tests)

Often referred to as nucleic acid amplification tests (NAATs), these assays rely on amplification of a targeted genetic region of the *Mycobacterium tuberculosis* (*M. tb*) complex, typically by Polymerase Chain Reaction (PCR). Molecular tests can detect TB and resistance to key anti-TB drugs, such as rifampicin (R) and isoniazid (H), fluoroquinolones (FQ) and second-line injectable drugs (SLID) more quickly than conventional C&DST. They are also available at different levels of health-care systems. Molecular methods however cannot be used for determining response to treatment *(11).*

i) **The Xpert MTB/RIF** is a cartridge-based NAAT (CB-NAAT) for simultaneous detection of TB and RR-TB. It detects DNA sequences specific for the M. tb complex and mutations in the RNA polymerase beta (rpoB) gene, which is associated with RR. Results are obtained from unprocessed sputum samples in 90 minutes, with minimal biohazard and very limited technical training required to operate. The instrument requires an ambient room temperature of below 30 degrees centigrade for optimal functioning.

ii) **The Xpert MTB/XDR** to be introduced as a follow-on test to molecular tests that detect M. tb/ RR, post endorsement by WHO *(12)* and in-country evaluation and operational feasibility studies. Refer to box 3.1 for additional information on Xpert MTB/XDR.

iii) **Truelab real-time quantitative micro PCR system by Molbio.** Truenat MTB and Truenat MTB-Rif Dx are chip-based, micro real-time PCR-based NAAT for TB detection and rifampicin resistance detection respectively.

- Truenat MTB assays detect *M. tb* bacilli in sputum after DNA extraction, using the separate TruePrep instrument and kits. Results are obtained in 1 hour;
- Truenat MTB-Rif Dx is used sequentially for RIF resistance detection;
- Truelab, which comes in Uno-, Duo-, and Quattro-throughput formats designed to be used at POC, as it does not need air conditioning and UPS to operate. Multiple micro pipetting steps necessitate a trained technician for its operation. It also requires centrifuging of large volume specimens like gastric lavage/ aspirates.

iv) **Line probe assays (LPA)** use PCR and reverse hybridization methods for detection of mutation isoniazid is associated with drug resistance. FL LPA detects mutations in the *rpo*B gene for R resistance; in the *Kat*G gene and the *Inh*A promoter region for H [and ethionamide (Eto)] resistance. SL LPA detects mutations in genes gyrA & gyr B for FQ resistance and rrs and eis (low level kanamycin resistance) for SLID resistance.

- Results of LPA are interpreted based on development/ absence of Wild Type (WT) and Mutant (MUT) bands. When all WT probes in the regions of the gene known to confer resistance to the drug are developed and none of the MUT probes in the corresponding region are developed, the result is reported as “Resistance not detected” *(13)*.
- The term “Resistance inferred” is used whenever one or more WT probes in regions of the gene known to confer resistance to the drug are not developed and none of the MUT probes in the corresponding region are developed.
- The term “Resistance detected” is used whenever one or more MUT probes identifying specific mutations conferring resistance to the drugs are developed; regardless of whether WT probes are developed or not.
- Mutations associated with low level increase in MIC and those associated with high level increase in MIC have been identified to aid in dosing drugs such as Isoniazid

and Moxifloxacin (Mfx). Detailed interpretation of the mutations is part of the laboratory training curriculum. A brief summary of test results and corresponding clinical interpretation is provided in **Table 3.1.**

v) **Growth-based drug susceptibility testing (DST) (phenotypic tests)** entail DST on solid culture (Lowenstein –Jensen) which was being performed earlier has been discontinued due to the longer turnaround time. Laboratories certified by NTEP perform DST on BACTEC MGIT 960 – an Automated Liquid Culture System. Liquid culture enables a higher rate of MTB isolation and requires a shorter turnaround time for mycobacterial growth than solid culture. *Mycobacteria* Growth Indicator Tube (MGIT) liquid culture system uses an oxygen quencher for fluorescence detection as a growth index. MGIT is the preferred method for DST. It can be used for testing both the pulmonary & EP specimens for sensitivity to first as well as second-line anti-TB drugs. Liquid culture is also used to monitor response to treatment and for long-term follow-up of patients on drug resistant TB treatment *(14)*. Due to the higher rate of contamination in liquid culture, an LJ slope is inoculated as a backup for every MGIT culture.

Box 3.1: Xpert MTB/XDR

Xpert MTB/XDR detects mutations associated with resistance towards isoniazid (INH), fluoroquinolones (FQ), second-line injectable drug (SLI) (amikacin, kanamycin, capreomycin) and ethionamide (Eto) in a single test. The test uses a semi quantitative nested PCR followed by high resolution melt technology. Results are available in less than 90 minutes. The test can run on GeneXpert platforms equipped with 10-colour modules. The 10-colour modules can independently monitor 10 or more signals and enable detection of a broader spectrum of drug resistance. The 10-colour modules are compatible with all other test cartridges. The test has been evaluated by WHO (Rapid Communication- January 2021). When endorsed, the test is suited to follow molecular tests that detect *M. tb*/ rifampicin resistance. It can potentially improve access to rapid drug susceptibility testing, especially for ruling out fluoroquinolone resistance, which is required before starting the shorter oral Bedaquiline-containing MDR/RR-TB regimen. Key features of the test include:

Drug resistance	Target region
Isoniazid	inhA promotor, katG,fabG1, oxyR- ahpC intergenic region
Ethionamide	inhA promotor
Fluoroquinolone	gyrA, gyrB
Amikacin, Kanamycin, Capreomycin	rrs, eis promotor

Drug resistance	Vs phenotypic DST		Vs sequencing	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Isoniazid	91.4	99.1	98.8	98.7
Fluoroquinolone	93.1	98.5	93.3	100
Amikacin	91.9	99.4	96.4	100
Kanamycin	87.9	99.6	96.7	100
Capreomycin	84.0	100	96.3	100
Ethionamide	64.7	98.3	97.2	100

Table 3.1: LPA results and their clinical interpretation for programmatic use

Drug	Gene	Test results	Clinical interpretation
Rifampicin	rpoB	Resistance inferred or detected	R is not effective
Isoniazid	katG	Resistance to high level H inferred or detected	H is unlikely to be effective even at high dose
	InhA	Resistance to low level H inferred or detected	H at high dose is likely effective. Eto/Pto are not effective
Fluoroquinolones	gyrA	Resistance to Lfx and low level Mfx inferred Resistance to Lfx and low level Mfx detected	Lfx is not effective. Mfx could be used at higher dose. The regimen should be reevaluated based on phenotypic DST results to Mfx at clinical breakpoint
		Resistance Lfx and high level Mfx detected (MUT 3B, MUT 3C, MUT 3D)	Lfx / Mfx is not effective
	gyrB	Resistance to Lfx and low level Mfx inferred Resistance to Lfx and low level Mfx detected	Lfx is not effective. Mfx could be used at higher dose. The regimen should be re-evaluated based on phenotypic DST results to Mfx at clinical breakpoint.
Second-line injectable drugs	rrs	Resistance inferred or detected	Am, Km and Cm are not effective
		Resistance to Am inferred (mutation at 1402)	Km and Cm are likely not effective. Phenotypic DST result should guide the choice to use Am in the treatment regimen
	eis	Resistance inferred or detected	Am and Cm are likely effective. Km is not effective

3.1.2. Reliability of DST

Effective management of DR-TB stresses the need for reliable, quality-assured DST, to be provided by laboratories certified by NTEP. Rapid molecular testing is making it increasingly feasible to detect MDR/RR-TB and to use the results to guide treatment decisions. WHO approved rapid molecular DST is recommended as the initial test to detect drug resistance before the initiation of appropriate treatment for all TB patients, including new patients and patients with a previous history of TB treatment.

Line probe assay (LPA) can detect mutations commonly associated with resistance to R, H, FQ and SLI agents. No rapid molecular testing is currently available for E or Z. Results from LPA can be used to decide upon the initial regimen for treatment of H mono/poly DR-TB, or some other forms of mono-resistant or poly-resistant TB. LPA can also provide information on the mutation patterns, which can influence the choice of treatment (e.g. if only the InhA mutation is present, it is likely that H can still be effective at high dose, whereas if the KatG mutation alone or both InhA and KatG are present, H is no longer effective, even at high dose). If RR is detected, rapid molecular tests for resistance to H and FQ should be performed promptly, to inform the decision on which regimen to use for the treatment. Susceptibility to Eto may in part be inferred from the results of molecular testing for H resistance (i.e. presence of mutations in the InhA promotor region) using LPA. DST to H, R and FQ are most useful for clinical decision making on the choice of regimen. Methods for phenotypic DST – on MGIT – for Bdq, Lzd, clofazimine (Cfz), pyrazinamide (Z) and Dlm have now also been validated *(15)*. The DST available in India is given in box 3.2.

Box 3.2: DST available in India

Quality assured DST to R, H, Z, Mfx, Lfx, Lzd, Am, Km and Cm are available across the country.

Panel testing for Cfz will be conducted shortly and the DST made available across the country in 2021.

NIRT and NITRD have cleared SNRL panel for DST to Bdq and Dlm. These DSTs will be expanded to other national laboratories in 2021.

Phenotypic DST for E, Eto may be inaccurate and not reproducible. Moreover, no agreed DST methods have been established for some other second-line drugs (e.g. cycloserine (Cs), imipenem-cilastatin/meropenem (Imp-Cln/Mpm) and PAS).

Phenotypic DST performed in MGIT, is known to miss well established RR associated mutations (disputed mutations) and hence is not useful as a confirmatory test. WHO in its recently published (Feb 2021) technical report has indicated lowering the critical concentration in MGIT from 1µg/ml to 0.5 µg/ml. This is expected to reduce the discordance between genotypic tests and phenotypic DST in MGIT (2). Genetic sequencing can be used when reliable DST is not available. Refer box 3.3 for information on genetic sequencing (14).

Box 3.3: Genetic sequencing

Since drug resistance in MTB is mainly conferred through point mutations in specific gene targets, targeted NGS offers great promise for rapid diagnosis of DR-TB. Targeted sequencing can be achieved through Pyrosequencing, Sanger sequencing as well as Next-generation sequencing (NGS).

Advances in NGS technology have enabled the routine use of NGS for both targeted NGS and WGS of *Mycobacterium tuberculosis* complex (MTBC) samples, especially in high resource settings. 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. Although targeted NGS and WGS both rely upon the same basic NGS workflow, and both applications may be run on the same NGS instrument, the sample type input requirements and processing steps can vary widely according to the desired application.

NGS has great potential for rapidly diagnosing drug- resistant tuberculosis (DR-TB) in diverse clinical reference laboratory settings. The NGS approach overcomes many of the significant challenges associated with conventional phenotypic testing as well as the limitations of other less comprehensive molecular tests by providing rapid, detailed sequence information for multiple gene regions or whole genomes of interest. NGS may be used for:

i. detection of genomic sequence variants to predict TB drug-resistance phenotypes;
ii. identification of strain lineage and resistance mechanisms for TB surveillance; and
iii. recognition of genetically related strains for resolution of transmission chains.

However, the uptake of these technologies for DR-TB diagnosis have been hindered by concerns regarding costs, integration into existing laboratory workflows, technical

training and skill requirements for utilization of the technology, computational expertise and the need for expert guidance regarding the management and clinical interpretation of sequencing data.

Thus, implementation of NGS-based DST is to be focused, at least initially, on capacity-building at the National TB Reference Laboratories and at well-performing Intermediate TB Reference Laboratories.

Although many NGS technologies will require additional optimization to further simplify workflows for the clinical diagnosis of DR-TB, they are on the path to early commercialization, and certain NGS platforms are already CE-IVD marked for in vitro diagnostic use and have been successfully integrated to reference laboratory workflows for routine DR-TB diagnosis and surveillance. Following additional optimization and commercialization, the next step for all NGS platforms is to achieve stringent regulatory approval, WHO endorsement, and local regulatory support for widespread implementation as in vitro diagnostic devices.

Studies demonstrating the impact of these NGS technologies on improved DR-TB patient diagnosis and treatment outcomes will also be critical to further reduce obstacles to NGS implementation and promote technology uptake in intended use settings. Amplification-based targeted NGS assays for detecting DR-TB directly from sputum specimens are in the pipeline. These assays have not yet been reviewed or approved by WHO.

These tools would offer unmatched flexibility in regard to the options for various targeted NGS and WGS applications as well as possibilities for routine molecular epidemiological investigations, assessment of laboratory cross-contamination and diagnosis of other infectious diseases, such as HIV or other drug-resistant, priority pathogens on the same platform.

Five WGS platforms (Illumina Miseq.), and one Pyrosequencer (Quaigen, PyroMark 48) have been deployed at National and State-level TB Laboratories. These will initially be used for sentinel surveillance of drug resistance. Targeted sequencing for determining resistance to drugs can be performed on both the systems. While Pyrosequencing detects known mutations, targeted sequencing in Illumina allows detection of novel mutations also. Algorithm for clinical management based on sequencing will be developed over time.

3.1.3. Turnaround time (TAT)

Laboratory TAT refers to the time taken from receipt of a specimen at the laboratory to issuing a laboratory test result. The overall TAT (from specimen collection to receipt of the result by the clinician) may be much longer, and is dependent on a number of factors including speed of referral of specimens to the laboratory and delivery of results to the clinician. Both these TATs need to be monitored to ensure prompt sample collection, transportation and efficient processes in the laboratories. Table 3.2 provides laboratory TAT of the different tests used under NTEP and their summarized description *(16).*

Table 3.2: Laboratory turnaround time for various TB tests performed under NTEP

Test	Description	Laboratory turnaround time	Comments
Solid culture	Löwenstein–Jensen medium	3 weeks (average) for smear-positive samples 4–8 weeks (average) for smear-negative samples	Egg-based medium Acceptable level of contamination 3–5%
Automated liquid culture	Commercial test systems	8–10 days for smear-positive samples 2–6 weeks for smear-negative samples	BACTEC MGIT 960 TB system automated liquid TB culture reference method for bacteriological confirmation. Acceptable level of contamination 8–10%
Phenotypic DST	Liquid medium - Commercial test systems	1–3 weeks from positive culture (indirect DST)	
Molecular testing	Line-probe assay for detection of drug resistance (Rifampicin, Isoniazid; Fluoroquinolones, second-line injectable drugs)	1–3 days	LPA is performed directly on AFB smear-positive specimens or indirectly on culture isolates if the smear is negative. DNA targets are amplified by PCR and hybridized to immobilized oligonucleotide targets; results can be read visually or using an automated reader
	CBNAAT. Xpert MTB/RIF assay detects *M. tuberculosis* and resistance to rifampicin using real-time PCR	2 hours (testing time)	The Xpert MTB/RIF is a fully automated assay Operational requirements include uninterrupted power supply and temperature controlled setting
	Truenat. Uses quantitative real time PCR for detection of *M. tuberculosis* A reflex test is performed for rifampicin resistance among *M. tb* detected.	1 hour (for TB detection) and 1 hour for rifampicin resistance detection	Truenat is a two-step assay for TB and rifampicin resistance detection respectively It is battery operated and amenable for placement in peripheral settings
Rapid TB identification tests	Immunochromatographic assay to be performed on solid or liquid culture growth	15 min (testing time)	Rapid identification of *M. tuberculosis* isolated from conventional solid or liquid culture Example: Capilia TB, SD Bioline's TB Ag MPT64, Becton Dickinson's TBcID©

3.2. Integrated drug-resistant TB algorithm

Effective management of DR-TB relies on detection of drug resistance followed by appropriate treatment. Genotypic testing is much faster than phenotypic methods. As these are not growth-based tests, timely diagnosis and prompt treatment initiation is possible. These include:

- Nucleic Acid Amplification Tests (NAAT) which includes CBNAAT and Truenat. These tests detect R resistance; and
- Line Probe Assay (LPA) which detects resistance to R, H, FQ and SLI drugs.

Rapid molecular tests such as NAAT are the preferred method for initial detection of RR. This is followed with LPA for detection of resistance to FQ and SLI drugs.

Phenotypic DST includes performing DST using MGIT system which is the preferred method for DST to many anti –TB drugs. The following drugs are tested using this method:

- Group A - Levofloxacin, Moxifloxacin, Bedaquiline**, Linezolid
- Group B- Clofazimine*
- Group C- Delamanid**, Pyrazinamide, Amikacin, Streptomycin

** will be available across laboratories in 2021;*
*** will be made available in all NRLs in 2021*

The integrated diagnostic and treatment algorithm for DR-TB is placed at **Figure 3.1.**

The first tier of the integrated diagnostic algorithm begins with three groups of patients classified as all presumptive TB or key population, all TB patients and non-responders to treatment, who are all subjected to NAAT. Upfront NAAT will be offered to all presumptive TB patients in areas that have transitioned from smear microscopy to molecular tests for diagnosis of TB. Key population includes PLHIV, children, EP-TB, smear negative/NA with CXR suggestive of TB, contacts of DR-TB patients and other vulnerable groups. While presumptive TB and key population as well as non-responders to treatment are offered upfront NAAT for TB/ RR-TB detection respectively; all TB patients in whom an appropriate specimen can be collected are to be offered NAAT for bacteriological confirmation of TB and RR-TB & further test for FQ. The subsequent time points when NAAT is offered for determining additional / acquired rifampicin resistance are as follows:

- bacteriologically positive during the course of DS-TB or H mono/poly DR-TB treatment;
- failure to respond to treatment;
- for patients who are retrieved after loss to follow-up; and
- any other reason as per treating physician's advice.

The algorithm is designed to segregate patients based on NAAT results as RR detected or RR not detected and offer DST guided treatment. As soon as NAAT results are available, the report must be updated in Nikshay.

For patients with NAAT result as MTB detected (irrespective of R status) the second specimen will by reflex be transported in cool chain from the NAAT facility to the C&DST laboratory. In rare circumstances, if the second specimen is used at the NAAT facility itself to repeat the test, a fresh specimen will be collected from the patient and transported in cool chain to the concerned C&DST laboratory. However, this will not always be possible for EP specimens.

Note: All fluid EP samples can be processed in CBNAAT in the periphery. However, EP TB samples such as tissue biopsy and lymph nodes require homogenization, which is to be performed in a TB containment facility available at NRL, IRL, C& DST labs. High volume samples

such as gastric aspirate/lavage may need to be concentrated by bio-safe centrifugation for obtaining valid results in laboratory tests including NAAT. Processing BAL, plural fluid and peritoneal fluid in Truenat requires bio-safe centrifugation available only at the laboratories with TB containment facilities. No attempt should be made to perform aerosol generating procedures such as centrifugation and homogenization in the peripheral labs. Precious samples such as FNAC and CSF although can be processed at the peripheral NAAT, may be escalated to laboratories with TB containment facility (if volumes are very low) for testing by multiple methods. CSF must be processed as quickly as possible after collection; therefore, the laboratory must be informed by a phone call immediately. Samples must not be collected in formalin.

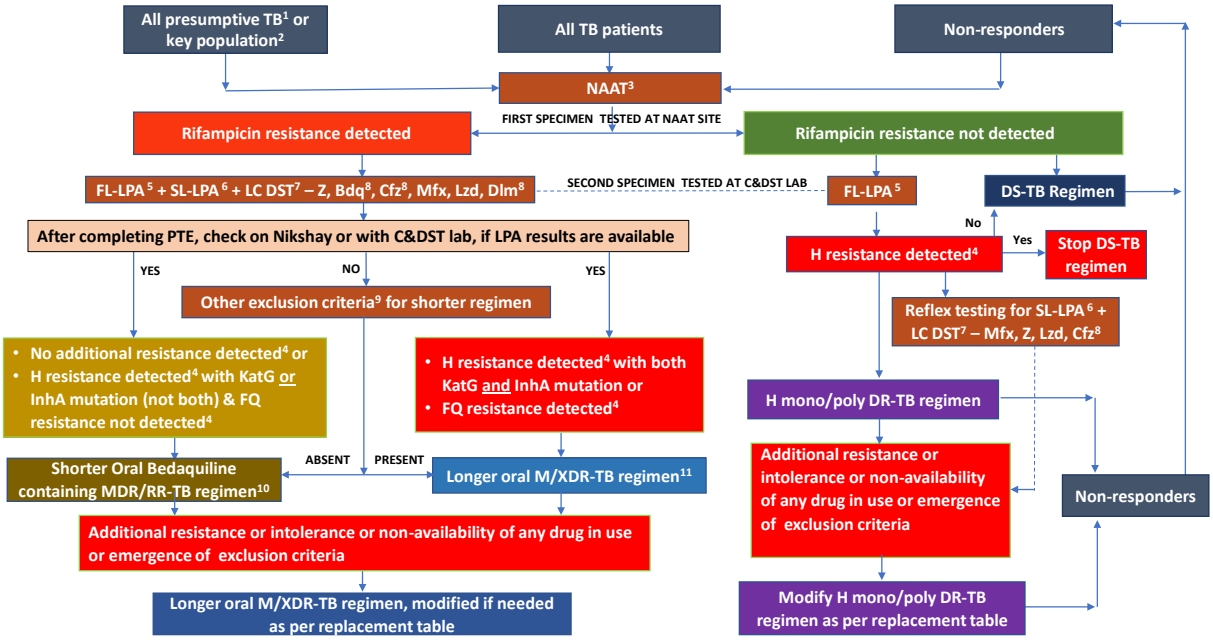


Figure 3.1 Integrated diagostic and treatment algorithm for drug resistant tuberculosis

Footnotes:

1. In areas transitioned to NAAT for TB diagnosis.
2. Key population includes PLHIV, children, EP-TB, smear –ve/NA with CXR suggestive of TB, contacts of DR-TB patients, other vulnerable groups.
3. CBNAAT or Truenat. All EP-TB specimen except FNAC of peripheral LNs & CSF to be sent directly to C&DST laboratory for further processing. For processing FNAC & CSF specimen at NAAT sites, refer to the text.
4. As per mutation pattern, includes resistance inferred.
5. Discordance in RR results between NAAT & FL-LPA to be resolved with a repeat NAAT at C&DST lab and microbiologists will provide the final decision. InhA mutation associated with Eto resistance. Use other exclusion criteria to decide regimen if FL-LPA is done on culture isolates for patients with smear negative specimen.
6. To assess Lfx, Mfx and Am resistance.
7. Start treatment based on LPA results and modify based on LC&DST results later.
8. Whenever DST is available.
9. Other exclusion criteria for shorter oral Bedaquiline-containing MDR/RR-TB regimen includes:
   - History of exposure for > 1 month to Bdq, Lfx, Eto or Cfz, if result for DST (Bdq, FQ, Inh A mutation, Cfz & Z) is not available;

- Intolerance to any drug or risk of toxicity from a drug in the shorter oral Bedaquiline-containing MDR/RR-TB regimen (e.g. drug–drug interactions);
- Extensive TB disease – presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, presence of cavities or bilateral disease on chest radiography;
- Severe EP-TB disease - presence of miliary TB or TB meningitis or CNS TB. In children aged under 15 years, extra-pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression);
- Pregnant and lactating women (with conditional exceptions); and
- Children below 5 years.

10. This portion applies as states move to shorter oral Bedaquiline-containing MDR/RR-TB regimen under guidance of NTEP.
11. Patients who were initiated on longer oral M/XDR-TB regimen based on h/o exposure for > 1 month and in whom resistance is not detected to H or FQ may be switched to shorter oral Bedaquiline-containing MDR/RR-TB regimen based on the FL & SL LPA results, if the duration of longer oral M/XDR-TB regimen drugs consumed is < 1 month.

The left arm: Rifampicin resistance detected.

When rifampicin resistance is detected, the patient is offered first-line (FL) and second-line (SL) LPA. RR detected in a new case with no risk factors for DR-TB needs to be retested if only *M. tb* detected was very low as that could be false positive. If there is a discordance in rifampicin resistance between NAAT and LPA, a second NAAT is performed at the C & DST laboratory using the decontaminated deposit and microbiologist will provide the final decision. Direct LPA can be performed only on smear positive specimen. In instances where the smear is negative, a culture is set up and if the culture is positive, an indirect LPA is performed on the isolate. While FL LPA provides information on InhA mutations associated with Eto resistance, SL LPA provides information on resistance to Lfx, Mfx and Am. LC DST would be set up for Z, Mfx (if resistance detected by LPA), Lzd, Cfz*, Bdq* and Dlm* (* when available). Treatment is initiated based on the results of LPA and if required modified based on the LC DST results which would be available later.

If FQ resistance is not detected and H resistance is detected due to mutations either in katG or InhA (but not both) the patient is eligible for shorter oral Bedaquiline-containing MDR/RR-TB regimen described in detail in the respective treatment chapter. If FQ resistance is detected or H resistance is due to mutations in both katG and InhA, the patient is eligible for longer oral M/XDR-TB regimen, described in detail in the respective treatment chapter.

The right arm: Rifampicin resistance not detected

When rifampicin resistance is not detected, the patient is offered FL LPA for detecting resistance to H. If there is a discordance in rifampicin resistance between NAAT and LPA, a second NAAT is performed at the C & DST laboratory using the decontaminated deposit and microbiologist will provide the final decision. Direct LPA can be performed only on smear positive specimen. In instances where the smear is negative, a culture is set up and if the culture is positive an indirect LPA is performed on the isolate. If H resistance is not detected, the patient is continued on a DS TB regimen. If H resistance is detected, the patient is eligible for H mono/Poly DR-TB regimen, described in detail in the respective treatment chapter. SL LPA will be performed for detecting resistance to FQ and LC DST will be performed for Mfx (if resistant by SL LPA), Z, Lzd and Cfz* (*when available). Treatment is initiated based on LPA results and modified based on the LC DST results which would be available later.

3.3. Specimen flow and operational processes

The HF doctor confirms that the patient is presumptive DR-TB. S/he should arrange for sending two sputum specimens (one early morning & one "supervised" spot specimen) from the patient to the assigned NAAT laboratory along with the Laboratory request form (TB bacteriology request form - **Annexure 7**). Patient ID and Test ID are generated in Nikshay for the patient. If the patient prefers to return back with early morning specimen, then spot specimen can be collected. Alternately, specimens can be collected from the patient by the health-care worker and transported in a cool box to the nearest NAAT facility on the same day.

At the NAAT facility, one specimen will be used for the test. If TB is detected (R resistant detected or not detected), the other specimen is packaged and transported in a cool box through courier or speed post to the linked C&DST laboratory. LT at NAAT facility will generate the test request for the second sample to be tested at the C&DST lab. If there is likely to be a delay in transporting the specimens, these should be stored in a refrigerator at the peripheral TB detection centre/ HF with biosafety precautions. All necessary materials for specimen collection and transportation need to be made available at the specimen collection centre and the NAAT facility by the DTO.

At the C&DST lab, smear positive specimen would be subjected to FL and /or SL LPA and further for LC DST as per the diagnostic algorithm. Smear negative specimen will be inoculated in liquid culture and the isolate obtained subjected to LPA. Tests results (LPA and DST) are updated in Nikshay. The C&DST lab may request for additional specimen from the patient, in case of early contamination (within 4 days) or for other reasons. The referring centres must ensure that fresh specimen are collected from the patient and transported to the C&DST labs within 3 days of request **(Figure 3.2).**

Specimen will be rejected at the C&DST laboratory in the following situations:

- Unlabelled or mislabelled specimens
- Specimen sent without test request ID in Nikshay
- Mismatch in the name on the specimen and test request in Nikshay

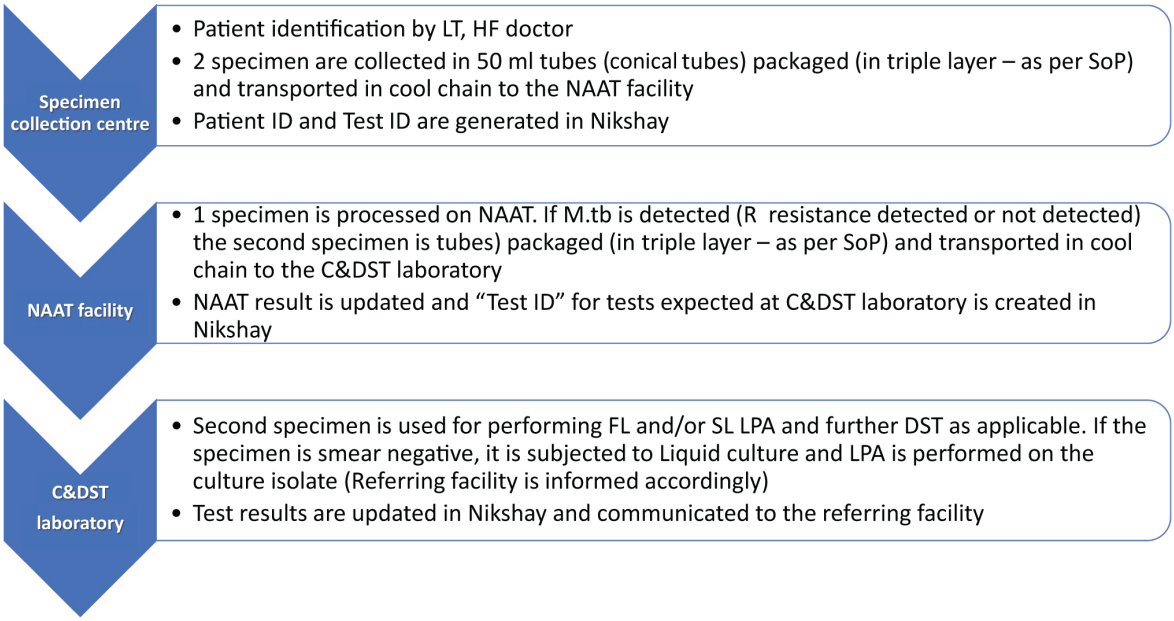


Figure 3.2 Specimen flow and operational processes

- If the container is full up to the lid with the specimen
- Sample is not collected in an appropriate container
- Specimen container is broken
- Leakage of specimen

3.3.1. Specimen collection and transportation

Obtaining good quality specimens of adequate volume is critical to ensuring correct diagnosis. The Laboratory technician needs to explain the process of collecting "a good quality sputum specimen" while adhering to Airborne Infection Control (AIC) measures. Sputum must always be collected in an open well-ventilated area identified for the purpose.

Programme recommends collection of sputa one spot and one early morning, or 2 spot specimens collected with a gap of at least one hour (if the patient is coming from a long distance or s/he is unlikely to return to give the second specimen). Alternatively, samples can be collected by the health-care worker and transported in cool chain to the nearest NAAT facility.

Good quality specimen. Volume of 2-5 ml, preferably mucopurulent and not heavily blood stained or contaminated on visual appearance. The patient must be advised to collect the specimen in a sterile container (50 ml conical tube) after thorough rinsing of the mouth with clean water. Triple layer packaging procedure is to be followed for transporting samples. Specimens should be transported to the NAAT or C&DST laboratory as soon as possible after collection. If a delay is unavoidable the specimens should be refrigerated to inhibit the growth of other micro-organisms *(17).* (**Annexure 8** on Health & safety guidelines for staff involved in sputum transportation)

Specimen collection container. Sterile 50 ml screw capped and graduated conical bottom polypropylene tube.

Collection of extra-pulmonary specimen. Specimens must be collected in sterile saline with no other preservatives added. Specimen for TB diagnosis must NOT be collected in formalin. In case histopathological examination is also required, the specimen must be divided into two tubes/ two specimens collected. Extra pulmonary specimens are to be transported to the linked laboratory as soon as it is collected not exceeding 4 hours. The laboratory must be informed as soon as the specimen is collected *(18)*. (**Annexure 9** on Standard operating procedures for collection, transportation, processing and inoculation of extra-pulmonary specimens)

Labelling of specimen containers. Specimen containers to be labelled legibly with details such as the patients' name, date and time of specimen collection, TB detection centre/ DTC, lab no, specimen A or B.

For every TB patient referred by HF doctor, date of referral and transport of specimens to C&DST laboratory should be entered in Nikshay and generate test request preferably.

Material required for packing the specimen for transportation. Specimen collection tubes containing the sputum samples; 5% phenol; test tube rack; tongs; parafilm; absorbent cotton; tissues; self-sealing covers; thermocol boxes; gel packs; permanent marker pens; scissors; rubber bands; scotch tapes; biohazard stickers *etc.* It is to be ensured that the coolant gel packs have been frozen prior to packaging samples for transportation **(Figure 3.3a & 3.3b)**.

Figure 3.3a Material required for packing the specimen for transportation

Thickness of box-2.5 cm

Outer dimensions: Length-18.5cm, breadth-13cm, height-12 cm (without lid), height-14 cm (with lid)

Inner dimensions: Length-14.5cm, breadth-8cm, height-12cm (without lid), height-13cm (with inner part of lid)

No. of gel pack required:2, weight of fully packed consignment box: 400 grams

Gel packs maintain a temperature between 12-20° C for up to approximately 48 hours in tightly packed thermocol boxes (average outside temperature 35° C). If conditioned in the deep freezer (temperature between -20 to -15° C) for a minimum 48 hours to a maximum 72 hours before use. (This is a one-time use box since thermocol boxes and gel packs are not reused)

Figure 3.3b Technical specifications of transport box for sputum specimen transportation in cool chain

3.3.2. Standard operating procedure for specimen packaging (triple layer packaging)

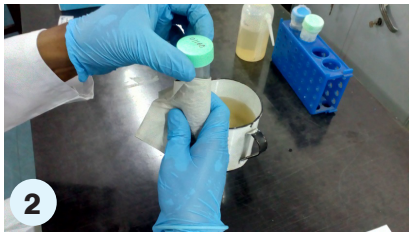
Step 1. Make sure that the specimen collection tube is tightly closed after the sample has been collected from the patient.

Step 2. Wipe the outer surface of the 50 ml conical tube with 5% phenol followed by absorbent tissues and allow it to air dry.

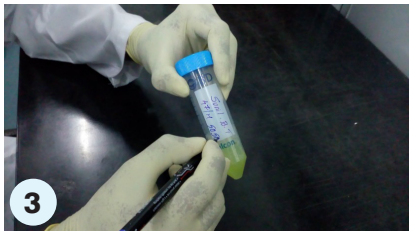
Step 3. Write the patient details on the opaque area (white area) of the specimen collection tube using a permanent marker pen, clearly in capital letters.

Step 4. Cut the parafilm strip, wrap one of the strips at the joint between the cap and the neck of the specimen collection tube such that a secure seal is formed. (primary receptacle/ package)

Step 5. Open the absorbent cotton roll and spread out on the work bench; separate the cotton into two equal layers. Roll the specimen collection tube containing the sample tightly in the absorbent cotton such that the tube is covered completely.

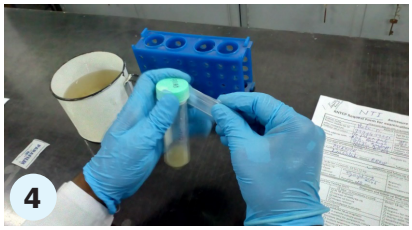


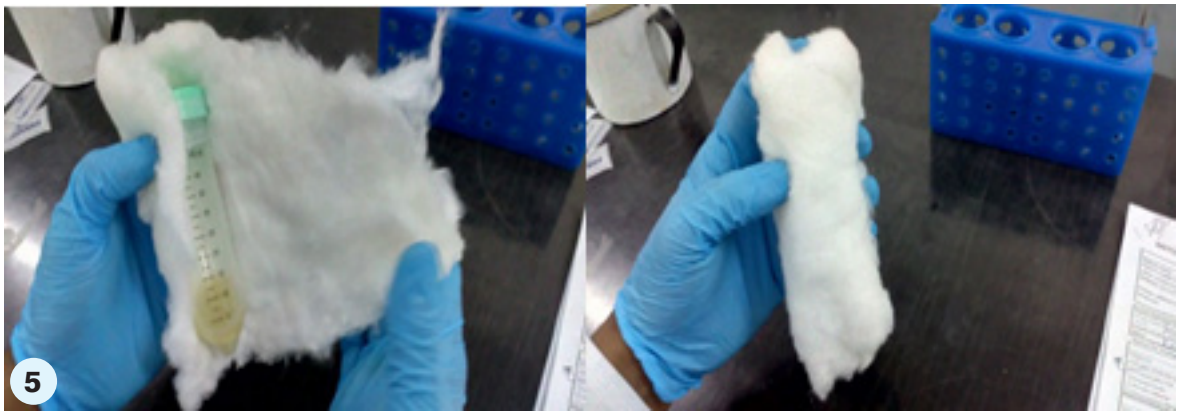
Step 6. Put this roll containing the specimen collection tube into the ziplock pouch. Roll the whole into a tight bundle, ensuring that there is no air in the pouch. This bundle should be secured with the rubber bands. (secondary receptacle/ package)

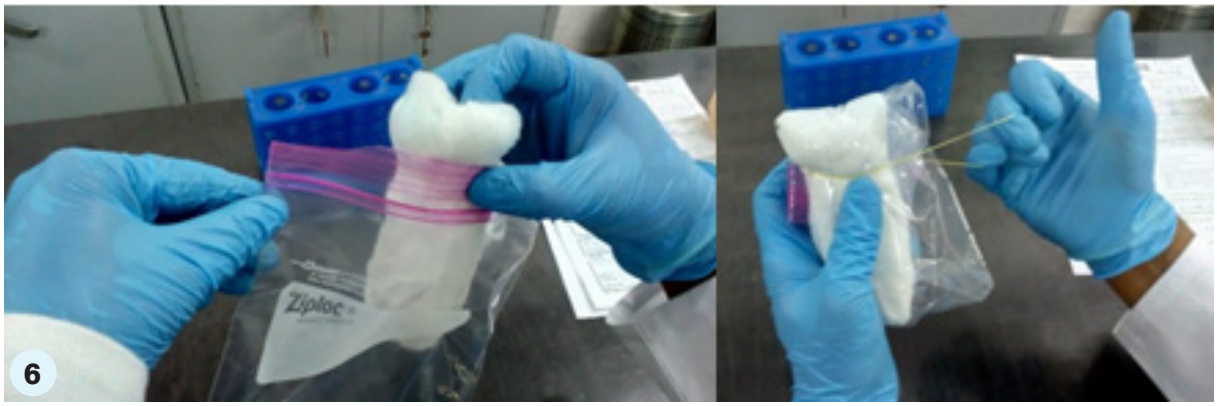


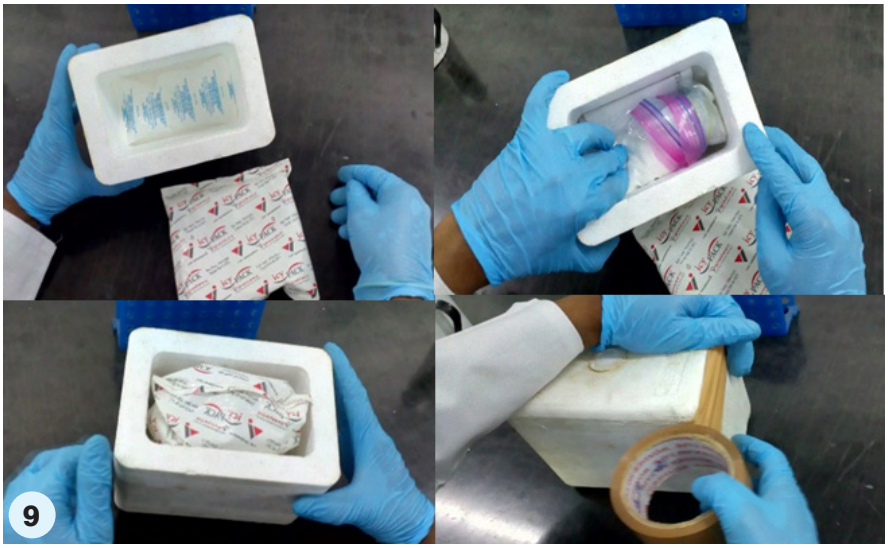
Step 7. Repeat Steps 5–7 for the second sample of the patient.

Step 8. Insert the Test Request form printed from Nikshay in to the zip lock pouch after ensuring that the details on the form and the sample tubes match, with the writing facing outside (details visible though the package). Seal the ziplock on the pouch.









Step 9. Place the cooled gel packs into the thermocol box, place the sample tubes packed in zip lock pouches on the frozen gel packs (frozen for 48 hrs at -40°C) and also keep the pouch containing the Test Request form printed from Nikshay on top. Stick the BIOHAZARD sign over the lid and "To and From" stickers on the exterior of the thermocol box or box used to pack the specimen. Close the lid of the box and wrap tightly with brown duct tape. (Tertiary receptacle/ package)

Step 10. Complete the 'From' and 'To' addresses on the stickers, using a permanent marker pen.

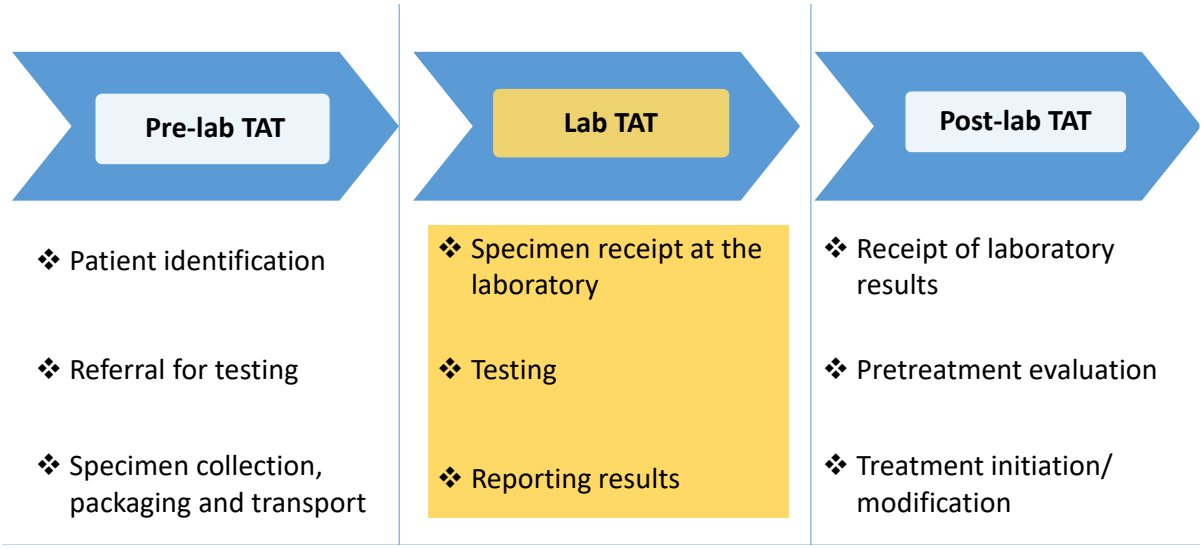


Figure 3.4 Patient turnaround time

LT of the collection centre /NAAT facility should promptly inform the specimen transport agency such as courier/ speed post service to collect and transport the specimens.

3.3.3. Patient turnaround time (P-TAT)

Patient turnaround time (TAT) is defined as the elapsed time in days between identifying the eligible patient to initiating the patient on treatment, based on the laboratory result. The patient TAT has been divided into pre-lab, lab and post-lab TAT **(Figure 3.4).** TAT serves as a quality indicator to assess efficiency of field services as well as the diagnostic cascade in the patient pathway. Despite the introduction of rapid molecular tests, the overall patient turnaround time has not reduced significantly chiefly due to insufficient supervision of field-level activities and laboratory services. It is important to consistently achieve benchmark TAT and to periodically review process indicators for achieving quality improvement. **Table 3.3** describes benchmarks for each part of the TAT.

Table 3.3 Benchmark for TATs

Test	Pre Lab TAT in Days	Lab TAT in Days	Post Lab TAT in Days	Total Patient TAT (P-TAT) in Days*	Remarks
NAAT	1–2	1–2	2–3	4–7	Pre-lab TAT includes patient identification, counselling, collection and transport of 2 specimens to NAAT facility Post-lab includes accessing test results, pre-treatment investigation and treatment initiation
LPA	1–3	2–3	2–3	5–9	Pre-lab TAT includes time from collection to NAAT and further transport of second specimen to C&DST labs
LC DST**	NA	Time till LPA testing 5–7 days + *22– 48 (in most cases 30 days)	2–3	29–58 (in most cases 40 days)	No pre-lab time, cultures are set up using decontaminated deposit *Includes culture and growth days for DST set up ** for Z DST additional 7 days will be needed
Liquid culture (Follow-up)	2–3 days (for tracing the patient and collecting specimen for follow-up culture)	8–42	1–2	11–45	Fresh sample is collected from the patient and transported

3.4. Laboratory recording and reporting

Results of all laboratory tests such as smear, culture and DST / LPA/ NAAT are entered in Nikshay and downloaded as the C&DST register for all laboratories of the network. All results must be communicated to the concerned DTO, DR-TBC/ private provider through Nikshay as soon as results are available. However, alternative means (email, SMS *etc.,*) for communicating the results may additionally be utilized.

Lab information and management system (LIMS)

NTEP has implemented the LIMS in C&DST laboratories to improve efficiency, automate workflows, integrate instruments and manage information associated with the samples.

LIMS has been integrated with Nikshay through API. It is currently functional offline and being developed to provide real-time information. With complete integration, the diagnostics module under development in Nikshay, would have features such as sample collection time, transit and delays, tests requested for a particular laboratory, results reported, *etc.*

3.5. Quality assurance

NTEP has a very well established quality assurance (QA) mechanism which follows the WHO system of hierarchal control from the highest level of National Reference laboratories to State Intermediate Reference laboratories, to the district/sub district level and then TB diagnostic centre at the most peripheral level. The QA has all elements of internal quality control, on-site evaluation and external quality control. EQA for sputum smear microscopy includes on-site evaluation, panel testing and random blinded rechecking (RBRC).

The components of QA for C & DST include Internal Quality Control (IQC) and EQA mechanisms. IQC of LJ media involves testing each batch of media for contamination as well as the use of control strain (H37RV) for growth parametres. IQC for MGIT is instrument guided. IQC of DST involves use of control strain (H37RV) as well as mono resistant strains with every batch of DST performed. The EQA for DST is through structured panel testing and retesting exercises *(19).*

3.5.1. Certification

Proficiency testing (PT) exercise is conducted annually for certification of laboratories in all technologies used for determination of drug resistance. PT for LPA includes benchmarks for invalid results, contamination in negative control, internal as well as external concordance. The proficiency testing schedule for phenotypic DST as well as LPA is annual in nature and the certification process is biennial for all technologies.

Quality Assurance for CBNAAT had earlier been limited to instrument guided internal controls. However, External Quality Assurance of CBNAAT using dried tube specimen has been expanded across the country. These panels will be used for quality assurance of Truenat also. Coordination of the EQA activity, manufacture and validation of the panels is undertaken by National TB Institute, Bangalore.

3.5.2. Accreditation

Accreditation is a procedure by which an independent, authorized body gives formal recognition to a laboratory certifying it as competent to perform specific tasks. Laboratory accreditation recognizes a laboratory's technical capability and is usually specific to the systems, products, components or materials for which the laboratory claims proficiency. Accreditation allows a laboratory to determine whether it is performing its work correctly and according to appropriate standards. This does not guarantee that a given analytical result is correct, but it does establish standards that must be met and a framework within which non-conformities are identified and addressed.

The accreditation of clinical or medical laboratories is achieved by measuring performance against ISO (International Organization for Standardization) 15189, which addresses quality systems essentials.

Laboratories that confirm to ISO 15189 are accredited by the National Accreditation Board for Testing and Calibration Laboratories (NABL). TB laboratories certified by NTEP through proficiency testing protocols are also encouraged to proceed towards NABL accreditation.

3.6. Infection prevention and control (IPC)

Infection prevention and control (IPC) is essential in health-care services and other settings where the risk of *Mycobacterium tuberculosis* transmission is high. IPC practices are vital to

reduce the risk of *M. tuberculosis* transmission, by reducing the concentration of infectious droplet nuclei in the air and the exposure of susceptible individuals to such aerosols. IPC measures are implemented in a systematic and objective way that prioritizes consideration of the hierarchy of administrative and environmental controls, and personal protection *(20)(21)*.

Administrative controls measures include triaging of people with signs and symptoms of TB, or with TB disease; separation of people with presumed or demonstrated infectious TB; prompt initiation of effective TB treatment of people with TB disease and respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB. These measures aid in reducing *M. tuberculosis* transmission to health workers, persons attending health-care facilities or other persons in settings with a high risk of transmission.

Environmental controls measures include ventilation systems (natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air [HEPA] filters) and upper-room germicidal ultraviolet (GUV) systems.

Personal protection is provided by using appropriate Personal Protective Equipment (PPE) mainly by the particulate respirators.

3.7. Biomedical waste management

Biomedical waste includes all waste generated from the health-care facility which can have any adverse effect to the health of a person or to the environment in general if not disposed properly. All such wastes are considered infectious and require management **(Annexure 10).** Biomedical wastes are segregated in colour coded bags:

Yellow bags are used for:

- Human anatomical waste human tissues, organs, body parts and foetus below the viability period;
- Animal anatomical waste;
- Soiled waste items contaminated with blood, body fluids like dressings, plaster casts, cotton swabs and bags containing residual or discarded blood and blood components;
- Discarded or expired medicine;
- Chemical waste and chemicals used in production of biological and used or discarded disinfectants; chemical liquid waste;
- Discarded linen, mattresses, beddings contaminated with blood or body fluid, routine mask & gown; and
- Microbiology, biotechnology and other clinical laboratory waste (pre-treated) microbiology, biotechnology and other clinical laboratory waste that includes blood bags, laboratory cultures, stocks or specimens of microorganisms, live or attenuated vaccines, human and animal cell cultures used in research, industrial laboratories, production of biological, residual toxins, dishes and devices used for cultures.

Red bags are used for:

- Wastes generated from disposable items such as tubing, bottles, intravenous tubes and sets, catheters, urine bags, syringes without needles, fixed needle syringes with their needles cut, vacutainers and gloves.

White boxes are used for:

- Waste sharps including metals, needles, syringes with fixed needles, needles from needle tip cutter or burner, scalpels, blades, or any other contaminated sharp object that may

cause puncture and cuts. This includes both used, discarded and contaminated metal sharps.

Blue bags are used for:

- Broken or discarded and contaminated glass including medicine vials and ampoules except those contaminated with cytotoxic wastes.

3.7.1. Use of colour-coded bags for waste segregation, in TB laboratories

Yellow bag. Truenat chips (MTB/RIF), used mask /gowns.

Red bag. Specimen collection tubes, sputum cups, CBNAAT cartridges, infected plastic, contaminated tips, pasteur pipettes, Truenat cartridges, PCR tubes, used gloves, MGIT tubes, disposable LJ tubes.

Blue bag. Glass slide in Truenat machine, used microscopy slides. Slides should not be broken.

Waste generated in the C&DST laboratory are autoclaved prior to segregation in colour coded bags. Personnel handling/segregating biomedical wastes must use appropriate PPE and should be trained in spill management. Laboratories must also acquaint themselves with amendments made from time-to-time in the biomedical waste management rules.

3.7.2. Sputum disposal

- In the inpatient facility, spittoons are to be disinfected with 5% phenol for one hour and then emptied into the routine drain (preferable to have effluent treatment plant, if not ensure running tap water). The spittoons can be reused after sterilization (autoclaving) and provided to the patient after adding disinfectant (5% phenol).
- At the patient's home. The contents are to be drained and the spittoon boiled. These can be reused after adding the disinfectant (5% phenol).

At the sputum collection centre, biomedical waste segregated in colour coded bags are deposited at the common collection facility. All BMW are handed over to the authorized waste collectors within 48 hours. If facilities for waste collection are not available, all soiled/ contaminated gloves/ masks /sputum cups/soiled paper are wrapped in autoclavable red/ yellow /blue bags and buried in the pit in an isolated area, identified for the purpose.

3.8. Private sector and IPAQT

Diagnostic services are provided free of cost at all public health laboratories to referrals from the private sector. Laboratory services are also purchased from the certified private sector laboratories through partnership schemes. Private sector laboratories are certified by NTEP upon clearing mandatory proficiency testing exercise conducted by the National Reference Laboratory.

Back in 2012, TB diagnosis in the private sector was driven by the excessive use of unreliable serological tests concurrent with issues of low availability and high costs of quality-assured diagnostics tests. The IPAQT was initiated by the Clinton Health Access Initiative (CHAI) in 2013 to bring WHO-approved tuberculosis tests at affordable prices to patients in the private sector. IPAQT is an initiative of not-for-profit stakeholders and private sector labs/hospitals (collection centres) with a pan-India presence that have come together to provide WHO approved tests for TB.

IPAQT brought together various private laboratories with the support of test manufacturers and other major stakeholders to:

- bring down the price for quality TB tests up to 50% in the private sector; and
- promote the use of these tests by building awareness among health providers, laboratories and patients.

IPAQT has set a ceiling price for 4 WHO-endorsed TB tests as follows:

- GeneXpert Test – Rs 2200
- Hain genotype test – Rs 1800
- MGIT AFB culture – Rs 900
- BacT/ALERT AFB culture – Rs 900

For further details, refer to https://www.ipaqt.com

DTOs are to ensure that patients diagnosed through IPAQT laboratories are notified to NTEP surveillance system and appropriate public health action is initiated.

3.9. Diagnosis of DR-TB in children

Very limited data is available for MDR-TB in children. In children, it largely results from transmission of drug-resistant bugs by the source case (usually adolescents and adults). Less commonly, it can result from previous inadequate TB treatment too. MDR-TB in children mirrors MDR-TB in adults and thus is common in settings where MDR-TB pool exists in adults and is associated with higher morbidity and mortality compared to drug-sensitive disease.

3.9.1. Approach to diagnose DR-TB in children

DR-TB is a bacteriological diagnosis and there are no clinical patterns marking presence of drug resistance in a given case. Epidemiological markers are important pointers towards likelihood of DR-TB and therefore a careful history of patients is paramount. This includes contact with a known or presumptive MDR, drug and dose history as well as adherence. Any patient not responding to treatment could be harbouring a drug-resistant strain. However, the causes for non-response to anti-TB treatment are many including incorrect diagnosis of TB, poor adherence, associated immunodeficiency such as HIV. Paradoxical upgrading reactions and inter current infections which could be the other reason for an apparent non-response.

Presumptive MDR-TB in children (Figure 3.5) - Children who are contacts of adults with MDR-TB/ drug resistant TB, who are lost to follow-up after initiating treatment, those who present with recurrence of disease after previous treatment, those who do not respond to treatment with first-line drugs and those living with HIV (CLHIV).

It is pertinent to mention here that in the current U-DST strategy, every patient of TB gets upfront testing for presence of resistance to rifampicin and thus this definition has become less relevant from an operational view point.

It is important to get appropriate body fluid samples for both pulmonary or EP-TB patients for mandatory bacteriological confirmation and drug susceptibility testing. For this, sputum (or other relevant samples e.g. gastric aspirate, induced sputum, bronchoscopic lavage, lymph node aspiration, CSF, tissue biopsies) must be collected in all children with presumed DR-TB for NAAT or LPA and culture and drug susceptibility testing. This may even imply

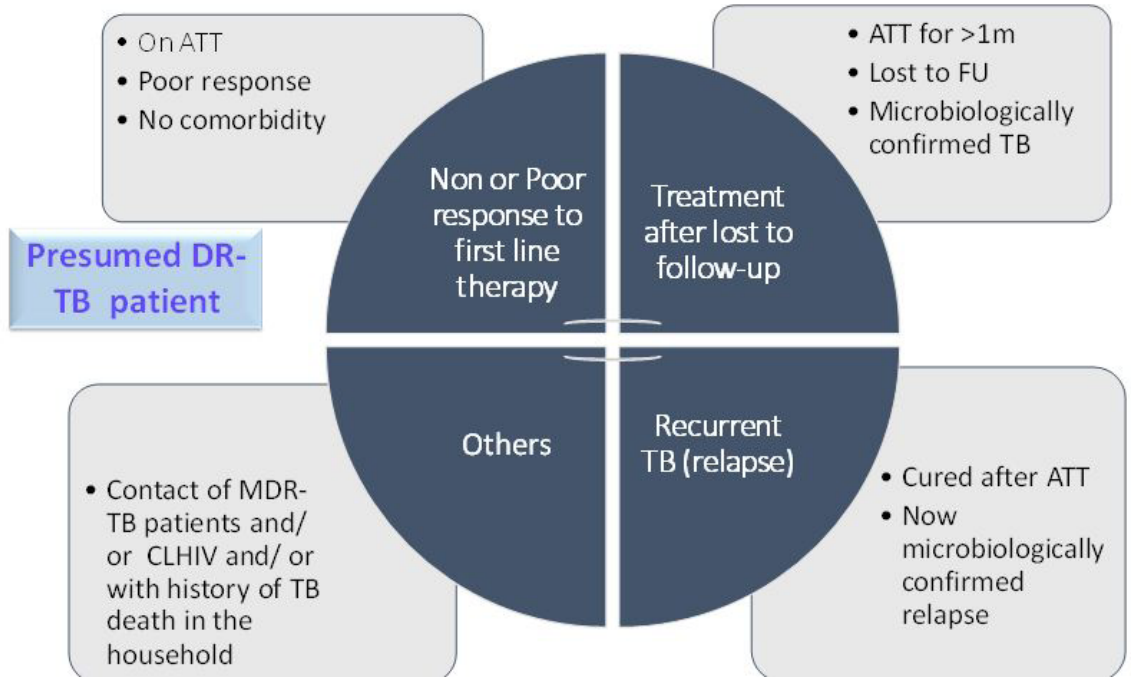


Figure 3.5: Presumptive MDR-TB in children

referral to a higher centre to facilitate invasive testing. (Refer to **Annexure 9** on collection and transport of extra-pulmonary specimen).

Diagnosis of DR-TB in the absence of bacteriological confirmation must be thoroughly reviewed as it may often be untenable. In a presumptive DR-TB patient, if there is no bacteriological confirmation, bacteriologically negative clinically diagnosed probable DR-TB can be considered after ruling out alternative diagnosis.

3.9.2. Probable MDR-TB among children

The term probable MDR-TB in children would be applied to children wherein DR-TB is clinically suspected strongly but there is no bacteriologic confirmation and the decision regarding diagnosis and initiation of treatment is taken by the N/DDR-TB committee **(Figure 3.6).**

Criteria for diagnosis of "Probable MDR-TB" include children with sign and symptoms of active TB disease who in addition have the following risk factors:

- Close contact with a known case of MDR-TB
- Close contact with a person who died whilst on TB treatment
- Close contact with a person who failed TB treatment
- Non-response or failure of a first-line regimen
- Previous treatment with second-line medications.

and their appropriate specimens fail to demonstrate *M. tb* and thus the resistance pattern cannot be determined (culture negative TB) or an access to specimen is not easily possible (tuberculomas or abdominal tuberculosis, *etc.*). This consideration of initiation of appropriate DR-TB regimen without bacteriological confirmation does not replace the need for a thorough and ongoing diagnostic evaluation, including consideration of non-TB causes, prior to initiation of DR-TB treatment. Children with a central nervous system disease and/or those with other life-threatening manifestations with risk factors for DR-TB may be treated as probable MDR-TB

A pediatric patient of TB with clinical non response with or without radiological deterioration despite adherence to ATT by the end of 4 weeks, with one or more of the following risk factors:

- **exposure to an MDR/RR-TB** patient and/or history of recent death in family due to TB
- children who were **earlier lost to follow-up**

AND

Whose microbiological **tests are negative** for *M.tb* or there is no possible access to specimen

In view of the prolonged duration and risks of second line drug therapy, decision for such a situation should be made on recommendation of the DR-TB Committee

Figure 3.6 Probable MDR-TB in children

even when their DST tests are awaited. They should be initiated on treatment immediately, in consultation with the paediatrician in the NDR-TBC committee, given the high risk of mortality. Further continuation of treatment can be decided based on their test results when available.

Presumptive DR-TB is a patient who needs to be subjected to genotypic (NAAT, LPA) or phenotypic (LC&DST) DSTs while probable MDR-TB is a patient, who after getting the results of the above tests, cannot be bacteriologically confirmed and needs to be started DR-TB regimen based on their clinical and /or radiological deterioration (clinically diagnosed case of MDR-TB). All patients considered to have 'probable' MDR-TB should be presented to and discussed with a DR-TBC Committee followed by a decision to treat which ought to be made in consultation with the paediatrician. The algorithmic approach to diagnose DR-TB in children is shown in **Figure 3.7.**

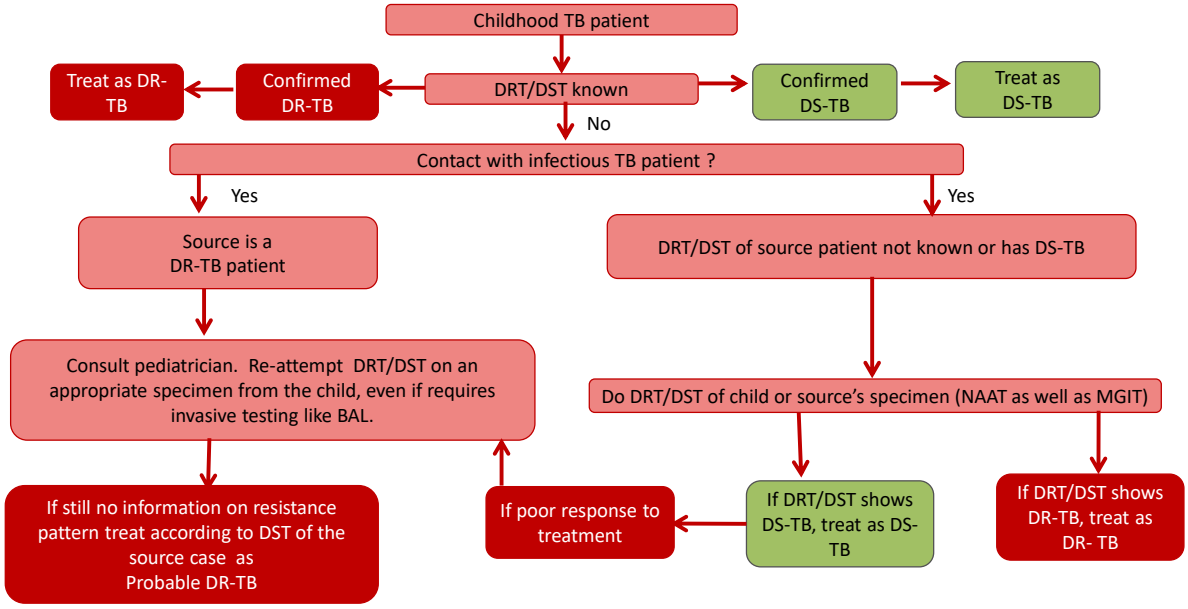


Figure 3.7 Algorithmic approach to diagnosis of DR-TB in children

3.9.3. Confirmed drug resistant patient

A patient is confirmed to have drug-resistant TB, only when the results suggesting drug resistance are from a NTEP quality assured culture and DST laboratory and/or by a NTEP-endorsed testing method (NAAT/LPA).

MDR-TB patients can often have additional resistance to other anti-TB drugs and therefore all such cases must undergo further testing for presence of resistance to other first and second-line drugs so that can be put on an optimized treatment. If an appropriate specimen is available from the child, the specimen processing will be in accordance to the integrated DR-TB diagnostic algorithm.

POINTS TO REMEMBER

- ✓ Two specimens are to be collected and sent to the NAAT facility. SoP for triple layer packaging must be strictly adhered to and the sample transported in cool chain.
- ✓ Samples must not be batched but transported immediately after collection to the linked laboratory for appropriate testing.
- ✓ Presumptive TB or key population, all diagnosed TB patients and non-responders to treatment, are all subjected to NAAT. If R resistance is detected with very low level of M. tb in a patient with low clinical suspicion, a repeat NAAT may be ordered by the physician.
- ✓ If R resistance is detected on NAAT, the patient is offered first-line (FL) and second-line (SL) LPA followed by LC DST as indicated in the algorithm.
- ✓ If R resistance is not detected on NAAT, the patient is offered FL LPA for detecting resistance to H. All H resistant patients are subsequently offered SL LPA followed by LC DST as indicated in the algorithm.
- ✓ Phenotypic DST for ethambutol, ethionamide may be inaccurate and not reproducible. No agreed DST methods have been established for some other second-line drugs (e.g. cycloserine/terizidone, imipenem-cilastatin/meropenem and PAS).
- ✓ Treatment is initiated based on LPA results and modified based on the LC DST results which would be available later.
- ✓ EP-TB samples should not be collected in formalin for bacteriological tests (genotypic as well as phenotypic).
- ✓ DR-TB in children, largely results from transmission of drug-resistant bacteria from the source case (usually adolescents and adults). Less commonly, it can result from previous inadequate TB treatment.
- ✓ AIC measures pertinent to the setting must be followed at all times. Biomedical waste management must be ensured at all settings.
- ✓ WHO approved diagnostics are also available in the private sector.
- ✓ Monitoring turnaround time is important for better treatment outcomes.

CHAPTER 4

TREATMENT OF DRUG-RESISTANT TB

Learning objectives

In this chapter, we will learn about:

- Goals of TB treatment, grouping of drugs, health education and counselling.
- Treatment of shorter/longer oral MDR-TB regimen as well as rifampicin-susceptible and Isoniazid-resistant TB (including poly DR-TB) covering.
  - o Pre-treatment evaluation
  - o Technical and operational aspects of treatment
  - o Follow-up monitoring
  - o Management of DR-TB in children
  - o Management of special situations and comorbid conditions
- Prevention and management of adverse drug events.
- Treatment outcomes.
- Implementation considerations and flow of patients along DR-TB care cascade.

Drug resistant TB (DR-TB) continues to be a public health problem, taking a heavy toll on patients, their families, communities and health-care systems. Compared to the treatment for drug susceptible TB (DS-TB), DR-TB regimens require a longer course, higher pill burden and higher toxicity profile, resulting in lower adherence and poorer treatment outcomes, including deaths. This chapter contains sub-sections for two arms of oral regimens for rifampicin resistant TB – shorter and longer as well as oral regimen for rifampicin susceptible with Isoniazid resistant TB. As any H mono resistant TB serves as a surrogate for first-line poly drug resistance in India based on prior drug resistance survey and surveillance data, the oral regimen will be applicable to poly DR-TB as well and hence, it is termed as H mono/poly DR-TB regimen in these guidelines.

4.1. Goals of TB treatment

- Render the patient non-infectious, break the chain of transmission and decrease pool of infection.
- Decrease TB deaths and related comorbidity by ensuring relapse-free cure.
- Minimize & prevent development and amplification of drug resistance.

4.2. Grouping of drugs

The anti-TB drugs recommended for treatment of MDR/RR-TB patients are grouped based on efficacy, experience of use, drug class and aligned with revised classification as per WHO Consolidated Guidelines for TB Module 4: Treatment of Drug Resistant TB (2020) *(15)*. WHO guidelines development group assessed the individual contribution to patient outcomes of drugs used in longer oral M/XDR-TB regimen using primarily the estimates of effect from the 2018 individual patient data–meta analysis (IPD-MA) and Trial 213 (delamanid) and summarized the evidence for each drug as well as the evidence-to-decision framework. Following a thorough assessment of the relative benefits and harms, recommendations were made for each drug and they were classified into three groups as explained in the **Table 4.1.**

Other drugs that are not included in Groups A–C are:

- Kanamycin and capreomycin, which were associated with poorer outcomes when used and are therefore no longer recommended for use in MDR-TB regimens.
- Gatifloxacin and high-dose Isoniazid (H^h) were used in very few patients and thioacetazone was not used at all. Quality-assured preparations of gatifloxacin are not currently available following its withdrawal from the market due to concerns about dysglycaemias. Thioacetazone is unlikely to have a role in contemporary longer regimens and is not currently available in a quality-assured formulation.
- Clavulanic acid should be included in MDR/RR-TB regimens only as a companion agent to the carbapenems (Imp-Cln and Mpm). When used in this way, it should be given with every dose of carbapenem and should not be counted as an additional effective TB agent.

Table 4.1: Grouping of anti-TB drugs and steps for designing longer MDR-TB regimen

GROUPS & STEPS	MEDICINE	ABBREVIATION
Group A **Include all three medicines**	Levofloxacin or Moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine or Terizidone	Cs Trd
Group C **Add to complete the regimen and when medicines from Group A and B cannot be used**	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or Meropenem	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)	Am (S)
	Ethionamide or Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Bedaquiline (Bdq) is a diarylquinoline that specifically targets mycobacterial ATP synthase, an enzyme essential for the supply of energy to *Mycobacterium* TB. Strong bactericidal and sterilizing activities against *M.tb* have been shown in pre-clinical, laboratory and animal experiments. The drug has a high volume of distribution, with extensive tissue distribution, highly bound to plasma proteins and is hepatically metabolized. The drug has an extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping Bdq. Bdq has shown significant benefits in improving the time to culture conversion in MDR-TB patients *(22)*. Bdq is now well incorporated within NTEP as a part of standard longer oral M/XDR-TB regimen for eligible patients.

Delamanid (Dlm) is the first approved drug in the class of nitro-dihydro-imidazo-oxazoles for the treatment of MDR-TB. It is bactericidal drug with 36 hours of half-life and act with two different mechanism of action. It blocks the synthesis of mycolic acids (i.e., stopping the bacteria from creating building blocks important for their cell walls) as well as poison the bacilli with nitric oxide, which the drugs release when metabolized *(23).*

The risk–benefit considerations for the use of Bdq in patients aged 5–17 years and Dlm in patients aged 3–5 years are similar to those considered for adults. On the basis of findings in adults and on the pharmacological and safety data reviewed, extrapolations on efficacy and safety of Dlm should be restricted to children aged 3–5 years but not to children younger than 3 years *(15).*

The prioritized order of the drugs in the groups has been derived from the evidences on efficacy and safety of the second-line anti-TB drugs **(Annexure 11).**

4.3. Treatment care cascade

It is crucial that patients with DR-TB be referred for treatment as soon as possible. Patients detected with any form of DR-TB should immediately be traced with help of the Community Health Officer (CHO) of the Health and Wellness Centres (HWC), health facility doctors and staff (including TB health visitor [TBHV] and Senior Treatment Supervisor [STS]). They must counsel and promptly refer for treatment initiation to the nearest facility. **Figure 4.1** below

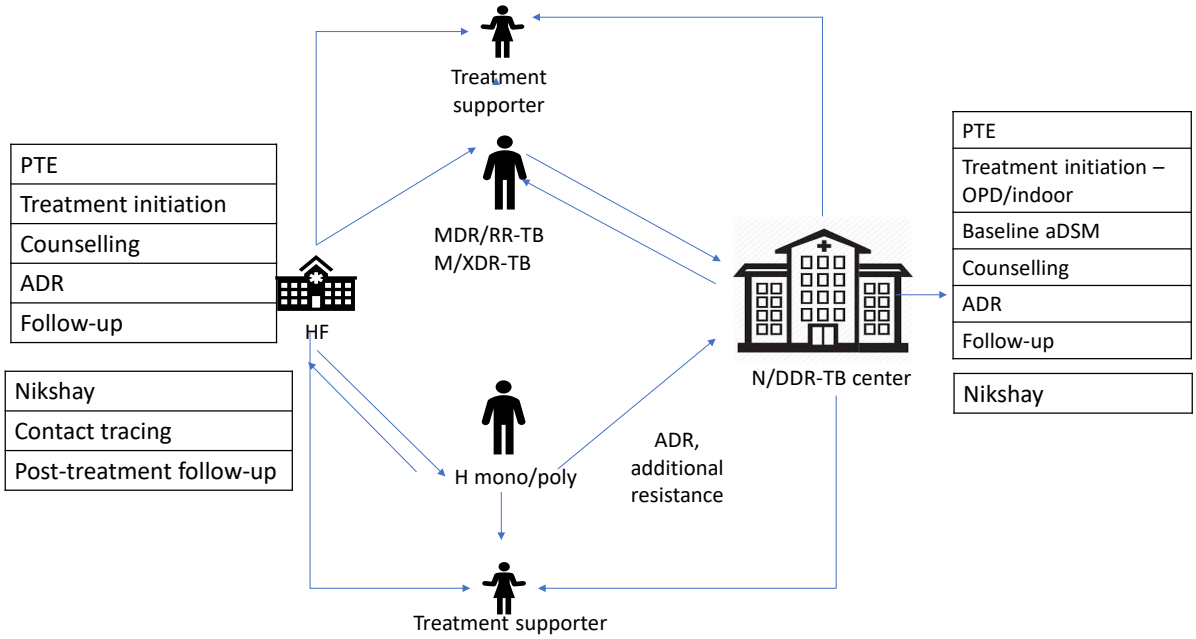


Figure 4.1 Patient flow in the DR-TB treatment care cascade

elaborates the processes for the prompt initiation of treatment in DR-TB patients. Patients with H mono/poly DR-TB may be initiated on treatment at any of the health facilities (HF) after the pre-treatment evaluation. Patients with MDR/RR-TB or XDR-TB need to be referred for necessary pre-treatment evaluations, basis which their treatment is initiated at the N/DDR-TBC. Counselling of the patient and his/her family is done at home or over phone by the health workers and doctor at the health facility. An appropriate treatment supporter needs to be identified in consultation with the patient and trained to monitor treatment adherence, maintain records, identify and report minor side effects of DR-TB patients. In case of severe ADRs, the patients will be referred to N/DDR-TBC. The contacts of the MDR/RR-TB patient with FQ susceptible, upon ruling out active TB are initiated on preventive treatment as per the guidelines. HFs are responsible to update the information of DR-TB patients in Nikshay on real-time basis. All the process as mentioned in the care cascade needs to be monitored by the TB unit (MO-TU) and senior DR-TB TB-HIV supervisor.

4.4. Health education & counselling to patients and their family/caregiver

Health education and counselling to the DR-TB patients and their family members about the disease, the mechanism of transmission and necessity of taking regular and adequate treatment, is of utmost importance. Effective counselling for all patients and their family members from the time of treatment initiation with DS-TB is found to be effective in preventing the development of drug resistance. In all circumstances, counselling should start at the initial point of contact as soon as the diagnosis is established and continued during all visits by the patient to a health facility as well as by the health-care workers to the patients' home or through the national TB call centre (Nikshay Sampark).

The DR-TB counsellor at the NDR-TBC would provide specialized counselling through the care cascade to the DR-TB patients. Although, NTEP provides a counsellor at every NDR-TBC for this purpose, all counsellors and health-care workers in the health system need to know the key points of counselling to DR-TB patients as per the DR-TB Counselling Tool **(Annexure 12)** as counselling may not just be needed at the facility level but at the field and household level as well during visits. The key points of counselling also need to be used by the executives of the national TB call centre (Nikshay Sampark). Confidentiality and informed decision-making process is paramount when performing education and counselling to patients and their family members.

4.4.1. Pre-treatment counselling

Pre-treatment counselling must serve as an informed decision-making process that enables patients to make a duly informed decision regarding the use of all anti-TB drugs and regimen. No separate written consent is needed for any treatment regimen under NTEP.

The counsellors need to be trained exclusively with a counsellor training module on an e- learning platform by NTEP. This covers the various approaches involved in counselling, tools, activities to be undertaken as well as the records and reports to be maintained by the counsellors. A counselling register must be maintained for all patients for recording information about the patients' situation and counselling services provided from the time of diagnosis till post-treatment follow-up period. The key points to be covered during pre-treatment counselling are depicted in **Figure 4.2.**

4.4.2. Counselling during treatment

Counselling during treatment offers an opportunity to explore and address past and present difficulties faced by patients in a confidential and supportive environment, especially while

Figure 4.2: Key points to be covered during pre-treatment counselling of DR-TB patients

dealing with life issues. The role of counselling in the management of DR-TB is significant.

A counsellor can help the patient to better understand importance of regular treatment as well as consequences of deviation from the treatment. Her/his role is to empower patients with disease related information and enable the patient to take informed decisions related to treatment adherence. Treatment duration of any DR-TB regimen is long enough for the patient which needs multiple sessions of counselling, preferably more frequently in the initial phase of treatment. Documentation helps the counsellor in being aware about the progress of the sessions and gives space to record his/her observations. The DR-TB counselling register serves the purpose of such documentation **(Annexure 13).**

4.5. Treatment algorithm of M/XDR-TB

Rifampicin resistance (RR) is primarily being diagnosed in the field using NAAT among all the presumptive TB patients in areas that have transitioned to rapid molecular tests for TB diagnosis and in areas yet to transition, among key populations (PLHIV, children, EPTB, smear negative or NA with X-ray suggestive of TB, contact of DR-TB patient, other vulnerable groups) or in all TB patients or among the non-responders of DS-TB or H mono/poly DR-TB patients.

MDR-TB patients get diagnosed among the H mono/poly DR-TB patients or among RR-TB patients which are subjected to FL-LPA during their treatment or if the specimen is directly tested for UDST on FL-LPA occasionally. Refer to integrated diagnostic and treatment algorithm in **Chapter 3** for more details. The treatment algorithm for RR-TB patients is detailed in **Figure 4.3** below. It will be further detailed in the subsequent sub-sections of the chapter.

4.6. Shorter oral Bedaquiline-containing MDR/RR-TB regimen

This section deals with the guidance on transitioning from the current shorter injectable containing MDR/RR-TB regimen to the shorter oral Bedaquiline-containing MDR/RR-TB regimen in patients >5 years of age weighing 15kg or more in a phased manner starting with selected states to gain programmatic experience to guide future expansion within 2021.

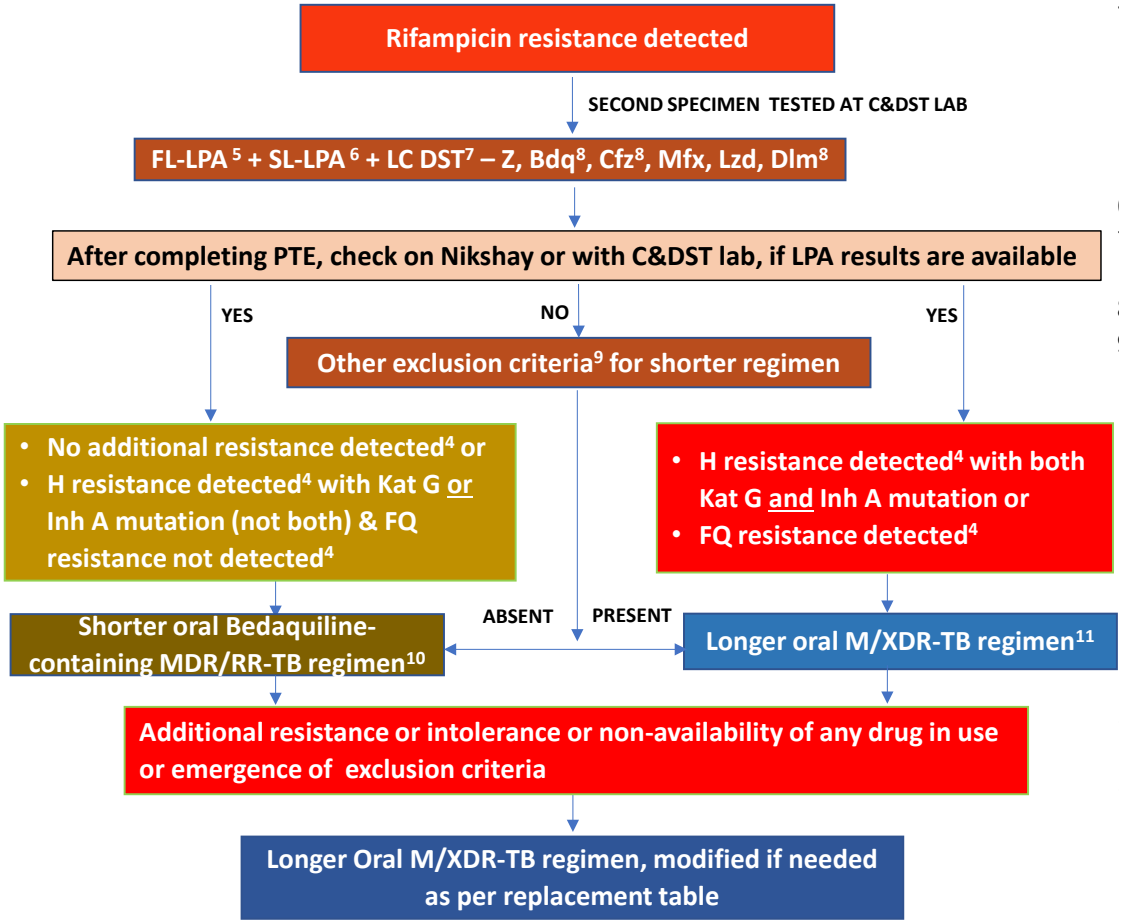


Figure 4.3: Treatment algorithm for Rifampicin resistant tuberculosis (MDR/RR-TB)

4. As per mutation pattern, includes resistance inferred
5. Discordance in RR results between NAAT & FL-LPA to be resolved with a repeat NAAT at C&DST lab and microbiologists will provide the final decision. Inh A mutation associated with Eto resistance. Use other exclusion criteria to decide regimen if FL-LPA is done on culture isolates for patients with smear negative specimen.
6. To assess Lfx, Mfx and Am resistance
7. Start treatment based on LPA results & modify based on LC&DST results later.
8. Whenever DST is available
9. Other exclusion criteria for shorter regimen include
   - History of exposure for > 1 month to BDQ, Lfx, Eto or Cfz, if result for DST (BDQ, FQ, Inh A mutation, Cfz & Z) is not available
   - Intolerance to any drug in the shorter MDR TB regimen or risk of toxicity from a drug in the shorter regimen(e.g. drug–drug interactions)
   - Extensive TB disease – presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, presence of cavities or bilateral disease on chest radiography.
   - Severe EP-TB disease - presence of miliary TB or TB meningitis or CNS TB. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)
   - Pregnant and lactating women
   - Children below 5 years
10. This portion applies as states move to shorter oral Bedaquiline-containing MDR/RR-TB regimen under guidance of NTEP.
11. Patients who were initiated on Longer oral regimen based on h/o exposure for > 1 month and in whom resistance is not detected to H or FQ may be switched to Shorter oral regimen based on the FL & SL LPA results, if the duration of Longer oral regimen drugs consumed is < 1 month.

4.6.1. Eligibility criteria

Shorter oral Bedaquiline-containing MDR/RR-TB regimen is recommended for those MDR/RR-TB patients in whom resistance to the component drugs has been excluded or those who have not been previously treated for more than one month with second-line drugs used in shorter oral Bedaquiline-containing MDR/RR-TB regimen and have no other exclusion criteria. The criteria to include or exclude the patients from offering shorter oral Bedaquiline-containing MDR/RR-TB regimen are given below.

4.6.1.1. Inclusion criteria

1. **DST based inclusion criteria**
   - Rifampicin resistance detected/inferred
   - MDR/RR-TB with H resistance detected/inferred based on InhA mutation only or based on KatG mutation only (not both)
   - MDR/RR-TB with FQ resistance not detected
2. **Other inclusion criteria**
   - Children, aged 5 years to less than 18 years of age and weighing at least 15 kg, given their special needs, in consultation with the pediatrician
   - No history of exposure to previous treatment with second-line medicines in the regimen (Bdq, Lfx, Eto or Cfz) for more than 1 month (unless susceptibility to these medicines is confirmed)
   - No extensive TB disease
   - No severe extra-pulmonary TB
   - Women who are not pregnant or lactating (**further details in 4.7.7.1**)

4.6.1.2. Exclusion criteria

1. **DST based exclusion criteria**
   - MDR/RR-TB patients with H resistance detected with both KatG and InhA mutation; and
   - MDR/RR-TB patients with FQ resistance detected.
2. **Other exclusion criteria**
   - If result for FL-LPA, SL-LPA and DST to Z, BDQ* & Cfz* is not available after pre-treatment evaluation is completed and it is a time to initiate the first dose of the regimen, then, exclude those with history of exposure for > 1 month to Bdq, Lfx, Eto or Cfz;
   - Intolerance to any drug or risk of toxicity from a drug in shorter oral Bedaquiline-containing MDR/RR-TB regimen (e.g. drug–drug interactions);
   - Extensive TB disease found in presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, presence of cavities or bilateral disease on chest radiography;
   - Severe EP-TB disease where there is a presence of miliary TB or TB meningitis or central nervous system (CNS) TB. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression);
   - Pregnant and lactating women (**refer further details in 4.7.7.1);** and
   - Children below 5 years (**refer further details in 4.6.6).**

4.6.2. Pre-treatment evaluation (PTE)

This section details about the processes to be considered while evaluating the MDR/RR-TB patients for initiation of treatment. Since the drugs used for the treatment of DR-TB have significant adverse effects and to rule out any underlying co-morbid conditions or radiological or ECG or biochemical derangements, a pre-treatment evaluation is essential to identify patients not eligible for shorter oral Bedaquiline-containing MDR/RR-TB regimen, those requiring special attention and regimen modifications from the beginning of treatment.

In majority of MDR/RR-TB patients, pre-treatment evaluation can be done on an outpatient basis as per **Table 4.2** below. The DTO and MO-TU can arrange PTE at N/DDR-TBC or at sub-district level health facility, wherever feasible. The PTE carried out at the time of treatment initiation can be considered valid for 1 month from the date of test result and patient can be re-initiated on subsequent regimen considering the previously conducted pre-treatment tests. Active drug safety management and monitoring (aDSM) treatment initiation form needs to be completed for all DR-TB patients at the time of initiation of each new episode of treatment.

Table 4.2: PTE for MDR/RR-TB patients

Clinical evaluation	Laboratory based evaluation
History and physical examination	Random blood sugar (RBS)
Height	HIV testing following counselling
Weight	Complete blood count (Hb, TLC, DLC, platelet count)
Psychiatric evaluation if required	Liver function tests (including serum proteins)
	TSH levels
	Urine examination – routine and microscopic
	Serum electrolytes (Na, K, Mg, Ca)
	Urine pregnancy test (in women of reproductive age group)
	Chest X-ray
	ECG

4.6.3. Treatment

This section deals with the evidence, regimen composition, its duration, dosages, administration, treatment extension and additional consideration for Bdq use.

4.6.3.1. Evidence

The evidence on shorter oral Bedaquiline-containing MDR/RR-TB regimen is primarily based on the programmatic data from South Africa, which was reviewed by WHO for the performance of standardized shorter regimen whereby injectable agent was replaced by Bdq, in combination with Lfx (or Mfx), Cfz, H^h, E, Z and Eto (or Pto). The preliminary analysis suggested that a 13% higher treatment success rates among the shorter oral Bedaquiline-containing MDR/RR-TB regimen group as compared to the shorter injectable containing regimen and similar treatment success rates compared to longer oral M/XDR-TB regimen *(15).*

4.6.3.2. Regimen and duration

A shorter oral Bedaquiline-containing MDR/RR-TB regimen of 9–11 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.

Shorter oral Bedaquiline-containing MDR/RR-TB regimen will be introduced in the country in a phased manner to gain programmatic experience to guide future expansion. Till the complete geographical coverage, the states yet to transition to implementing shorter oral Bedaquiline-containing MDR/RR-TB regimen will continue to use shorter injectable containing regimen for MDR/RR-TB **(see box 4.1 below).**

The regimen consists of an initial phase of 4 months that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9–11 months. Bdq is used for a duration of 6 months.

(4-6) Bdq $_{(6\ m)}$, Lfx, Cfz, Z, E, H^h, Eto	(5) Lfx, Cfz, Z, E,

The composition or the duration of the initial or continuation phase cannot be changed.

Points to remember

- From start to end of 4th month – Bdq, Lfx, Cfz, Z, E, H^h, Eto
- From start of 5th month to end of 6th month – (If IP not extended) – Bdq, Lfx, Cfz, Z, E
- From start of 7th month to end of 9th month – Lfx, Cfz, Z, E
- If the IP is extended up to 6 months then all 3 drugs Bdq, H^h and Eto are stopped together.

4.6.3.3. Treatment extension

- Total duration of shorter oral Bedaquiline-containing MDR/RR-TB regimen is for 9-11 months, depending on IP duration.
- IP should be given for at least 4 months. After 4th month of treatment, if the result of sputum microscopy is negative then CP should be initiated with Bdq continued for another 2 months.
- If sputum smear microscopy does not become negative by the 4th month of treatment, subject the patient to FL-LPA and SL-LPA and culture & DST and the IP should be extended. IP can be extended to 5th or 6th month based on smear results at the end of 4th and 5th month of treatment. This will be done for a maximum of 2 months (*i.e.,* total duration of IP is not more than 6 months). If any additional resistant to Z/Cfz on C&DST of the baseline sample is detected or to FQ/InhA & KatG mutation of the 4th month sample is detected, the patient needs to be reassessed at N/DDR-TBC for stopping shorter oral Bedaquiline-containing MDR/RR-TB regimen and initiation of longer oral M/XDR-TB regimen, immediately on receiving the report.
- Duration of CP is fixed for 5 months.

4.6.3.4. Additional considerations for the use of Bdq

Inclusion criteria

- Bdq can be provided to adults and children aged 5 years to less than 18 years of age and weighing at least 15 kg, given their special needs, in consultation with pediatrician.
- Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation
- Pregnancy & lactating women (**refer further details in 4.7.7.1).**

Exclusion criteria

- Currently having uncontrolled cardiac arrhythmia that requires medication.
- Having any of the following QTcF interval characteristics at screening **(Annexure 14**).
  - QTcF > 500 at baseline & normal electrolytes, ECG to be repeated after 6 hours and if both ECGs show QTcF >500 then the patient should not be challenged with cardiotoxic drugs; and
  - History of additional risk factors for Torsade de Pointes, e.g. heart failure, hypokalemia, family history of long QT syndrome.

If results of the serum chemistry panel, hematology or urinalysis are outside the normal reference range (including above listed parametres), the patient may still be considered if the physician judges that the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable. Hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to a patient receiving any QTc prolonging drugs.

Till the complete geographical coverage, the states yet to transition to implementing shorter oral Bedaquiline-containing MDR/RR-TB regimen will continue to use shorter injectable containing regimen for MDR/RR-TB (see **Box 4.1** below).

Box 4.1: Shorter injectable containing regimen

Exclusion criteria

1. DST-based exclusion criteria
   - MDR/RR-TB patients with H resistance detected with both Kat G and Inh A mutation; and/or
   - MDR/RR-TB patients with FQ or SLI resistance detected.
2. Other exclusion criteria
   - If result for FL, SL LPA and DST to Z & Cfz* is not available after pre-treatment evaluation is completed and it is time to initiate the first dose of the regimen, then, exclude those with history of exposure for > 1 month to Km/Am, Mfx^{h}, Eto or Cfz.
   - Intolerance to any drug in the shorter MDR-TB regimen or risk of toxicity from a drug in the shorter regimen (e.g. drug–drug interactions)
   - Extensive TB disease where bilateral cavitary disease or extensive parenchymal damage on chest radiography is present. In children aged under 15 years, presence of cavities or bilateral disease on chest radiography is seen.
   - Severe EP-TB disease where presence of miliary TB or TB meningitis or central nervous system (CNS) TB. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are seen.
   - Pregnant and lactating women (refer further details in 4.7.7.1).

Regimen composition and duration

- (4-6) Mfx^{h}, Km/Am, Eto, Cfz, Z, H^{h}, E/ (5) Mfx^{h}, Cfz, Z, E
  - If the intensive phase is prolonged, the injectable agent is only given three times a week in the extended intensive phase;

- Neither replacement of drug (except the use of Am instead of Km) nor extension of treatment duration (beyond 11 months) is permitted; and
- Pyridoxine is to be given as per weight band.

Pre-treatment evaluation and follow-up investigation

- In addition to the test listed in **Table 4.2** above (except serum electrolytes) till injectables are continued:
  - Audiometry – baseline and then every 2 months till SLI course is completed and then as and when clinically indicated; and
  - Serum creatinine – baseline and then monthly till SLI course is completed.

Rest of their management would be the same as for shorter all oral Bedaquiline containing MDR/RR-TB regimen detailed in the guidelines.

4.6.3.5. Drug dose administration

The dosage for drugs used in the regimen by weight bands for adults are enumerated in the Table 4.3 below. These are in accordance with the WHO recommended doses of anti-TB drugs for adult patients.

- The dosage of drugs would vary as per weight of the patients.
- Adult patients (≥ 18 years) would be classified in weight bands of <16 kg, 16-29 kg, 30-45 kg, 46-70 kg and >70kg.
- All drugs in the regimen are to be given daily under observation.
- All morning doses are to be supervised by the treatment supporter.
- In patients of drug intolerance – Cs, Eto and Na-PAS can be given in divided doses (twice a day).
- Pyridoxine should be provided as part of regimen till the end of treatment all patients.
- For adult DR-TB patients whose weight increases or decreases by 5 kg or more compared to baseline weight and crosses the current weight band during the course of the treatment, the weight band must be changed at the time of issuing next month box to the treatment supporter of the patient.
- For pediatric patients, the drug dosage should be adjusted immediately once the weight of the patient crosses the range of weight band. Patient must be counselled regarding the change in weight band and demonstrated the change in number of pills need to be consumed.

Table 4.3: Dosage of shorter oral Bedaquiline-containing MDR/RR-TB regimen drugs for adults

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	High dose H (H^h)	300 mg	600 mg	900 mg	900 mg
2	Ethambutol(E)	400 mg	800 mg	1200 mg	1600 mg
3	Pyrazinamide(Z)	750 mg	1250 mg	1750 mg	2000 mg
4	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
5	Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
6	Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
7	Ethionamide (Eto)*	375 mg	500 mg	750 mg	1000 mg
8	Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

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

Key considerations for newer drugs

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

The following medications are not allowed during the 24-week administration of Bdq and up to one month after the last dose of Bdq because of potential drug–drug interactions:

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

Drugs that can be used safely or which are to be avoided along with Bdq are listed in **Table 4.4.**

Table 4.4: List of the drugs that can be used safely or are to be avoided along with Bdq

Group	Safe to use	Drugs to be avoided
Antiemetics	Metoclopramide	Domperidone, Ondansetron
Analgesics	NSAIDs, Paracetamol	Tramadol
Antacids	Ranitidine, Milk of Magnesia	Pantoprazole, Omeprazole
Anti-histaminics	Pheniramine, Fexofenadine, Cetirizine	Diphenhydramine, Loratadine
Anti-malarials	Artesunate	Chloroquine
Antibiotics	Penicillins, Cephalosporins, Tinidazole	Ciprofloxacin, Norfloxacin, Cotrimoxazole, Metronidazole
Anti-fungals	Terbinafine	Fluconazole, Ketoconazole, Itraconazole
Anti-epileptics	Sodium Valproate	Phenytoin, Carbamazepine, Phenobarbital
Anti-diabetics	Mostly safe	
Anti-hypertensives	Safe (except diuretics)	Diuretics
Lipid lowering agents		Statins Best to avoid
Anti-arrhythmics	Diltiazem, Lignocaine	Amiodarone, Procainamide, Digoxin
Other cardiac drugs	Nitroglycerine, Sorbitrate	Sotalol

Group	Safe to use	Drugs to be avoided
Anti-retrovirals	Tenofovir, Zidovudine, Nevirapine, Dolutegravir	Efavirenz, Lopinavir, Ritonavir
Anxiolytics	Benzodiazepines (Alprazolam)	Avoid other sedatives
Anti-psychotics	Risperidone, Lurasidone	Haloperidol, Clozapine, Quetiapine, Olanzapine
Anti-depressants	Best to be avoided, give only if essential with ECG monitoring	Citalopram, Fluoxetine, Sertraline

Bdq should be used with caution in PLHIV infection treated with ARVs that exhibit drug-drug interactions with Bdq (efavirenz) or prolong the QT interval (lopinavir/ ritonavir) as well as in patients with comorbidities (such as diabetes) or persons with drug or alcohol use, due to limited or no information. Frequent clinical and cardiac evaluation is required in these patients.

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

4.6.4. Replacement sequence

Need for stopping/ replacing any drug in the shorter oral Bedaquiline-containing MDR/RR-TB regimen warrants stopping the regimen and evaluating the patient to switch to longer oral M/ XDR-TB regimen.

4.6.5. Follow-up monitoring

4.6.5.1. Clinical monitoring

- A day may be identified by N/DDR-TBC for all monthly follow-up visits for every patient. Patients on any DR-TB regimen should be seen by a doctor trained in NTEP PMDT guidelines for clinical evaluation on a monthly basis.
- The responsible doctor at N/DDR-TBC should assess clinical, bacteriological and radiological response to treatment, measure weight, assess possible adverse events and encourage the patient to continue treatment. Sharing care responsibilities with a pediatrician for children on shorter oral Bedaquiline-containing MDR/RR-TB regimen is strongly advised. The follow-up visit should result in updating of treatment cards and Nikshay.
- Close monitoring of patients is necessary to ensure that the patient is adhering to treatment, progressing well and any adverse effects are recognized early by the treatment supporter.
- Other relevant investigations may be done as and when clinically indicated. These investigations can be done at N/DDR-TBC or any institute as per local arrangement, however patients should not be charged for these investigations. Some patients may need to be hospitalized during treatment for medical/psychosocial reasons.

4.6.5.2. Follow-up evaluations

Apart from clinical evaluation, the patients initiated on shorter oral Bedaquiline-containing MDR/RR-TB regimen need to be closely monitored for bacteriological and radiological improvement on treatment and also for any derangements in bio-chemical, ECG and other systemic disorders indicating drug induced adverse events or co-morbidities to enable timely interventions to address these and improve the probability of treatment success, survival and quality of life **(Table 4.5).**

Table 4.5: Follow-up evaluation schedule of MDR/RR-TB patient during treatment by regimen

Regimen Class	Shorter oral Bedaquiline-containing MDR/RR-TB regimen
Duration	9 – 11 months (4-6m IP, 5m CP)
Clinical + Wt.	Monthly in IP or extended IP if previous month S+ve, quarterly in CP
Smear Microscopy	Monthly from 3rd month onwards till end of IP Monthly in extended IP only if previous month S+ve Conduct SM within 7 days, if the smear at 6 months is positive to rapidly ascertain bacteriological conversion/reversion
Culture	At the end of month 3, end of month 6 and/or end of treatment If the culture results of month 6 is positive, collect one repeat sample immediately to rapidly ascertain the bacteriological conversion/reversion If the repeat sample is culture negative, then do end of treatment specimen collection
DST	FL-SL LPA (Lfx, Mfx, Eto) and LC&DST (Z, Bdq*, Cfz*, Mfx, Lzd, Dlm*) if any • culture +ve (end of month 3 or later and end of treatment) or • smear +ve at end of IP, end of extended IP and end of treatment
UPT	As and when clinically indicated
CBC	As and when clinically indicated
TSH & LFT#	At end of IP, then as and when clinically indicated
CXR	At end of IP, then as and when clinically indicated, end of treatment
ECG$	At 2 weeks, then monthly in first 6 months, then as and when clinically indicated
S. Electrolytes (Na, K, Mg, Ca)	As and when indicated and in case of any QTcF prolongation
Specialist consultation	As and when clinically indicated
Color vision test	Once in two months (in children)

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

$ In case of baseline ECG abnormality or QTcF ≥450ms with shorter oral Bedaquiline-containing MDR/RR-TB regimen that contains Bdq & Cfz, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG

** DST whenever available*

- The most important evidence of response to DR-TB treatment is conversion of sputum smear and culture to negative. Good quality sputum specimen is therefore essential to get reliable results that form the basis of monitoring bacteriological response to treatment.
- Smear microscopy would be continued on monthly basis from 3rd month onwards. IP needs to be extended if the previous month's smear is positive up to a maximum of 6 months while follow-up culture will be done at the end of month 3 and 6 and at the end of treatment. If smear/ culture remains positive at the end of month 3/end of IP respectively and/or extended IP, a fresh specimen/culture isolate of that time will be subjected to FL-LPA and SL-LPA to check for amplification of resistance to FQ and/or H (both inhA and katG

mutation). If no additional resistance is detected, the IP will be extended on monthly basis up to a maximum of 6 months. If the smear and/or culture at month 6 or later is positive, one fresh sample must be sent to the C&DST lab for repeat culture to rapidly ascertain bacteriological reversion. If bacteriological reversion is ascertained or if any resistance is detected by FL-LPA or SL-LPA or if found to be smear/culture positive at the end of 6 months or later, the patient will be declared as 'treatment failed'. The patient is then re-evaluated for longer oral M/XDR-TB regimen with appropriate modification, if required.

- FL-LPA and SL-LPA (Lfx, Mfx, Eto) on fresh specimen and LC&DST to Z, Bdq*, Cfz* to ascertain amplification and Mfx, Lzd, Dlm* to assess susceptibility (*whenever available) will be set up on the LPA deposits for MDR/RR-TB patients on shorter oral Bedaquiline-containing MDR/RR-TB regimen who remains culture +ve at end of month 3 and 6 and at the end of treatment or smear +ve at end of IP, end of extended IP and end of treatment if the patient has not reached bacteriological reversion.
- A patient once treated with the shorter oral Bedaquiline-containing MDR/RR-TB regimen for more than one month, will never be reinitiated on it again.
- Long-term follow-up will be done with 6 monthly cultures among symptomatic patients till two years after completion of any DR-TB regimen i.e. months 6, 12, 18 and 24 post treatment.

Follow-up culture results will be the basis for declaring the final treatment outcome of all MDR/RR-TB patients.

4.6.6. MDR/RR-TB in children

The principles for treatment of MDR/RR-TB in children is quite similar to adults and uses the same second-line drugs. The treatment outcomes for MDR/RR-TB often lower and associated with higher mortality when compared to drug-sensitive TB in children.

4.6.6.1. Principles for management of MDR/RR-TB in children

- Always treat in consultation with an expert, preferably pediatrician available/linked to DR-TBC.
- Include at least 4-5 effective medicines from group A and B to which the *Mycobacterium tuberculosis* strain is known or likely to be susceptible.
- Do not add a single drug to a failing regimen to avoid amplification of resistance.
- Strict monitoring of treatment by clinical examination, radiology and culture response to be undertaken by pediatrician/ expert available/ linked to DR-TBC.

The principles of designing a WHO recommended regimen detailed in the previous section also applies to children. Children, aged 5 years to less than 18 years of age and weighing at least 15 kg, are eligible for both shorter or longer oral MDR/RR-TB regimen. Child-friendly (i.e. dispersible and palatable) formulations of the medications should be used whenever available. Bdq tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole, and can therefore be used to treat drug-resistant TB in children until a child-friendly formulation becomes available. Child-friendly formulations of most of the component drugs of shorter and longer MDR-TB regimen will be made available under NTEP. The shorter oral Bedaquiline-containing MDR/RR-TB regimen will be introduced in a phased manner. Children below 5 years are not excluded from short course but instead get short course injectable till further evidence on use of Bdq is available.

The dosages for drugs used in various DR-TB regimens by weight bands for paediatric DR-TB patients are as recommended in the WHO consolidated guidelines for TB – Module 4: Treatment of Drug Resistant Tuberculosis *(15)* and enumerated in **Annexure 15.**

The monitoring of DR-TB treatment in children is same as that in adults, however, for probable MDR-TB patients, the paediatrician available at or linked to the N/DDR-TBC must regularly evaluate the progress of the child on treatment and initiate any other investigations as deemed necessary.

4.6.7. Special situations

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

4.6.7.1. Pregnancy and lactation

Ethionamide is contraindicated during the first 32 weeks of pregnancy because animal reproduction studies have shown an adverse effect on the foetus, and there are no adequate and well-controlled studies in humans. Hence, the shorter oral Bedaquiline-containing MDR/RR-TB regimen cannot be administered in pregnant women before 32 weeks due to Eto led potential teratogenicity in first trimester and risk of hypothyroidism in the infant in second trimester. Beyond 32 weeks, the choice of regimen needs to be a consultative decision between the obstetrician and physician at the N/DDR-TBC **(refer further details in 4.7.7.1).** Although more compelling evidence on toxicity causes attributed to the use of specific anti-TB drugs during pregnancy and lactation is needed, longer oral M/XDR-TB regimen can be designed to avoid known toxicities until better safety profiles are established.

4.6.7.2. People living with HIV

The presentation of MDR/RR-TB in the PLHIV does not differ from that of DS-TB. Early diagnosis of drug- resistant TB and HIV, prompt initiation of appropriate second-line anti-TB drugs and ART, sound patient support and infection control measures are essential components in the management of drug-resistant TB in PLHIV.

The shorter or longer oral MDR-TB regimen can be used in PLHIV, including those who are receiving ART. In PLHIV with pulmonary MDR/RR-TB, additive toxicities or drug-drug interactions between anti-TB and ART medicines potentially overlap e.g. Mfx and Cfz or Efavirenz and Bdq, ritonavir may potentially increase the risk of Bdq related adverse events and hence combined use should be avoided or used with caution. In South Africa, most PLHIV received ART (95%) together with the shorter oral Bedaquiline-containing MDR/RR-TB regimen. Close monitoring of people on the two regimens is advised.

Initiating ART in patients with DR-TB

- The use of ART in HIV infected patients with TB improves survival for both drug-resistant and susceptible disease. However, HIV infected DR-TB patients without the benefit of ART may experience mortality rates exceeding 90%.

- As in any other PLHIV, those receiving the shorter oral Bedaquiline-containing regimen should also receive prophylactic medication for opportunistic infections (OI), support for TB and ARV medication adherence and close monitoring of biomarkers of immune status.
- Co-trimoxazole can be provided to all patients with HIV as per WHO recommendation.
- Based on NACO Guidelines on ART for HIV infection in adults and adolescents; irrespective of CD4 cell counts, patients co-infected with HIV and TB should be started on ART as soon as possible after initiating TB treatment. The ART should be initiated as soon as possible in all HIV/TB co-infected patients with active TB. Second-line anti-TB drugs should be initiated first, followed by ART as soon as second-line anti-TB drugs are tolerated. Generally, this should be within the first two weeks of initiating DR-TB treatment. On the other hand, undue delay in starting ART could result in significant risk of HIV related death amongst DR-TB patients.
- It is critical that the ART medical officer and physician of N/DDR-TBC collaborate closely to decide on the ART regimen composition to adjust to the shorter oral Bedaquiline-containing MDR/RR-TB regimen that is recommended to be used as a package with no scope of any modifications. However, regimen modification may be considered on a case to case basis in longer oral M/XDR-TB regimen based on drug-drug interactions and synergistic side effects between the component drugs of both regimen.
- Occasionally, patients with HIV related TB may experience a temporary exacerbation of symptoms, signs, or radiographic manifestation of TB after beginning TB treatment. This paradoxical reaction occurs in HIV infected patients with active TB and is thought to be a result of immune restitution due to the simultaneous administration of ART and tuberculosis medication (IRIS syndrome). Symptoms and signs may include high fever, lymphadenopathy, expanding intrathoracic lesions and worsening of chest radiographic findings. The diagnosis of a paradoxical reaction should be made only after a thorough evaluation has excluded other etiologies, particularly where TB treatment has failed. For severe paradoxical reactions prednisone (1–2 mg/kg for 1–2 weeks, then gradually decreasing doses) may be used.
- Patients with drug-resistant TB and HIV may suffer from severe wasting, diarrhoeal diseases and malabsorption syndromes. Wherever possible, patients with drug-resistant TB living with HIV should be offered socioeconomic and nutritional support. NTEP also monitors treatment outcomes separately for HIV-TB patients.
- Considering the risk of developing primary DR-TB among susceptible close contacts, effective TB infection control measures are mandatory. If the patient shows signs of TB treatment failed, further evaluation is warranted. In addition, the ART regimen should be evaluated for possible treatment failed as described in other WHO guidelines.

4.6.7.3 Role of surgery

- In DR-TB patients with localized disease, surgery, as an adjunct to chemotherapy, can improve outcomes provided skilled thoracic surgeons and excellent postoperative care is available.
- When unilateral resectable disease is present, surgery should be considered in the following patients:
  - Absence of clinical or bacteriological response to chemotherapy despite six to nine months of treatment with effective anti-TB drugs;

- High risk of treatment failed or relapse due to high degree of resistance or extensive parenchymal involvement;
- Morbid complications of parenchymal disease e.g. haemoptysis, bronchiectasis, broncho-pleural fistula, or empyema; and
- Relapse after completion of anti-TB treatment.

- WHO has recommended surgical procedures like wedge resections or lobectomy in patients with localized lesions. If surgical option is under consideration, at least six to nine months of chemotherapy is recommended prior to surgery to ensure culture conversion.
- Linkages may be established with existing institutions with thoracic surgical facilities in the state (government/ private through partnership options) where patients can be referred for expert opinion and decisions taken to provide surgical options after a detailed review of the patient. AB-PMJAY is a potential national insurance that can be leveraged to cover the cost of surgery.
- States need to identify institutes with capacity to conduct thoracic surgery and link up DR-TBCs to such institutes with support to the patient to cover costs involved for surgery through innovative mechanisms.

4.6.7.4. Renal impairment

Renal insufficiency due to longstanding TB disease itself, previous use of aminoglycosides or concurrent renal disease is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal impairment. Drugs which might require a dose or interval adjustment in the presence of mild to moderate renal impairment are E and Lfx. In the presence of severe renal impairment, Lfx can be replaced with normal dose Mfx (200/400 mg based on the patients' weight) and many other drugs that may require adjustments as indicated in **Table 4.6.**

Table 4.6: Dose adjustment of anti-TB drugs of shorter oral Bedaquiline-containing MDR/ RR-TB regimen in presence of renal impairment

Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving hemodialysis (unless otherwise indicated dose after dialysis)
Isoniazid	No adjustment necessary
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Ethionamide	No adjustment necessary
Bedaquiline	No dosage adjustments required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Clofazimine	No adjustment necessary

Estimated creatinine clearance calculations: Men: Ideal Body Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dl), Women: 0 85 X Ideal Body Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dl))

4.6.7.5. Pre-existing liver disease

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

Once a patient on second-line anti-TB drugs develops hepatitis, other etiologies should be excluded such as viral hepatitis, alcoholic hepatitis, drug induced hepatitis by non-TB drugs etc. Further management should be on the same line as in non-DR-TB patients. MDR/RR-TB patients having deranged liver function test (LFT) during pretreatment evaluation should be strictly monitored as clinically indicated while on treatment. However, routine LFT is not recommended in all patients.

In patients with pre-existing liver disease with persistently abnormal liver function test, a shorter oral MDR/RR-TB regimen will be avoided due to presence of H(h), Eto and Z.

4.6.7.6. Seizure disorders

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

In the regimen, Eto and FQ have been associated with seizures and hence should be used carefully amongst MDR/RR-TB patients with history of seizures. Though the seizure is not common with Bdq, it should also be considered while assessing the causality assessment.

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

4.6.7.7. Psychiatric illness

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

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

H(h), FQ and Eto have been associated with psychosis. Pyridoxine prophylaxis may minimize the risk of neurologic and psychiatric adverse events. When any patient on DR-TB treatment develops psychosis, other etiologies such as psychosocial stresses, depression, hypothyroidism, illicit drug and alcohol use, should also be looked for.

All health-care workers treating drug-resistant TB should closely work with the psychiatrist at the DR-TBC and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patients being a danger to him/herself or others. Mechanisms to deal with psychiatric emergencies (often inpatient psychiatric hospital admissions) should be available 24X7.

4.6.8. Adverse drug events

- This section focuses on the measures to promote patient safety that contributes to improving quality of care during the treatment of drug-resistant TB, relieving unnecessary suffering.
- Patients and their family members should be encouraged to report voluntarily if the patient experiences any adverse effects, though patients should not be asked any leading question to elicit any adverse reaction. However, if the patient makes any complaint, the patient should be evaluated in detail and necessary action taken.
- The treatment supporter should be trained to recognize adverse events like nausea, vomiting, diarrhoea, skin rash, loss of hearing, reduced sensation, psychiatric symptoms and jaundice. Training should also be provided on the management of minor reactions and when the patients should be referred to the doctor. Severe adverse events (SAEs) should be referred to an appropriate clinical facility, which may include D/NDR-TBC coordinating care for the patient.
- Poor management of adverse effects increases the risk of treatment interruption and LTFU which may result in death or permanent morbidity. The ability to monitor patients for adverse effects daily is one of the major advantages of having a treatment supporter over self-administration of drug-resistant TB treatment.
- The programme has developed an ADR tool kit which contains the material to build the capacity of treatment supporter to screen and manage common ADRs during the course of treatment. The toolkit consists of a training guide for health workers; posters on common ADRs, causality assessment, grading and management protocol of common ADR; and ready reckoner for the doctor.
- The CHO or HF doctor may advice the patients to temporarily suspend intake of certain offending drug/s which are causing side effects. The drugs should not be withheld continuously for more than 60 days for them to be re-introduced.
- Adverse effects are easy to recognize and are usually reported by patients when they experience them. However, few effects may not be reported by patients in the presence of other major adverse effect/s. Certain laboratory investigations are required on routine basis during treatment to monitor the ADR (**Table 4.7**).

Table 4.7: Additional monitoring for patients on shorter oral Bedaquiline-containing MDR/RR-TB regimen

Laboratory Investigations	Recommended action in specific situations beyond routine follow up evaluation schedule (refer Table 4.5)
S. electrolytes (Na, K, Cl)	Every, one to three weeks in HIV infected patients, diabetics, and other high-risk patients
S. Mg & Ca	Check magnesium and calcium blood levels whenever hypokalaemia is diagnosed. Repeat if any electrocardiogram (ECG) abnormalities develop (prolonged QT interval)
Thyroid stimulating hormone (TSH)	Every six months. TSH is sufficient for screening for hypothyroidism and it is not necessary to measure hormone thyroid levels. Monthly monitoring for clinical signs/symptoms of hypothyroidism is also necessary
Liver function test	Periodic monitoring every six months for patients at risk for or with symptoms of hepatitis. For HIV- infected patients, monthly monitoring while on Bdq, with viral hepatitis, monitoring every two weeks for the first month and then every month is recommended
HIV testing	Repeat if clinically indicated
Lactic acid	Indicated for work up of lactic acidosis in patients on ART receiving shorter oral Bedaquiline-containing MDR/RR-TB regimen
Fasting blood glucose	In diabetic patients, monitor fasting blood glucose at baseline and monitor monthly. Educate/remind patients on signs and symptoms of hypoglycaemia and hyperglycaemia monthly
Vision tests	Perform at least a visual acuity test with Snellen charts and colour vision test at baseline (as a small percentage of the population has colour blindness). Repeat the test for any suspicion of change in acuity or colour vision due to E & Lzd
Educational, mental health and social consultation	At baseline by personnel trained in health education, mental health, and social issues relevant to DR-TB management; during treatment and repeat as indicated. Refer to social worker, psychologist or psychiatrist when indicated

Below in **Table 4.8** possible adverse drug events due to drugs used in shorter oral Bedaquiline-containing MDR/RR-TB regimen are depicted. The detailed management of these adverse events is mentioned in **Section 4.10.**

Table 4.8: Possible adverse events due to drugs in shorter oral Bedaquiline-containing MDR/RR-TB regimen

Adverse Drug Events	Drugs	Adverse Drug Events	Drugs
QT prolongation	Bdq, FQ, Cfz	**Psychotic symptoms**	H, FQ,
Rash, allergic reaction and anaphylaxis	Any drug	**Suicidal ideation**	H, Eto
Gastrointestinal symptoms	Eto, Z, E, Bdq, Cfz, FQs, H	**Seizures**	H, FQ
Diarrhoea and/or flatulence	Eto	**Tendonitis and tendon rupture**	FQ

Adverse Drug Events	Drugs	Adverse Drug Events	Drugs
Hepatitis	Z, H, Eto, Bdq	**Vestibular toxicity (tinnitus and dizziness)**	FQs, H, Eto
Giddiness	Eto, FQ, Z	**Optic neuritis**	E, Lzd, Eto, Cfz, H
Hypothyroidism	Eto	**Metallic taste**	Eto, FQs
Arthralgia	Z, FQ, Bdq	**Gynaecomastia**	Eto
Peripheral neuropathy	H, FQ, rarely Eto, E	**Alopecia**	H, Eto
Headache	Bdq	**Superficial fungal Infection and thrush**	FQ
Depression	FQ H, Eto	**Dysglycaemia and hyperglycaemia**	Eto

4.7. Longer oral M/XDR-TB regimen

4.7.1. Eligibility criteria

- Longer oral M/XDR-TB regimen is recommended for MDR/RR-TB patients who are excluded from shorter oral Bedaquiline-containing MDR/RR-TB regimen including for the XDR-TB patients. Refer to **Section 4.6.1** for the exclusion criteria of shorter oral Bedaquiline-containing MDR/RR-TB regimen.
- In case of additional resistance or intolerance or non-availability of any drug in use or emergence of exclusion criteria to shorter oral Bedaquiline-containing MDR/RR-TB regimen or any longer regimen, the patient would be re-evaluated and initiated on longer oral M/XDR-TB regimen at N/DDR-TBC with any modifications, if additional resistance to any second-line drugs especially Lfx, Mfx, Bdq*, Lzd, Cfz*, Dlm* and Z (*whenever available). The regimen modification would be done using replacement sequence from group C detailed in the later section.

4.7.2. Pre-treatment evaluation (PTE)

This section details the processes to be considered while evaluating the M/XDR-TB patients for initiation of treatment. In majority of M/XDR-TB patients, pre-treatment evaluation can be done on an outpatient basis. The DTO can arrange pre-treatment evaluation at N/DDR-TBC or at sub-district level health facility, wherever feasible. The list of investigations enumerated for shorter oral Bedaquiline-containing MDR/RR-TB regimen (Table 4.2) will remain applicable to longer oral M/XDR-TB regimen with the following additional investigations specific to group C drugs that may be required in situations where the longer oral M/XDR-TB regimen may need to be modified.

- Blood urea & serum creatinine – if Am needs to be added
- Ophthalmologist opinion (for linezolid)
- Surgical evaluation for consideration after culture conversion is achieved

The pre-treatment evaluation carried out at the time of treatment initiation can be considered valid for 1 month from the date of test result and the patient can be re-initiated on subsequent regimen considering the previously conducted pre-treatment tests. The active drug safety management and monitoring (aDSM) treatment initiation form needs to be completed for all DR-TB patients at the time of initiation of each new episode of treatment.

4.7.3. Treatment

This section outlines details regarding longer oral M/XDR-TB regimen.

4.7.3.1. Regimen and duration

In MDR/RR-TB patients on longer oral M/XDR-TB regimen, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective and that at least three agents are included for rest of the treatment if Bdq is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it as recommended by WHO. *(15)*

However, in India the experts concurred to start with all 5 drugs of Group A and B and continue with 4 drugs in the latter part of the regimen (beyond 6-8 months) if the patient can tolerate the drugs and for operational ease in the field.

Longer oral M/XDR-TB regimen is of 18-20 months with no separate IP or CP. Although standardization in the design of longer regimens is possible, in many cases, the modification of the composition and duration of a regimen to make it individualized could enhance regimen effectiveness or safety (or both).

Once a patient is placed on a longer oral M/XDR-TB regimen for at least 4 weeks, normally that patient can no longer be switched to the shorter oral Bedaquiline-containing MDR/RR-TB regimen because this 4-weeks treatment would represent an exposure to second-line medicines.

(18-20) Lfx Bdq $_{\text{(6 month or longer)}}$ Lzd# Cfz Cs
#dose of Lzd will be tapered to 300 mg after the initial 6–8 months of treatment *Bdq will be given for 6 months & extended beyond 6 months as an exception* *Pyridoxine to be given to all DR-TB patients as per weight band* *For Pre-XDR-TB and XDR-TB patients the duration of longer oral XDR-TB regimen would be for 20 months with appropriate modifications*
Caution to be exercised while choosing group A and B drugs • Bdq & Cfz may lead to cardiotoxicity particularly QtcF prolongation. Hence, baseline ECG, serum electrolytes must be assessed and corrected and if QtcF is between 450 to 500 ms, a cardiologist consultation must be taken prior to treatment initiation. • Lzd may cause anaemia, thrombocytopenia, peripheral neuritis and optic neuritis. Adequate precaution may be taken accordingly. • Cs should be used carefully in pre-existing seizure disorders not adequately control with medication. Neurologist consultation should be taken prior to initiation of Cs in such patients, also psychiatrist opinion should be taken in patients with signs of severe depression as Cs can aggravate depression and lead to suicidal tendency. • Cfz also causes dark brown discoloration of the skin. Accordingly, the patient should be counselled prior to initiation of treatment.

4.7.3.2. Treatment extension

- Total duration of longer oral M/XDR-TB regimen is 18–20 months.
- After month 6 of treatment, the patient must be reviewed based on month 5 culture results. If month 5 culture result is not available at the end of month 6, decision to taper the dose of Lzd to 300 mg will be based on month 4 culture result. If the month 5 or 4 culture result (whichever applicable) remains positive, the dose of Lzd (600 mg) and the regimen is

extended by 1 month to month 7 and for a maximum till month 8 based on monthly culture results of month 6 and 7 respectively and clinical/radiographic response. If the month 8 culture is also positive, subject the culture isolate to FL-LPA, SL-LPA and C&DST. If any additional resistant to Group A, B or C drugs in use is detected, the patient needs to be reassessed at N/DDR-TBC for modification of longer oral M/XDR-TB regimen immediately on receiving the report.

- The duration of Bedaquiline is limited to 6 months. Extension beyond 6 months is to be considered in patients in whom an effective regimen cannot otherwise be designed if only 2 of 5 drugs are available from Groups A & B and adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST.
- Maximum duration of treatment is not more than 20 months. A treatment duration of 15–17 months after culture conversion is suggested for most patients. The duration may be modified according to the patient's response to treatment.

4.7.3.3. Additional considerations for the use of newer drugs

Some points to consider in addition to details outlined in **Section 4.6.3.4** are as follows**:**

- Dlm can be provided to adults and children aged 6 years to less than 18 years, given their special needs in consultation with a pediatrician. Dlm will be considered only for longer oral M/XDR-TB regimen.
- If taking a light meal with Dlm and other anti-TB drugs, patients should not consume milk-containing products at the same time, as the calcium in these can decrease the absorption of FQs.
- It is important that Dlm be taken daily preferably after a standard meal to improve bioavailability
- Other second-line drugs that are likely to be administered with Bdq/Dlm, notably FQs and Cfz may potentially increase the risk of cardiotoxicity.
- Drug-drug interaction studies of Dlm with tenofovir, efavirenz and lopinavir/ritonavir, respectively, suggested that no dose adjustments were needed when Dlm was used with any of these ARV agents. No new or significant drug-drug interactions between Dlm and ARV drugs were observed in Trial 213, although the number of participants receiving dual treatment was low and results should be interpreted with caution. *(24)* Therefore, PLHIV who will be receiving Dlm as part of DR-TB treatment should have their ART regimens designed in close consultation with HIV clinicians and ART specialists.

4.7.3.4. Drug dose administration

The dosage of M/XDR-TB drugs for adults used in longer oral M/XDR-TB regimen with replacement drugs from group C in the order of priority customized for India by national experts are enumerated in **Table 4.9.** For further details including key considerations for Bdq and drugs to be avoided with Bdq and Dlm, refer to **Table 4.4**.

Table 4.9: Dosage of M/XDR-TB drugs
for adults in longer oral M/XDR-TB regimen (with replacement drugs)

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
2	Moxifloxacin (Mfx)	200 mg	400 mg	400 mg	400 mg
3	High dose Mfx (Mfx^{h})	400mg	600mg	800mg	800mg

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

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

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

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

4.7.4. Replacement sequence

In case of the need for replacement of any of the component(s) in the longer oral M/XDR-TB regimen, the following broad principles apply:

- The drugs are replaced according to their efficacy, no demonstrable resistance, prior use, side-effects profile and background resistance to the replacement drug in the country as per the NDRS report *(4)*.
- The regimen should preferably be fully oral. However, in certain circumstances, injectables may have to be used for the need of efficacy and side-effect profile.
- At least 4-5 drugs are to be used in the initial 6 to 8 months. In situations where no replacement of any drug is required in the first 6 or 8 months of treatment in MDR-TB or XDR-TB patients, continue with at least 3 drugs after this depending upon resistance, tolerability, availability, contraindication etc. of any one of Group A or B drugs.
- Replacement sequence of Group C drugs for longer oral M/XDR-TB regimen was recommended in the order of - delamanid, amikacin, pyrazinamide, ethionamide, PAS, ethambutol, penems.
- Combined use of Bdq and Dlm in the regimen is recommended for those M/XDR-TB patients in whom an appropriate regimen cannot be designed using all 5 drugs from Group A and B.

- In the final 12 months, at least 3-4 drugs are to be used from Group A & B. In situations where this can not be done, the remaining drugs from Group C may be added as per the replacement sequence to complete 4 drugs (except Dlm and Am).
- Dlm and Am will not be started in the final 12 months of treatment.
- The duration of new drugs (Bdq or Dlm) is limited to 6 months. Extension beyond 6 months to be considered in patients in whom an effective regimen cannot be otherwise designed if only 2 of 5 drugs are available from Groups A & B and adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST.
- Though Imp-Cln is 4th in the sequence of drugs of group C in WHO guidelines (15), it will only be used as the last resort for designing the regimens, operational issues of a Peripherally Inserted Central Catheter (PICC) placement for the entire duration of its use, need for admission.
- In individual patients for whom the design of an effective regimen is not possible as per recommendations, BPaL can be considered as a last resort under prevailing ethical standards, if Bdq and Lzd are available for use.
- To modify the longer oral M/XDR-TB regimen, the N/DDR-TBC physician must review the resistance pattern, tolerability history, contraindications and availability of first and second-line drugs to identify the number of drugs from Group A and Group B that need to be replaced and then refer to the **Table 4.10** below.

Table 4.10: Sequence of using replacement drugs to modify the longer oral M/XDR-TB regimen

Sr. No	Drugs to be replaced	No. of drugs to include from			Final Regimen after replacement
		Group A (3 drugs)	Group B (2 drugs)	Group C (7 drugs)	
1	None$^{\$}$	3	2	-	6-8 Lfx, Bdq, Lzd, Cfz, Cs / 12 Lfx, Lzd, Cfz, Cs
2	1 group A drug$^{@}$	2	2	1	**No FQ,** then 6-8 Bdq, Lzd, Cfz, Cs, Dlm / 12 Lzd, Cfz, Cs $^{\$}$ **No Bdq**$^{\$}$**,** then 6-8 Lfx*, Lzd, Cfz, Cs, Dlm / 12 Lfx*, Lzd, Cfz, Cs **No Lzd,** then 6-8 Lfx*, Bdq, Cfz, Cs, Dlm / 12 Lfx* Cfz, Cs
3	1 group B drug	3	1	1	**No Cfz,** then 6-8 Lfx* Bdq, Lzd, Cs Dlm / 12 Lfx* Lzd, Cs **No Cs,** then 6-8 Lfx* Bdq, Lzd, Cfz, Dlm / 12 Lfx* Lzd, Cfz
4	1 group A drug$^{@}$& 1 group B drug	2	1	2	**No FQ & Cfz** then 6-8 Bdq, Lzd, Cs, Dlm, Am$^{\#}$ / 12 Lzd, Cs, Z$^{\#}$, Eto$^{\#}$ **No FQ & Cs** then 6-8 Bdq, Lzd, Cfz, Dlm, Am$^{\#}$ / 12 Lzd, Cfz, Z$^{\#}$, Eto$^{\#}$ **No Bdq & Cfz** then 6-8 Lfx* Lzd, Cs, Dlm, Am$^{\#}$ / 12 Lfx* Lzd, Cs **No Bdq & Cs** then 6-8 Lfx* Lzd, Cfz, Dlm, Am$^{\#}$ / 12 Lfx* Lzd, Cfz **No Lzd & Cfz** then 6-8 Lfx* Bdq, Cs, Dlm, Am$^{\#}$ / 12 Lfx*, Cs, Z$^{\#}$, Eto$^{\#}$ **No Lzd & Cs** then 6-8 Lfx* Bdq, Cfz, Dlm, Am$^{\#}$ / 12 Lfx*, Cfz, Z$^{\#}$, Eto$^{\#}$

Sr. No	Drugs to be replaced	No. of drugs to include from			Final Regimen after replacement
		Group A (3 drugs)	Group B (2 drugs)	Group C (7 drugs)	
5	2 group A drugs[@]	1	2	2	**No FQ & Bdq** then 6-8 Lzd, Cfz, Cs, Dlm, Am[#] / 12 Lzd, Cfz, Cs, Z[#] **No FQ & Lzd** then 6-8 Bdq, Cfz, Cs, Dlm, Am[#] / 12 Cfz, Cs, Z[#], Eto[#] **No Bdq & Lzd** then 6-8 Lfx*, Cfz, Cs, Dlm, Am[#] / 12 Lfx*, Cfz, Cs, Z[#]
6	2 group B drugs	3	0	2	**No Cfz & Cs** then 6-8 Lfx* Bdq, Lzd, Dlm, Am[#] / 12 Lfx*, Lzd, Z[#], Eto[#]
7	3 or more from group A drugs[@]& group B drugs	Use the remaining drugs		3 or more	Remaining drugs from Group A and B plus 3-5 drugs from Group C using the conditions/sequence# below to make a regime with at least 5-6 drugs known to be effective. If Bdq and Dlm can be used, their combined use in the regimen with at least 4 -5 drugs or its extended use beyond 6 months till clinical and bacteriological conversion is achieved. If Bdq and Lzd can be used, explore the possibility of using BPaL regimen under prevailing ethical conditions.

[$] No replacement required if any one drug is dropped in the last 12 months of treatment.

[@] FQs would be counted together as one drug of group A if neither Lfx nor Mfx[h] can be used

* if Lfx can't be used, use Mfx[h] if SL LPA pattern suggests and continue if Mfx(1.0) sensitive on LC&DST

[#] if sensitive on LPA or LC&DST . inhA mutation would indicate Eto resistance. If resistance detected, then the drugs to be used in the order of Dlm, Am[#], Z[#], Eto[#], PAS, E and as a final resort Imp-Cln or Mpm in combination with Amoxiclav. Dlm & Am may not be introduced after initial 8 months of treatment and during this later phase the replacement sequence would be Z[#], Eto[#], PAS, E

4.7.5. Follow-up monitoring

4.7.5.1. Clinical monitoring

For clinical monitoring of any DR-TB patient, refer to section 4.6.5.1.

4.7.5.2. Follow-up evaluations

Apart from clinical evaluation, the patients initiated on longer oral M/XDR-TB regimen need to be closely monitored for bacteriological and radiological improvement on treatment and also for any derangements in bio-chemical, ECG and other systemic disorders indicating drug induced adverse events or co-morbidities to enable timely interventions to address these and improve the probability of success, survival & quality of life **(Table 4.11)**.

Table 4.11: Follow up evaluation schedule of longer oral M/XDR-TB regimen during treatment

Regimen Class	Longer Oral M/XDR-TB Regimen
Duration	18-20 months (no separate IP/CP)
Clinical + Wt.	Monthly up to month 6 or 7 or 8 if previous month S+ve Quarterly in from month 7 or 9 onwards
Smear microscopy	With culture at C&DST lab Conduct SM within 7 days, if any smear at 6 month or later is positive to rapidly ascertain bacteriological conversion/reversion C&DST lab to update the result on Nikshay and inform the concerned field staff of collection center on same day
Culture	Monthly from month 3 onwards to end of 6 months or 7 or 8 if the previous month's culture is +ve Quarterly month 6 or 7 or 8 onwards based on previous month's culture results If the culture results of month 6 or any of the quarterly culture is positive, collect one repeat specimen immediately and send it for culture to rapidly ascertain bacteriological conversion/reversion and if the repeat specimen is culture negative, then the subsequent quarterly or end of treatment specimen collection.
DST	FL & SL-LPA (Lfx, Mfx, Am, Eto) and LC&DST (Mfx, Lzd, Cfz*, Bdq*, Dlm*, Z) if culture +ve at the end of 6 months or any time beyond
UPT	As and when clinically indicated
CBC/platelets ^	Day 15, monthly in first 6 months, 6 or 7 or 8 if previous month S+ve, then as and when clinically indicated
TSH & LFT#	LFT quarterly, then as and when clinically indicated. TSH every 6 months
CXR	At the end of month 6, end of treatment and as and when clinically indicated
ECG$	At 2 weeks, monthly in first 6 months and till Bdq/Mfx/Cfz/Dlm is extended, then as and when clinically indicated.
S. electrolytes (K, Mg, Ca)	As and when indicated and in case of any QTcF prolongation

^ If Lzd is part of the regimen to rule out bone marrow suppression

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

$ In case of baseline ECG abnormality or QTcF ≥450ms with longer oral M/XDR-TB regimen that contains Bdq, Mfx, Cfz or Dlm, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG.

* DST whenever available.

- The most important evidence of response to DR-TB treatment is conversion of sputum smear and culture to negative. Good quality sputum specimen is therefore essential to get reliable results that form the basis of monitoring bacteriological response to treatment.
- Smear and culture will be done as per table above to decide on extension of regimen. Extension of treatment is based on the follow-up culture result of month 5 or 4 which would be available by end of month 6 of treatment. If month 4 culture result is negative, taper the dose of Lzd to half for subsequent period of treatment from month 6 onwards. If the follow-up culture result (month 4 or 5 whichever is available at end of month 6) is

positive, extend the treatment on monthly basis with monthly smears and cultures up to maximum of month 8, beyond which, taper the dose of Lzd to half for subsequent period in all the weight bands. Patient should have received minimum 8 months of treatment before declaring the patient as treatment failed if the patient is not converted.

- FL & SL LPA (Lfx, Mfx, Am, Eto) on fresh specimen and LC&DST (Mfx, Lzd, Cfz*, Bdq*, Dlm*, Z) (*whenever available) will be set up on the LPA deposits only for MDR/RR-TB patients if patient remains smear/culture positive at end of 6 months and beyond if the patient has not reached bacteriological conversion/reversion.
- If any change is required in the composition of longer oral M/XDR-TB regimen due to reasons like resistance, intolerability, unavailability or contraindication during the initial 8 months of treatment, re-initiation or re-registration is not required and patient will be continued with same registration date for that episode with the modifications as per replacement table above unless the patient is declared as 'treatment failed'. Total duration of treatment should not be extended beyond 20 months.
- Long-term follow-up will be done with 6 monthly cultures among symptomatic patients till two years after completion of any DR-TB regimen i.e. months 6, 12, 18 and 24 post treatment.

Follow-up culture results will be the basis for declaring the final treatment outcome of all MDR/RR-TB patients.

4.7.6. M/XDR-TB in children

- For management of DR-TB in children, please refer to section 4.6.6. In addition, Dlm is already approved for use and available under NTEP from 6 years onwards. Although the use of Dlm in the age group of 3-6 years has been approved by WHO, the regulatory approval in India is awaited. Achieving an appropriate dose in children aged 3–5 years will be easier when the special formulation dispersible 25 mg tablet used in trials in these age groups becomes available. The recent data review for the WHO guidelines *(15)* suggested that there are no additional safety concerns for concurrent use of Dlm with Bdq.
- As in adults, extension of Bdq beyond 6 months and concomitant use of Bdq and Dlm in special situations will apply to children as well. For children under 5 years of age where neither Bdq nor Dlm is approved yet, the longer oral M/XDR-TB regimen suitably modified as per the replacement drug **Table 4.10** will be used to design the regimen considering child-friendly formulations where Bdq can be replaced with Am, Z, Eto in the initial phase. 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 treatment and the treatment needs to be provided under strict monitoring to ensure early detection of ototoxicity. The avoidance of an injectable-containing regimen is particularly desirable in children. Shortening the total treatment duration to less than 18 months may be considered in the case of children without extensive disease. Seizures may be more common in children with meningitis treated with imipenem, and meropenem is preferred for cases of TB meningitis and in children.

4.7.7. Special situations

Certain associated special situations make the treatment of DR-TB more difficult. These include DR-TB in pregnancy; those co-infected with HIV; requiring surgery; in patients with

renal impairment; in patients with pre-existing liver disease; seizure disorders; psychiatric illnesses and in extra-pulmonary TB patients.

4.7.7.1. Pregnancy and lactation

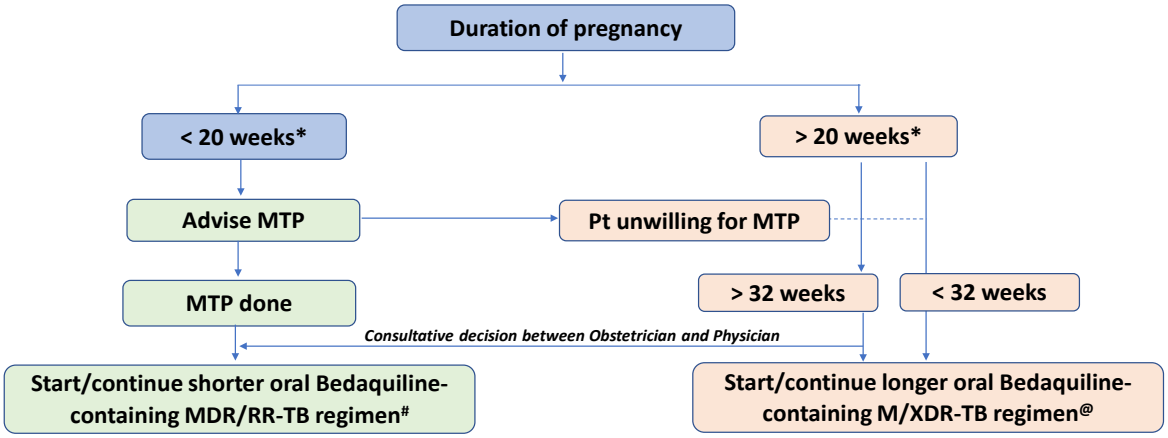
Pregnancy is not a contraindication for treatment of drug-resistant TB but poses great risk to both the mother and foetus. Second-line injectables are contraindicated throughout the pregnancy due to its effect on the 8th cranial nerve (auditory) of the foetus. Eto is contraindicated during the first 32 weeks of pregnancy due to teratogenic effects. For these reasons, shorter oral Bedaquiline-containing MDR/RR-TB regimen cannot be administered in pregnancy with DR-TB. It is prudent to solicit the opinion of an experienced gynecologist/obstetrician while treating such patients.

Knowledge about the safety of Bdq and Dlm in pregnancy and during breastfeeding is still sparse. However, there is now new evidence from an observational study in South Africa on the use of Bedaquiline during pregnancy. As part of their MDR/RR-TB regimen, 58 women received Bedaquiline and were compared to 50 women who had no Bedaquiline in their regimen. The observational cohort study between January 2013 and December 2017 demonstrated that treatment outcomes were 9% more favourable for pregnant women exposed to Bdq versus not exposed. The women in this study gave birth to 109 live infants, of whom 49 had Bedaquiline exposure in utero and 60 had no Bedaquiline exposure in utero. Clinical assessments were carried out at 2, 6 and 12 months after birth to document infant outcomes. The main objective of the study was to document treatment, pregnancy and infant outcomes among women treated for RR-TB with second-line TB drugs during pregnancy. The results of this study indicated that fetal exposure to Bdq in utero was associated with low birth weight (<2500 g), with no other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in infants until 1 year of age. Based on this evidence, WHO recommended that, in pregnancy, a longer oral M/XDR-TB regimen be individualized to include components with an established safety profile. The outcomes of treatment and pregnancy, and postpartum surveillance for congenital anomalies, should be documented to help inform future recommendations for MDR-TB treatment during pregnancy.

All women of childbearing age who are awaiting results of C&DST as well as those receiving DR-TB treatment should be advised and counselled intensively to use birth control measures because of the potential risk to both mother and foetus. It should be remembered that oral contraceptives might have decreased efficacy due to vomiting and drug interactions with DR-TB drugs.

All women of childbearing age should be tested for pregnancy as part of the pre-treatment evaluation and whilst on treatment. DR-TB patients found to be pregnant prior to treatment initiation or whilst on treatment must be evaluated in consultation with a gynecologist or obstetrician, considering factors such as risks and benefits of DR-TB treatment; severity of DR-TB; gestational age; and potential risk to foetus.

In pregnant women, strict counselling needs to be done for MTP, especially regarding the risk of delaying treatment, potential effects of new drugs on the foetus including fetal abnormalities (if MTP not opted) and the need for more intense maternal-fetal-neonatal follow-up. Appropriate counselling and informed decision making process for consent needs to be undertaken in each case with electronic data management in Nikshay including active drug safety monitoring.



* 24 weeks will apply wherever the bill is passed.
# Regimen: 4-6 Bdq (6m) Lfx, Cfz, Eto, Hh, Z, E / 5 Lfx, Cfz, Z, E. No modifications allowed.
@ Regimen:18-20 Lfx, Bdq(6m or longer) Lzd#, Cfz, Cs. Lzd dose to be tapered to half after 6-8 months based on bacteriological response. Modify regimen if one or more drug cannot be used due to reasons of resistance, tolerability, contraindication, availability etc.

- in the order of Z E PAS.
- Eto may be considered after 32 weeks' gestation.
- Am may be considered in post-partum period only. Am will not be started in the final 12 months of treatment.

Figure 4.4: Management of MDR-TB patients during pregnancy

The pregnant women with MDR-TB should be jointly managed by OB/GY and pulmonologist/ physician at DR-TBC. Further management of DR-TB patients who are pregnant prior to initiation of treatment or whilst on treatment are based on duration of pregnancy **(Figure 4.4).**

In pregnant women diagnosed with DR-TB, if the duration of pregnancy is <20 weeks*, the patient should be advised to opt for a medical termination of pregnancy (MTP) in view of the potential severe risk to both mother and foetus. If the patient is willing, she should be referred to a gynecologist or obstetrician for MTP following which a shorter oral Bedaquiline-containing MDR/RR-TB regimen can be initiated (if the patient has not started treatment) or continued (if the patient is already on treatment) by the DR-TBC committee.

In women of reproductive age who have been initiated on shorter oral Bedaquiline-containing MDR/RR-TB regimen and who become pregnant, the risk to the mother and foetus needs to be explained clearly. If the pregnancy is ≤20 weeks*, the decision on continuing shorter oral Bedaquiline-containing MDR/RR-TB regimen would depend upon the willingness of the patient to opt for an MTP. If she is unwilling for MTP or has a pregnancy >20 weeks* duration, she needs to be shifted to a longer oral M/XDR-TB regimen. For patients who are unwilling for MTP or have pregnancy of >20 weeks* (making them ineligible for MTP), the risk to mother and foetus needs to be explained clearly and the pregnant DR-TB patients need to be monitored carefully, both in relation to the treatment and progress of the pregnancy. This approach should lead to good results, since the patient should be smear/culture negative at the time of parturition and mother and infant do not need to be separated. Breastfeeding should be encouraged if the patient is smear/culture negative.

Bdq and Dlm both are not recommended during lactating period, unless the mother is willing to replace breastfeeding with formula feed. Pregnant women initiated on Bdq must be encouraged to provide formula feeds to their newborn child, till further evidence on safety of this drug during lactation is available.

The following additional monitoring is recommended for pregnant women managed with shorter/longer oral MDR-TB regimen including foetal and neonatal monitoring:

1. If the basal TSH in pre-treatment evaluation is deranged then TSH must be done monthly and once it is normal (less than 2.5) then quarterly during treatment. Check infant for early evidence of hypothyroidism.
2. In case PAS and Eto are given (which cause hypothyroidism and Lzd causes myelosuppression)to a newborn who has been exposed to a cocktail of drugs, certain baseline investigations at birth like CBC, TSH should be done.
3. These mothers should deliver in a tertiary care institute or at least at a place where a paediatrician is available.
4. USG foetal anomalies scan at 18 weeks and USG growth scan at 32 weeks.
5. Option of 2nd trimester MTP can be considered if the mother is fit for it, based on fetal scan of 2nd trimester.
6. Foetal echo to be done only if there is an abnormality on scan.
7. Strict active drug safety monitoring and management to be done.
8. More frequent ECG, serum electrolytes and CBC may be considered as clinically indicated.
9. ANC registration & OB/GY follow-up to be done regularly.

4.7.7.2. HIV-TB co-infection

Refer to **Section 4.6.7.2**. that also applies to longer oral M/XDR-TB regimen.

4.7.7.3. Role of surgery

Refer to **Section 4.6.7.3** that also applies to longer oral M/XDR-TB regimen.

4.7.7.4. Renal impairment

Renal insufficiency due to longstanding TB disease itself, previous use of aminoglycosides or concurrent renal disease is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal impairment. Care must be taken to see if DR-TB patients require aminoglycosides for 6 months or more. Other drugs, which might require a dose or interval adjustment in the presence of mild to moderate renal impairment, are E, FQ, Cs and PAS. In the presence of severe renal impairment, many other drugs may require adjustments **(Table 4.12).**

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

Table 4.12: Dose adjustment of anti-TB drugs in presence of renal impairment

Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)

Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Amikacin	12-15 mg/kg per dose two or three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Cycloserine	250 mg once daily, or 500 mg / dose three times per week
Ethionamide	No adjustment necessary
PAS	4 g/dose, twice daily maximum dose
Bedaquiline / **Delamanid**	No dosage adjustments required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/ clavulanate	For creatinine clearance 10-30 ml/min dose 1000 mg as amoxicillin component twice daily; For creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily
Imipenem / **Cilastatin**	For creatinine clearance 20-40 ml/min dose 500 mg every 8 hours; For creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20-40 ml/min dose 750 mg every 12 hours; For creatinine clearance <20 ml/min dose 500 mg every 12 hours

4.7.7.5. Pre-existing liver disease

In various DR-TB regimens under NTEP, R, H, Z, PAS, Eto and Bdq are potentially hepatotoxic drugs. For more details, refer to **section 4.6.7.6**.

4.7.7.6. Seizure disorder

Among second-line drugs, Cs, Eto and FQ have been associated with seizures and hence should be used carefully amongst DR-TB patients with history of seizures. Though the seizure is not common with newer drugs, it should also be considered while assessing the causality assessment. Pyridoxine should be given with Cs to prevent seizures. Cs should, however be avoided in patients with active seizure disorders that are not well controlled with medication. In patients where no other drug is appropriate, Cs can be given, and the anti-seizure medication adjusted as needed to control the seizure disorder. The risk and benefits of using Cs should be discussed with the patient and the decision on whether to use Cs are made together with the patient. Antiepileptic drugs may have drug interactions with Cs and FQ. Refer to **Section 4.6.7.7** for further details.

4.7.7.7. Psychiatric illness

Refer to section **4.6.7.8**. In addition, Cs, H(h), FQ and Eto have been associated with psychosis. Pyridoxine prophylaxis may minimize the risk of neurologic and psychiatric adverse events. Cs may cause severe psychosis and depression leading to suicidal tendencies. However, the use of Cs is not absolutely contraindicated for the psychiatric patient. Adverse effects of Cs may be more prevalent in the psychiatric patient but the benefits of using this drug often outweighs the potential higher risk of adverse effects. Close monitoring is recommended if Cs is used in patients with psychiatric disorders. If patient on Cs treatment develops psychosis,

anti-psychotic treatment should be started, and Cs treatment should be temporarily suspended. Once symptoms resolve and patient is stabilized, Cs treatment may be resumed. Such patients may require antipsychotic treatment till anti-TB treatment is completed.

4.7.7.8. Severe form of EP-TB and TB Meningitis

Longer oral M/XDR-TB regimen can be given to patients with extrapulmonary disease. Adjustments may be required, depending on the specific location of disease. Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by the ability of TB medicines to cross the blood–brain barrier. Group A FQs (Lfx, Mfx) and Lzd have good penetration across the blood–brain barrier (i.e. the CNS), as do Eto, Cs, and Imp-Cln. Seizures may be more common in children with meningitis treated with Imp, and Mpm is preferred for patients of TB meningitis and in children. H^h and Z can also reach therapeutic levels in the CSF, and may be useful if the strains are susceptible. Am and Sm only penetrate the CNS in the presence of meningeal inflammation. There are few data on the CNS penetration of Cfz, Bdq or Dlm. PAS and E do not penetrate the CNS well and should not be counted on as effective agents for MDR-TB meningitis. Hence the longer oral M/XDR-TB regimen must be modified as per the replacement table to consider this important factor and also other sites of the diseases.

4.7.8. Adverse drug reactions

The possible adverse drug events due to drugs used in longer oral M/XDR-TB regimen and the replacement drugs are depicted in **Table 4.13**. The detailed management of these adverse events is mentioned in **section 4.10.**

Table 4.13: Adverse drug events to drugs used in longer oral M/XDR-TB regimen and the replacement drugs

Adverse Drug Events	Drugs
QT prolongation	Bdq, FQ, Cfz
Rash, allergic reaction and anaphylaxis	Any drug
Gastrointestinal symptoms	Eto, PAS, Z, E, Bdq, Cfz, Lzd, FQs
Diarrhoea and/or flatulence	PAS, Eto
Hepatitis	Z, Eto, PAS, Bdq
Giddiness	Am, Eto, FQ and/or Z
Haematological abnormalities	Lzd
Hypothyroidism	Eto, PAS
Arthralgia	Z, FQ, Bdq
Peripheral neuropathy	Lzd, Cs, Am, FQ, rarely Eto, E
Headache	Bdq, Cs
Depression	Cs, FQ, Eto
Psychotic symptoms	Cs, H, FQ,
Suicidal ideation	Cs, Eto
Seizures	Cs, H, FQ

Adverse Drug Events	Drugs
Tendonitis and tendon rupture	FQ
Nephrotoxicity (renal toxicity)	Am
Vestibular toxicity (tinnitus and dizziness)	Am, Cs, FQs, Eto, Lzd
Hearing loss	Am
Optic neuritis	E, Lzd, Eto, Cfz,
Metallic taste	Eto, FQs
Electrolyte disturbances (Hypokalaemia and Hypomagnesaemia)	Am
Gynaecomastia	Eto
Alopecia	Eto
Superficial fungal infection and thrush	FQ
Lactic acidosis	Lzd
Dysglycaemia and Hyperglycaemia	Eto

4.8. Bedaquiline, Pretomanid, Linezolid (BPaL) regimen

Box 4.3: BPaL regimen for MDR-TB with additional FQ resistance

New WHO recommendations

- A treatment regimen lasting 6-9 months, composed of Bedaquiline, pretomanid and linezolid (BPaL) may be used under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones, who have either no previous exposure to Bedaquiline and linezolid or have been exposed for no more than 2 weeks; and
- This is a new recommendation for a defined patient group; it is to be used under operational research conditions, and thus does not apply to routine programmatic use.

Evidence (Conradie F, et al NEJM. 2020 Mar 5;382(10):893-902 (Nix TB trial)**):**

- BPaL showed 90% favourable outcomes among XDR (89%), MDR with FQ resistance, treatment intolerant /non responders (92%); and
- Peripheral neuropathy 81%, myelosupression 48%, all managed often with dose reductions or interruptions in treatment with linezolid.

For inclusion/exclusion criteria, sub-group and other details, WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis, 2020 can be referred.

Dosage & duration

- Pretomanid - 200 mg once daily for 26 weeks, Bedaquiline - 400 mg once daily for the first 2 weeks of treatment (days 1–14) and then 200 mg three times a week for 24 weeks, and linezolid - 1200 mg once daily for 24 weeks (after 1 month, dose and duration modification for linezolid is permissible), with an option to extend treatment to 39 weeks if they were culture-positive at week 16.

NTEG recommendation

- BPaL research proposal may be considered with flexibility to adapt with anticipated results of ZeNix trial with 4 arms of reduce dosage and duration of Linezolid in BPaL; and
- In exceptional cases, BPaL can be considered as a last resort by NTEP under prevailing ethical standards in individual patients for whom the design of an effective regimen is not possible as per WHO recommendations

Implementation considerations

- Pretomanid is approved by DCGI for use as part of BPaL regimen for conditional access under NTEP;
- In exceptional cases where an effective longer oral M/XDR-TB regimen cannot be designed with available drugs, NDR-TBC/state DT3C may send their case to national DT3C for clinical decision support and recommendations for BPaL;
- Initial hospitalization for 15 days at NDR-TBC ward is necessary to closely monitor tolerability;
- Active pharmacovigilance and proper management of adverse drug reactions, and prevention of complications from drug–drug interactions;
- Drugs to be made available by NTEP through state drug stores to NDR-TBC and refill to be done by NDR-TBC on monthly follow up visits by the patient; and
- Data management to be real time in Nikshay.

4.9. Isoniazid (H) mono/poly DR-TB regimen

This chapter deals with the technical and operational aspects of the treatment services provided under NTEP for H mono/poly DR-TB patients.

4.9.1. Treatment algorithm H mono/poly DR-TB regimen

The treatment algorithm for H mono/poly DR-TB patients is detailed in **Figure 4.5** below. Refer to Integrated diagnostic and treatment algorithm in Chapter 3 for more details.

Ruling out rifampicin resistance (RR) is primarily being done in the field using NAAT among all presumptive TB patients in areas that have transitioned to rapid molecular tests for TB diagnosis and in areas that are yet to transition, among key populations (PLHIV, children, EPTB, smear -ve/NA with X-ray suggestive of TB, contact of DR-TB patient, other vulnerable groups) or in all TB patients or among non-responders of DS-TB or H mono/poly DR-TB patients.

Once the patient is found to be rifampicin sensitive, the second specimen available must be sent immediately by the NAAT technician to the C&DST laboratory for FL-LPA test and the patient is initiated on standard regimen for DS-TB by the concerned CHO at HWC/ health facility doctor or private health-care provider. If H resistance is not detected, the patient will be continued on DS TB regimen and monitored for response to treatment. If H resistance is detected on FL-LPA (serves as a surrogate of first-line poly resistance as per NDRS), the LPA deposit must be subjected to SL-LPA and LC&DST to Mfx, Z, Lzd, Cfz* and the test result must simultaneously be uploaded by a microbiologist at the C&DST lab on Nikshay on the

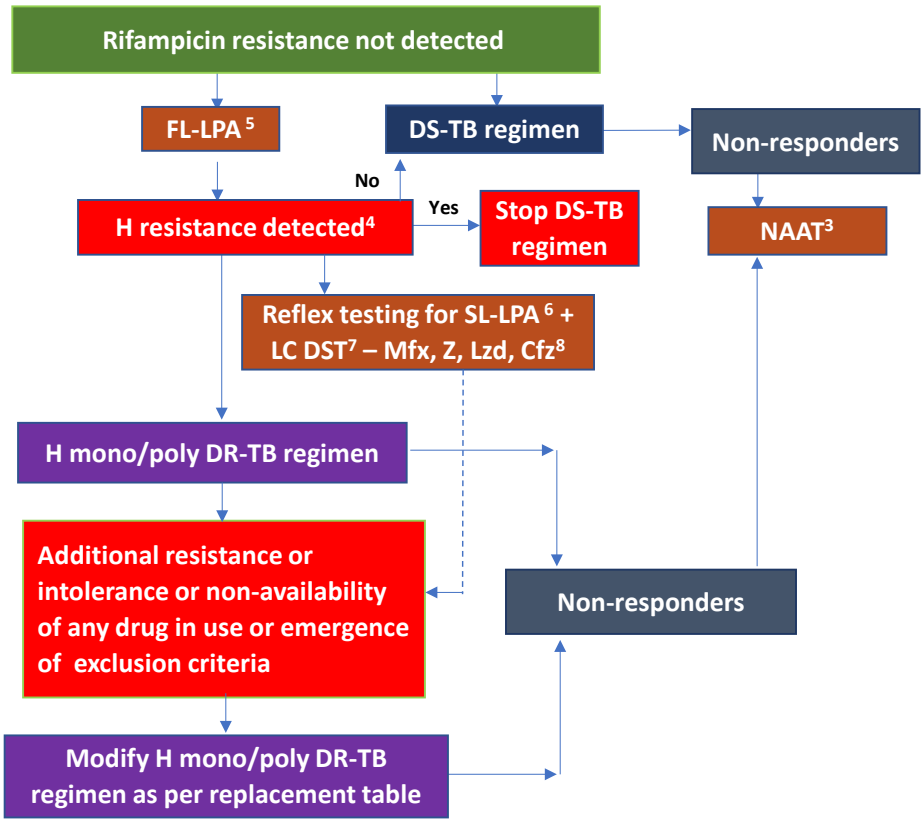


Figure 4.5 Treatment algorithm for H mono/poly drug resistant tuberculosis

4. As per mutation pattern, includes resistance inferred
5. Discordance in RR results between NAAT & FL-LPA to be resolved with a repeat NAAT at C&DST lab and microbiologists will provide the final decision. Inh A mutation associated with Eto resistance. Use other exclusion criteria to decide regimen if FL-LPA is done on culture isolates for patients with smear negative specimen.
6. To assess Lfx, Mfx and Am resistance
7. Start treatment based on LPA results & modify based on LC&DST results later.
8. Whenever DST is available

same day and the health facility doctor and staff to login on Nikshay at least once daily to check for results and inform the patient and concerned field staff on the same day. If H mono/poly DR-TB is detected, appropriate clinical evaluation is conducted by the treating doctor and H mono/poly DR-TB regimen is initiated at the respective health facility itself while waiting for the results of SL-LPA and LC&DST . These patients need not be sent to the DDR-TBC, unless deemed necessary on medical or other grounds.

As soon as the results of SL-LPA and LC&DST are available, the microbiologist at C&DST lab must upload them on Nikshay and inform the concerned health facility and DTO about the same. According to the results, the treating doctor may need to modify the regimen using the replacement sequence detailed later in the event of additional resistance or intolerance or non-availability of any drug in use or emergence of exclusion criteria. At any time during the treatment with DS-TB or H mono/poly DR-TB regimen with or without modifications, if there are signs of non-response, the patient must be subjected to NAAT again to rule out amplification of rifampicin resistance and further LPA and DST at specific time points as detailed in the follow-up monitoring **Section 4.9.5.2.**

4.9.2. Pre-treatment evaluation

Pre-treatment evaluation for any TB patient must include a thorough clinical evaluation by a doctor with

- History and physical examination
- Height/weight
- Random blood sugar (RBS)
- Chest X-ray
- HIV test.

No additional investigations are required for H mono/poly DR-TB patients unless clinically indicated. The pre-treatment evaluation carried out at the time of treatment initiation can be considered valid for 1 month from the date of the test result and the patient can be re-initiated on a subsequent regimen considering the previously conducted pre-treatment tests. Active drug safety management and monitoring (aDSM) treatment initiation form needs to be completed for all DR-TB patients at the time of initiation of each new episode of treatment.

4.9.3. Treatment

TB patients with rifampicin resistance not detected will be initiated on first-line DS-TB treatment regimen while awaiting the results of FL-LPA and continued on first-line treatment if Isoniazid resistance is not detected. If Isoniazid is found to resistant (with rifampicin sensitive), the patient will be initiated on H mono/poly DR-TB regimen at the health facility level while awaiting the results of SL-LPA and the regimen would be appropriately modified as detailed above.

4.9.3.1. Evidence

- **Treatment with rifampicin, ethambutol and pyrazinamide.** For patients with rifampicin susceptible, Isoniazid resistant TB, the evidence focused on determining whether treatment outcomes in H mono/poly DR-TB patients receiving (H)REZ treatment regimens of variable duration could be improved with the addition of a fluoroquinolone or streptomycin.
- **Duration of (H)REZ.** The analysis comparing (H)REZ treatment regimens for 6 months (6(H)REZ) and more than 6 months (>6(H)REZ) demonstrated that a 6(H)REZ regimen had a higher likelihood of treatment success than a >6(H)REZ regimen.
- **Duration of levofloxacin use.** The median duration of fluoroquinolone use was observed to be 6.1 months (interquartile range [IQR]: 3.5; 8.4), and for REZ it was 9 months.
- **Addition of a fluoroquinolone.** In patients with H mono/poly DR-TB, treatment success rates were higher when fluoroquinolones were added to (H)REZ regimens than when patients were treated with 6(H)REZ or >6(H)REZ without the addition of fluoroquinolones (aOR: 2.8; 95% CL: 1.1–7.3). With the addition of fluoroquinolones in patients receiving (H)REZ, the number of deaths was reduced (aOR: 0.4; 95% CL: 0.2–1.1). Acquisition of additional resistance with progression to MDR-TB was also reduced when fluoroquinolones were added to a ≥6(H)REZ regimen (aOR: 0.10; 95% CL: 0.01–1.2), albeit with small absolute numbers.
- **Management of patients.** Fundamental principle behind management of patients diagnosed with drug-resistant TB is careful selection of patients. Ahead of starting the (H)REZ–Lfx regimen, it is essential that resistance to rifampicin be excluded with NAAT. Empirical treatment of H mono/poly DR-TB is not advised.

4.9.3.2. Inclusion and exclusion criteria

- **Inclusion.** H mono/poly DR-TB with confirmed result for rifampicin resistance not detected
- **Exclusion.** No specific exclusion criteria

4.9.3.3. Regimen, duration and dosage

H mono/poly DR-TB regimen (R resistance not detected & H resistance detected) under NTEP:

(6 or 9) Lfx R E Z

H mono/poly DR-TB regimen is of 6 or 9 months with no separate IP/CP. In exceptional situations of unavailability of loose drug R or E or Z, the use of 4 FDC (HREZ) with Lfx loose tablets may be considered as an option rather than not starting the H mono/poly DR-TB patients on treatment.

The dosage of drugs would vary as per weight of the patients. Adult patients (≥ 18 years) would be classified in weight bands of <16 kg, 16-29 kg, 30-45 kg, 46-70 kg and >70kg. All drugs in the regimen are to be given on a daily basis under observation. The dosage for drugs used in H mono/poly DR-TB regimen by weight bands for adults are enumerated in the **Table 4.14** below for adult patients. Refer to **Annexure 15** for dosage for children.

Table 4.14: Dosages for drugs used in H mono/poly DR-TB regimen by weight bands for adults

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

4.9.3.4. Treatment extension

Total duration of H mono/poly DR-TB regimen is 6 months. It can be extended directly to 9 months in certain conditions. In patients with extensive disease; uncontrolled comorbidity; extra- pulmonary TB; if smear at the end of month 4 is found positive and when regimen is modified, the treatment may be directly extended to 9 months. There would be no monthly extensions in this regimen. In patients who remain sputum smear positive at the end of month 5 or later, the treatment outcome will be declared as 'treatment failed' and the patient will be re-evaluated as per the diagnostic algorithm as a non-responder.

4.9.4. Replacement sequence

Drugs of the component regimens will require to be replaced in case of additional resistance, intolerance, unavailability or contraindication of the component drugs of the regimen. In such situations, modification of H mono/poly DR-TB regimen may be done using the sequence of using replacement drugs as per **Table 4.16**.

Table 4.16: Replacement sequence of drugs to modify H mono/poly DR-TB regimen

Situation	Sequence of using replacement drugs
If Lfx can't be used	Replace with Mfx^{h} if SL LPA pattern suggests. Do LC DST for detection of resistance to Mfx^{h}, Z, Lzd & Cfz*
If Mfx^{h} or Z can't be used	Replace with Lzd. If Lzd also cannot be given, replace with Cfz* + Cs
If both Mfx^{h} and Z can't be used	Add 2 drugs of the 3 – Lzd, Cfz*, Cs in order of preference based on resistance, tolerability & availability
If R resistance	Switch to appropriate shorter or longer regimen

*whenever DST is available

In the first three situations above, treat for a total duration of 9 months. Treatment duration of H mono/poly DR-TB regimen can be longer in extensive pulmonary TB diseases up to 9 months. The use of new drugs is not yet recommended in the treatment of H mono/poly DR-TB due to lack of evidence.

4.9.5. Follow-up monitoring

This section provides information on the clinical and laboratory monitoring for patients on treatment for H mono/poly DR-TB.

4.9.5.1. Clinical monitoring

For clinical monitoring of any DR-TB patient, refer to **Section 4.6.5.1.**

4.9.5.2. Follow-up evaluations

Apart from clinical evaluation, the patients initiated on H mono/poly DR-TB regimen need to be closely monitored for bacteriological and radiological improvement on treatment and also for any derangements in bio-chemical and other systemic disorders indicating drug induced adverse events or co-morbidities to enable timely interventions to address these and improve the probability of treatment success, survival and quality of life **(Table 4.17).**

Table 4.17: Follow-up evaluation schedule of H mono/poly DR-TB patients

Regimen class	H mono/poly DR-TB regimen
Duration	6 or 9 months (no separate IP/CP)
Clinical + Wt.	Monthly till the end of treatment
Smear microscopy	Monthly from month 3 onwards till the end of treatment Conduct SM within 7 days, if the smear at month 4 or later is positive to rapidly ascertain bacteriological conversion/reversion
Culture	At end of month 3, end of treatment (month 6 and/or 9 if applicable) If the culture results of month 3 are positive, collect one repeat specimen for culture to rapidly ascertain bacteriological conversion/ reversion. If the repeat specimen is culture negative, then ensure specimen collection at the end of treatment
DST	NAAT, FL LPA, SL LPA (R, Eto, Lfx, Mfx) and LC DST (Mfx, Z, Lzd & Cfz*) if smear/ culture +ve at month 3, end of treatment (month 6 and/or 9 if applicable)

Regimen class	H mono/poly DR-TB regimen
UPT	As and when clinically indicated
CBC/platelets ^	As and when clinically indicated
TSH & LFT#	As and when clinically indicated
CXR	As and when clinically indicated and at end of treatment
ECG$	As and when clinically indicated
S. Electrolytes (K, Mg, Ca)	As and when clinically indicated
Specialist consultation	As and when clinically indicated
Colour vision test	Once in two months (in children)

^ Lzd containing regimen to rule out bone marrow suppression

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

$ In case of baseline ECG abnormality or QTcF ≥450ms for regimen contains Mfx^h or Cfz, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG.

* DST whenever available

- Smear examination would be used on a monthly basis from month 3 onwards to guide the decision on extension of treatment from 6 months to 9 months for H mono/poly DR-TB regimen.
- Treatment will be extended from 6 months directly to 9 months if the smear is positive at month 4 and as per the replacement drug sequence mentioned above. If the follow-up smears remain positive at end of month 5, declare the patient as 'treatment failed'. Follow-up culture would be done at month 3, 6 and 9 (if applicable).
- For adult DR-TB patients whose weight increases or decreases by 5 kg or more compared to baseline weight and crosses the current weight band during the course of the treatment, the weight band must be changed at the time of issuing the next month's box to the treatment supporter of the patient. For pediatric patients, the drug dosage should be adjusted immediately once the weight of the patient crosses the range of weight-band. Patient must be counselled regarding the change in weight band and also demonstrated the change in number of pills that need to be consumed.
- The most important evidence of response to DR-TB treatment is conversion of sputum smear and culture to negative. Good quality sputum specimen is therefore essential to get reliable results that form the basis of monitoring bacteriological response to treatment.
- It must be noted that the final treatment outcome of H mono/poly DR-TB patients will be declared based on follow up culture results.
- NAAT, FL LPA, SL LPA (R, Eto, Lfx, Mfx) on fresh specimen and LC&DST (Mfx, Z, Lzd, Cfz*) (*whenever available) will be set up on the LPA deposits only for if patient remains smear/culture positive at end of month 4 and beyond if the patient has not reached bacteriological reversion.
- If any change is required in the composition of H mono/poly DR-TB regimen due to the reason like resistance, intolerability, unavailability or contraindication during initial 4 months of treatment, re- initiation or re-registration is not required and patient will be continued

with same registration date for that episode with the modifications as per replacement table above unless the patient is declared as 'treatment failed'.

- Long-term follow-up will be done with 6 monthly cultures among symptomatic patients till two years after completion of any DR-TB regimen i.e. months 6, 12, 18 and 24 post treatment.

Follow-up culture results will be the basis for declaring the final treatment outcome of H mono/poly DR-TB patients.

4.9.6. H mono/poly DR-TB in children

Management of H mono/poly DR-TB in children will be the same as adults and child-friendly formulations can be used.

4.9.7. Special situation

4.9.7.1. Pregnancy and lactation

In pregnant women, the H mono/poly DR-TB regimen may be started or continued. In women of reproductive age, treated for H mono/poly DR-TB, the use of rifampicin may interacts with contraceptives, resulting in decreased efficacy of protection against pregnancy. Use of an oral contraceptive pill containing a higher dose of estrogen (50 μg); and use of another form of contraception like barrier methods (condoms/diaphragms), intrauterine devices or IUDs (CuT) or depot-medroxyprogesterone (depo-provera) are recommended, based on individual preference and eligibility, if rifampicin is being used.

4.9.7.2. Patients with extensive disease

The prolongation of the H mono/poly DR-TB regimen to more than 6 months could be considered on an individual basis for patients with extensive disease up to a maximum of 12 months.

4.9.7.3. People living with HIV

The H mono/poly DR-TB regimen is recommended in HIV reactive TB patients. In TB patients with HIV coinfection, the first priority is to ensure that they are started on ART within 8 weeks of TB treatment initiation (regardless of CD4 count). This applies to H mono/poly DR-TB patients as well.

4.9.7.4. Extra-pulmonary disease

The treatment of patients with extra-pulmonary TB should be designed in close consultation with appropriate specialists (e.g. infectious disease physicians and neurologists), to decide upon individual variations in treatment duration and supportive care as needed. In CNS, skeletal and miliary TB, treatment may be given up to a year.

4.9.8 Adverse drug events

The possible adverse drug events due to drugs used in H mono/poly DR-TB regimen and the replacement drugs are depicted in **Table 4.18**. The detailed management of these adverse events is mentioned in **Section 4.10.**

Table 4.18: Possible adverse events due to drugs in H mono/poly DR-TB regimen and the replacement drugs

Adverse Drug Events	Drugs
Hepatitis	R, Z
QT prolongation	FQ, Cfz
Rash, allergic reaction and anaphylaxis	Any drug
Gastrointestinal symptoms	Z, E, Cfz, FQs
Giddiness	FQ, Z
Arthralgia	Z, FQ
Peripheral neuropathy	FQ, E
Depression	FQ
Psychotic symptoms	FQ
Seizures	FQ
Tendonitis and tendon rupture	FQ
Vestibular toxicity (tinnitus and dizziness)	FQs
Optic neuritis	E, Lzd, Cfz
Metallic Taste	FQ
Superficial fungal infection and thrush	FQ

4.10. Management of adverse drug reactions

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

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

- if adverse effect is mild and not serious, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option;

- most adverse effects of several second-line drugs are dose-dependent. Reducing the dosage of the offending drug or terminating it is another method of managing adverse effects; and
- psychosocial support is an important component of the management of adverse effects. This may be provided through patient education and motivation by treatment supporter, patient support groups like patient's association/organization or through group discussions while in the hospital.

Management of some important adverse events is described in the paragraphs below.

4.10.1. QT prolongation

Suspected agent(s): Bdq, FQ, Cfz

Suggested management strategies

- QT interval is measured from the start of the QRS complex to the end of the T wave on a standard ECG. The QT is corrected for heart rate, which is referred to as the QTc and calculated by most ECG machines. Values above QTc fridericia correction (QTcF) 450ms in male and 470ms in female are referred to as prolonged. Patients with prolonged QTcF are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life threatening. FQ may cause prolongation of the QTcF. Mfx and Gfx cause the greatest QTcF prolongation, while Lfx and Ofx have a lower risk. Currently, ECG monitoring prior to initiation and during DR-TB treatment is only required with the use of Bdq or when two drugs known to prolong QTcF (e.g. Mfx, Cfz) are combined in the same regimen.
- Low serum levels of potassium, calcium and magnesium are associated with QTc prolongation. Electrolyte levels should be maintained in the normal range in any patient with an elevated QT interval. Also avoid other drugs that increase the QT interval. Patient's renal and hepatic function should also be monitored.
- QT prolongation can result in ventricular arrhythmias (Torsades de Pointes) and sudden death. It is therefore imperative that ECGs be used to monitor the QT interval regularly during use of the suspected drugs.
- Management of increased QTcF entails looking at the algorithm for reintroduction of anti-TB drugs (Bdq/ Dlm/ FQ/ Cfz) once prolonged QTc has normalized as shown in **Table 4.19** and **Figure 4.6.**

Table 4.19: Management of QT prolongation by grade of severity of ADR

Normal Value	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life threatening)
QTcF M: < 450 F: < 470	M: 450-480 ms F: 470-480	481-500 ms	> 500 ms on two separate ECGs	> 500 ms and life threating consequences
Condition	Asymptomatic	Asymptomatic, transient rhythm abnormality	Recurrent, persistent, symptomatic arrhythmia	Unstable dysrhythmia

Normal Value	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life threatening)
Action	Check electrolytes and correct it, as necessary Monitor ECG more closely	Check electrolytes. If abnormal, hold all QTcF prolonging drugs and correct the electrolytes before restarting them. Monitor ECG more closely	Consider hospitalization, hold QTcF prolonging drugs and correct electrolytes as necessary Repeat ECG after 24 hours and reintroduce the drugs if QTcF remains below 500 ms	-Hospitalize and replete electrolytes as necessary -Stop the offending drug -Repeat ECG after 24 hours

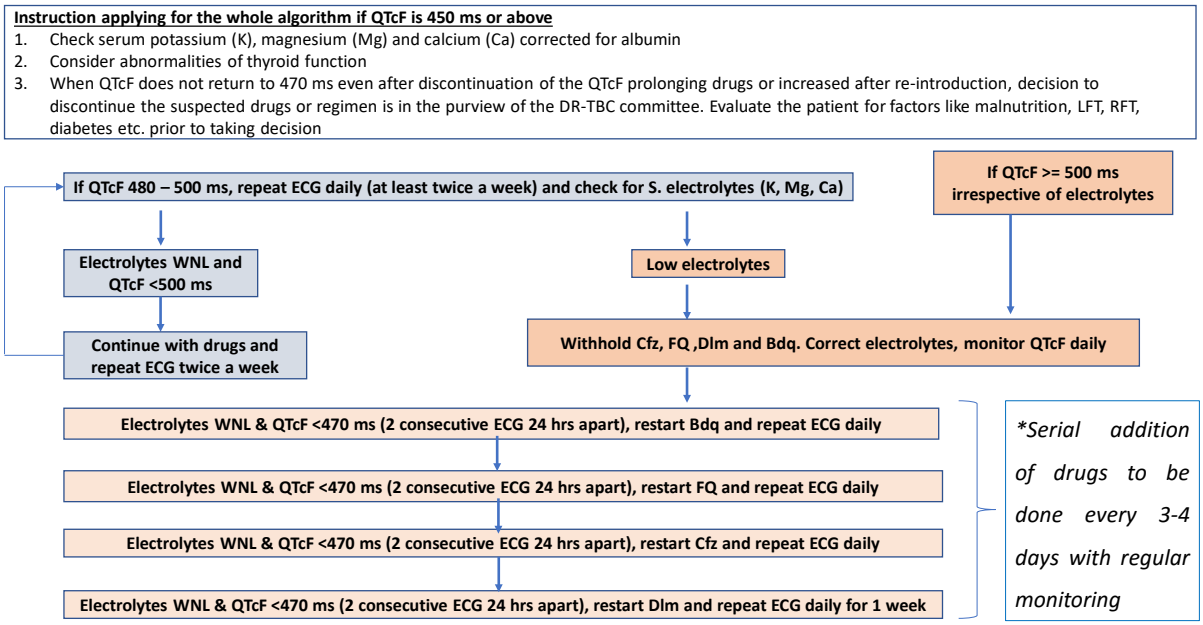


Figure 4.6 Management of prolonged QTcF during treatment with shorter/longer oral MDR-TB regimen

4.10.2. Rash, allergic reaction and anaphylaxis

Suspected agent (s): Any drug

Suggested management strategies:

- Hypersensitivity reactions such as pruritus or rash, can occur with any of the drugs used and are commonly managed with antihistamines.
- At the health facility or field level, if the case is of a mild reaction, the patient will be assured and managed symptomatically by the PHC MO.
- For serious allergic reactions, it will be important to stop all therapies pending resolution of reaction and refer the patient to Nodal DR-TB centre/ tertiary centre for further

management. In case of anaphylaxis, the condition will have to be managed with standard emergency protocols; other potential causes of allergic skin reactions (like scabies or other environmental agents) will need to be eliminated.

- For minor dermatologic reactions, various agents can be helpful. In this case medication must be continued. This could include antihistamines, hydrocortisone cream for localized rash, prednisone in a low dose of 10 to 20 mg per day for several weeks if other measures are not helpful and phototoxicity (may respond to sunscreens but can also cause rash). Dry skin may cause itching (especially in diabetics). In which case, a liberal use of moisturizing lotion is recommended, since dry skin is a common and significant problem with Cfz.
- Once rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. The order of reintroduction will be H, Z, Eto, E, FQ.
- Consider not reintroducing even as a challenge any drug that is highly likely to be the cause; and suspend permanently any drug identified to be the cause of a serious reaction.

Points to note

- History of previous drug allergies to be carefully reviewed. Any known drug allergies should be noted on the treatment card.
- Flushing reaction to Z is usually mild and resolves with time. Anti-histamines can be used. Hot flushes, itching, palpitations can be caused with H and tyramine containing foods (cheese, red wine). If this occurs, advise patients to avoid foods that precipitate reaction.
- Any of the drugs can cause hives (urticaria). To identify the drug, introduce drugs one at a time; and in case of hives, a desensitization attempt can be made.
- Any drug that results in anaphylaxis or Stevens–Johnson syndrome should never be reintroduced (not even as a challenge).

4.10.3. Gastrointestinal symptoms (nausea and vomiting)

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

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

Suggested management strategies:

- if vomiting persists, drugs will be administered one hour after one tablet of domperidone and/or a course of proton pump inhibitor (Omeprazole) or H2 receptor inhibitor (famotidine, ranitidine);
- other antacids are usually not given, since they interfere with absorption of FQ;
- in case of severe vomiting, the hydration status of the patient should be monitored, and rehydration treatment initiated if required;
- if the offending drug is Eto, the drug is more acceptable if administered with milk, or after milk, or at bedtime to avoid nausea;
- if vomiting is severe, drugs can be withheld temporarily, and tests can be conducted to rule out other causes of vomiting like hepatitis;
- assess for danger signs including dehydration, electrolyte disturbance and hepatitis. Initiate rehydration treatment if indicated and correct any electrolyte disturbance. If there is blood in the vomit, check hemoglobin and treat for possible bleeding ulcers; and
- with Bdq, metoclopramide is preferred over ondansetron; ranitidine is preferred over omeprazole. Other ancillary drugs need to be chosen with Bdq as mentioned in **Table 4.4.**

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

- **Step 1.** Adjust medication and conditions without lowering overall dose. Give Eto at night; Eto or PAS twice or thrice daily; light snack (biscuits, bread, rice, tea) before medication; and PAS two hours after other anti-TB drugs.
- **Step 2.** Start antiemetic(s) like metoclopramide 10 mg, 30 minutes before anti-TB medication; Ondansetron 8 mg, 30 minutes before anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide (if ondansetron is not available, promethazine can be used). For refractory nausea give 24 mg, 30 minutes before the dose.
- **Step 3.** Decrease dose of suspected drug by one weight class (except Bdq and Dlm) if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.

Points to note

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

4.10.4. Gastrointestinal symptoms (gastritis & abdominal pain)

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

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

Suggested management strategies:

- if symptoms are associated and consistent with gastritis (epigastric burning or discomfort, sour taste in mouth associated with reflux) initiate medical treatment with the use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) better than proton-pump inhibitors (omeprazole 20 mg once daily) which should be avoided along with Bdq. Avoid use of antacids as they decrease absorption of FQ;
- for severe abdominal pain, stop suspected agent(s) for short periods of time (1–7 days);
- lower the dose of the suspected agent, if this can be done without compromising the regimen; and
- discontinue suspected agent if this can be done without compromising the regimen.

Points to note

- severe gastritis, as manifested by blood in the vomit or stool is relatively rare, but should always be treated to facilitate adherence to treatment;

- if antacids must be used, they should be carefully timed to not interfere with absorption of FQ (take two hours before or three hours after anti-TB drugs);
- stop any non-steroidal anti-inflammatory drugs the patient may be taking;
- diagnose and treat for *Helicobacter pylori* infections; and
- severe abdominal distress has been reported with use of Cfz. Although these reports are rare, if this occurs, Cfz should be suspended.

4.10.5. Diarrhoea and/or flatulence

Suspected agent(s): PAS, Eto

Suggested management strategies:

- motivate patients to tolerate some degree of loose stools and flatulence;
- encourage fluid intake;
- treat uncomplicated diarrhoea (no blood in stool and no fever) with Cap Racecadotril 1 stat followed after 8 hours;
- check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe; and
- fever and diarrhoea and/or blood in the stools indicate that diarrhoea may be secondary to something other than the simple adverse effect of anti-TB drugs.

Points to note

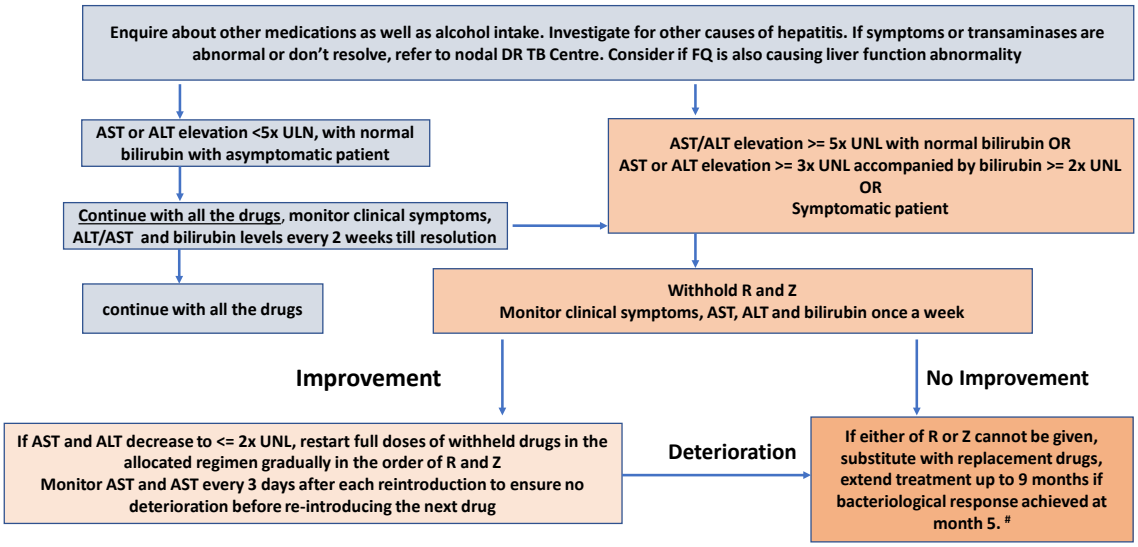
- consider other causes of diarrhoea;
- know that pseudo-membranous colitis related to broad-spectrum antibiotics (such as FQ) is a serious and even life-threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are warning signs of possible pseudomembranous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

4.10.6. Hepatitis

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

Suggested management strategies:

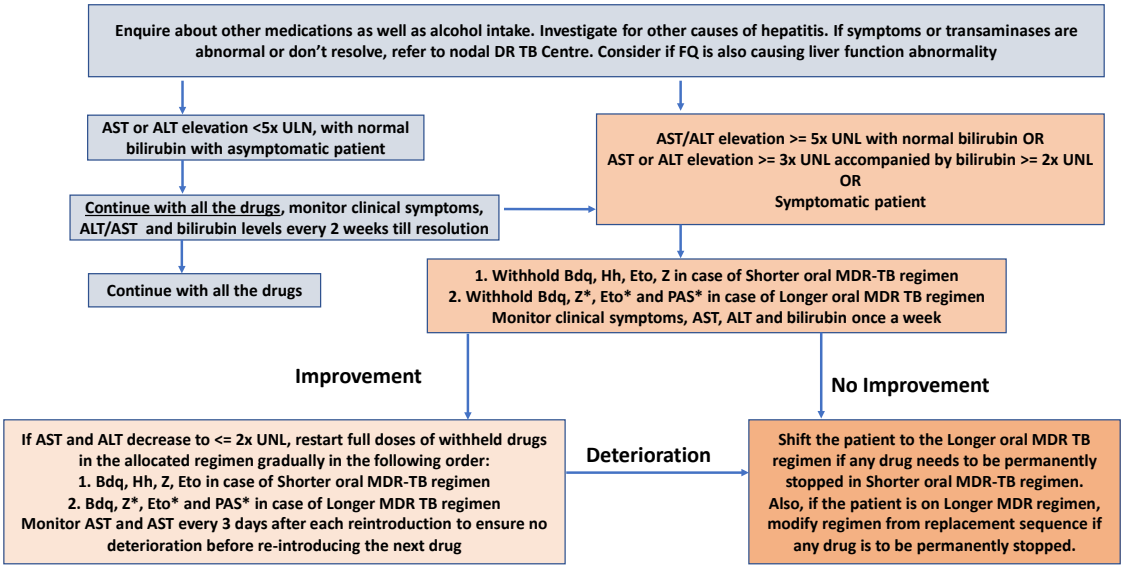
- in cases where patient is very sick i.e., meningitis, sputum smear grade 3+, administer ATT e. g. Streptomycin, FQ and Cs. Where patient is not seriously ill and one can wait, introduction of ATT can be done once enzyme levels are near normal;
- if enzymes are more than five times the upper limit of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



***The schedule followed for adult - R is start with 150 mg, repeat LFT after 3 to 5 days, if no increase and no symptoms, increase to 300 mg, repeat same as above and then full dose. For Z process is the same, it is 250 mg initially then 500 mg, 750 mg, 1 gm then full dose*

 # Refer to the nodal DR-TB centre for further management as necessary

Figure 4.7 Management of hepato-toxicity during treatment with H mono/poly DR-TB regimen



**If used*

Introduction can be tried from lower doses of each drug with gradually increasing to full dose while monitoring the LFT and symptoms.

Figure 4.8 Management of hepato-toxicity during treatment with shorter/longer oral MDR-TB regimen

Points to note

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

Management of hepatotoxicity during treatment with DR-TB regimen are described in **Figure 4.7** and **Figure 4.8.**

4.10.7. Giddiness

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

Suggested management strategies:

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

Point to note

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

4.10.8. Haematological abnormalities

Suspected agent(s): Lzd

Suggested management strategies:

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

Points to note

- hematological abnormalities (leukopenia, thrombocytopenia, anemia, red cell aplasia, coagulation abnormalities and eosinophilia) can rarely occur with several other anti-TB drugs; and
- there is little experience with prolonged use of Lzd.

4.10.9. Hypothyroidism

Suspected agent(s): Eto, PAS

Suggested management strategy: In cases of hypothyroidism, opinion of general physician/ endocrinologist may be taken. Eto/ PAS can be continued with introduction of thyroxine supplements.

Points to note

- symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair and constipation, as well as occasional depression and inability to concentrate;
- in cases with abnormal weight gain, hypothyroidism may be ruled out;
- it is completely reversible upon discontinuation of PAS and/or Eto; and

- combination of Eto with PAS is more frequently associated with hypothyroidism than when each individual drug is used.

4.10.10. Arthralgia

Suspected agent(s): Z, FQ, Bdq

Suggested management strategies:

- Initiate with paracetamol in the beginning.
- Treatment with nonsteroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day).
- Lower the dose of the suspected agent (most commonly Z) if this can be done without compromising the regimen.
- Discontinue the suspected agent if this can be done without compromising the regimen.

Points to note

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

4.10.11. Peripheral neuropathy

Suspected agent(s): Lzd, Cs, H, Am, FQ, rarely Eto, E

Suggested management strategies:

- To prevent occurrence of such adverse reaction, all patients on an NTEP regimen for MDR-TB should receive daily pyridoxine.
- The commonest offending agent is Lzd, almost 60–70% of the patients on Lzd 600 mg/day may develop neuropathy and pyridoxine does not help in preventing Lzd induced neuropathy. Early recognition of neuropathy symptoms and early dose reduction of Lzd helps to prevent the progression. If there is no improvement or symptoms worsen, amitriptyline 25mg will be added (to be avoided with Bdq) and if there is still no improvement, the patient should be referred to a neurologist;
- correct any vitamin or nutritional deficiencies and maximum daily dose (100 mg/day);
- consider whether the dose of Cs can be reduced without compromising the regimen. If H is being used (especially H^h), consider stopping it;
- initiate medical treatment:
  - non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms;
  - treatment with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime, the dose may be increased to a maximum of 150 mg) can be tried. Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors and Bedaquiline.
  - in such a patient, refer to specialist for further management; and
  - and rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.

Points to note

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

4.10.12. Headache

Suspected agent(s): Bdq, Cs

Suggested management strategies:

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

Points to note

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

4.10.13. Depression

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

Suggested management strategies:

- Assess and address underlying emotional and socioeconomic issues.
- Assess patients for coexisting substance abuse and refer to treatment if appropriate.
- Initiate individual counselling (or group counselling if the patient is sputum smear and culture negative).
- When depression is more significant, initiate antidepressant treatment with amitriptyline (not with Bdq), fluoxetine or similar.
- Tricyclic antidepressants and selective serotonin reuptake inhibitors and Bedaquiline should NOT be given together.
- Lower the dose of the suspected agent if this can be done without compromising the regimen (reducing dose of Cs and Eto to see if depression is lessened is a common strategy).
- Discontinue suspected agent if this can be done without compromising the regimen.

Points to note

- socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression;

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

4.10.14. Psychotic symptoms

Suspected agent(s): Cs, H, FQ

Suggested management strategies:

- Stop the suspected agent for a short period (1–4 weeks) while psychotic symptoms are brought under control.
- The most likely drug is Cs followed H[h].
- If moderate to severe symptoms persist, initiate antipsychotic treatment (haloperidol).
- Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others.
- Lower the dose of the suspected agent (if it can be done without compromising the regimen).
- Discontinue suspected agent if this can be done without compromising the regimen.
- Once all symptoms resolve and patient is off Cs, antipsychotic treatment can be tapered off. If Cs is continued at a lower dose, antipsychotic treatment may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist trained in the adverse effects of second-line anti-TB drugs.

Points to note

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

4.10.15. Suicidal ideation

Suspected agent(s): Cs, H, Eto

Suggested management strategies:

- Hospitalize the patient and put under 24-hour surveillance.
- Discontinue Cs.
- Request psychiatric consultation.
- Initiate antidepressant treatment.
- Lower the dose of Eto until the patient is stable.

Points to note

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

4.10.16. Seizures

Suspected agent(s): Cs, H, FQ

Suggested management strategies:

- Hold Cs, FQ and H pending resolution of seizures.
- Initiate anticonvulsant treatment -carbamazepine, phenytoin or valproic acid (relatively safe with Bdq) are most commonly used.
- Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride.
- When seizures have resolved, restart medication, one at a time. Cs should not be restarted unless it is absolutely essential to the regimen. If Cs is reinitiated, start a dose one weight band lower.

Points to note

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

4.10.17. Tendonitis and tendon rupture

Suspected agent(s): FQ

Suggested management strategies:

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

Points to note

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

4.10.18. Nephrotoxicity (renal toxicity)

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

Suspected agent(s): Am

Suggested management strategies:

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

Points to note

- during treatment, blood urea and serum creatinine should be done every month for the first three months after treatment initiation and then every three months thereafter whilst injection Am is being administered;
- silent renal toxicity may be picked up by these routine follow-up biochemical examinations;
- if at any time, the blood urea or serum creatinine becomes abnormal, treatment should be withheld, and further management decided upon in consultation with the DR-TBC committee;
- an example of how to calculate a creatinine clearance based on the serum creatinine is provided in **Table 4.12**; and
- history of diabetes or renal disease is not a contraindication to the use of agents listed here, although patients with these comorbidities may be at increased risk for developing acute kidney injury.

4.10.19. Vestibular toxicity (tinnitus and dizziness)

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

Suggested management strategies:

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

Points to note

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

4.10.20. Hearing loss

Suspected agent(s): Am

Suggested management strategies:

- Common cause is aminoglycosides if the reason like wax and middle ear infection is ruled out.
- Document hearing loss and compare with baseline audiogram if available (some degree of hearing loss occurs with most patients starting with high frequency loss).
- If early symptoms of hearing loss are documented, change dosing of the injectable agent to twice/thrice a week.
- Discontinue injectable agent if hearing loss continues despite dose adjustment and add additional drugs to reinforce the regimen. Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient's desire to maintain hearing.

The management of ototoxicity during treatment with injectables are described in **Figure 4.9.**

Points to note

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

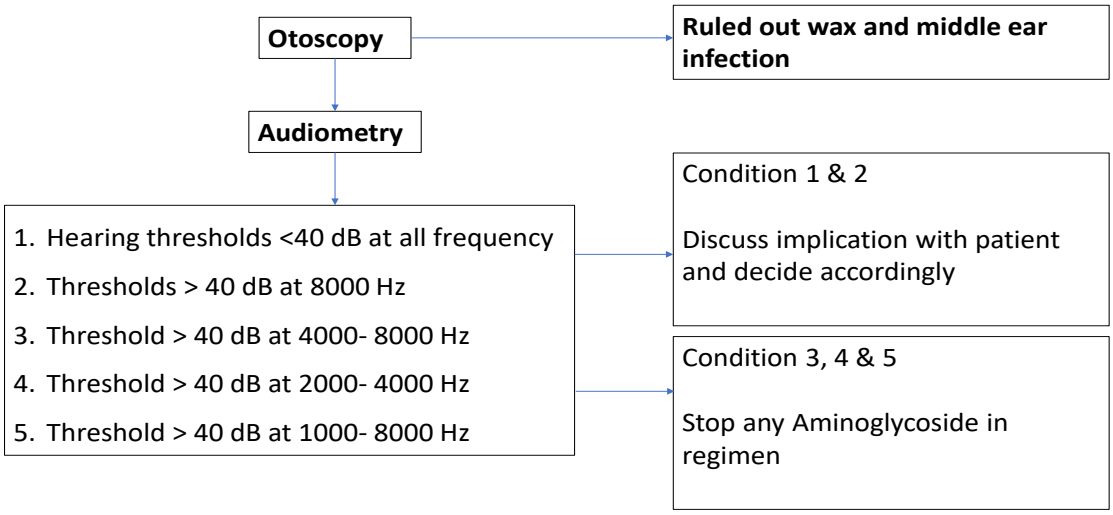


Figure 4.9: Management of hearing loss during course of treatment

4.10.21. Optic neuritis

Suspected agent(s): E, Lzd, Eto, Cfz, H, S

Suggested management strategies:

- Stop E and Lzd. Do not restart.
- Refer patient to an ophthalmologist.

Points to note

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

4.10.22. Metallic taste

Suspected agent(s): Eto, FQs

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

Point to note

- Normal taste returns when treatment is stopped.

4.10.23. Electrolyte disturbances- hypokalaemia and hypomagnesaemia

Suspected agent(s): Am

Suggested management strategies:

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

Points to note

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

4.10.24. Gynaecomastia

Suspected agent(s): Eto

Suggested management strategies:

- Breast enlargement can be a troublesome side effect of Eto treatment, especially for male patients. Galactorrhoea has also been reported.
- Encourage patients to tolerate this side effect.

Point to note

- Resolution occurs after treatment is stopped.

4.10.25. Alopecia

Suspected agent(s):H, Eto

Suggested management strategies:

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

Point to note

- Significant cosmetic change has not been reported.

4.10.26. Superficial fungal infection and thrush

Suspected agent(s): FQ

Suggested management strategies:

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

Point to note

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

4.10.27. Lactic acidosis

Suspected agent(s): Lzd

Suggested management strategy: Stop Lzd if lactic acidosis occurs.

Point to note

- Lactic acidosis can be managed at the Nodal DR-TB centre as per standard protocol and monitored with a blood test that measures lactic acid.

4.10.28. Dysglycaemia and hyperglycaemia

Suspected agent (s): Eto, FQ

Suggested management strategy: Replace the offending drug with a suitable drug.

Point to note

- Treat diabetes as needed. Good glucose control is important during treatment.

ADR management is crucial to improve treatment compliance of DR-TB patients. Majority of the side effects and ADR management are possible with a simple intervention which can be easily executed even at peripheral level. Drugs that can be used for managing common side effects or ADR reported by patients are given in **Table 4.20.**

Table 4.20: Drugs used in management of adverse event

ADRs	Suggested drugs to manage the ADR
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate, domperidone
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, *etc.*,), Proton pump inhibitors (omeprazole, lansoprazole, *etc.*,) Avoid antacids because they can decrease absorption of fluoroquinolone eg. aluminum hydroxide

ADRs	Suggested drugs to manage the ADR
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges, Nystatin suspension, itraconazole liquid
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline) (to be avoided with Bdq)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Any hypnotic
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal Effects), Buromazine, Thioridazine
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline (to be avoided with Bdq)
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, Promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine, diclofenac
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity Reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, *etc.*,), inhaled corticosteroids (beclomethasone, *etc.*,), oral steroids(prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium, magnesium and calcium replacement treatment (oral and intravenous formulations)

4.11. Treatment outcome of DR-TB

The progress of the patient on treatment would be monitored using interim as well as final treatment outcomes which are detailed below in the technical guidelines section. The operational aspects and the processes that needs to be adopted for declaring the treatment outcome is dealt in the operational guidelines section. The following definitions are the most recent outcome definitions recently revised by WHO and would apply to all forms of DR-TB patients.

4.11.1. Interim outcomes

Bacteriological conversion. After bacteriological confirmation of TB at least two consecutive cultures (applicable for DR-TB and DS-TB) or smears taken on different occasions at least 7 days apart (applicable for DS-TB only) are found to be negative.

Bacteriological reversion. At least two consecutive cultures (applicable for DR-TB and DS-TB) or smears (applicable for DS-TB only) taken on different occasions at least 7 days apart are found to be positive either after the initial conversion or for patients without bacteriological confirmation of TB.

- For defining treatment failed, bacteriological reversion is considered only when it occurs in the continuation phase.
- Time-to-culture conversion is calculated as the interval between the date of DR-TB treatment initiation and date of the first of these two negative consecutive cultures taken 7 days apart (date of sputum specimens collected for culture should be used).

4.11.2. Final outcomes

Treatment failed. A patient whose treatment regimen needs to be terminated or permanently changed[1] to a new regimen option or treatment strategy.

Cured. A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response[2] and no evidence of treatment failed.

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

Died. A patient who died[3] before starting or during the course of treatment.

Lost to follow-up. A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

Not evaluated. A patient for whom no treatment outcome was assigned[4].

[1] Reasons for the change include:

a) No clinical and/or bacteriological response*
b) Adverse drug reactions (ADRs),
c) Evidence of additional drug resistance to medicines in the regimen.

* Bacteriological response – bacteriological conversion with no reversion.

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

[3] *Patient died of any reason*

[4] *This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown and excludes lost to follow up.*

- In case of change in regimen within the scope of guidelines for the purpose, from shorter to longer or vice-versa in the initial months before any definitive treatment outcome applies, the outcome of only the changed regimen needs to be reported. The patient needs to be moved out of the denominator of the previous regimen.
- Patients who are still on treatment due to frequent short interruptions (less than 2 consecutive months) due to patient or provider requirements can be reported as not evaluated as outcome is not assigned at the time of reporting to NTEP and WHO but the data can be cleaned and updated later when the outcome is available.

4.12. Implementation considerations and patient flow

Quality of services with prompt diagnosis and treatment initiation of DR-TB patients requires a highly coordinated effort and efficient systems between different health facilities of public and private sector, laboratories (specimen collectors/ transporters, NAAT sites, C&DST labs), support staff (TB Unit, PPSA), supervisors (DTO, MOTU, Senior DR-TB TB-HIV supervisor) and treatment centres (health facilities including N/DDR-TBC). Nikshay serves as a common tool for prompt information and communication system that needs to be effectively used in real-time to improve quality of care for every DR-TB patient by all staff at the above listed

facilities. It is also necessary that every staff should be equipped and empowered under NHM with the necessary digital tools (tablets with internet), logistics (50 ml conical tubes, forms, DR-TB counselling tool), mobility support (travel allowances)/ training (e-modules/ videos/ virtual or in-person trainings) to provide quality care for DR-TB in their respective jurisdictions.

4.12.1. Mobilizing DR-TB patients for availing treatment

Mobilizing DR-TB patients for availing diagnosis and treatment of DR-TB is the primary responsibility of the staff at HWC and HF (public and private) with support from TB Unit staff (MOTU, STS, TBHV) as well as PPSA staff under guidance and monitoring of DTO and senior DR-TB TB-HIV supervisor.

A. Referral for pre-treatment evaluation

- Once DR-TB is confirmed, the laboratory staff will update the information about the diagnostic results in Nikshay on the same day and the patient should be traced with help of CHO/ HF-doctor/ Private health care provider and staff, TBHV, PPSA staff and STS under monitoring of MO-TU, Senior DR-TB TB-HIV supervisor and DTO.
- Patients should be informed about the diagnostic results, counselled and referred to the sub-district level health facility earmarked for pre-treatment evaluation and then to HF- doctor or N/DDR-TBC with pre-treatment evaluation results for initiation of treatment for H mono/poly DR-TB or M/XDR-TB respectively within the shortest possible time.
- While referring the patient to N/DDR-TBC, the CHO/ HF staff must update the DR-TB facility in Nikshay in health facility tab to make the patient details accessible and editable to the N/DDR-TBC.
- The HF doctor or physician at N/DDR-TBC may decide for initiation of treatment for H mono/poly DR-TB or M/XDR-TB respectively on in-patient (admitting to the ward) or out-patient basis. A specialist consultation along with reports of pre-treatment evaluation tests can be arranged, if required.

B. Counselling

- Health education and counselling should be provided to all patients and family members at different levels of health care, from the HWC/ HF and DR-TBC level. Patient must be counselled by the staff of HWC/ HF/ Private health care provider/ TBHV/ STS to visit the HF or N/DDR-TBC with a family member for further evaluation and management without further delay. It should be started at the initial point of contact and continued during all the visits by the patients to a health facility using the DR-TB counseling tool. **(Annexure 12)**
- After counselling, the DR-TB patient should be referred by CHO after completing the data entries in Nikshay to the HF doctor or N/DDR-TBC with DST results and PMDT referral for treatment form, for pretreatment evaluation and initiation of standard regimen for DR-TB as appropriate.

C. Preparing for ambulatory care

- While the DR-TB patient is undergoing pretreatment evaluation, the CHO/ HF doctor/ private health-care provider and staff, TBHV, PPSA staff and STS should ensure an initial home visit/ virtual contact with patient and family members using video call to verify the address, provide counselling, update bank account details for DBT, contact investigation to rule out TB/DR-TB and offer TPT as applicable to eligible contacts. This must be monitored by MO-TU, senior DR-TB TB-HIV supervisor and DTO.
- A treatment supporter (who can either be a health-care worker, community worker/ volunteer or private practitioner or family member) should be identified in consultation

with the patient during pre-treatment evaluation. The family member, if identified as treatment supporter should be trained to give medication under supervision at the residence, under close monitoring by CHO/ ASHA/ ANM/ MPW with support from TBHV/ STS. The treatment supporter should also be given training for drug administration and adherence monitoring, identification of adverse effects during treatment, frequency of follow-up, use of digital adherence technology like MERM, access to Nikshay Sampark, TB Aarogya Sathi app, provide TPT to the eligible contacts of DR-TB patient, record keeping and maintaining constant touch with concerned CHO/ health staff and TBHV/ STS.

4.12.2. Pre-treatment evaluation

Each of the HF and N/DDR-TBC must ensure that capacity to carry out PTE for H mono/poly DR-TB and M/XDR-TB patients respectively, consultancy services of various specialists must be available at N/DDR-TBC, either in-house supported under institutional/ state government mechanism or through outsourced mechanisms including tie-up under free diagnostic initiative of NHM. Alternatively, outsourcing with private facility under Guidance document on Partnership 2019 *(10)* should be undertaken for investigations that are not available in-house. The DTO needs to organize the availability of PTE and specialist consultation services for every HF (through linkages) and N/DDR-TBC (in-house or linkages) for serving H mono/ poly DR-TB and M/XDR-TB patients respectively in accordance to the details provided in the respective sections above.

The PTE and baseline aDSM assessment must be updated in Nikshay by the concerned HF or N/DDR-TBC staff. The PTE done would be considered valid till one month. However, the PTE would be repeated if clinically indicated.

4.12.3. Treatment initiation and management

The LT must enter the results of NAAT done on the first specimen in Nikshay on the same day. Once the patient is found to be rifampicin sensitive, the second specimen available must be sent immediately by the NAAT technician to the C&DST laboratory for FL LPA and the patient should be initiated on standard regimen for DS-TB by the concerned CHO/HF doctor/ Private health care provider. If H mono/poly DR-TB is detected on FL-LPA, the LPA deposit must be subjected to SL-LPA and LC&DST to Mfx, Z, Lzd, Cfz*. The FL-LPA test result must be entered by microbiologist/ staff at C&DST lab in Nikshay on the same day. The HCW/ HF staff need to login daily to check for the results and inform the patient and the treating doctor at the concerned health facility on the same day. If H mono/poly DR-TB is detected, appropriate clinical evaluation is conducted by the treating doctor and all oral H mono/poly DR-TB regimen can be initiated by the trained HF doctor/private health-care provider at the respective health facility itself while waiting for the results of SL-LPA and L- DST. These patients need not be sent to the DDR-TBC, unless deemed necessary.

As soon as the results of SL-LPA and LC&DST are available, the microbiologist/ staff at C&DST lab must enter the results in Nikshay and inform the concerned health facility and DTO on the same day. According to the results, the treating doctor may need to modify the regimen using the replacement sequence detailed earlier. At any time during the treatment with DS-TB or H mono/poly DR-TB regimen with or without modifications, if there are signs of non-response, the patient must be subjected to NAAT again to rule out amplification of rifampicin resistance and further LPA and DST at specific time points as detailed in the follow-up monitoring earlier. If MDR/RR-TB is detected, the patient must be sent to the N/DDR-TB centre for evaluation and treatment initiation with shorter oral Bedaquiline-containing MDR/ RR-TB regimen or longer oral M/XDR-TB regimen as per the eligibility criteria.

In all DR-TB patients, if additional resistance is reported after treatment initiation either on the baseline sample or any time subsequently on the basis of FL/SL-LPA to FQ, Am, Eto or LC&DST to Z, Lzd or whenever standardized WHO endorsed DST methods for Cfz, Bdq and Dlm are available under NTEP, the patient should be counselled by the CHO/ HF doctor or Private health care provider, field staff/ TBHV/ STS and referred to the N/DDR-TBC immediately for necessary regimen modification. Regimen modification must not be attempted by HF doctor without consulting the concerned N/DDR-TBC physician. The standard shorter oral Bedaquiline-containing MDR/RR-TB regimen shall be stopped and the N/DDR-TBC committee would consider initiating longer oral M/XDR-TB regimen with or without modifications as appropriate. As the patient would still be in early IP, the patient would be re- classified and re-registered for a new episode of treatment and updated on Nikshay against same Patient ID by creating subsequent Episode ID. Such patients will not be accounted for in the final treatment outcomes as detailed earlier in **Section 4.11.**

The first dose is given under supervision at the treatment initiating facility for ambulatory patients. All doses are to be supervised by the treatment supporter. Empty blisters of drugs taken unsupervised in the evening and on Sundays are to be collected by treatment supporter.

The results of SL-LPA (Lfx / Mfx[h]) resistance are expected to be available within a week of specimen submission. Based on results, if no additional resistance is detected, the patient will be continued on the same regimen.

The DTO, MO-TU and the Senior DR-TB TB-HIV supervisor need to ensure that the patient turn-around time (P-TAT) from diagnosis, PTE to treatment initiation relative to the laboratory technology used should be well within the minimum acceptable timeline as detailed in **Table 4.21** below. This need to be intensively monitored for every district and TB unit.

Table 4.21: Patient turnaround time (P-TAT) from identification to treatment initiation relative to the laboratory technology used

Technology	Pre Lab TAT in Days*	Lab TAT in Days**	Post Lab TAT in Days***	Total Patient TAT in Days
NAAT	1-2	1-2	2-3	4-7
LPA	1-3	2-3	2-3	5-9
LC DST[#]	NA	Time till LPA testing – 5-7 days + [@]22 – 48 (in most cases 30 days)	2-3	29-58 (in most cases 40 days)
LC for follow up	2-3 days (for tracing patient and collecting specimen)	8-42	1-2	11-45

Remarks:

* Pre lab TAT for NAAT includes time from patient identification, counselling, collection and transport of 2 specimens to NAAT facility. Pre lab TAT for LPA & LC&DST includes time from collection to NAAT and further transport of second specimen to C&DST labs.

** Lab TAT includes the time from specimen receipt to results by technology.

***Post lab TAT included time from accessing test results, pre-treatment evaluation to treatment initiation.

[#] For Z DST additional 7 days will be needed.

@ Includes culture and growth days for DST set up.
Fresh samples are collected from the patient and transported for follow-up on liquid culture.

While patient-centric outpatient/ ambulatory care is the primary strategy for care of DR-TB patients with otherwise good general condition, hospitalization is essential for severely ill patients and for those with complications or associated conditions requiring closer clinical monitoring. It might also be an alternative, especially during the initial phase of treatment, for a small number of patients for whom other means of ensuring treatment adherence and support are not available. Hence, it is important to assess the general condition of every DR-TB patient to identify those who may need hospitalization upfront to prevent any adverse outcome.

If any patient at a PHC/private clinic has one or more of the following features, s/he should be referred for inpatient care at N/DDR-TBC. The HF doctor/private doctor should identify patients who required hospitalization using the Technical Guidance for Comprehensive Package for Differentiated Care of TB patients and the N/DDR-TBC Committee can decide on a patient-to-patient basis, the need for admission of DR-TB patients for initiation of treatment based on clinical, radiological and psycho-social assessment. The following conditions warrant initial hospitalization of the DR-TB patient for a period of 7-14 days:

1. Children under 5 years with DR-TB
2. Extensive TB disease – presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, presence of cavities or bilateral disease on chest radiography
3. Severe EP-TB disease - presence of miliary TB or TB meningitis or CNS TB. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)
4. Intolerance to any drug in the shorter/longer oral MDR-TB regimen or risk of toxicity from a drug (e.g. drug–drug interactions)
5. Severely malnourished (HB < 7 g/dl, BMI < 16 with pedal edema, MUAC < 16cm)
6. Hypotension (Diastolic below 60mm)
7. Oxygen saturation (SPO2 below 85%)
8. Haemoptysis >100 ml
9. General condition – drowsy state of consciousness
10. Pregnancy related complications with DR-TB
11. Patients exceptionally being considered for BPaL regimen
12. Underlying severe co-morbid or other systemic disease (hepatitis, nephritis, underlying cardiac conditions etc.)
13. Any surgical intervention required in the chest for any emergency like pleural complications and elective surgeries for patients with localized lesions after bacteriological conversion.

The patient can be initiated on shorter oral Bedaquiline-containing MDR/RR-TB regimen at N/DDR-TBC on in-patient or out-patient basis and further decision can be made upon availability of reports of sample sent for SL-LPA or LC&DST . Once the PTE is completed and it is time to initiate the patient on treatment, the physician at N/DDR-TBC and support staff must ascertain if the FL-SL LPA results are available on Nikshay or call up the microbiologist of C&DST lab to ensure appropriate choice of regimen based on LPA results.

Shorter/longer oral MDR-TB regimen can be initiated on out-patient basis if the patient is satisfying all following risk assessment criteria:

- QTcF < 450 ms in males and <470 ms in females at baseline
- Normal serum K, Mg, Ca at baseline
- No history of structural cardiac abnormalities (LVH or RVH secondary to hypertension can also cause ECG changes, however mere presence of LVH need not be an exclusion criteria) or ECG abnormalities
- Patients with QTcF between >450 to 500 ms in male and > 470 to 500 ms in female require daily monitoring of ECG for 3 days along with evaluation and correction of any electrolyte abnormalities. A cardiologist opinion may need to be taken.

The first dose is given under supervision at the treatment initiating facility for ambulatory patients. In patients who are admitted, the duration of indoor management would be decided by N/DDR-TBC committee as clinically indicated.

On discharge, the patient will be provided the current monthly patient box with rest of the drugs including newer drugs to complete the first month of the treatment course. The patient/ family member will carry the box with drugs including newer drugs and hand it over to the treatment supporter under supervision/guidance of the senior DR-TB TB-HIV supervisor, STS and DTO. The monthly patient box including new drugs will remain under custody of the treatment supporter till the patient completes the treatment course while the box with other drugs would be refilled on a monthly basis. The bottle of Bdq will be supplied for the full course and tablets should not be removed from the bottle assigned to the patient.

Once patient is initiated on treatment, CHO/ HF doctor/private health-care provider staff/ TBHV/ STS to identify and prepare the treatment supporter and supply 2 monthly patient boxes, training, counselling tool and records to the treatment supporter and 2 more monthly patient boxes corresponding to that patient at the HWC/HF concerned. Senior DR-TB TB-HIV supervisor, MO-TU and DTO to coordinate for advance information to concerned HWC or HF.

While referring the patient back to the HWC/HF of public or private sector for ambulatory treatment, s/he should be referred after updating all relevant information by N/DDR-TBC staff in Nikshay with remaining current monthly patient box initiated at N/DDR-TBC and a copy of the PMDT treatment book and referral form under intimation of the DTO. The respective DTO/ MO-TU/ HF doctor/ CHO/ Private health care provider should be informed by the concerned staff of N/DDR-TBC on referral of patients for ambulatory care in advance, by means of the NTEP PMDT referral for treatment form via Nikshay, email or mobile phone.

Confirmation that the patient has reported to the concerned DTO/ HF doctor/ CHO/private health-care provider from the respective N/DDR-TBC must be received by N/DDR-TBC including acceptance by the current HF of the district as soon as the patient reaches home and is initiated on ambulatory care with a patient TAT of within 1 week of referring the patient. Drugs consumed by the patients to cover for transit period may be accounted as unsupervised doses. The monthly patient-wise box with remaining quantity of drugs should be handed over to the treatment supporter as early as possible. DTO should arrange for availability of the monthly drug box to the treatment supporter (via the TU staff like STS/TBHV) for subsequent months and intimate the respective CHO/HF doctor/private health-care provider immediately. CHO/ HF doctor will be responsible for supplying patient records, training and drugs to the designated treatment supporter.

Treatment must be provided under direct observation by the trained treatment supporter complemented by digital adherence technologies like MERM, video observation of treatment

(VoT) etc. Other modalities of treatment adherence like monthly refill monitoring, empty blister or pill counts and interview of patient and treatment supporters could be used by various levels of supervisors to assess treatment adherence. Treatment supporters must also be educated about the potential side effects and then need for timely reporting the side effects to the CHO/ HF doctor for timely and prompt resolution at HF or if required at N/DDR-TBC level. This is also critical to ensure treatment adherence and successful completion of treatment. Also, special needs of patients for vocational, psycho-social support, social welfare, surgical interventions, palliative care.

Community engagement and peer support systems through trained TB champions and community volunteers must be leveraged upon for encouraging patients to avail DR-TB services early, promote treatment adherence and stigma reduction efforts through the HWCs, community based organizations (CBO) and local self-help groups (SHG).

CHO/ HF doctor must ensure that follow-up smears are done at the nearest TB detection centres while specimen for follow-up cultures need to be collected and sent to the concerned C&DST lab from the specimen collection centres through the suitable transportation system arranged by the DTO. All other biochemical, radiological, ECG and specialist assessments must be arranged for all DR-TB patients by the DTO/ MO-TU and HF doctor as per the follow-up schedule for each regimen through the designated mechanisms at HF or N/DDR-TBC or free diagnostic schemes of NHM or through the outsourced mechanism. Patient's information as per PMDT treatment book and aDSM treatment review form as detailed later must be regularly updated and uploaded on Nikshay (at least weekly) by the concerned field staff responsible.

Towards the end of treatment, it is desirable that the DR-TB patients are sent to the concerned HF or N/DDR-TBC for end of treatment assessment and declaration of final treatment outcome. Treatment outcome is determined by reviewing the patient PMDT treatment card. The treatment outcome and date the patient stopped treatment is written in the appropriate section in the TB treatment card. The transferred-out patients should be tracked vigorously before declaring them as not evaluated or lost to follow-up. The date on which the patient stopped treatment is the date of the last dose of drugs taken. The HF doctor or physician at N/DDR-TBC should record the treatment outcome in Nikshay. Details of treatment outcome should be updated in Nikshay on the same day of declaring the final treatment outcome by the concerned HF doctor or N/DDR-TBC respectively. If required, the hard copy of the treatment card can be printed from the Nikshay (if required). Every patient started on treatment must be given one and only one treatment outcome for each episode of treatment regimen. Once the outcome is declared, all successfully treated DR-TB patients must be followed up at 6 monthly intervals to screen for signs and symptoms of TB, chest X-ray if possible and smear/ cultures among symptomatic until 24 months post treatment to ascertain relapse free cure.

Overall responsibility of monitoring the patient's progress on treatment, including follow-up and follow-up investigations is with the CHO/ HF doctor/ TBHV/ STS where patient is being treated with support of the respective TU team. Nikshay Sampark toll free Helpline number **1800-11-6666** can be contacted anytime by patients and their families for any concerns or issues.

The flow of patients from diagnosis to treatment initiation and follow up till final treatment outcome submission is depicted in **Figure 4.14** for H mono/poly DR-TB and **Figure 4.15** for shorter oral Bedaquiline-containing MDR/RR-TB regimen /longer oral M/XDR-TB regimen.

Figure 4.14: Flow of H mono/poly DR-TB patients from diagnosis to treatment initiation and follow-up till final treatment outcome submission

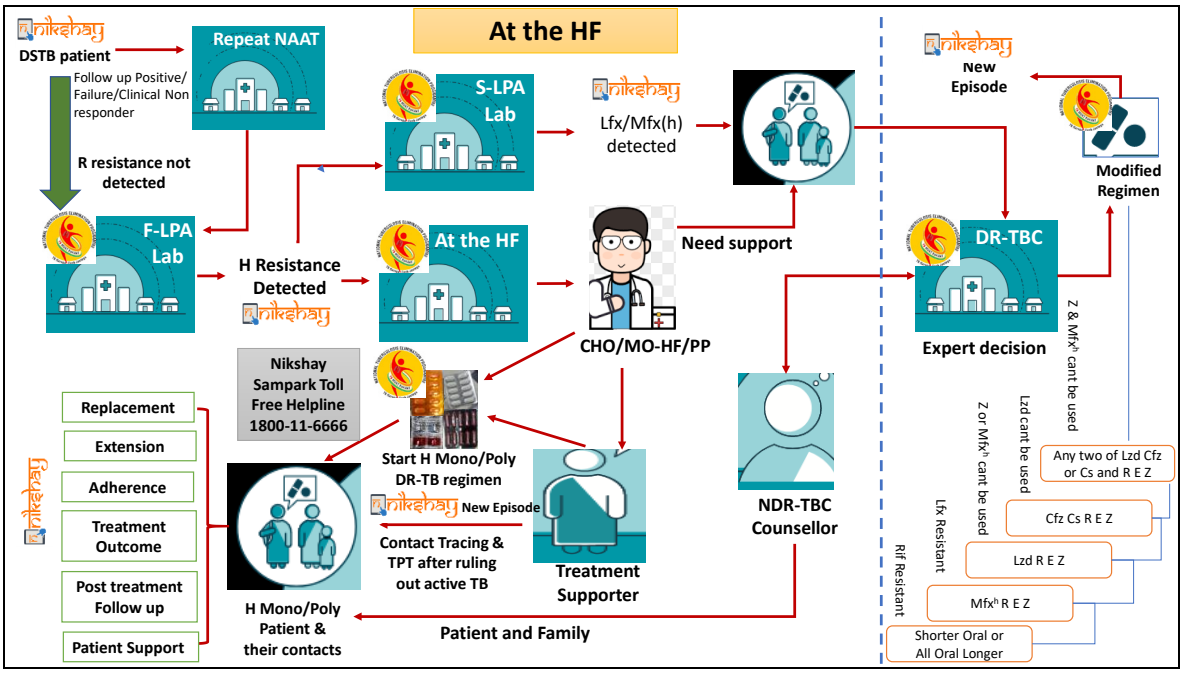
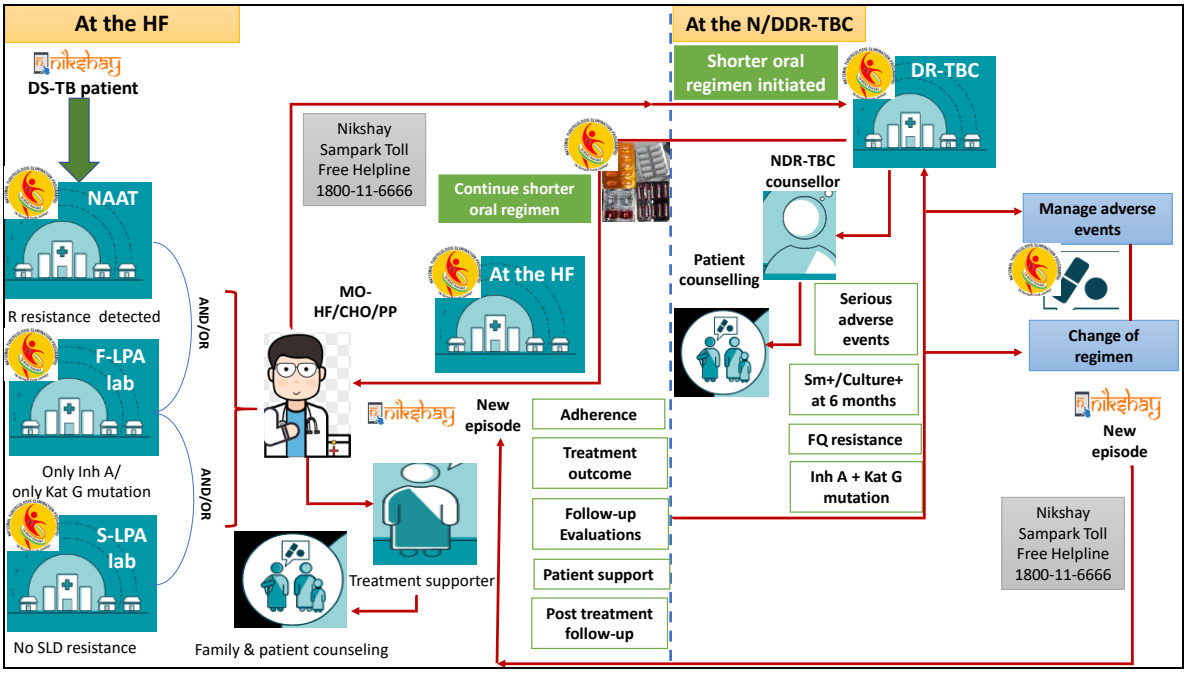
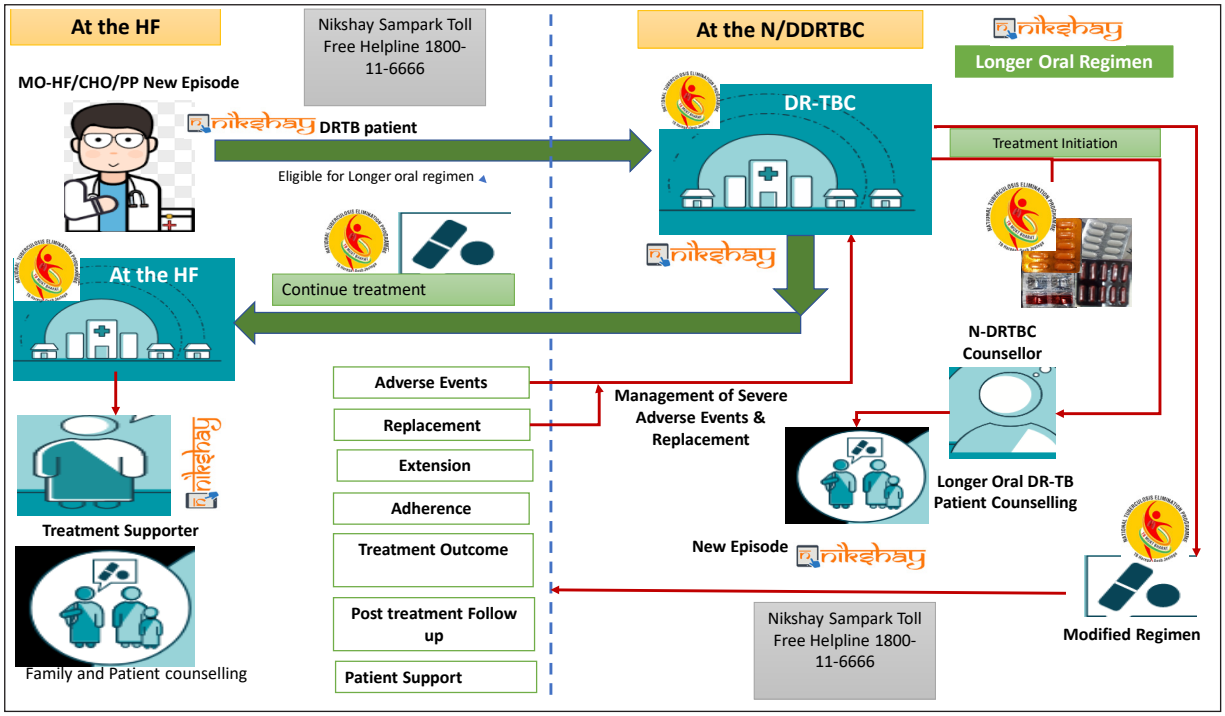


Figure 4.15: Flow of M/XDR-TB patients from diagnosis to treatment initiation and follow up till final treatment outcome submission





4.12.4. Management of treatment interruptions and lost to follow-up

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

The following strategies are applicable for patients who interrupt treatment:

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

Patients who interrupt treatment for less than two months. When the patient returns to resume treatment, the treatment will be continued and the duration of treatment will be extended to complete the regimen. The follow-up cultures will be done as per the schedule. An additional culture may be considered if the patient returns between one to two months of treatment and has clinically deteriorated. If the culture is positive, repeat FL/SL LPA and LC DST need to be done as per diagnostic algorithm. If additional resistance is detected to any component drugs, the MDR/RR-TB patient will be switched to longer oral M/XDR-TB regimen with a fresh PTE. If the interruption is in IP the outcome will be accounted for this patient for the longer oral M/XDR-TB regimen only and if the interruption is in CP the outcome for shorter oral Bedaquiline-containing MDR/RR-TB regimen will be declared 'treatment failed'.

Patients who are "lost to follow-up" (interrupt treatment continuously for two months or more) and return back for treatment: Such patients will be given an outcome of "lost to follow-up". The patient would be subjected to repeat NAAT & FL/SL-LPA and LC&DST as per the diagnostic algorithm to restart with appropriate treatment. If there are signs of impending treatment failed for any MDR/RR-TB patient with or without additional resistance to second-line drugs, the patient should be switched to longer oral M/XDR-TB regimen and evaluated

further to modify appropriately based on DST results if required. If a patient has received the shorter oral Bedaquiline-containing MDR/RR-TB regimen for more than one month and returns for treatment after continuous interruption of two month or more, the patient is not restarted on a shorter oral Bedaquiline-containing MDR/RR-TB regimen.

Patients on newer drug containing regimen and interrupt treatment or are "lost to follow-up" or recurrent DR-TB

- Patients who interrupt Bdq during the first two weeks of Bdq course and returns to resume the treatment:
  - if interruption is up to 7 days, Bdq will be continued to complete the doses and the duration of treatment will be extended to complete full course of Bdq. Follow-up cultures will be done as per the revised schedule; and
  - if interruption is more than 7 consecutive days, Bdq course will be reloaded (started afresh with a new bottle and old bottle sent for reconstitution). Follow-up cultures will be done as per the revised schedule.
- Patients who interrupt Bdq during 3-24 weeks of Bdq course and return to resume treatment:
  - if interruption is up to two months, Bdq containing regimen will be continued to complete the doses and duration of treatment will be extended to complete full course of Bdq. Follow-up cultures will be done as per revised schedule; and
  - if interruption is more than two months, the regimen will be permanently discontinued. Such patients will be given an outcome of "Lost to follow-up" (LTFU), registered afresh and initiate longer oral M/XDR-TB regimen with appropriate modification if needed after a re-evaluation with FL-SL LPA, LC&DST as per algorithm and PTE.
- Patient who are required to be shifted from shorter oral Bedaquiline-containing MDR/RR-TB regimen to longer oral M/XDR-TB regimen due to reasons of resistance, tolerability, availability and emergence of exclusion criteria, need to be re-evaluated for necessary modification of longer oral M/XDR-TB regimen as required and initiated on a full course of longer oral M/XDR-TB regimen. Bedaquiline should be given for the entire 6 months duration without the loading dose.
- Similarly, patients who are placed on a longer oral M/XDR-TB regimen based on history of exposure to second-line drugs for > 1 month awaiting LPA results and later found to be eligible for the shorter oral Bedaquiline-containing MDR/RR-TB regimen (and in whom resistance is not detected on baseline specimen to H i.e. both inhA and katG or to FQ or Z, Cfz*, Bdq*) can be switched, provided that treatment has not lasted for more than 1 month. If patients are switched in this way, the shorter oral Bedaquiline-containing MDR/RR-TB regimen is given for the full duration, without any changes to its composition or duration. Bedaquiline should be given for the entire 6 months duration without the loading dose.
- In both of the above situations, the remaining drugs of the regimen stopped should be returned back for reconstitution and a new box of regimen changed should be initiated. Bdq can be reinitiated with the loading dose, if the interruption, if any, is up to two months.
- In such patients with change in regimen within the scope of guidelines for the purpose, from shorter to longer or vice-versa in the initial months before any definitive treatment outcome applies, the outcome of only the changed regimen needs to be reported. The patient moves out of the denominator of the previous regimen.

- If the patient misses one or more doses of Dlm during treatment up to a maximum of two month, one should continue the treatment and complete the Dlm for rest of the period which may prolong the Dlm containing phase beyond 24 weeks from initiation of treatment to make the adjustment of missed dosage.
- Patients who have consumed more than one month of any regimen with Bdq or/and Dlm and return after treatment interruption of two month or more will be declared as "lost to follow up". Such patients would not be considered eligible for administration of same drug (Bdq/ Dlm) anymore, unless they are found to be susceptible on DST whenever available under NTEP.
- Where further treatment is concerned, if the patient has any indication of a treatment failed or recurrence, the NDR-TBC Committee will be contacted to discuss the appropriate regimen design. The decision will be made on an individual patient-to-patient basis, using all available bacteriological, clinical, radiological, biochemical, ECG, h/o exposure to drugs and most recent resistance pattern data to all drugs in group A, B and C from which a reliable DST method is available.
- If a DR-TB patient on treatment decides to move and informs the health-care worker, the patient can be transferred out to the HWC or HF anywhere in India where the patient wishes to migrate maintaining continuum of care during the transit.
- Transfer out should be brought to the notice of the N/DDR-TBC by the concerned CHO, HF doctor, private provider, MO-TU and DTO.
- The current health facility for the patient needs to be updated for a patient from transferring health facility to the receiving health facility under the transfer module of Nikshay while referring health facility is still able to fetch the patient details through Nikshay. This should preferably be done before or as soon as the physical movement of patient happens.
- Suitable treatment supporter should be identified and updated in Nikshay by the receiving health facility. The details of treatment adherence follow up and treatment outcome need to be updated against same episode ID from the receiving health facility.
- If the patient is migrating to other district that is not being served by the same DR-TBC, the patient may be formally transferred out with 7 days of drugs for transit period to a suitable treatment supporter at that place where s/he proposes to move.
- The receiving DR-TBC for the patient need to be updated in Nikshay along with the linked current health facility.
- During transfer to other N/DDR-TBC, the patient should be transferred along with the referral for treatment form, copy of the PMDT treatment card downloaded and printed from Nikshay, the PMDT treatment book, aDSM treatment initiation & review forms as applicable, pre-treatment & follow-up investigations from the concerned DR-TBC transferring the patient by the DTO who initiates the transfer-out process to the DR-TBC and DTO of the district receiving the patient with coordination support of Senior DR-TB TB-HIV supervisors of both districts. This would be in prior consultation with DTO of that district and under intimation of DR-TBC concerned.
- The patient must be motivated to carry the PMDT treatment book to the receiving N/DDR-TBC.

It is the responsibility of the receiving DTO and N/DDR-TBC to receive the patient on Nikshay transfer module, arrange for treatment supporter and send feedback/update status on Nikshay for the transferring DTO and N/DDR-TBC to establish a link for future exchange of information about interim reports, culture conversion and treatment outcomes with support of the Senior DR-TB TB-HIV supervisors of both districts.

4.13. Palliative care

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

Need of palliative care

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

Challenges in palliative care

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

Services under palliative care

Palliative care would be necessary for care of patients who are chronically ill, with extensive drug resistance, with extensive fibro-cavitary or disseminated bilateral lung disease, who have

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

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

Supportive measures in palliative care

The details on palliative care supportive measures are summarized below:

- ***Respiratory rehabilitation.*** Relief from dyspnoea with oxygen may be used to alleviate shortness of breath in some patients but there is no significant evidence to generalize its practice. Physiotherapy, evaluation for surgery, respiratory rehabilitation including yoga *etc.,* need to be considered in such patients. (Refer to **Annexure 16** for an example of pulmonary rehabilitation) Morphine provides significant relief from respiratory insufficiency and should be offered according to established clinical protocols available in the medical literature.
- ***Relief from pain and other symptoms.*** Paracetamol or Tramadol with paracetamol gives relief from moderate pain. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable.
- ***Infection control measures.*** The patient who is taken off anti-TB treatment because of failed often remains infectious. Infection control measures should be continued with reinforcement of administrative, environmental and personal measures, including N-95 mask use for caregivers.
- ***Nutritional support.*** Small meals as needed are often best for a terminally ill patient. It should be accepted that the intake will reduce as the patient's condition deteriorates and during end- of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support, should be treated.
- ***Regular medical visits.*** When DR-TB treatment stops, regular visits by healthcare providers and the support team should be continued to address medical needs and ensure that infection control practices are being followed. Early identification, periodic assessment and management of post treatment sequelae could be beneficial for the patient.
- ***Vocational rehabilitation.*** Wherever possible, based on the interest of the patient, an appropriate linkage for vocational rehabilitation and new skill learning opportunities through various NGOs may be explored to help the patient regain his/her source of livelihood and move towards socio-economic sufficiency. This would also have an indirect impact on improving the patient's nutritional, psychological and mental wellbeing.
- ***Continuation of ancillary drugs.*** All necessary ancillary medications should be continued as needed. Opioids help control cough, as well as pain. Other cough suppressants can be added. Bronchospasms can be controlled with a metered dosed inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed. Antiemetic may still be needed, and fever treated if the patient is uncomfortable. Appropriate use of alternative drug may be considered through expert consultation.

- ***Preventive measures.*** Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important. Additionally, patients must be encouraged to move their bodies in bed if able. Keeping beds dry and clean are also important.
- ***Provide psychosocial support.*** Psychological counselling to the patient and family caregivers is critical at this stage, especially to assist patients in the planning of decisions related with the end-of-life stage. Also, emotional support, especially in settings in which strong stigma is attached to the disease would be necessary.
- ***Respect for patient's beliefs and values.*** It is common for the patient and family caregivers to develop or increase their interest in spiritual and religious matters while passing through this situation. Health-care providers should respect those beliefs and should not impose personal values and practices that prevent the patient to seek and find comfort in services delivered by faith-based organizations (FBO).

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

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

Need for human resource and infrastructure

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

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

All health workers must receive training in palliative care to enable them extend support to family members or caretakers providing home-based palliative care and to undertake regular contact tracing and extend support to address their problems. Existing expertise from palliative care, HIV and respiratory medicine can, therefore, translate directly to TB. Delivery of palliative care from within respiratory clinical services by existing staff with additional training, with clear criteria for referral to palliative care specialists for complex patients, is to be established. NDR-TBCs should link up with local palliative care and hospice teams from the network of Pallium India and Indian Association of Palliative Care. However, it is of paramount importance from the infection control perspective to avoid sending infectious patients to these palliative care centers where immunocompromised cancer or stroke patients could potentially be infected.

Effective control of the various problems faced by patients and their families is possible across many settings (hospital, hospice, primary care and home-based care) and flexibility in place of delivery need to be established. Palliative and end-of-life care should be delivered to the patient and their family in the setting where they are receiving care, whether an inpatient, an outpatient, or at home. Community-based workers could be trained in palliative care to scale-up existing health care delivery to include pain and symptom control. Having a patient die at home can be difficult for the family and the other way around. Home-based care should be offered to patients and families who want to keep the patient at home, whenever appropriate infection control practices can be followed. Institution-based end-of-life care should be available to those for whom home care is not feasible or desirable.

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

POINT TO REMEMBER

- ✓ Shorter oral Bedaquiline-containing MDR/RR-TB regimen (recommended by WHO) to be introduced in a phased manner in adults (>18 years) as well as in children (5 years to 18 years) in individuals confirmed with pulmonary MDR/RR-TB, with uncomplicated extra-pulmonary TB disease and in PLHIV in selected states to gain programmatic experience to guide future expansion;
- ✓ Only those patients with mutations in both InhA and katG will not be eligible for shorter oral Bedaquiline-containing MDR/RR-TB regimen. However, patients with only InhA or only katG mutations will be eligible for the shorter oral Bedaquiline-containing MDR/RR-TB regimen provided other conditions are met;
- ✓ Child-friendly formulations of second-line drugs including newer drugs are now available under NTEP;
- ✓ Longer oral M/XDR-TB regimen with Bdq will be used to treat patients who are not eligible for shorter oral Bedaquiline-containing MDR/RR-TB regimen including pregnant women with stringent aDSM;
- ✓ For longer oral M/XDR-TB regimen, the revised replacement drugs sequence recommended would be delamanid, amikacin, pyrazinamide, ethionamide, PAS, ethambutol, carbapenems;
- ✓ Extension of Bdq beyond 6 months to be considered in patients in whom an effective regimen cannot be otherwise designed if only 2 of 5 drugs are available from Groups A & B and adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST;
- ✓ Combined use of Bdq and Dlm in the regimen is recommended for those M/XDR-TB patients in whom an appropriate regimen cannot be designed using all 5 drugs from Group A and B;
- ✓ BPaL can be considered as a last resort by NETP under prevailing ethical standards in individual patients for whom the design of an effective regimen not possible as per recommendations.

- ✓ Post-treatment completion follow-up of all successfully treated TB patients at 6th, 12th, 18th and 24th months to be initiated under NTEP;
- ✓ Health and Wellness Centres and HF staff need to be trained to improve quality of last mile service delivery to DR-TB patients and all medical colleges to establish DR-TB centres to improve quality of clinical care of DR-TB patients;
- ✓ Patient turnaround time for early diagnosis and prompt treatment initiation on appropriate regimen need to be closely monitored for all district and TB units;
- ✓ Strengthen mechanisms for improved patient follow-up and aDSM for quality implementation of PMDT guidelines; and
- ✓ Build capacity of all providers (labs, DR-TBC, field staff) in optimally utilizing Nikshay for real-time data entry as well as monitoring at state and district level in order to improve the quality of care and timely regimen change in DR-TB patients.

CHAPTER 5

PREVENTIVE TREATMENT FOR CONTACTS OF DR-TB

Learning objectives

In this chapter, we will learn about:

- Rationale and evidence
- Integrated algorithm for screening and ruling out active TB among HHC of DR-TB patients
- Policy on TPT for DR-TB contacts in India
- Treatment, drug dosages, adherence and follow-up
- Managing ADRs and referring to DR-TB centres

5.1. Rationale and evidence

MDR-TB is a serious form of TB and is less easy to treat than other types of TB disease. Mathematical modelling suggests 3 in every 1000 people globally carry MDR-TB infection and prevalence of MDR-TB in those with TBI is more than double among those younger than 15 years. *(25)*

HHC of patients with MDR/RR-TB or H mono/poly DR-TB are at higher risk of TBI than contacts exposed to drug-sensitive TB, however the risk of progression to TB disease does not differ among contacts in both groups. *(26)*

Recent evidence from systematic review & meta-analysis, and cost-effectiveness of treatment of latent tuberculosis to reduce progression to multidrug-resistant tuberculosis revealed. *(27)*

- a reduced risk of TB incidence with treatment for MDR-LTBI, suggesting effectiveness in prevention of progression to MDR-TB, and confirmed cost-effectiveness;
- estimated MDR-TB incidence reduction was 90% (9%-99%) using data from 5 comparison studies;
- high treatment discontinuation rates due to adverse effects in persons taking pyrazinamide-containing regimens; and
- cost-effectiveness was greatest using a fluoroquinolone/ethambutol combination regimen.

The rationale for four-month daily rifampicin (4R) in contacts of H resistant R sensitive DR-TB patients is that R has an excellent efficacy and safety profile compared to H and the cost is lower than rifapentine. This regimen is useful to give to contacts of people with bacteriologically confirmed isoniazid-resistant, rifampicin-susceptible TB disease. One of the main challenges with 4R however may be to deal with the perception that R needs to be protected for use as a first-line TB medicine and concerns that its use in TPT may increase levels of R resistance

in the community or promote misuse of the agent as monotherapy for TB disease. There is however no evidence till date demonstrating the significant increase in R resistance levels due to scale-up of TPT services. *(26)*

Other challenges to consider are drug–drug interactions with ARVs (refer to the section on drug–drug interactions). Child-friendly formulations are not available currently and the supply of single dose formulations may be limited due to widespread availability of FDCs of first-line TB treatment. However, studies have shown that in adults, 4R has been shown to be safer (lower frequency of grade 3 or 4 hepatotoxicity) and to have better adherence rate than 9H. Also, inadequately powered TB prevention trials involving adults, 3R was found to be non-inferior to 6H and 3HP was found to be non-inferior to 9H. In the study *(28)*, 829 children were randomly assigned to receive 9H or 4R, with drugs administered by the participants or their caretakers. Of these children, 79 were under the age of 2 years, an age group with the highest risk of life-threatening TB disease. No significant safety concerns were identified with either regimen, but the R group had better treatment-completion rates.

5.1.1. WHO recommendations on TPT among contacts of DR-TB patients

WHO recommends *(26)* TPT among contacts exposed to MDR-TB with FQ sensitive or H resistant with R sensitive DR-TB patients following consideration of intensity of exposure; confirming the source patient and her/his drug resistance pattern confirmed bacteriologically and ascertaining TBI using IGRA or TST.

Among contacts exposed to patients with known MDR-TB with FQ sensitive, WHO suggests *(26)* the use of levofloxacin for six months (pediatric formulation for child contacts) if tolerated. If H susceptibility is confirmed in RR-TB index patients, contacts may be given 6H. Among contacts exposed to individuals with known H-resistant TB with R sensitive, the use of rifampicin for four months is proposed. Regardless of whether treatment is given or not, clinical follow-up should be done for two years and any emergent signs and symptoms suggestive of TB should be actively investigated and curative regimens started as needed.

5.1.2. Studies in the pipeline

Randomized controlled trials on MDR-TB preventive treatment are urgently needed to improve the evidence base. Results from following three RCTs of TPT among HHC of MDR-TB patients are expected to become available in the next few years:

- **TB CHAMP.** Testing six months of levofloxacin (Lfx) vs placebo in infants and young children less than five years of age exposed to MDR-TB (South Africa; ongoing recruitment and intending to publish by end 2021).
- **V-QUIN.** Testing 24 weeks of Lfx vs placebo in all ages with evidence of infection (Viet Nam; recruitment completed; date of ending data collection is March 2022).
- **PHOENIx.** Testing 26 weeks of delamanid vs isoniazid in all ages (11 countries; estimated completion in mid-2025)

5.2. Integrated algorithm for screening and ruling out active TB among HHC of DR-TB patients

The integrated algorithm for screening and ruling out active TB among HHC of DR-TB patients is detailed in **Figure 5.1** below. It is critical to know the DST pattern of the index DR-TB patients to guide the TPT regimen choice in those found eligible to received TPT for among DR-TB contacts.

The following are the salient features of the integrated algorithm:

- Once a DR-TB patient is identified, all HHCs are counselled, screened and evaluated to rule out active TB;
- NAAT will be used upfront among contacts with symptoms or abnormal chest X-ray to diagnose TB;
- If the result is MTB detected with no resistance, the treatment for DS-TB is initiated;
- If the result is MTB detected with H and/or R resistance, manage as per DR-TB guidelines;
- If the result is MTB not detected, in HHC <5 years, assess for TPT and check for any contraindications;
- If the result is MTB not detected, in HHC >5 years of age with TBI test positive or unavailable and chest X-ray is normal or unavailable check for any contraindications;
- If contraindications to TPT drugs exists, defer TPT and if no contraindication exists, offer TPT regimen as appropriated based on DST pattern of the index patient; and
- Follow-up for active TB as necessary, even for patients who have completed preventive treatment irrespective of TPT offer.

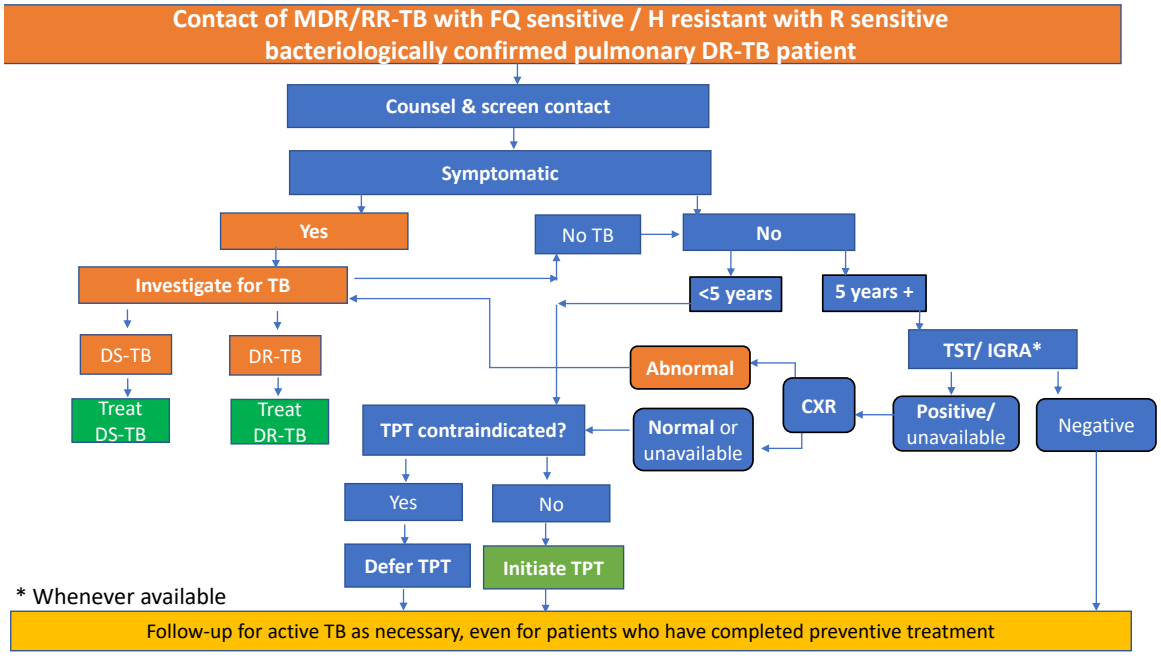


Figure 5.1: Integrated algorithm for screening and ruling out active TB among HHC of DR-TB patients

5.3. Policy for TPT in DR-TB contacts in India

Preventive treatment among HHC of MDR-TB index patients (in whom FQ resistance has been ruled out) and among HHC of H resistant index patients (in whom R resistance has been ruled out), the target population, using 6Lfx and 4R respectively to be introduced in a phased manner for all age groups to gain programmatic experience to guide future expansion while awaiting results of ongoing studies. This recommendation may be considered for children given their special needs pan-India.

5.4. Treatment, drug dosages, adherence and follow-up

The recommended dosage of medicines for TB preventive treatment among contacts of DR-TB index patients after ruling out active TB and testing for TBI by age and weight is given in **Table 5.1** below.

Table 5.1: TPT regimen options and recommended dosages of medicines for contacts of DR-TB index patients

Regimen	Dose by age and weight band
Six months of daily levofloxacin (6Lfx) for contacts of R resistant FQ sensitive patients[#]	Age > 14 years, by body weight: < 45 kg, 750 mg/day; ≥ 45 kg, 1g/day Age < 15 years (range approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day 10–15 kg: 200–300mg/day 16–23 kg: 300–400mg/day 24–34 kg: 500–750mg/day
Four months of rifampicin daily (4R) for contacts of H resistant R sensitive patients*	Age 10 years & older: 10 mg/kg/day[@] Age <10 years: 15 mg/kg/day (range, 10–20 mg)

[#] Levofloxacin 100 mg dispersible tablets available for children. Children receiving 6Lfx should be watched for joint abnormalities.

* In children from 0-14 years, 4R should only be used after ruling out active TB in limited geographies/ populations for evidence generation to guide future scale up for country wide implementation.

[@] Maximum dose of R would be 600 mg/day.

Note: 6H can be considered as the TPT regimen option for contacts of index patients with RR-TB with FQ and H sensitive, after ruling out active TB in them.

Once TPT is initiated, the individuals will be monitored by the Doctor for clinical and laboratory parameters as below.

- Screening with 4S symptoms (cough, fever, night sweats and weight loss)
- Any side effects
- If any of the sign/ symptoms of TB emerge, the person may be referred to the DR-TB centre for further evaluation for active TB/DR-TB disease
- In the above case the person may be subjected to NAAT & LPA for diagnosis of TB & DR-TB and appropriately managed if found to have developed active TB/DR-TB disease.

Develop a personal adherence plan with the support of the family member, caregiver or health worker as per treatment regimen being provided. Treatment support and adherence monitoring will be similar to that of the index patient. Give first preference to the family member to be the treatment provider in consultation with the person. Use of digital platforms (tele/video calls, 99DOTS/MERM), counting empty blisters, refill monitoring etc, to strengthen adherence monitoring.

Adherence to the TPT course and treatment completion are important determinants of clinical benefit, both at individual and population levels. Irregular or inadequate treatment reduces the

protective efficacy of TPT regimen. Poor adherence or early cessation of TPT can potentially increase the risk of the individual developing TB including drug-resistant TB (although not supported by existing evidence from research settings). It is known that the efficacy of TPT is greatest if at least 80% of the doses are taken within the duration of the regimen. The total number of doses taken is also a key determinant of the extent of TB prevention. The criteria for completion of TPT among DR-TB contracts is given in **Table 5.2** below.

Table 5.2: Criteria for completion of TPT with 6Lfx and 4R

	Total duration in months	Expected no. of doses	80% of recommended doses (days)	Extended time for treatment completion (days) (treatment duration +33% additional time)
6Lfx (daily)	6	180	144	239
4R (daily)	4	120	96	160

5.5. Managing adverse events

Levofloxacin

- Many people using this medication do not have serious side effects. Nausea, diarrhoea, headache, dizziness, light-headedness, or trouble sleeping may occur.
- If any of these effects last or get worse, the doctor may be consulted promptly.
- If any serious side effects are observed, including unusual bruising/bleeding, signs of kidney problems (such as change in the amount of urine), signs of liver problems (such as nausea/vomiting that doesn't stop, loss of appetite, stomach/abdominal pain, yellowing eyes/skin, dark urine), the treating physician should be consulted immediately.
- Very serious side effects, include chest pain, severe dizziness, fainting, fast/irregular heartbeat, signs of a tear/break in the main blood vessel called the aorta (sudden/severe pain in the stomach/chest/back, cough, shortness of breath).
- This medication may rarely cause a severe intestinal condition (clostridium difficile-associated diarrhoea) due to a type of resistant bacteria. This condition may occur during treatment or weeks to months after treatment has stopped. The doctor must be intimated right away if the patient develops diarrhoea that doesn't stop, abdominal or stomach pain/ cramping, blood/mucus in the stool.
- Do not use anti-diarrhoea or opioid medications in case of any of these symptoms because these products may make them worse.
- Use of this medication for prolonged or repeated periods may result in oral thrush or a new yeast infection. The doctor may be contacted if white patches are noticed in the mouth, or there is a change in vaginal discharge or any other new symptoms.
- A very serious allergic reaction to this drug is rare. However, medical help must be taken right away if any symptoms of a serious allergic reaction are noticed, including rash, itching/ swelling (especially of the face/tongue/throat), severe dizziness or trouble breathing.

Rifampicin

- The potential adverse events associated with R are summarized in **Table 5.3** below.

Table 5.3 Possible adverse events associated with rifampicin

Drug	Known adverse events	Rare adverse events
Rifampicin	• Gastrointestinal reactions (abdominal pain, nausea, vomiting) • Hepatitis • Generalized cutaneous reactions • Thrombocytopenic purpura • Discoloration of body fluids	• Osteomalacia • Pseudomembranous colitis • Pseudoadrenal crisis • Acute renal failure • Shock • Haemolytic anaemia • Flu-like syndrome

- Patients with moderate and severe ADRs may be referred to the linked DR-TBC with all necessary documents/ records; and
- These cases may be referred to the N/DDR-TBC as appropriate for further management.

For details on implementation strategy, effective person-centered strategy to promote adherence, adverse events and their management pertaining to R, drug supply chain management, recording & reporting using Prevent TB India app till Nikshay TPT module is developed, treatment outcomes, private sector engagement, supervision monitoring evaluation and community engagement, please refer to the Guidelines for TB preventive treatment in India – 2021.

POINTS TO REMEMBER

- ✓ Preventive treatment among HHC of MDR-TB with FQ sensitive or H resistant R sensitive bacteriologically confirmed pulmonary index patients using 6Lfx or 4R respectively to be introduced in a phased manner for all age groups to gain programmatic experience to guide future expansion while awaiting results of ongoing studies.
- ✓ The person on TPT with 6 Lfx/4R may be referred to the DR-TB centre in case s/he develops any of the signs/ symptoms of TB for further evaluation and management.

CHAPTER 6

OPERATIONAL MANAGEMENT OF DR-TB PATIENTS SEEKING CARE IN PRIVATE SECTOR

Learning objectives

In this chapter, we will learn about:

- Understanding of the sequence of flow of a patient seeking care in the private sector from notification to successful treatment completion.
- Mechanism of establishing linkages between public and private sector.
- Introduce concept of purchase of services.

NTEP recognizes the fact that although free quality diagnostic, treatment and patient support services are available in the public health sector, a significant number of patients are seeking health services from the large unorganized private health sector. Reaching out to these patients is important, especially to deliver essential public health services to prevent the spread of disease, emergence of drug-resistance, to support TB patients on treatment and address comorbidities which adversely affect treatment outcomes. Additionally, health-care seeking is also guided by the willingness on part of the patient as well as the provider.

A TB patient seeking care in the private sector may come in the purview of NTEP through notification or referral. Both these scenarios and the steps to be followed in their operational management are listed below:

6.1. Scenario 1: Patient notified from the private sector

It is assumed that a TB/DR-TB patient who has been notified on Nikshay from the private sector is seeking care from a health facility that is already engaged by NTEP. This engagement could have been established by the NTEP or public health department directly or through a Patient Provider Support Agency (PPSA) or any other NGO/partner agency. It is the responsibility of the local public health and NTEP staff to reach out to the private provider directly or through PPSA and ensure that the TB care cascade is followed for the patient as per NTEP guidelines or standards of TB care.

6.2. Scenario 2: DR-TB patient referred for treatment from the private sector

6.2.1. With bacteriological confirmation in the private sector

Many times, DR-TB patients diagnosed in the private sector will wish to avail services from the public sector (NTEP). NTEP strongly recommends bacteriological confirmation of any DR-TB patients before initiation of treatment and discourages any empirical treatment. DST results

available from private laboratories for such patients will be considered acceptable under the following situations:

- NAAT results from labs that regularly undertake annual calibration of machines and/or are a part of the EQA mechanism of quality assurance under NTEP; and
- C&DST labs who participate in the annual proficiency testing through NRLs under NTEP for the respective DST technology.

For patients who do not have results in accordance with the above, DST would be offered under NTEP as per the updated integrated DR-TB algorithm.

6.2.2. With clinical diagnosis of DR-TB in the private sector

In presumptive or clinically diagnosed DR-TB patients from the private sector, all attempts should be made to bacteriologically confirm the diagnosis of DR-TB, however, if no bacteriological confirmation is possible due to lack of specimen, decision to treat for DR-TB may be taken. This can only be done in consultation with the DR-TB Committee.

6.2.3. With treatment initiated in the private sector

In a situation when patients may have consumed some duration of anti-TB drugs, such prior anti-TB treatment is not likely to be uniformly reliable as far as the quality or quantity and duration of drugs consumed is concerned. Given that uncertainty, the basic principle is that duration of the DR-TB regimen under NTEP need not be reduced. There may be exceptional circumstances that the DR-TBCs may consider where prior treatment is very well-documented, adequate and effective. The DR-TBC committee can, exceptionally, adjust the duration after detailed patient review, approval and documentation of decisions taken.

If such a referral from the private sector has taken place without notification on Nikshay, the patient would be freshly notified after due confirmation of diagnostic results.

The private health facilities or laboratories which did not notify TB/DR-TB patients, health facilities or laboratories which are not engaged through any partnership options and the laboratories which are not engaged under NTEP laboratory certification process, would be considered 'not engaged'. In such a situation, while ensuring that the care cascade is followed, the local public health staff such as STS, TBHV, and PPM coordinator at the district level, should reach out to the private health facility to establish linkages with NTEP. In places where a PPSA is operational, the public health authorities should coordinate with the PPSA to initiate engagement with that private health facility.

In both scenarios (notification/referral), if the patient prefers to continue clinical services from the private provider, the health staff/NTEP staff should support it by coordinating with the treating clinician(s) and hospital management. All patients are also eligible for receiving public health action (detailed later), irrespective of where they choose to seek TB care from.

6.3. Flow of a patient seeking care in the private sector through the care cascade

The DR-TB care cascade is to be ensured for every patient notified/ referred from the private sector. The care cascade includes DST (first-line or second-line drug resistance testing as per NTEP guidelines), counselling, pre-treatment evaluation, treatment initiation and adherence support, follow up clinical assessment, bacteriological, radiological and biochemical testing at prescribed intervals, interrupter retrieval, active drug safety monitoring and management (aDSM), co-morbidity management, NPY, contact tracing and TB preventive treatment for contacts as applicable, reporting of treatment outcomes and post-treatment follow-up.

With expansion of NAAT services up to district level, states need to arrange for DST of notified TB patients from the private sector. They need to ensure that all notified TB patients (bacteriologically confirmed and clinically diagnosed) undergo DST at least for R, H and SL-DST as per the DR-TB diagnostic algorithm.

To avail services available under NTEP, efficient specimen collection and transport system should be established from the private/other providers to the nearby NTEP certified NAAT/ DST laboratory.

Second-line anti-TB drugs including shorter oral Bedaquiline-containing MDR/RR-TB regimen and newer all oral MDR-TB regimens along with digital adherence technology available under NTEP can be systematically offered to patients seeking care in the private/ other sector.

A strong and sustainable partnership between NTEP and providers is necessary to establish linkages to ensure availability of the above mentioned services for any DR-TB patient in the private sector. These services may be extended through:

6.3.1. Local public health facilities

PMDT services for patients seeking care in the private/other sectors can be accessed from NTEP at all levels of the health system. This includes from the field level care offered through the network of Health & Wellness Centres (HWCs) under Ayushman Bharat, to tertiary care available in medical colleges / nodal DR-TB centres/CoE.

It would be the responsibility of the District TB Officers (DTOs) to reach out to all private providers of the respective district and make them aware of the free of cost services including drugs, diagnostics and patient support available through the public sector. The decision to avail these services depends on the willingness of the patient as well as provider, nevertheless, the availability of these services should always be explained to the private providers. Similarly, patients should be made aware of free services through private providers and communities (like TB champions). The DTO should be supported by PPSAs (if present), PPM coordinators, STS, TB-HV and the senior DR-TB TB-HIV supervisor in this task.

Private practitioners should be made aware on the newer protocols of DST, newer and latest drug regimen through clinical CMEs on case studies, difficult to treat TB clinics and other virtual meets with well accepted experts from local and external clinical communities. Such clinical summit should be organization at a regular frequency with private providers. In parallel, one to one consultations should be organized with individual health facilities to set up linkages of services like sample transport services, free pre-treatment and follow-up investigations, drug supply chain and information exchange through Nikshay in a well-coordinated manner. Wherever external agencies are involved like PPSA, DTO should ensure coordination among health facilities and PPSA for DR-TB services.

Role of private provider

- Liaise with the public health officials/staff and the PPSA (if any) of the District to ensure all TB services are made available to patients; and
- Alternatively, refer the patient to the public health facility where TB services can be availed.

6.3.2. Purchasing services from the private sector

One of the options for such linkages available within NTEP currently is the Guidance Document on Partnerships (2019) *(10)*. It provides options for purchasing services for diagnosis, specimen transportation, laboratory services for C&DST of first and second-line drugs.

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

For increasing capacity of DR-TB treatment services and utilizing experts/health institutes in expanding access, the State should consider engaging private health institutes or provider for DR-TB centres. There are at least three different ways that programme officers can expand DR-TB treatment services using the Guidance Document on Partnerships. These are namely, i. DR-TB centre inpatient services; ii. DR-TB centre on an outpatient basis; and iii. provision of consultation charges for private specialist to support public sector DR-TB centres in clinical management. Local programme officers can innovate and create other options also using the guidance from the document.

If the provider has the capacity to initiate an appropriate DR-TB treatment regimen as per WHO recommended principles of designing a regimen and is willing to avail treatment support services, including second-line drugs from NTEP, efforts should be made to partner with such institutes to serve as a DR-TB Centre as per Guidance Document on Partnerships (2019) *(10).*

Role of private provider

- The private providers which NTEP enters into a partnership with, and from whom TB services are purchased must make sure that quality diagnostics, treatment and care are offered to the patient.
- It would also be their responsibility to make programmatic and performance data available to NTEP, to ensure all agreements are upheld.

6.3.3. DR-TB services through private sector health facilities

Availing health-care services from the private sector is a choice of the patient. Many such choices are dependent on services available in local settings. If private health-care settings have the capacity of clinical management (diagnose, treat and follow-up) of drug-resistant TB, such available capacity should be utilized to expand DR-TB services in such area.

6.3.3.1. Private-private partnership and the hub and spoke model of care

One way is to utilize existing health-care facilities or build a referral network of private facilities (private-private partnership facilitated by NTEP) for expanding DR-TB services for patients who seek care from them, as per prevailing standards. In such a mechanism, NTEP needs to identify a few private health facilities to function as a hub or referral centre and organize referral linkages from other health facilities to the hub for management of DR-TB. The identified hub should be engaged and all the DR-TB management services should be ensured as per the PMDT guidelines while referring to the requirement of the DR-TB centre. Peripheral health facilities (spoke) should be identified as network providers for smooth referral and linkages. Any patient diagnosed as DR-TB at spoke would refer patients to the hub for further management. The functions of hubs and spokes are given in **Table 6.1** below.

Table 6.1 Functions of hub and spokes in management of DR-TB patients

Functions of hub	Functions of spokes
• Manage DR-TB patients as per PMDT guidelines and standards • Conduct pre-treatment evaluations • Treatment as per the latest recommendations of DR-TB • Follow-up examination of DR-TB patients • Manage ADR in DR-TB patients • Maintain DR-TB treatment register • Report in Nikshay	• Notify every TB patient in Nikshay • DST of all notified TB patients • Patients with DR-TB to be referred to the Hub • Maintain referral register • Facilitate follow-up examination of patients • Counselling for adherence support • Report in Nikshay

Efforts should be made by DTO to make sure services from the hub must be free of cost. A person (hub agent/TB Mitra) may be supported for coordination of DR-TB patients and engagement with NTEP. Cost of such personnel support to be incorporated within the package of engagement that includes cost for consultation, indoor and investigations.

Role of private provider

- Adopt a hub and spoke model where all involved private parties liaise with each other to ensure smooth flow of data and information;
- Clearly demarcate the activities which the spoke and hub would undertake in the TB care cascade . and
- Ensure proper liaison with NTEP officials and PPSA (if present).

6.3.4. Accountability of DR-TB service provision to patients

The accountability to ensure quality of care and to reduce out-of-pocket expenditure for all DR-TB patients notified from the private sector and/or continuing DR-TB treatment from the private sector, rests with the DTO. It is therefore necessary that the DTO, supported by the District and TU staff, and PPSA (if present), to monitor all patients over their entire care cascade and ensure that appropriate measures are taken by their treating physician (public or private) over the course of their treatment and care.

6.3.5. Access to new regimens to patients seeking care in private/other sector

PMDT services including latest recommended treatment regimens and new drugs like Bedaquiline, Delamanid or any other in future, would be available from NTEP and can be provided to the patient seeking services in the private/other sector. This regulation is to prevent indiscriminate use of these drugs that could lead to emergence of resistance against them. To expand access of PMDT services, including new regimens and drugs, for patients seeking care in the private sector, the following mechanisms are applicable:

- Interested and potential providers/institutions are expected to fulfil the requirements to serve as a DR-TBC and undertake a MoU/Agreement with the State/District as per the Partnership Guidance following which the private providers/institutions are empowered to provide PMDT services including new regimens. The collaboration will be implemented as per conditions detailed under the MoU/Agreement;
- For providers not in a position to fulfil such requirement, their patients can still be provided access to PMDT services, including new regimens, through a mechanism that entails engaging with NTEP. They can approach the concerned District TB Officer (DTO) for

linkage with the concerned District and Nodal DR-TBC for access to DR-TB treatment as per guidelines and with a commitment to partner with NTEP for complete patient care throughout the treatment course, including decisions around patient eligibility, treatment initiation, follow-up schedule, active drug safety monitoring and management (aDSM), treatment outcomes, long-term follow-up and information exchange as per programme guidelines. To locate the nearest N/DDR-TBC, providers can contact the DTO of their concerned districts. List is available at https://reports.nikshay.in/Reports/DtosDirectory. For assessing eligibility for specific regimens, all relevant medical records and reports of the patient should be shared with N/DDR-TBC to facilitate a decision on the regimen design that would suit the patient's condition; and

- Based on mutual understanding between patient, provider and N/DDR-TBC, DR-TB patients can be initiated on treatment on OPD basis or IPD at N/DDR-TBC or private institute with requisite monitoring. For continuation of treatment, the private provider (if not already a N/DDR-TBC) can continue to be the treatment supporter and monitor the patient in close coordination with N/DDR-TBC. The monthly drug supply and follow-up investigations need to be undertaken as per guidelines. Moreover, patients would be notified under NTEP and follow the recording and reporting system for monitoring, including long term follow-up. The state/district TB officers should provide public health support to all private providers entering into such partnerships for DR-TB care.

6.3.6. Public health action for DR-TB patients notified

All DR-TB patients in the private sector are eligible for the entire range of public health action extended to patients in the public sector. This includes patient counselling, contact tracing, extending preventive treatment to eligible contacts of the DR-TB patients, co-morbidity testing, provision of nutritional support, adherence support through regular follow-up and/or access to Digital Adherence Technologies and active drug safety monitoring and management.

The responsibility of providing these services rests with the local public health facility, either from their own public sector services through established linkages with private facility directly or through PPSA, or from purchased services from private service providers as per the Partnership Guidance (2019). The decision to extend public health action from public sector or through purchased services would depend on the local context of accessibility of services and patient/provider willingness.

Partnership linkages should be established between the private health facility (from where the patient seeks care) and the facility providing the public health action (public or private). This can be done by mobilizing the services of the PPSA, if present, or the STS, TB/HV, District PPM coordinator, senior DR-TB TB-HIV supervisor or whichever staff that has been given the responsibility of private sector engagement by the MO-TC and DTO.

6.4. Enablers and incentives

All private patients are eligible for Rs 500 per month as nutritional support under Nikshay Poshan Yojana (NPY) for the entire duration of their DR-TB treatment. The STS, TB/HV or staff-in-charge should ensure collection of bank details of the patient from the field-level and seeding into Nikshay for further processing. Alternatively, bank details may be collected at the DR-TB centres when the patients present themselves for pre-treatment evaluation.

Private providers who notify the patients are eligible for Rs 500 for every patient notified and Rs 500 for outcome reporting. While all attempts must be made to ensure successful

treatment outcomes, as of now, reporting of any outcome ensures eligibility of the provider for and incentive of Rs 500. This is to promote complete reporting and ensure support care for patients in the private sector.

In situations, where the patient from one district is seeking care from a private provider in another district, the 'current HF' should be marked as the public health facility catering to the residence of the patient and one that would be responsible for extending all local public health action, including incentives to the patient. The private health facility from the other district can be 'linked' to the patient using the Nikshay feature of linking a private health facility in addition to the current HF (similar to linked ART/ DR-TB centre). This would ensure that the private health facility can still enter the treatment outcome and be eligible for incentives. Close coordination would be required between PPM coordinators, DR-TB/HIV-TB supervisor, STSs and Public Financial Management System (PFMS) agencies of the two districts involved to enable smooth payment of incentives to the private provider.

If both districts have the same PPSA agency, Direct Benefit Transfer (DBT), Public Health Action (PHA) etc should be managed by the PPSA. If the two districts have different PPSA agencies, coordination would be required between the field staff of the two agencies.

Private health facilities would also be eligible for treatment supporter Incentive of Rs 5000 per DR-TB patient for ensuring support for the entire course of treatment to the DR-TB patient. Treatment supporters of DR-TB patients on the 6 months long H mono/poly DR-TB regimen would be eligible for incentive of Rs 1000 per patient for ensuring support for the entire course of treatment.

Likewise, any private provider/health facility referring a new DR-TB treatment episode to the public sector (with diagnosis made in the public sector laboratory), would be eligible for the informant incentive of Rs 500.

6.5. Sensitization and capacity building of private providers

Regular sensitization and training should be conducted for all private providers on DR-TB diagnosis, treatment and patient support. Private providers may also be given access to e-modules in Swasth e-gurukul which give an understanding of treatment and management of DR-TB patients. The providers can take the course and get certified, which can further aid them in managing DR-TB patients in consultation with N/DDR-TBC. Channels for communication between the private providers and specialists at the DR-TB centres should be established for teleconsultation like difficult-to-treat clinics to aid in making clinical decisions that are in-line with NTEP guidelines.

A list of contact details of local public health staff/officers and PPSA (where present) should be made available to all private providers. Use of Nikshay Sampark (Toll free number: 1800-11-6666) for feedback/concerns should also be promoted from private providers as well as patients.

6.6. Monitoring indicators for DR-TB patients from the private sector

Monitoring of programmatic functions of DR-TB patients in private sector should be carried out similar to those patients who are seeking care from public sector. Refer to **Chapter 8** and **Annexure 17.**

POINTS TO REMEMBER

- ✓ A DR-TB patient notified in the private sector must receive all services and benefits that are available for public sector patients. Access to testing, public health action, patient support enablers and drugs must be ensured for all patients in the private sector;
- ✓ Linkages must be well established between the private sector health facility and the local public health authorities at the TU/district to ensure smooth flow of information and services for the benefit of the patient;
- ✓ Depending on the context and need, eligible services may be procured from private sector service providers to ensure minimal out-of-pocket expenditure to the patient;
- ✓ Access to Nikshay login, Recording & Reporting formats, IEC material, drugs and incentives for private providers must be ensured; and
- ✓ Responsibility of establishing linkages with the private sector should be clearly established by the local public health authorities- a coordinated effort of all State/ District PPM coordinators, senior DR-TB TB-HIV supervisor, STS, TB-HV, and staff from PPSA (if present) is needed.

CHAPTER 7

SUPPLY CHAIN MANAGEMENT OF SECOND-LINE ANTI-TB DRUGS AND LOGISTICS

Learning objectives

In this chapter, we will learn about:

- Procedures for inventory management of second-line drugs.
- Management of NAAT cartridges/chips used in diagnosis, treatment and prevention of drug-resistant TB.

7.1. Drug distribution system

Continuous and smooth supply of good quality assured anti TB drugs and all related commodities is an essential activity under NTEP. The procurement of anti TB drugs is planned, coordinated and conducted centrally on an annual basis through a well-defined procurement mechanism while the procurement of diagnostics and equipments done be partly by centre and partly decentralized and given to the States to procure at state level.

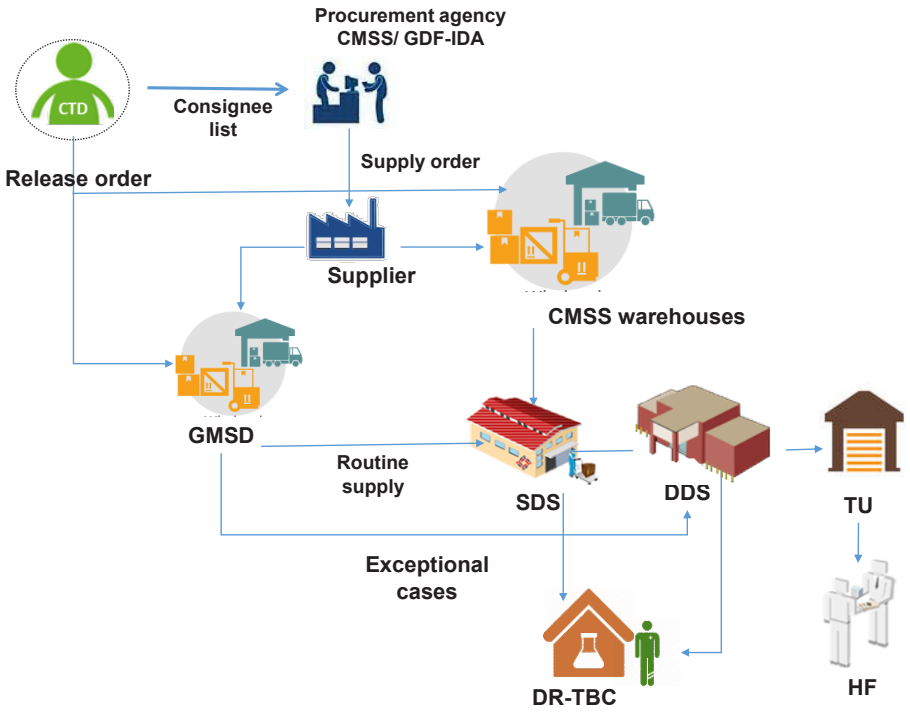


Figure 7.1: Drug distribution flow

7.2. Drug management cycle of second-line anti-TB drugs

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

Inventory management. Procedures for ongoing tracking and replenishment of the inventory of second-line anti-TB drugs at SDS and all subordinate stocking points ensures these are maintained at or close to the stocking norms presented in **Table 7.1.**

Table 7.1: Standards for stocking norms
for monthly patient wise boxes (PWB) at various stocking point

Level	Stock for utilization	Reserve stock	Drug requirements
Treatment supporter	2 months	0 month	Two-monthly PWB under utilization
Health facility*	0 month	2 months	Reserve stock in HF at end of the month
TU drug store	0 month	2 months	(Quarterly consumption/ 3) x 6 – (existing stock in TU including HF drug stores at end of the quarter)
DTC drug store	0 month	3 months	(Quarterly consumption/ 3) x 9 – (existing stock in DTC drug store including TU & HF drug stores at end of the quarter)
SDS	0 month	3 months	(Quarterly consumption/ 3) x 12 – (existing stock in SDS including stocks at all districts at end of the quarter)

**All health facilities may not have a reserve stock. Only HFs where patient/s are initiated or on treatment will have reserve stock of second-line drugs.*

7.3. Preparation of patient-wise drug boxes

All drugs used in the various DR-TB regimens shall be supplied through a centralized procurement system at the Central TB Division, MoHFW, GoI. Supplies of the second-line drugs shall be from the respective Government Medical Store Depot (GMSD) / Central Medical Services Society (CMSS) to the state drug store (SDS). An advance intimation of all drug supplies shall be communicated to the states for SDS to make available the requisite space in the drug store. The State/ SDS shall be supplied only the loose form of second-line anti-TB drugs (SLD). On receipt of drugs, the SDS shall acknowledge the receipt to CTD. The SDS shall repack the loose drugs into one-monthly patient-wise boxes for standard regimens in DR-TB as given below and supply them to the districts for treatment.

Shorter Oral MDR/RR-TB Regimen*

- (4-6) Bdq $_{(6\ m)}$ Lfx Cfz Z E Hh Eto / (5) Lfx Cfz Z E

Longer Oral M/XDR-TB Regimen

- (18-20) Lfx Bdq $_{(6\ month\ or\ longer)}$ Lzd# Cfz Cs

Isoniazid mono/poly DR-TB Regimen

- (6 or 9) Lfx R E Z

** Those DR-TB patients on longer/shorter injectable containing regimen should be supplied drugs continuously till the state/district fully transitions to all oral regimen.*

#dose of Lzd will be tapered to 300 mg after the initial 6-8 months of treatment

The drug box preparation would preferably be done at the SDS level. The DDS shall be supplied monthly patient-wise boxes as per the above standard regimens as well as loose medicines for replacement.

There may be circumstances when the drug box is required to be prepared at the district level, like unpacking of unused/partially used boxes, modification of regimen as per replacement advised by DR-TBC. The SDS shall supply additional quantity of SLDs to districts for necessary modifications which will be conducted at district level. Whenever the state has built the capacity of districts, exercise of preparation of standard patient-wise boxes shall be conducted at DDS under the guidance and supervision of DTO.

Additionally, SDS/DDS shall supply loose drugs to N/DDR-TBC for treatment initiation.

7.4. Constituents of monthly patient-wise box for DR-TB patients

7.4.1. Shorter oral Bedaquiline-containing MDR/RR-TB regimen

Table 7.2 Constituents of monthly type A & B patient wise box of shorter oral Bedaquiline-containing regimen

Type A box		(use in IP as well as CP)			
Drugs	**Strength**	**16-29 kg**	**30-45 kg**	**46-70 kg**	**>70 kg**
Tab. Levofloxacin*	250 / 500 mg	250 mg *30tab	250 mg *30tab + 500mg *30tab	500mg *60tab	500mg *60tab
Tab. Clofazimine	50 / 100 mg	50 mg *30tab	100 mg *30tab	100mg *20tab	100mg *60tab
Tab. Ethambutol	400 / 800 mg	400 mg *30tab	800mg *30tab	400 mg *30tab + 800mg *30tab	600 mg *60tab
Tab. Pyrazinamide	500 / 750 mg	750 mg *30tab	500mg *30tab + 750 mg *30tab	500mg *60tab + 750 mg *30tab	500mg *30tab + 750 mg *60tab
Tab. Pyridoxine	50/100 mg	50 mg*30tab	100 mg*30tab	100 mg*30tab	100 mg*30tab

Type B Box		(Use in IP)			
Drugs	**Strength**	**16-29 kg**	**30-45 kg**	**46-70 kg**	**>70 kg**
Tab. Isoniazid	100 / 300 mg	300mg *30tab	300mg *60tab	300mg *90tab	300mg *90tab
Tab. Ethionamide	125 / 250 mg	125mg *30tab + 250mg *30tab	250mg *60tab	250mg *90tab	250mg *120tab
Bedaquiline bottle	100 mg	1 Jar (Jar of 188 tablets for full course)			

** When moxifloxacin prescribed under exceptional condition instead of levofloxacin, the modified box with moxifloxacin (normal dose) can be prepared from standard box at DDS.*

Standard PWB for patient on shorter injectable containing regimen

Type A. Moxifloxacin – high dose (Mfx^h); Clofazimine (Cfz); Pyrazinamide (Z); Ethambutol (E)

Type B. Kanamycin (Km); Isoniazid – high dose (H^h); Ethionamide (Eto)

The patient on shorter oral Bedaquiline-containing MDR/RR-TB regimen shall be put on Type A and Type B box when initiated on treatment in monthly patient wise boxes. Bdq will be issued separately and stopped after 6 months. Patient should be provided Type A boxes when started on CP.

7.4.2. Longer oral M/XDR-TB regimen

There is no separate IP and CP in Longer oral M/XDR-TB regimen. A standard patient-wise boxes will be prepared by SDS/DDS as per composition below.

Table 7.3 Constituents of monthly standard patient wise box of Longer oral M/XDR-TB regimen

Standard PWB*		Continue till complete treatment			
Drugs	**Strength**	**16-29 kg**	**30-45 kg**	**46-70 kg**	**>70 kg**
Tab. Levofloxacin	250 / 500 mg	250mg *30tab	500mg *30tab + 250 mg *30tab	500mg *60tab	500mg *60tab
Tab. Linezolid#	600 mg	600mg *30tab#	600mg *30tab	600mg *30tab	600mg *30tab
Tab. Clofazimine	50 / 100 mg	50 mg *30tab	100 mg *30tab	100mg *30tab	100mg *60tab
Tab. Cycloserine	250 mg	250 mg *30tab	250 mg *60tab	250 mg *90tab	250 mg *120tab
Tab. Pyridoxine	50/100 mg	50 mg*30tab	100 mg*30tab	100 mg*30tab	100 mg*30tab
Bedaquiline bottle	100 mg	1 Jar (Jar of 188 tablets for full course)			
* No separate box for IP and CP					
# Tab. linezolid available in 600mg only. When prescribed with modified dose of 300mg OD, patient should be advised to divide the pill in half, consume half of the pill and may throw the rest half of the pill in drain					

7.4.3 H mono/poly DR-TB regimen

There is no separate IP and CP in H mono/poly DR-TB regimen. A standard patient-wise box will be prepared by SDS/DDS as per the composition below. In comparison to other DR-TB regimen, full treatment course should be prepared for the entire duration of 6 months.

Table 7.4 Constituents of standard patient wise box (6 months) of H mono/poly DR-TB regimen

Standard PWB		Continue for complete treatment			
Drugs	Strength	16-29 kg	30-45 kg	46-70 kg	>70 kg
Tab. Levofloxacin	250 / 500 mg	250 mg *180 tab	250 mg *180 tab + 500mg *180 tab	500mg *360 tab	500mg *360 tab
Tab. Rifampicin	150 / 300 / 450 mg	300mg *180 tab	450mg *180 tab	300mg *360 tab	300mg *360 tab + 150mg *180 tab
Tab. Ethambutol	400 / 800 mg	400mg *180 tab	800mg *180 tab	400mg *180 tab + 800mg *180 tab	800mg * 360 tab
Tab. Pyrazinamide	500 / 750 mg	750mg *180 tab	750mg *180 tab + 500mg *180 tab	750mg *180 tab + 500mg *360 tab	750mg *360 tab + 500mg *180 tab
Tab. Pyridoxine	50/100 mg	50 mg *180tab	100 mg*180tab	100 mg*180tab	100 mg*180tab
* No separate box for IP and CP					

7.5. Dosage and dispensation of child-friendly formulations of second-line anti-TB drugs

NTEP is procuring child friendly – dispersible formulations of second-line anti-TB drugs for use in the pediatric age group who are unable to swallow drugs.

- **Levofloxacin:** 100 mg; scored dispersible
- **Clofazimine:** 50 mg; uncoated tab, scored tablet, caps & film coated tablet available
- **Ethambutol:** 100 mg; scored dispersible, dispersible, scored, film coated available
- **Pyrazinamide:** 150 mg; scored dispersible, uncoated, scored tab
- **Isoniazid:** 100 mg; scored dispersible, scored, uncoated, film-coated tab
- **Ethionamide:** 125 mg; scored dispersible, film coated tab
- **Moxifloxacin:** 100 mg; scored dispersible available, No Syrup formulation
- **Cycloserine:** 125 mg; caps available
- **Bedaquiline:** 20mg; dispersible tablets (DT)

Dosing of medicines used in second-line MDR/RR-TB regimens by weight band (patient under 15 years) is presented in **Annexure 15.**

The regimen would be the same as that used in the adult regimen, however the drugs utilized will be of the child-friendly formulations.

7.6. Dispensation of child-friendly formulation of Bedaquiline 20 mg DT

- Pediatric BDQ is available as 20 mg dispersible tablets and the recommended dose is 200 mg daily for 2 weeks followed by 100 mg thrice a week for 22 weeks;

- Pediatric Bdq is supplied in a jar which contains 60 tablets of the whole course of 470 tablets;
- When a decision is taken to initiate the child patient on Bedaquiline 20mg DT, SDS shall allocate the entire course of 8 bottles to the patients. DTO shall make necessary arrangement to deliver entire course to the treatment supporter of the patient. When a family member is a treatment supporter, entire course can be handed over to the family member with instruction to monitor treatment adherence.

Note: when allocating entire course to the patients, SDS/DDS shall remove 10 tablets from any of 8 bottle course use for the patient and arrange dispatch of 8 bottles with total 470 tablets for consumption. 10 tablets shall be utilized for reconstitution.

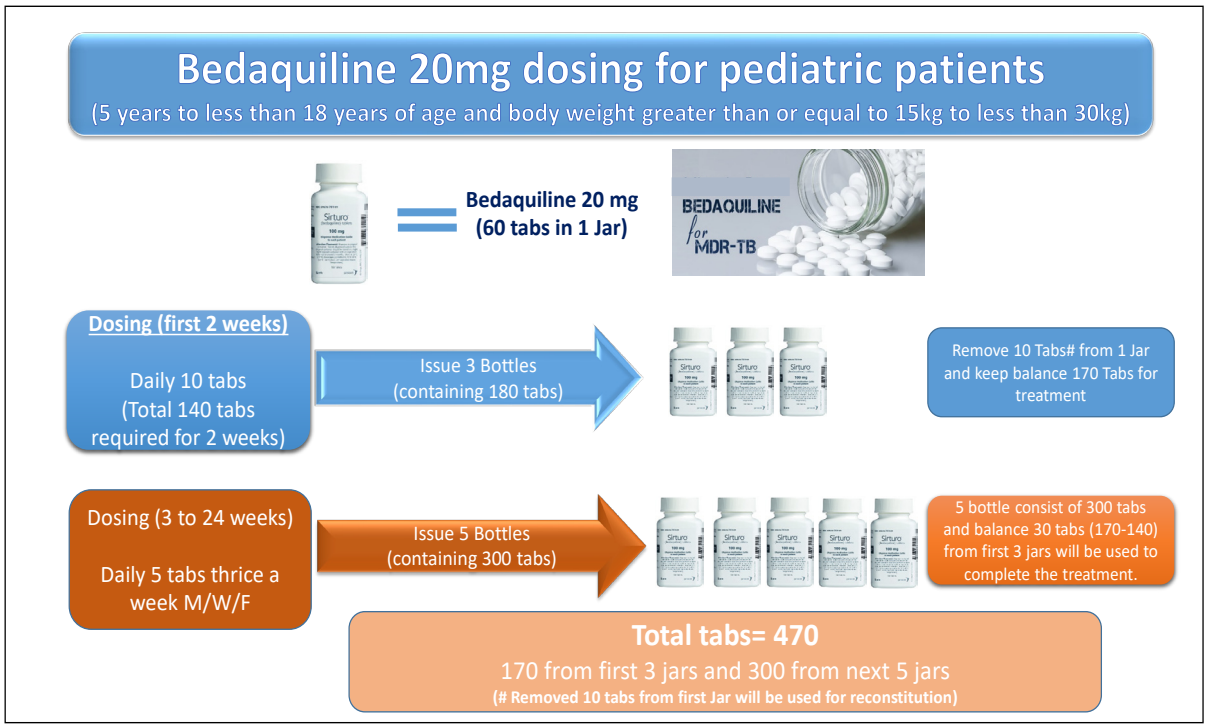


Figure 7.2 Bedaquiline 20 mg DT for children

7.7. Second-line drug anti-TB drug distribution and supply chain system

7.7.1. Distribution from centre to SDS

As mentioned in the overview of this chapter, loose SLD shall be supplied to SDS directly from the centre. The regular process of supply of new stock of drugs to the SDS begins only when the state submits their requirement to CTD. For effective reporting, NTEP has implemented a web-based real time Logistics Management Information System (LMIS) software i.e. Nikshay Aushadhi. This software is used at all levels for reporting of drugs availability, consumption and future requirement. The SDS pharmacist shall raise a request through Nikshay Aushadhi in the prescribed format available in the software. The request through Nikshay Aushadhi shall be verified by STO of all SDSs, in the state. The state shall facilitate in determination of drug stocks available with SDS (s) within the state. This requisition through Nikshay Aushadhi shall be submitted online to CTD by the state as per the reporting guidelines, by the 10thof every month / Qtr. In the event of more than one/ multiple SDSs within the state, all the requisition through Nikshay Aushadhi shall be forwarded to CTD within the timelines stated above. The request of the stocking units is to be submitted as per the scheduled mentioned below.

7.7.2. Distribution from SDS to district

The SDS will supply drugs to the DTCs in the form of monthly standard patient-wise drug boxes and loose second-line drugs, every quarter. It shall review the quarterly consumption report received from the linked districts through Nikshay Aushadhi and issue the boxes as well as loose medicines to the district. The DTC shall send the boxes to its implementing TU in a similar manner on a quarterly basis and then monitor through the TU quarterly SLD requirement report. Buffer stocks of PWB shall be held at all levels as per stocking norms. The district will ensure arrangement for supply of monthly drug boxes from the respective TUs to HFs and from HFs to the treatment supporters/centre. The STS shall identify the treatment supporter in consultation with the HF doctor and the patient. Considering further decentralization of services, SDS will supply loose oral SLD to the DDS for modification in regimen.

7.7.3. Distribution of SLDs to N/DDR-TBC

Loose drugs will be supplied to N/DDR-TBC from SDS/DDS as per consumption pattern in previous month and request given in Nikshay Aushadhi. On discharge, the patient will be handed over the remaining drugs for current one month of consumption for transit. Senior DR-TB TB-HIV supervisor under guidance of N/DDR-TBC, shall guide STS for arranging the treatment supporter. Entire course available with the patient shall be handed over to the treatment supporter.

- For patient put on Bdq containing regimen, the entire bottle of Bdq (188 tablets) shall be earmarked for each enrolled patient and handed over to the treatment supporter under the supervision of the senior DR-TB TB-HIV supervisor in every district.
- For the patients who are placed on the Dlm containing regimen**,** the entire course of Dlm treatment will be earmarked at the DDS level. However, drugs will be supplied on a monthly basis to TU and further to HF.

7.7.4. Distribution from DDS to TU drug stores

Buffer stock equivalent to two months will be kept at the TU. The drug boxes will be supplied from the TU to HF every month. These will be transferred from the TU to the respective HF as per the monthly consumption report submitted by the HF through Nikshay Aushadhi.

7.5.5. Distribution from TU drug store to HF

Buffer stock equivalent to two months will be kept at the HF at the beginning of each month. The drug boxes will be supplied from HF to treatment support centre/ treatment supporter. All HFs may not have reserve stock. Only HFs where patient/s are initiated or on treatment will have reserve stock of second-line drugs.

Details such as drugs received, distributed and balance stock are to be entered in Nikshay Aushadhi. Drug distribution mechanism is supported by Nikshay Aushadhi where drugs stock, dispatch and return of drug can be reported through tracking of the drug.

Scenario 1: Modification in regimen. If N/DDR-TBC committee decides on modification of regimen, DDS shall prepare modified PWB from available standard boxes using loose replacement SLD available at district level and arrange supply to treatment supporter. DTO needs to ensure that the drugs should be supplied as per the modified regimen for all subsequent months.

Scenario 2: Extension of intensive phase. If IP of the patient is required to be extended; the respective N/DDR-TBC committee shall inform DTO who will intimate the same to the

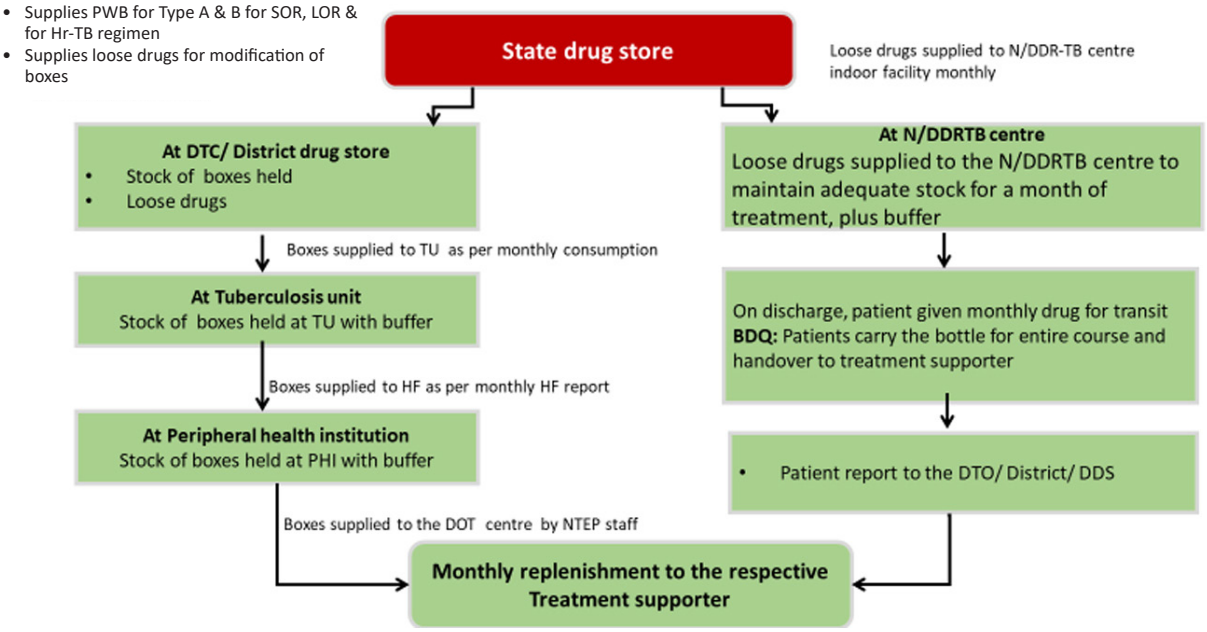


Figure 7.1 Second-line drug supply chain management

HF doctor and the respective TU. The HF will release one-month drug box to the respective treatment support centre from where the patient is taking treatment. When the patient is switched to CP in case of shorter oral Bedaquiline-containing MDR/RR-TB regimen, the DTO shall intimate the same to the HF doctor and the respective TU. On instruction of DTO, the HF will release one monthly PWB to the respective treatment support centre from where the patient is taking treatment. In the case of longer oral M/XDR-TB regimen, after completion of 6 to 8 months of treatment, the dosage of LZD should be reduced to 300 mg as per the directives of N/DDR-TBC. All patients must complete the monthly box before switching to subsequent box provided.

Scenario 3: Change in regimen. If DR-TBC committee decides to change the regimen then DDS shall arrange supply of new treatment regimen box from PWB/loose drugs supplied from the SDS and the unused drugs including Bedaquiline container should be sent back to DDS. In such situation patient should be immediately switched to the new regimen designed by N/DDR-TBC.

Box 7.1 Supply chain management of Bdq

For regimen containing Bdq, the patient will be initiated on treatment through bottle containing full course (188 tablets) of requirement. When the treatment support of the patient is being arranged and handed over monthly PWB of the regimen, entire course of Bdq should be handed over too. The treatment supporter should be adequately trained on drug dosages, dispatch, adherence and ADR monitoring. Unused Bdq tablets should be sent back to DDS in same container for reconstitution.

When Bdq extension is prescribed by N/DDR-TBC in any patients, required number of tablets to adjust extension is to be packed in plastic container or empty Bdq bottle and supplied to treatment supporter of the patients.

Box 7.2: Supply chain management of Delamanid

Once a patient is initiated on Dlm containing regimen it should be ensured that the entire course of treatment is secured for the patient. SDS shall issue loose Dlm strips to the DDS as requested.

- Dlm will be provided with other SL drugs for a period of 24 weeks, supplied on a monthly basis;
- Dlm is available as 50 mg tablets and the recommended dose is 50 mg twice a day for (6–11years) and 100 mg twice a day for 12–17 years for 24 weeks.
- 6 years to 11 years of age. 2 tablets a day. 7 boxes to be provided for full duration of treatment. Each box contains 48 tablets i.e. 6 strips of 8 tablets per strip. Patient is provided with 8 strips (64 tablets) every month for 5 months. The four extra tablets issued every month are carried over and in the sixth month only 2 strips are issued, thereby ensuring that the patient consumes only 36 tabs over 18 days.
- 12 years and above: 4 tablets a day. 14 boxes to be provided for full duration of treatment. Each box contains 48 tablets i.e. 6 strips of 8 tablets per strip. Each box contains 48 tablets i.e. 6 strips of 8 tablets per strip. Patient is provided with 15 strips (120 tablets) every month for 5 months. Only 9 strips are issued in the sixth month thereby ensuring that the patient consumes only 72 tablets over 18 days.
- In the event of loss to follow up or death or discontinuation of DLM for any reason, the leftover tablets will also be returned back to the DDS. These drugs would be taken back in stock.

7.8. Constitution of patient-wise boxes and role of various drug stores

7.8.1. At state drug store-level

SDS shall constitute drug boxes for shorter oral Bedaquiline-containing MDR/RR-TB regimen (Type A and B), longer oral M/XDR-TB regimen and H mono/poly DR-TB regimen and supply to respective districts. Loose drugs will also be supplied from SDS to DDS for modification and preparation of new boxes.

7.8.2. At district drug store-level

When modification in regimen is suggested by DR-TBC, district drug storekeeper/pharmacist shall take a call and prepare modified boxes from loose SLD supplied from SDS. The state shall provide necessary support for capacity building of DDS for carrying out entire exercise of preparing standardized/modified patient-wise drug boxes at DDS level.

Full time DDS store keeper/pharmacist is mandatory to be recruited/ placed for successful decentralized system of preparation of drug boxes at DDS level.

Whenever oral regimens are modified during the course of treatment, DDS needs to ensure that the change in regimen should be incorporated in supply of subsequent boxes.

7.9. Packing instructions

- Packaging of loose drugs into monthly patient-wise boxes should be done under guidance of the STO/medical officer/drug logistics In-charge at state level and district level;

- One monthly pouch of cap. Cs & tab. E each should be made from plastic bag with ziplock facility in which 1 gm. pouch of silica gel desiccant should be kept. In each Type A box, one pouch of silica gel desiccant of 4 gm weight should also be kept;
- Labels for the boxes should be developed with following information:
  - item-wise name of drugs with quantity of each drug in the box;
  - batch no. & DOE of individual drugs;
  - DOE of boxes-expiry date of the drug having shortest expiry;
  - date of issue of the box from SDS;
  - serial number of the box;
  - storage instructions on the box for ensuring adequate precautions in storage of the drugs, especially at Treatment supporter level. Some suggested messages are: “store in a cool and dark place, preferably in a clean cupboard”; “do not expose to direct sunlight”; “keep away from children/unauthorized persons”; and or “box to be closed properly every time after withdrawal of drugs”.

7.10. Reconstitution: Repackaging and use of partially used boxes

- In case of default/death/transferred-out/treatment stopped patients, unconsumed boxes shall be brought back from treatment support centre to HF to TU to DTC within the shortest possible time. The unconsumed box returned to the DTC should be updated in Nikshay Aushadhi. All loose drugs remaining in the boxes received back shall be accounted for in the stock register and Nikshay Aushadhi at the DDS and same will be issued as per FEFO principles to either N/DDR-TBC or for use as loose drugs or for repackaging into monthly boxes;
- Partially used BdQ bottle shall be sent back to SDS where repackaging will also be done. Remaining tablets in the bottle received back shall be accounted for in the stock register and Nikshay Aushadhi at SDS. Upon reconstitution, the bottle shall be accounted for in the stock register (loose tablets to be mentioned in remarks column) to be issued as per FEFO principles. When reconstitution is done, tablets of same expiry can be considered using same container to a maximum of 188 tablets. These reconstituted containers shall be used for treatment of subsequent patients found eligible for Bdq. This reconstitution exercise should be done at the SDS. All such drugs that are taken from the new containers shall be collected as a group of 188 tablets of same expiry and put in a light resistant container as per advice from the manufacturer. The actual expiry of tablets should be mentioned over the container;
- In the event of SDS falling short of 188 tablets from an expiry batch, reconstitution can still be done using number of tablets to complete 188 tablets with another expiry batch. In such a case, tablets of the respective expiry should be retained in their same respective containers and issued to patients and providers with counselling to consume the tablets with the nearest expiry first; and
- If expiry of remaining tablets is less than six months, the same shall be consumed at NDR-TBC for admitted patients. It will be adjusted from the new long expiry bottle on discharge.

7.11. Quality assurance of drugs

The quality assurance component of the NTEP drug supply system ensures that each drug used by a patient is safe, efficacious and has appropriate standards of quality. Maintaining

quality of drugs, a system of pre-dispatch & post-dispatch testing of drugs is established. As per the protocol developed by CTD, random samples of second-line anti TB drugs shall be picked from all stocking points in the field and sent for testing by an independent drug testing laboratory contracted by CTD to ensure quality of drugs is continuously maintained and remains the same throughout the supply chain of the drugs. This should be done based on communication sent by CTD to the concerned states and districts.

7.12. Waste disposal guidelines

If any drug expires due to reasons beyond control, it should be disposed of after writing off the loss as may be required under the rules and thereafter procedures laid down in the rules under the Drugs & Cosmetics Act and Biomedical Waste (management and handling) rules of GoI.

7.13. Guidelines for recording and reporting of SLD

The recording and reporting system for drug stock management from SDS to the N/DDR-TBC and to districts, TB units and HFs has been recently revised to suit the 1 monthly patient-wise boxes system. An ICT based recording and reporting systems i.e. Nikshay Aushadhi, has been implemented up to HF level for real-time data, inventory management, demand generation, analytical tools, drugs accountability, forecasting & anticipation.

7.13.1. Nikshay Aushadhi: Supply chain management software solution

Nikshay Aushadhi, is a web-based TB drug supply management system. It is a major step towards adapting technology to improve supply chain management of TB drugs in State level and district stores, TB unit (TU), Health facilities (HFs), DR-TBC and treatment supporter centres. These applications deal with demand and distribution of all essential anti-TB drugs and consumables required at State, district, TU, TB detection centre and HF level.

It also caters to data from Government Medical Stores Depot (GMSD) and the procurement agency, currently CMSS. The advantage of inventory automation is to get the complete detail of stock on hand at various levels, supplies in pipeline and distribution and consumption patterns in the state, up to higher management level. This will help in anticipation of future requirement while ensuring dramatic improvement in performance along with reducing costs.

Modules available in Nikshay Aushadhi

1. Quantification, forecasting (only at national-level dashboard)
2. Drug request management-routine request/additional drug request
3. Issue/dispatch (GMSDs to SDSs – DDSs – TUs –HFs-patients)
4. Receipt of drugs from store (HF, TU, DDS, SDS, GMSD)/acknowledge desk
5. Return from patient to concerned store for reconstitution
6. Stock management (like drug inventory, physical stock verification, expiry management etc)
7. Packaging/repackaging (second-line drugs box preparation & modification)
8. Quality control management
9. Miscellaneous (Reports)

Figure 7.4: Homepage presenting services available in Nikshay Aushadhi portal

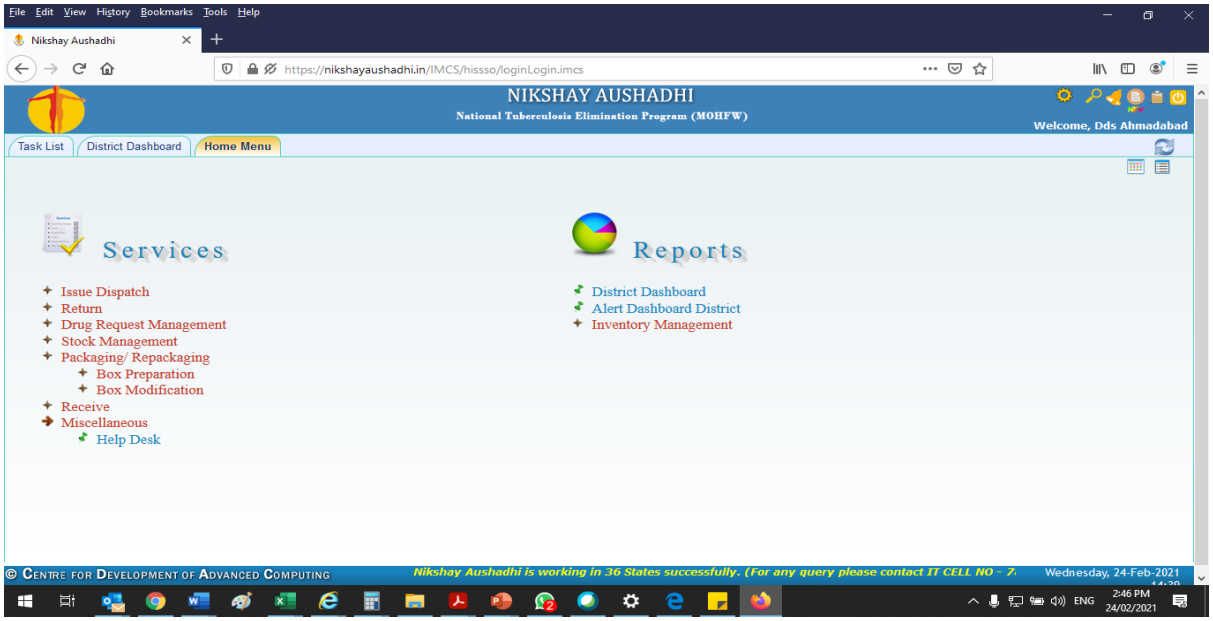


Table 7.5: Services in Nikshay Aushadhi and roles

Services	Function	Roles
Issue dispatch	Store can issue/dispatch the drugs to the lower hierarchical store.	Store keeper of SDS can issue the drugs to DDS; DDS issues the drugs to TU drug store; and TU drug store issues to HF store using this function The store can issue demand request from lower store whenever or even without request from lower store
Return	Drugs can be returned to the higher store for reconstitution	Store keeper of lower hierarchical store can return the drug to upper store. Unutilized drugs can be returned to the higher store using this function
Drug request management	The store can put the demand of drug using this function	Store keeper of lower drugs store can demand and generate request to higher drug store. The request could be routine or additional
Stock management	The store can manage the inventory and observe real time stock position through stock management function	The store keeper can review the stock status using stock management function
Receive	The store can receive the drug and can acknowledge the higher store	The store keeper can acknowledge the receipt of the drugs and adjust any mismatch in receipt
Issue to the patient	The medicine/PWB can be issues to the patient using this function	This function is available at HF level store and HF pharmacist can issue to the patient. This function is going to transition to Nikshay and will be available under prescription module as described below.
Miscellaneous	This is a help desk and linked with the trouble shooting desk at the back-end	The store keeper can raise the concern or query through this function.

The detailed guidance can be referred in SoP manual for Procurement & Supply Chain Management.

7.13.2. Dispensation module

NTEP will integrate Nikshay and Nikshay Aushadhi for dispensation of drugs. To enable this a dispensation module is being developed in Nikshay. The current HF module in Nikshay Aushadhi that is used for dispensing of drugs will eventually be moved to Nikshay under the name "Dispensation Module." On completion of the integration, the balance of drugs available can be accessed in Nikshay and the drug dispensation facility will be available through the dispensation module in Nikshay.

All other modules will continue to be available in Nikshay Aushadhi as detailed above.

For further understanding of the supply chain management of DS-TB, DR-TB & Nikshay Aushadhi refer to the supply chain management (SCM) Manual.

7.14. Inventory management of CBNAAT cartridges and Truenat chips

- Inventory of CBNAAT cartridges and Truenat chips supplied by the centre or procured by the States/Districts should be managed through Nikshay Aushadhi.
- The store keeper of SDS/DDS must enter the stock of cartridges/Truenat as received from third party.
- The store keeper of SDS/DDS will issue dispatch the cartridges/ chips to the NAAT site.
- NAAT site incharge will send monthly utilization report to SDS/DDS. The SDS will share quarterly utilization to central level through Nikshay Aushadhi.

7.15. Medication event reminder monitor (MERM) for DR-TB patients

The MERM is a digital pillbox that has been designed to monitor MDR-TB treatment in resource-constrained settings, using relatively affordable technology and drugs provided

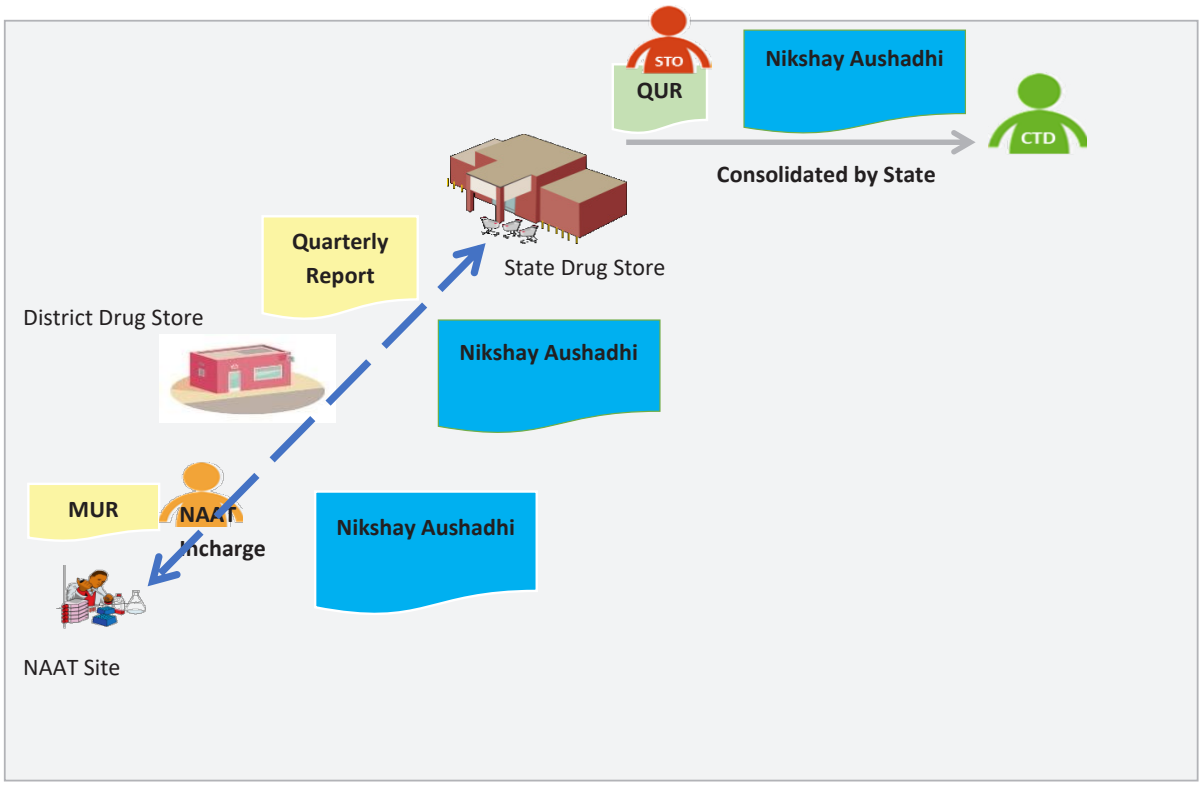


Figure 7.5: Inventory management of NAAT cartridges/chips in Nikshay Aushadhi portal

Figure 7.6: MERM Container for shorter/longer oral MDR-TB regimen

by NTEP. This system is specifically designed to be used with multiple blister-packaged TB medications in DR-TB regimens. The MERM provides programmable visual and audible reminders of daily dosing and of monthly refill by capturing data on pillbox opening as a proxy for dose ingestion, and transmits these data to a server so that healthcare providers (HCPs)/ treatment supporters can remotely visualize patients' dosing histories to support enhanced adherence counseling. In addition, by providing near real-time adherence data, the MERM can facilitate identification of high-risk patients and prompt early intervention by HF staff to reduce non-adherence. When compared to facility-based DOT in which patients travel to clinics to be observed taking their medications monitoring using the MERM may also reduce the required frequency of patient visits to TB clinics.

7.15.1. Technology enrolment

- Patient is notified in Nikshay at the HF/treating facility with required patient and treatment initiation details.
- At point of notification, the DR-TBC staff/STS/TB-HV/treatment supporter who has previously received MERM training) assigns MERM as adherence technology in Nikshay.
- Staff to check if the patient resides in an area where network connectivity is adequate.
- Staff will also provide orientation to the technology before allocating the MERM device to the patient. The charger is also handed over to the patient.

POINTS TO REMEMBER

- ✓ All second-line anti-TB drugs are procured and issued in loose forms. These drugs are then constituted to patient-wise boxes as per regimen and inventory can be managed in loose drugs.
- ✓ Inventory management should be handled through Nikshay Aushadhi.

CHAPTER 8

SUPERVISION, MONITORING AND EVALUATION

Learning objectives

In this chapter, we will learn about:

- Guidelines for supervision, monitoring and evaluation (SME) systems that are essential to ensure quality of care of DR-TB patients enrolled under NTEP.
- Standardized mechanisms and tools to facilitate optimal programme SME.
- The robust digital R&R system is in place along with provisions for multiple internal and external checks to ensure good quality data generation which, in turn, forms the basis for the NTEP SME strategy.
- Mechanisms to ensure that activities are implemented as planned and that the data recorded and reported is accurate and valid.
- Understand the overall goal of the SME strategy by putting into place systems that bring about greater transparency, accountability and efficiency by:
  - ensuring equitable provision of services to all sections of the community, including vulnerable areas and
  - populations such as urban slums, scheduled caste/tribal/minority pockets etc;
  - incorporating systems which lead to remedial action to improve performance; and
  - serving as a tool to facilitate commitment of higher authorities at different levels.

8.1. Leveraging Nikshay for strengthening SME

In line with the overall goal of shifting from paper-based to ICT based systems under the program, the SME too will be driven by Nikshay with user-based/ institute-based logins, facility-based supervisory checklists **(Annexures 18–29),** task lists & reminders, escalation matrix for enabling prioritization etc.

User friendly dashboards, generated from the digital R&R and supervisory systems will be used to look at the different areas under the program and prioritize remedial action and relevant escalations across different users like state level, district level, TU level, N/DDR-TBC, C&DST labs, NAAT labs, private health facility, PPSA etc.

Table 8.1: Framework of PMDT-SME

Stage	Tools
Supportive supervision	• Supervisory checklists for various levels (STC, STDC, C&DST labs, N/DDR-TBC, DTC, NAAT, PP, TU, TDC, HWC/HF, treatment supporter, DR-TB patient) • Interview questionnaire for patients
Monitoring	• Monitoring indicators with downloadable reports and dashboards on PMDT implementation
Evaluation	• Central & state internal evaluation (CIE and SIE) formats to include sections for evaluating all the aspects of PMDT implementation • Visits to N/DDR-TBC, NAAT Lab, C&DST Lab, DDS, SDS, patients' interview, template-based reviews at fixed intervals etc

Box 8.1: SME through Nikshay

1. Nikshay is the ICT enabled state-of-art recording, reporting, SME and surveillance system for managing all aspects of NTEP including PMDT.
2. Nikshay facilitates the continuous monitoring and treatment adherence for all registered TB patients, including DR-TB patients, across lifecycle, geographies, transfers and referrals.
3. The Nikshay dashboard functions to track activities and enables online monitoring of major programme indicators with tabular, graphical and geo-mapping displays.
4. Nikshay is the primary source of information for all monitoring indicators. Thus, validation of actual report and the entered report should be done at each level to sustain quality of information available digitally.
5. Patient-wise details and aggregated monitoring indicators for specified period is available within Nikshay.
6. It essentially uses a person-based approach to the TB lifecycle, enabling patient-based tracking and monitoring allowing for stakeholder integration, as well as timely and accurate reporting and real time decision support.
7. Nikshay will, in a phased manner, replace the paper-based system of R&R. The system is already enabled to capture the events at origin through provision of mobile/web applications, tablets and call centres on a real-time basis. This has brought about vast improvements in the reporting structures by augmenting agility and efficiency by providing relevant reports at relevant levels without the delays associated with paper-based collection, collation and compilation of reports.
8. Nikshay will generate user specific task lists on real time basis according to their job responsibilities aiding staff to prioritize tasks at various levels. For e.g., No. of patients not initiated on treatment, No. of patients adherence not updated since last >14 days, No. of patients cross the due date beyond expected outcome date, patient turnaround time, DBT task list etc. individualized event-based custom push notifications would also be made available to intimate the staff about the upcoming activities as per their ToRs. Summary views would be available for state, district & TU level to monitor the pending task list on a weekly/ fortnightly basis.
9. ICT enabled adherence mechanisms [99DOTS, MERM, refill monitoring, VOT (manual)] will feed treatment related information from patients and treatment supporter into Nikshay enriching it as a patient care and support platform to prioritize patients for differential care.

10. Nikshay will populate dashboards for all supervisory staff at various levels to aid in their day-to-day work by providing dashboards for different facilities and geographies. This will aid supervisors and programme managers in identifying areas both thematic and functional for intensive supervision.
11. Supervisory check-list built in the Nikshay will collect and maintain log of the real-time information entered by any supervisor. This will be available on https://forms.nikshay.in and will be maintained as continuum for every health facility to track actions taken on the recommendations of the supervisors made during prior visits.

8.2. Supportive supervision

Supportive supervision is a process of helping staff to improve their performance on a continuous basis. It is carried out in a polite and non-authoritarian way with a focus on using supervisory visits as an opportunity to improve knowledge and skills of health staff. Supportive supervision encourages open communication and team building approaches to facilitate real time handholding and problem-solving. It focuses on monitoring performance towards goals, and using data for decision-making, and depends upon regular follow-up with staff to ensure that assigned tasks are being implemented correctly. The objectives of supportive supervision are to:

1. Build capacity of health staff to implement PMDT procedures correctly
2. Ensure that the data recorded and reported is accurate and valid
3. Incorporate a system of analysis and review aimed at improving quality of programme implementation
4. Increase involvement and commitment of staff at different levels
5. Ensure field staff respond to Nikshay tasks, lists activities and updates missing information promptly
6. Provide actionable and timely feedback
7. Evaluate impact of training on performance of health staff
8. Assess retraining needs
9. Assess stocks and replenishment of supplies.

8.2.1. Process of supervision

8.2.1.1. Principles for supportive supervision

The general principles for supportive supervision are:

- To focus on processes and systems
- To nurture effective communication with staff
- To resolve conflicts, if any
- To encourage involvement and ownership of supervisor and those supervised.
- To optimize programme efficiency and delivery and make these target oriented
- To encourage continuous learning, development and capacity building of those supervised.

8.2.1.2. Preparation for supportive supervision

Following are the pre-requisites for an effective supervisory visit.

- Plan ahead. Tour should be planned in advance in monthly Advance Tour Planning (ATP) with the specific objective or follow up protocol.
- Inform about your visit. The concerned authority should be informed about the visit in advance through mail, letter, phone call (as per norm). Surprise visits should be discouraged.
- The supervisor should acquaint him/herself with baseline data of area/ facility to be visited. Use job aides, checklists & monitoring indicators.
- Analyze data beforehand assess situation so that preparatory activities for possible interventions may be undertaken.
- The supervisor may review the previous visit or evaluation report to update him/ herself for any pending follow up activity.
- Set an example by demonstrating correct practices.

Table 8.2: Recommended modalities for supervision of different levels of stakeholders and facilities

Stakeholder / Facility	To be supervised by (using standard checklists)	Frequency
DR-TB Patient	• TB HV • STS • Senior DR-TB TB-HIV supervisor • MO-TU • MO-DTC • DTO • State officials	• TB HV / STS. Visit all diagnosed DR-TB patients at their home within a month of treatment initiation and subsequently, at least once a quarter to monitor the treatment • Sr. DR-TB HIV Sup.At least once a quarter to monitor treatment • MO-TU. At least once a quarter • DTO/MO-DTC. Visit a sample of patients during TU visits • State officials. Visit a sample of patients during district visits
Diagnostic centre	• STS • STLS • Senior DR-TB TB-HIV supervisor • MO-TU • MO-DTC • DTO • State officials	• STS. At least once a week • STLS. At least once a fortnight • MO-TU. At least once a month • DTO/ MO-DTC, Sr. DR-TB HIV sup: Once a quarter • State officials: Visit a sample of TB detection centre during district visits
NAAT Lab	• STS • STLS • Senior DR-TB TB-HIV supervisor • MO-TU • MO-DTC • DTO • State officials	• STS. At least once a week • STLS. At least once a fortnight • MO-TU. At least once a month • DTO/ MO-DTC, Sr. DR-TB HIV sup. Once a month • State officials. Visit a sample of TB detection centre during district visits

Stakeholder / Facility	To be supervised by (using standard checklists)	Frequency
TU (incl. TU Drug Store)	• STS • MO-TU • MO-DTC • DTO • State officials	• STS. At least once a week • MO-TU. At least once a month • DTO / MO-DTC, Sr. DR-TB HIV sup. Once a month • State officials: Visit a sample of TUs during district visits
District Drug Store	• STS • Senior DR-TB TB-HIV supervisor • MO-TU MO-DTC • DTO • State officials	• HQ STS: At least once a fortnight • DTO/ MO-DTC, Sr. DR-TB HIV sup. Once a month • State officials. During district visits
DDR-TBC	• Senior DR-TB TB-HIV supervisor • MO-TU • MO-DTC • DTO • State officials	• Sr. DR-TB HIV sup. As and when a patient comes for treatment initiation • DTO/ MO-DTC. Once a month • State officials, During district visits
NDR-TBC	• Senior DR-TB TB-HIV supervisor of the district where NDR-TBC is situated • Senior DR-TB TB-HIV supervisors of the districts linked to NDR-TBC • Concerned DTO • State officials	• Concerned senior DR-TB TB-HIV supervisor and DTO. Once a fortnight • Quarterly coordination meeting with all senior DR-TB TB-HIV supervisors of districts linked to NDR-TBC • State officials. During district visits
C&DST Lab	• State officials • IRL microbiologist and team • Concerned HQ STLS • Concerned DTO	• Concerned HQ STLS & DTO. Once in a quarter • IRL team and state official. Twice a year
IRL	• State officials • NRL microbiologist and team • Concerned HQ STLS • Concerned DTO	• Concerned HQ STLS & DTO. Once a quarter • NRL team and state official. Once a year
State Drug Store	• Designated nodal officer from State/ State Chief Pharmacist • STO / Representative	• Once a month

8.3. Monitoring

Here we understand the process of utilization of the information recorded in Nikshay as well as various reports and registers at periodic intervals and monitor the performance of the various aspects of NTEP through these.

Monitoring is defined as the systematic ongoing collection, collation, analysis and interpretation of data with a view to detect any deviations from the expected norms and followed by dissemination of feedback for corrective actions.

Monitoring is the ongoing process of observing whether an activity or service is occurring as planned. It implies systematic and purposeful observation, aiming to identify any diversion from the planned course of action. A good monitoring strategy moves beyond the widely used detection and treatment outcome indicators and applies the concept of input, process, output, outcome and impact indicators for measurement of key programme activities on a regular and ongoing basis. This facilitates early identification of any diversions from a planned course of action thereby allowing timely solutions to problems.

8.3.1. Objectives of monitoring

The objectives of monitoring are as follows:

1. To ensure that activities are implemented as planned, and that the data recorded and reported is accurate and valid.
2. Incorporate a system of analysis, supervision and review which leads to remedial action to improve performance and improve indicators.
3. Serve as a tool to facilitate following:
   - Commitment of higher authorities at different levels;
   - Streamline newer programme initiatives in PMDT;
   - Engagement of all care providers which includes PP/other government health facilities/ medical colleges/NGOs; and
   - Ensure equitable provision of services to all sections of the community, including vulnerable populations.

8.3.2. Levels of monitoring

Monitoring, as an essential component of NTEP implementation, is undertaken at different levels as under:

1. National level – Central TB Division
2. State level – State Health Society and State TB Cell with the support of STDC
3. District level – District Health Society and District TB Officer
4. TB unit level – Medical Officer – TB unit
5. Health facility (PHC/ UPHC/ CHC/ UCHC/ district hospital/ medical college/private clinic/ private hospital/ dispensary) – doctor HF including CHO
6. Treatment supporter level

8.3.3. Monitoring indicators

- Various components of programme service delivery are fed in Nikshay from where various input, process and outcome indicators are drawn for different levels of health facilities.

- Analysis of these indicators helps the programme managers in monitoring improvement in programme performance.
- The list of monitoring indicators is placed at **Annexure 17.**

Monitoring of various PMDT related parametres under the programme are largely cohort based. A cohort comprises of a group of patients diagnosed and notified within a specified time period in facilities of specified geographic area. Cohort-based analysis allows monitoring by summarizing outcomes and other related risk factors within that group. This cohort, under the NTEP, is prepared by grouping notified patients from specified geographic location into quarters.

8.3.4. Nikshay-based monitoring system

In order to ensure uniformity of data for the purpose of SME across all levels, it has been decided that only data from Nikshay shall be considered as final. Moreover, all states/ UTs need to establish the mechanism for real-time data entry in Nikshay preferably at the source of data generation. Delay in the data entry needs to be monitored at district level regularly at least weekly to avoid any backlog in Nikshay data entry. It has been decided to provide a fixed time period, allowing sufficient time for the user to make entry into the system and after which, the reports on Nikshay would be considered as final and frozen. For further details, please refer to training modules for programme managers and medical officers (Module 8, page 184). *(29)*

8.3.5. PMDT review mechanism

Apart from monitoring through Nikshay there are review meetings to be organized which can provide the platform to discuss upcoming changes in guidelines and requirement for innovative solutions to address implementation challenges. The protocols and timelines for the PMDT related review meetings are as per **Table 8.3.**

Table 8.3: Protocols and timelines for the PMDT related review meetings

Meeting	Chair	Frequency	Participants
National level			
• Biannual National STO-Consultants' meeting • Regional PMDT review meeting	DDG- TB	Annual	STOs & state PMDT coordinators in the region WHO NTEP RTLs & consultants
State-level			
State PMDT committee meeting	Principal Secretary (Health)/ MD NHM	Quarterly	Members of state PMDT committee
DTO quarterly review meeting	MD NHM / STO	Quarterly	Concerned NHM and STC officials, STDC, IRL, C&DST lab and DTOs
NDR-TBC site coordination meeting	Nodal officer/ Senior medical officer – NDR-TBC	Quarterly (1st week of each quarter)	Concerned NDR-TBC staff & all senior DR-TB TB-HIV supervisors of the districts linked to NDR-TBC

Meeting	Chair	Frequency	Participants
District-level			
NTEP review meeting of the MO-TU	District magistrate/ Chief medical officer/ DTO	Monthly	District programme managers, MO-TU, medical college nodal officers, DR-TB nodal officers, In-charge/ microbiologists C&DST lab, STS, STLS, TBHV, LT, GHS staff
Block Level			
NTEP performance review	MO-TU/ block medical officer	Monthly	Block medical officer/ MO-TU, TU staff (STS, TBHV, STLS), HF staff
HF level			
NTEP performance review	MO-HF	Monthly	STS, TBHV, STLS, HF staff including CHO & team

8.3.6. Active drug safety monitoring and management

Whenever a patient has serious adverse events to any of the second-line anti-TB drugs, ideally, s/he is admitted at the DR-TBC and the committee decides on further management of the patient. This may require withholding or discontinuing the offending drug in the treatment regimen. The committee will be responsible for arranging the drugs to be given for managing these events. Timely and intensive monitoring for identifying and managing adverse events are essential components of the PMDT services. This will help improve the patient's adherence to treatment, reduce mortality, ensure timely management of ADR and obtain better treatment outcomes. Ancillary drugs for the management of adverse events should be made available to the patient free of cost. Proper training of staff and support to the patient are other important activities that are required. Timely, accurate and complete reporting and analysis of adverse events are required to be reported under the programme. This is crucial for the protection of patients. Also, any SAE should be managed at the appropriate health facility level and reported in Nikshay within 24 hours by the health facility managing the SAE/ parent health facility.

8.3.6.1. Adverse event definitions and classifications

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

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

- results in death;

- is life-threatening (subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it more severe);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a suspected transmission of any infectious agent via a medicinal product; and
- is medically important. (Medical and scientific judgment exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of other outcomes listed in the definition above. These is usually considered serious.)

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

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

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

8.3.6.2. Attribution definitions

Causality assessment will be done by the physician at DR TBC and are divided in five categories (mentioned below). The DR TBC committee, in coordination with ADR reporting centre (AMC) will review and confirm causality of all serious events/reactions in relation to therapy.

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

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

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

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

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

8.3.6.3. Severity criteria

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

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

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

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

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject, e.g. laboratory abnormalities. Safety assessment measure is the proportion of patients experiencing a Grade 3 or greater adverse event, as defined by DAIDS (Division of AIDS) criteria during treatment and follow-up:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

8.3.7.4. Reporting of AE and SAE

All SAEs and AE's (non-serious adverse events) which are possibly, probably or very likely related to administration of any anti-TB drug that fits the definition as detailed later and which relates to detailed formats for AE reporting and pregnancy occurring during the programme. They must be reported by the physician to NTEP as they occur. If pregnancy occurs during MDR-TB treatment, the regimen should be modified as per NTEP PMDT guidelines. Any death of a patient occurring during treatment, regardless of causality, must be reported as SAE and a verbal autopsy **(Annexure 30)** should be undertaken. Doctor - HF should carry out verbal autopsy for all DR-TB patient died during the course of treatment. It is recommended that the patient be questioned before commencement of treatment and at each subsequent consultation in order to obtain a detailed description of any sign of toxicity or adverse drug reaction, which they might have experienced. The standard prescribed formats for aDSM – treatment initiation form need to be maintained for every patient. And aDSM – treatment review form need to be maintained for all patients with SAE. NTEP will ensure that strict aDSM is implemented by all NDR-TBC and district physicians for ambulatory patients.

The treating physician at N/DDR-TBC and medical practitioners at periphery will observe patients for any adverse events (spontaneous reporting by patient and active screening) and manage as per laid down criteria in document. The SAE will be reported to ADR monitoring centre (AMC) and CTD within 24 hours. Patient details will be captured as baseline (before starting treatment) and will get updated at regular monthly intervals till completion of treatment. The primary responsibility of filling up above forms will be with the nodal officer with the help of SMO or MO designated by DTO for DR-TB centre. The nodal officer will be responsible for data entry in Nikshay with help of SA at NDR-TBC and senior DR-TB TB-HIV supervisor at DDR-TBC centre. Concerned DTO should make necessary arrangements for data entry in absence of abovementioned support staff. Records need to be maintained in hard copies at respective centres.

8.3.7. Death audits under PMDT

The diagnosis and treatment of DR-TB patients is definitely more challenging than the same for DS-TB. Both morbidity as well as mortality rates are significantly higher in DR-TB Patients. Hence, determining the cause of death of all DR-TB patients under treatment is a crucial first step towards designing appropriate and timely interventions to prevent avoidable deaths. Death audits using verbal autopsy as well as review of clinical records can be a valuable tool for understanding commonest causes of mortality and guide the program to optimize its service delivery mechanisms to address these identified causes. The doctor – HF in coordination with nodal/ district DR-TB sites should mandatorily review every patient of death

of diagnosed DR-TB patients irrespective of treatment and record these. A template of verbal autopsy is placed as **Annexure 30.**

8.4. Evaluation

Evaluation refers to the periodic assessment of the programmes/ projects activities. It involves systematic recording and review of information regarding the interventions and outcomes of programmes to improve programme effectiveness and support informed decisions on future strategies. Broadly, it helps:

1. To monitor progress towards achieving the programme's goals.
2. To determine whether desired progress on outcomes are being achieved.
3. To facilitate continuous quality improvement.
4. To ensure effective and optimum utilization of resources.

Evaluation is an integral component of NTEP SME strategy. It acts as a tool to evaluate if good programme practices are adopted and quality services are provided to the community. They also offer an opportunity for programme managers to look into all aspects of the programme and help them in understanding determinants of good as well as poor performance and institute prompt remedial measures if needed.

Central and State Internal Evaluations form the backbone of systematic programme evaluation under the NTEP. The objectives of these internal evaluations are, broadly, as under:

1. To provide a systematic framework for assessment of programme performance, financial & logistics management, R&R, and quality of care received by patients.
2. To give recommendations for improving the quality of programme implementation and performance with a realistic action plan and timeline.
3. To monitor efforts to improve and maintain programme quality and performance over time.

The evaluation of PMDT aspects of programme implementation forms a crucial part of these evaluations.

8.5. Training and re-training on PMDT guidelines

Broadly, there are 4 types of trainings envisaged under the NTEP which are listed below:

1. **Induction training.** Initial comprehensive training before assuming responsibilities of NTEP.
2. **Re-training.** Periodically retaining of already trained staff in NTEP need to be considered (once a year).
3. **Update training.** Newer initiatives or changes in the policy of NTEP are to be conveyed to the health personnel as short update trainings.
4. **Refresher training.** Based on training needs of identified personnel focused on specific deficits of knowledge or skills identified.

Details of frequency, duration, level and batch sizes prescribed for all trainings under the NTEP are described in the updated Training Modules for Programme Managers and medical officers (Module 5, pages 34 – 41). *(29)*

8.5.1. E-Training

The NTEP has launched extensive E-Training modules through carefully curated content designed by national experts. These e-learning modules help the participant undertake various trainings at their own convenience and at a pace best suited for them. In order to ensure quality training, all the chapters are followed by in-depth questionnaires. The participant can progress to the subsequent chapter only on successfully answering the questions from the preceding chapter. The participants would be awarded with a certificate on successful completion of training. These certificates would be valid for a pre-determined period of time, post which, the staff member will need to undergo a refresher training. It is envisaged that the E-trainings would be followed by an actual hands-on training for relevant staff, especially for the laboratory components, at an appropriate level.

The state will need to prepare detailed timetables for various cadres of staff to complete the E-trainings. These need to be monitored to ensure that all eligible staff undertake these trainings and are certified. These completion certificates need to be placed in the personnel files of all staff. The validity of these certificate needs to be recorded and monitored to ensure timely refresher and re-trainings. The e-training platform provides convenient timing and feasibility of its use to improve its access to the public and private sector. (http://swasth-egurukul.in/)

8.5.2. Supervision and evaluation of the training quality and needs

C&DST labs, N/DDR-TBC, district health units and peripheral levels of health services are visited to observe the performance of the staff related to NTEP activities. By this, the quality of the training imparted and training needs can be assessed. These visits must be utilized for handholding and updating of the staff in the areas of knowledge/ skill gaps and also in transmission of new knowledge/ policy changes.

POINTS TO REMEMBER

- ✓ NTEP has robust mechanisms for ensuring SME of all the components of the programme, including PMDT;
- ✓ Nikshay, the state-of-art recording, reporting, SME and surveillance system for managing all aspects of NTEP (including PMDT) will be leveraged to gradually enable a completely IT based and paperless SME mechanism;
- ✓ Standard checklists and IT based tools have been developed for facilitating supervision of the various facilities under the programme;
- ✓ Standard monitoring indicators have been finalized for all the major parametres under the programme; and
- ✓ Robust and standardized evaluation mechanisms have been established to review the programme performance at period intervals at all levels, namely national, state, district etc.

CHAPTER 9

RECORDING, REPORTING IN NIKSHAY

Learning objectives

In this chapter, we will learn about:

- To enable real-time access of the patient's details for management of individual patient at all level.
- To real-time generation of reports to track progress which allows managers at different levels in NTEP to follow overall programme performance through the distribution and trend in DR-TB notification; and the response to treatment in DR-TB patients treated with NTEP regimen.

This chapter describes the information system for patients that fall under NTEP PMDT. It also provides details on mostly electronic reporting and recording system with some paper-based elements yet to be developed in Nikshay.

9.1. Information system for NTEP PMDT

The information system for NTEP PMDT is based upon and is an extension of the basic NTEP information system. The forms are therefore made as similar as possible to the existing forms in NTEP. This chapter defines the minimum instruments and variables of the information system, necessary to satisfactorily implement and monitor treatment with various NTEP regimens for DR-TB.

In line with the aims of the information system elaborated above, NTEP has a preference for the Digital First, Paper Second Policy. Utilizing Nikshay, as a fully equipped tool for real time information management, two broad aims of the information system as above, namely i) Real time access to information at all levels and ii) Real time report generation, can be achieved with ease. Of the many benefits of the Digital First approach, a few are listed below:

1. Real-time access to information at all levels
2. Consistent, secure data management, with built in internal validations, aligning all stakeholders
3. Eliminates redundancy and duplication of data entry efforts
4. Ease of report generation for large datasets
5. Ease of data analysis.

NTEP is cognizant of the possibility of operational challenges towards real-time Nikshay-based recording and reporting, which may be variable for different states, districts and TUs. Accordingly, it is recommended that states, districts and TUs may strategically prioritize complete transition to Nikshay, the digital information management system, at the earliest

opportune moment. This transition may take place in bits and pieces, starting even at the grassroots level i.e. any HF which is ready for such a transition may do so without waiting for other HFs to transition. It should however be clearly noted that any paper-based records are only a stop-gap arrangement while awaiting complete transition to real time a Nikshay-based Digital Information management system. Accordingly, paper-based records should not circumvent and are not in lieu of Nikshay-based recording and reporting even during the transition period.

9.2. Data management of PMDT in Nikshay

The following section describes the digital information flow as well as digital reports and registers that will be used for NTEP PMDT to enable proper recording of diagnosis, monitoring and care, in addition to the reporting of outcomes.

The overall flow of information for data management of PMDT in Nikshay is depicted in the swim-lane diagram **(Figure 9.1)** below.

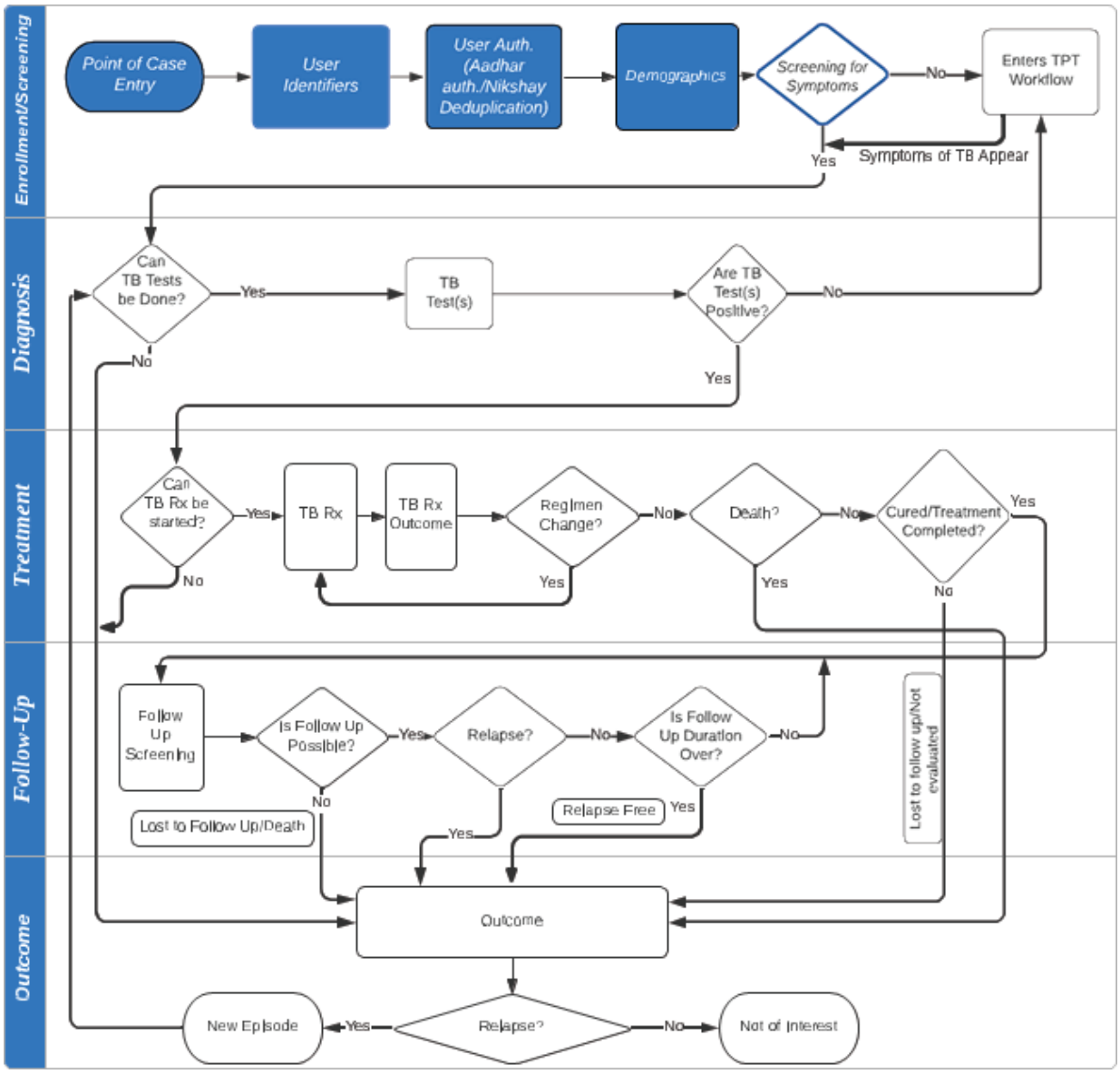


Figure 9.1 Swim-Lane diagram: Overall information flow for PMDT data management in Nikshay

9.2.1. Introduction to swim-lane diagram, enrolment/screening activity

The above swim-lane diagram illustrates five cardinal activities in the TB patient workflow:

1. Enrolment/screening
2. Workflow related to TB diagnosis
3. Workflow related to TB treatment
4. Workflow related to TB follow-up
5. Workflow related to assigning outcomes/creating a new diagnostic episode.

Each square in the diagram signifies a process and quadrangle signifies a decision point. There are data entry points associated with each process and decision point. Also, each of these five activities (swim-lanes) are connected to other activities (swim-lanes) in some way, which makes this flow an integrated workflow for TB patient information management.

Enrolment/Screening. The first swim-lane in the diagram illustrates the workflow around enrolment and screening of persons. At the first point of contact of the person, the process of enrolment begins. The person is authenticated through primary details like gender, phone number and going forward Aadhaar number (upcoming feature in Nikshay) and validated through the Nikshay Deduplication module. On confirming the person as unique in Nikshay, further demographic details would need to be entered, following which the process of screening kicks in. On entering symptom screening details, a decision point is reached. If the person does not have symptoms suggestive of TB then the person exits the TB workflow and enters the TPT workflow.

If the person has symptoms suggestive of TB, then the second activity (swim-lane) workflow begins related to TB diagnosis.

The field staff potentially assigned to the enrolment/screening activity and responsible for data entry is described in the operational guidelines below.

- Enrolment module in Nikshay enables registration of all kinds of new cases
  - Presumptive (including vulnerable populations) or confirmed patient
  - Taking treatment from public or private sector
  - DS-TB and DR-TB
- On enrolment, a unique numeric Episode ID is generated by Nikshay
- While enrolment, Nikshay shows duplicate records based on gender and mobile number. Very soon, Aadhaar integration would also be enabled for beneficiaries of Nikshay Poshan Yojna (NPY) which would enhance the deduplication process further. Users should review the possible duplicates carefully before enrolling a new case.

At the time of enrolment, following variables as shown in **Table 9.1** are captured in Nikshay. These variables, although can be updated to a limited extent, would be utilized across all the line-lists (registers) and reports for maintaining consistency.

Table 9.1 Variables captured in Nikshay at the time of enrolment

Variables for enrolment Set-1	Variables for enrolment Set-2	Variables for enrolment Set-3	Variables for enrolment Set-4
First name	HIV test status	Key population	Contact person's name
Last name	Fathers' name	- Contact of TB patients	Contact person's address
Gender	Pin code	- Diabetes	Contact person's phone
Age	Taluka	- Tobacco	
Occupation	Town ward	- Prison	
Address	Landmark	- Miner	
Primary phone	Area- Urban, rural, urban slum, tribal	- Migrant	
		- Refugee	
Type of patient- Public/Private	Marital status	- Urban Slum	
		- Health-care worker	
	Socio-economic status -APL,BPL	- Other	

The screenshots for data entry are as depicted below:

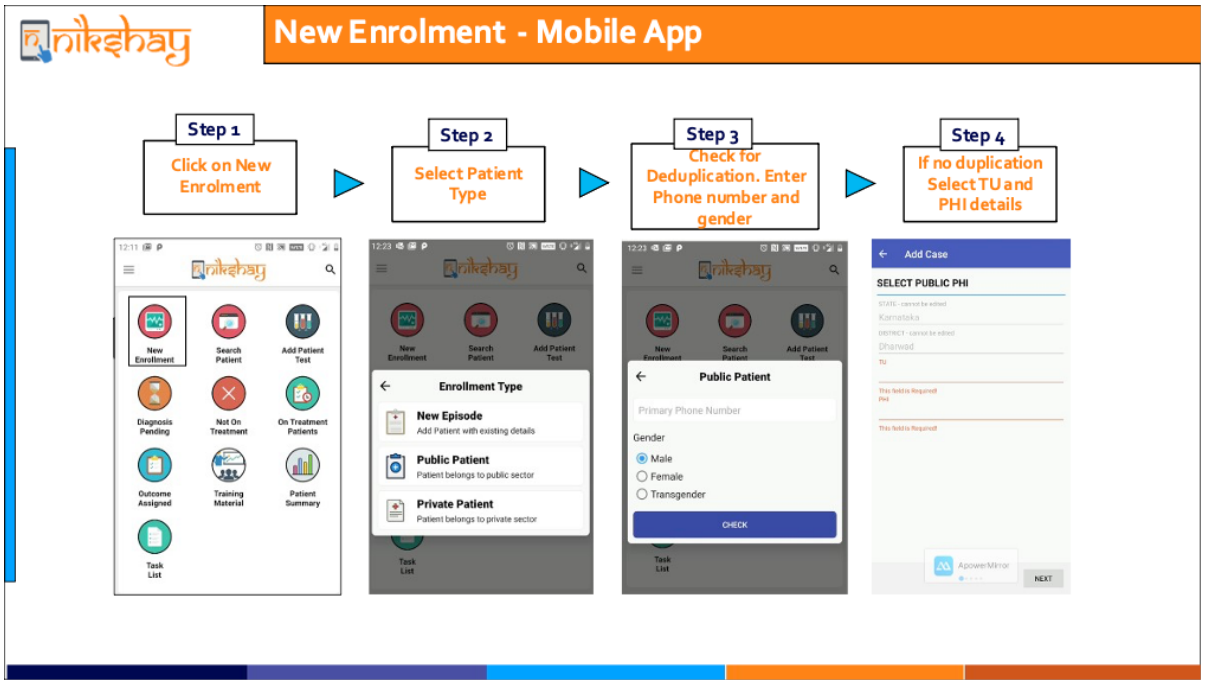


Figure 9.2 Enrolment dialogue box-mobile app-Part 1

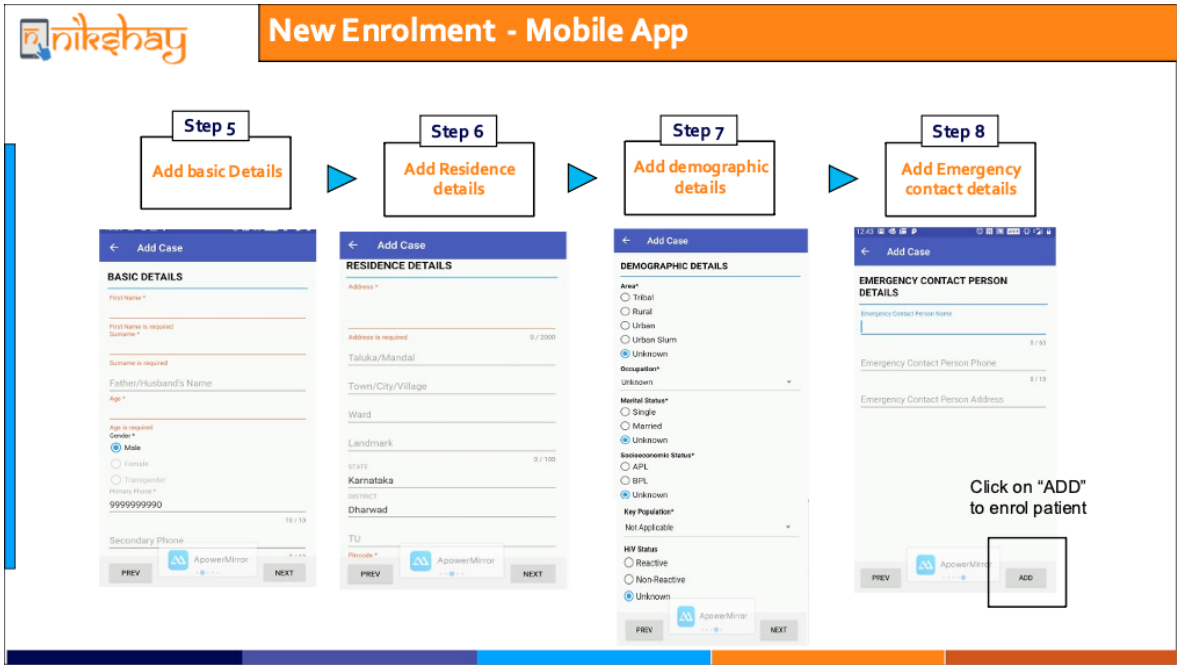


Figure 9.3: Enrolment dialogue box-mobile app-Part 2

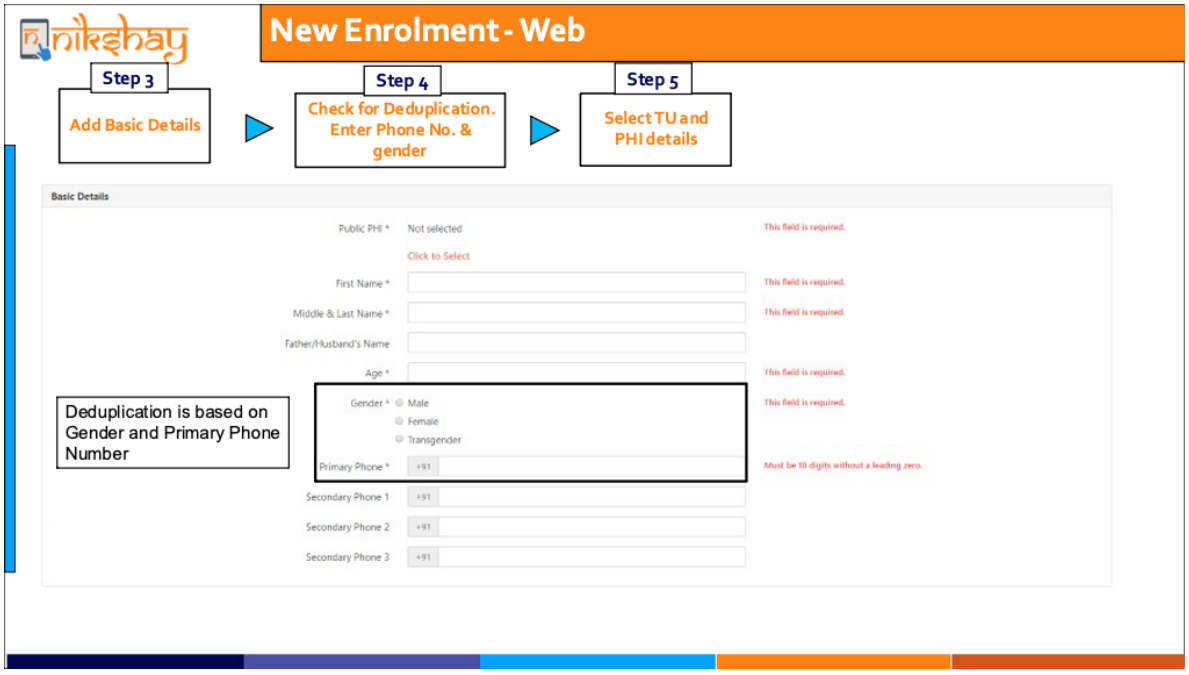


Figure 9.4: Enrolment dialogue box-web-Part 1

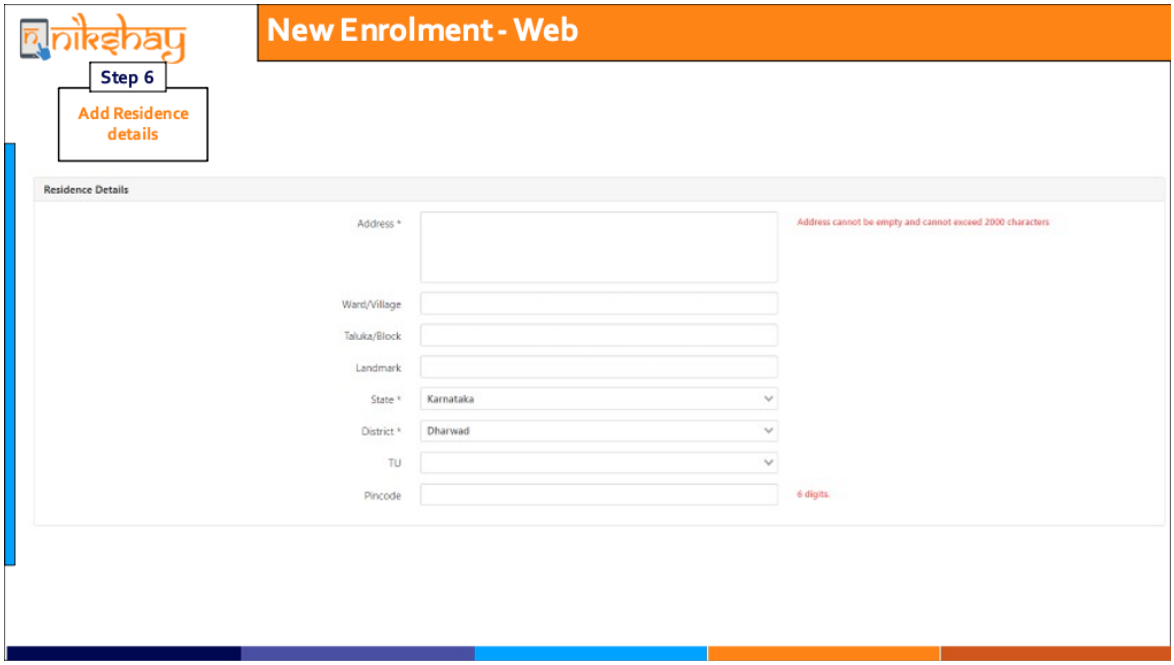


Figure 9.5: Enrolment dialogue box-web-Part 2

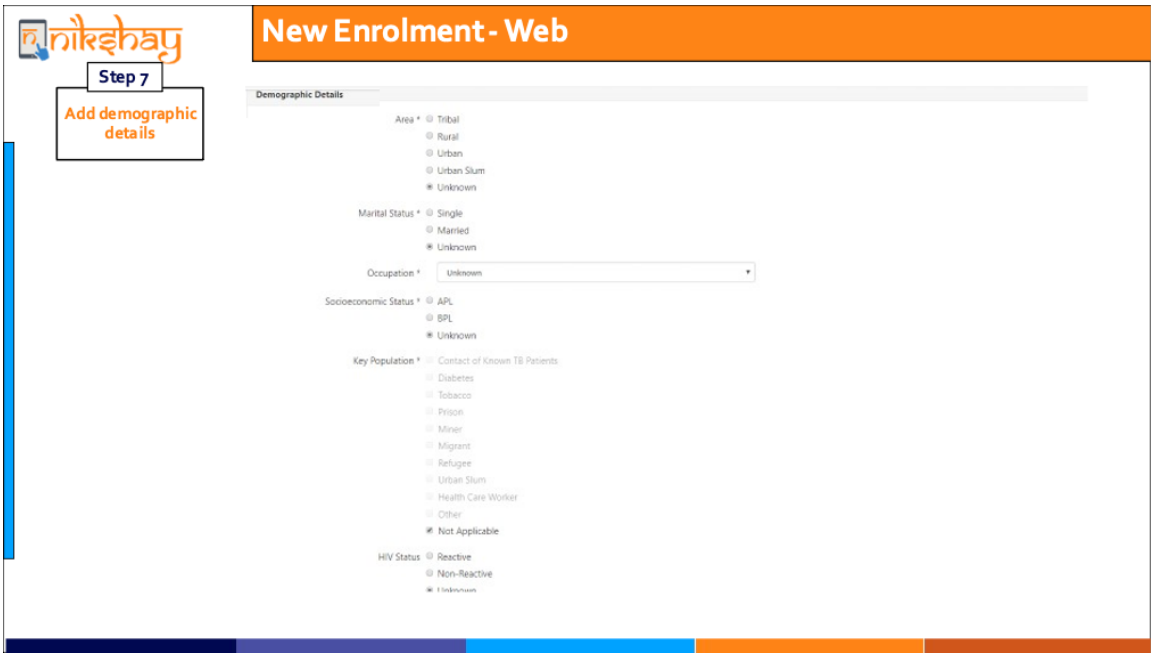


Figure 9.6: Enrolment dialogue box-web-Part 3

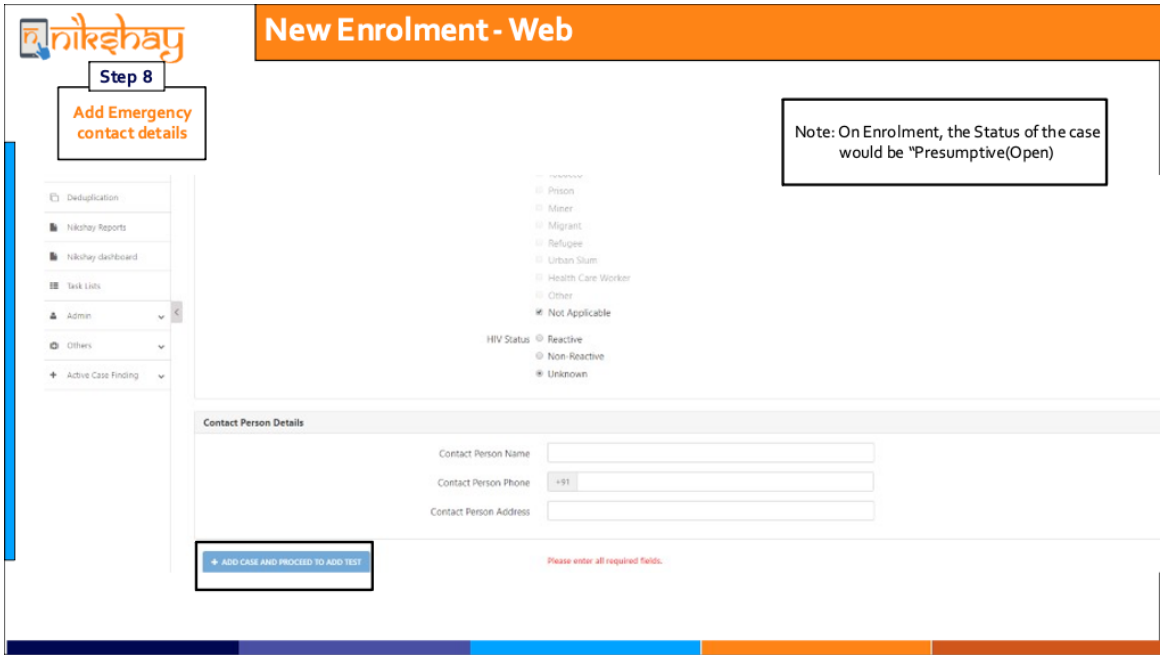


Figure 9.7: Enrolment dialogue box-web-Part 4

9.2.2. Workflow related to diagnosis and tools for maintaining records

In this activity the person is assessed for eligibility of TB tests and feasibility of TB tests. If the person is found eligible for TB tests and if the TB tests are feasible then the process of tests would be conducted. If the tests are positive for TB the person would be redirected for assessment of feasibility of initiating TB treatment and that workflow would be pursued further as above. However, if the TB tests are not feasible to be conducted then a diagnostic outcome would be assigned.

In cases where TB tests are negative then the person would exit the TB workflow and enter the TPT workflow.

For all specimens sent from health facilities, test requests should be generated from the specimen collecting health facility for the corresponding patient episode ID in Nikshay. This will enable instant online intimation about the upcoming specimen to the health facility (particularly NAAT site or C&DST laboratory) where these tests are requested prior to receipt of the specimen while it is in transit. The result will be updated at the testing health facility in Nikshay against the test ID requested from the field to save time required to scan results and send it to the concerned health facility. Real-time data entry helps NTEP to disseminate information at all levels like C&DST labs, N/DDR-TBC, district, TU and HF to initiate reflex actions for further patient management on real-time basis.

All individuals who are presumptive TB or presumptive DR-TB are required to have a sputum or an appropriate EP specimen examination for diagnosis. The erstwhile used comprehensive 'Request form for examination of biological specimen for TB' may be discontinued and real-time entries in Nikshay are encouraged which is expected to be the norm going forward. Should it be required to have physical form for such specimen collection requests, it may be printed from Nikshay once the relevant entries are made in Nikshay. The feature to print specimen examination form would be available in Nikshay soon. Till then the TB bacteriology request form **(Annexure 7)**, will be used by HF staff to be send along with the specimen collected in periphery during the last mile specimen transport from HF to TDCs where the

LT will raise the test request in Nikshay. Also with the revamp of the diagnostic module in Nikshay, it is also expected to have lab-centric features with tools to track lab samples as well. These features in Nikshay are under development.

Nikshay has the ability to request tests for most of the tests to be requested to the lab like microscopy, NAAT test, C&DST test, X-ray and others. The variables collected while adding a test request over and above other variables collected for the person/patient in Nikshay are given in **Table 9.2**

Table 9.2 Variables captured in Nikshay while adding a test request

Test Variables	
Id (Test request ID)	**Status**
Patient Id (Episode ID)	- Results pending
Type	- Results pending
Specimen	Reason
Visual appearance sputum	- Diagnosis of DR-TB
Reported By	- Diagnosis of DS-TB
Date tested	- Diagnosis of TB
Date reported	- Follow-up of DR-TB (Smear and Culture)
Testing facility name	- Follow-up of DS-TB (Smear)
Test result	Predominant symptom
Stage	Predominant symptom duration
- End IP / Extended IP	HF visited
- End treatment	Previous ATT
- Other	Date specimen collected
- Pre-treatment	

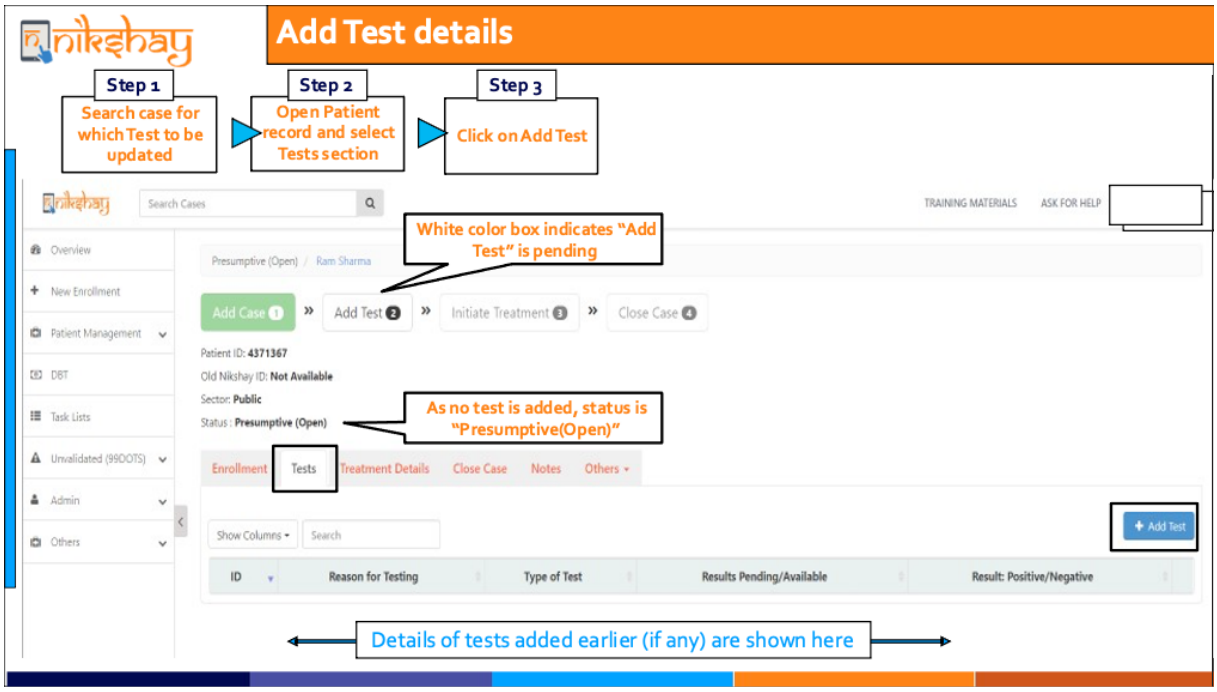


Figure 9.8 Add test dialogue box-web-Part 1

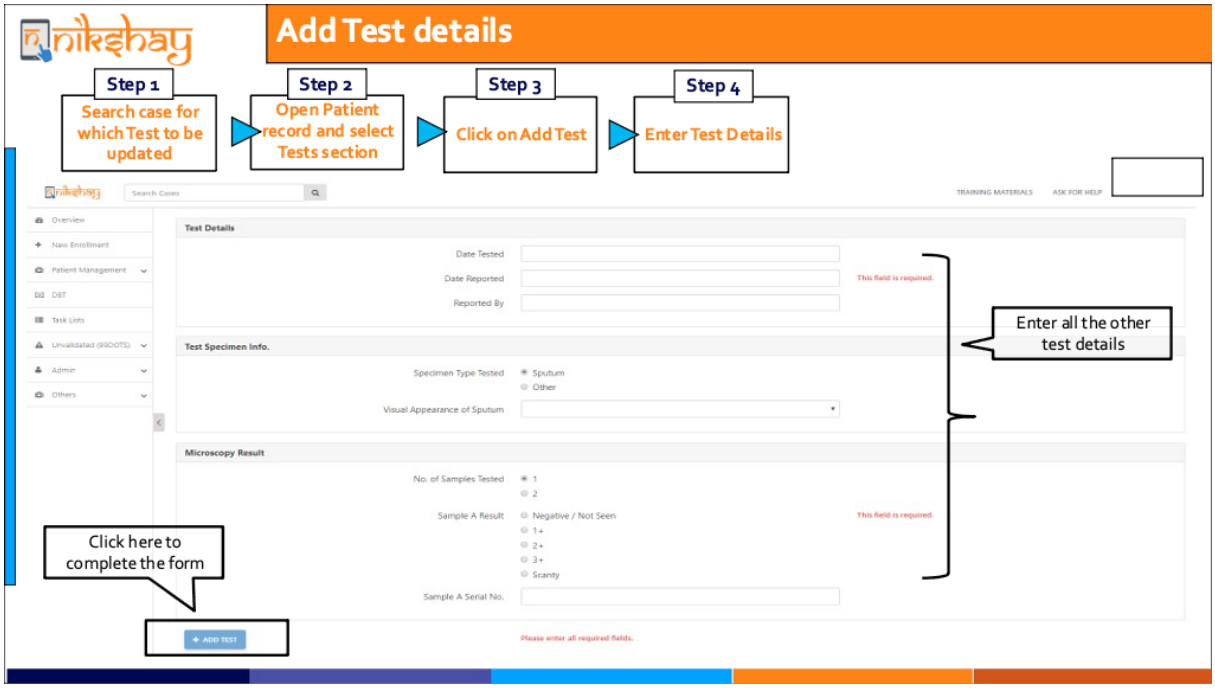


Figure 9.9 Add test dialogue box-web-Part 2

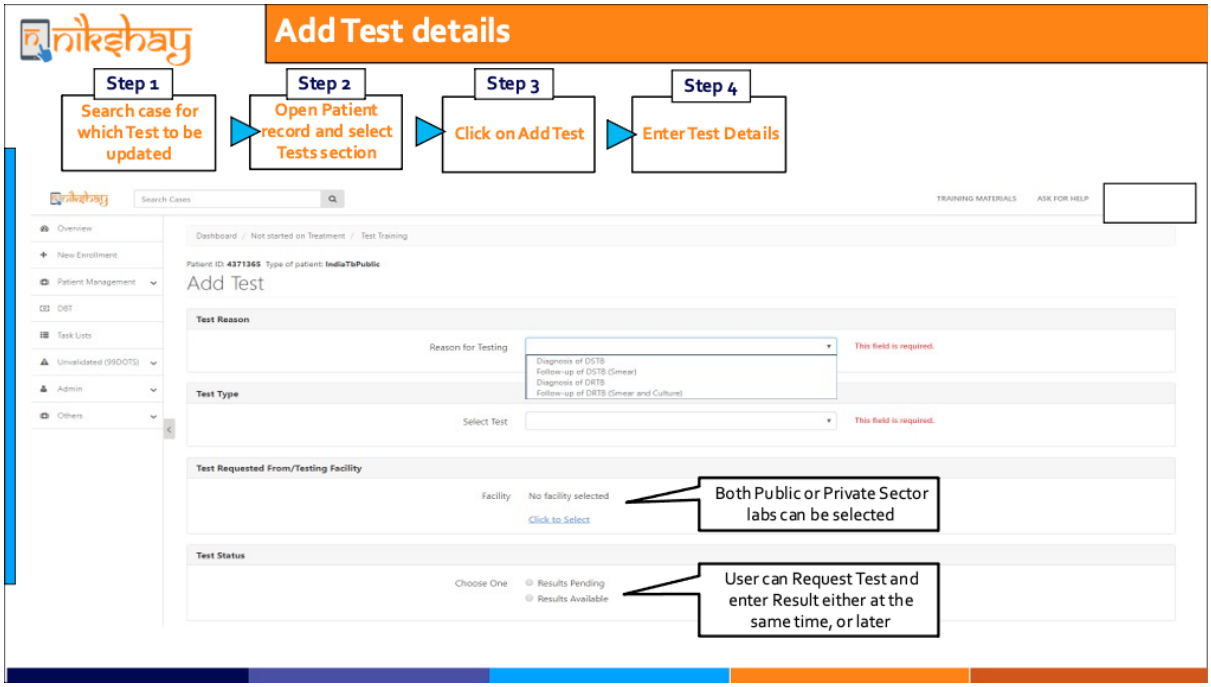


Figure 9.10 Add test dialogue box-web-Part 3

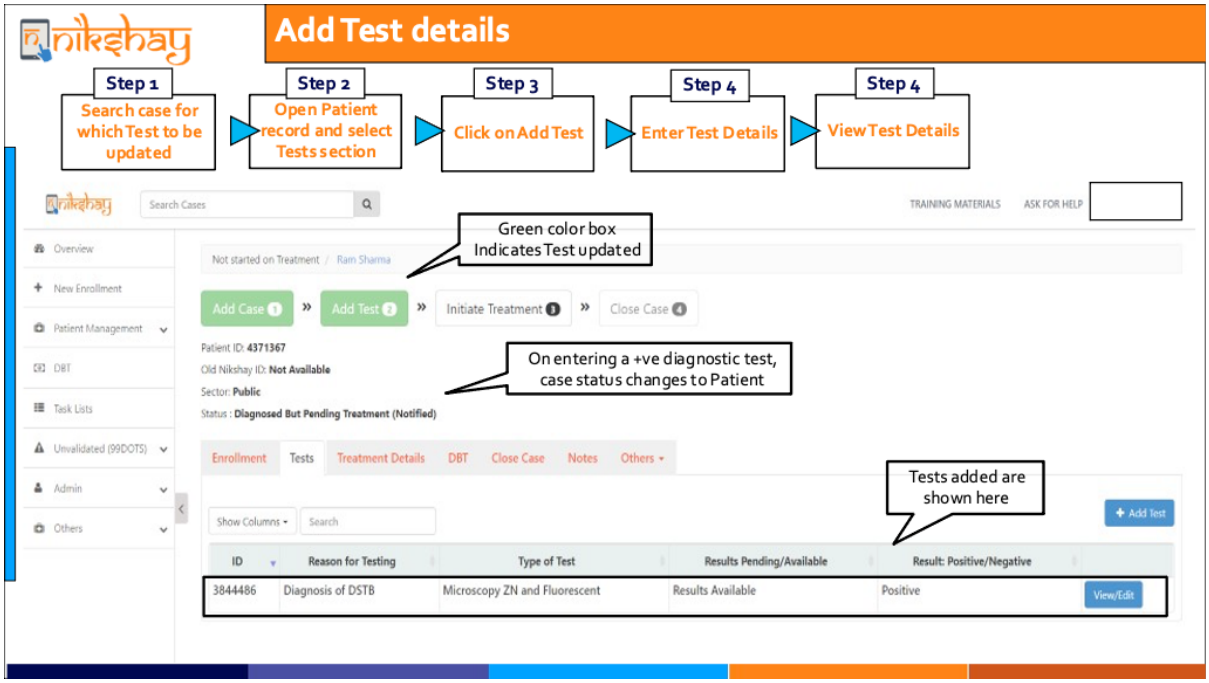


Figure 9.11 Add test dialogue box-web-Part 4

9.2.3. Workflow related to treatment

If the person has tested positive for TB from the above workflow then a decision point is reached. Assessment for feasibility of TB treatment would be conducted and if the TB treatment could be initiated then TB treatment would be initiated. If, however the TB treatment cannot be started despite the person being eligible for TB treatment, then a treatment outcome would be assigned.

Pursuing the persons for whom TB treatment has been initiated, the next process is assessment of treatment outcome across the following:

1. Regimen change
2. Death
3. Cure/treatment completed

For persons started on TB treatment and assessed for regimen change would re-enter the process of TB treatment initiation.

For persons started on TB treatment and assessed as dead would end up with an outcome.

For persons started on TB treatment and assessed as cured/treatment completed would enter the next activity-Assessment for follow-up criteria. However, if the patient is assessed as not belonging to any of these categories (Lost-to-follow-up/Not evaluated) would end up having an outcome assigned.

Treatment details can be updated in Nikshay real-time. Details about contact tracing which includes aggregate household contacts found, screened, evaluated for active TB, diagnosed

with active TB, put on treatment for TB as well as details about others put on TPT for both persons under 5 years and above 5 years can be recorded. Further adherence details as far as manual update is concerned can also be done through the adherence calendar. The set of variables collected for treatment details including co-morbidity details in Nikshay are as under:

Table 9.3 Variables captured in Nikshay at while adding treatment details

Treatment Variables	
Type of case	Comorbidity details variables
New	HIV status
Retreatment-Recurrent	Date of HIV testing
Retreatment-Treatment after failure	PID no.
Retreatment-Treatment after lost-to-follow-up	Date of CPT delivered
Retreatment-Others	Date of referral to ART centre
PMDT	Initiated on ART
Drug regimen -DR-TB regimen	Date of ART initiation
- H mono/poly DR-TB regimen	CD4 count
- Shorter oral Bedaquiline-containing MDR/RR-TB regimen	Pre-ART number
- Longer oral M/XDR-TB regimen (MDR/PreXDR/ XDR)	ART number
- BPaL regimen (MDR/PreXDR)	Diabetes status
TB treatment start date	RBS
Diagnosis basis	FBS
Monitoring method	End of IP
- 99DOTS	End treatment
- MERM	Initiated on anti-diabetic treatment
Treatment type	Date of Initiation
- First-line drugs	Other co-morbidity
- Second-line drugs	COVID status
Refill monitoring	Current tobacco user
Height	Tobacco type
Weight band	Linked for cessation
New or previously treated	Status of tobacco use at the end of treatment
Site of disease	H/O alcohol intake
EP site	Linked for de-addiction
Weight	Status of pregnancy during episodes
Type of DOT	RCH Id
- Institutional treatment supporter	
- Community treatment supporter	
- Family DOT	

Figure: 9.12 Treatment details dialogue box-web-Part 1

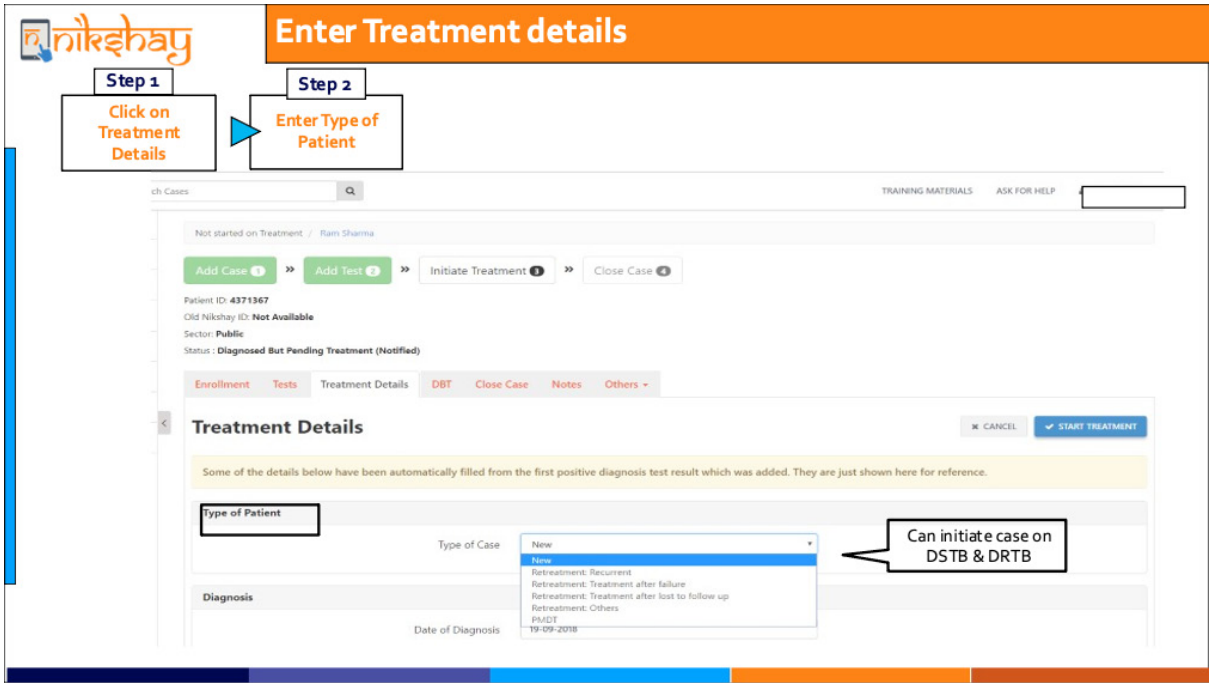


Figure 9.13 Treatment details dialogue box-web-Part 2

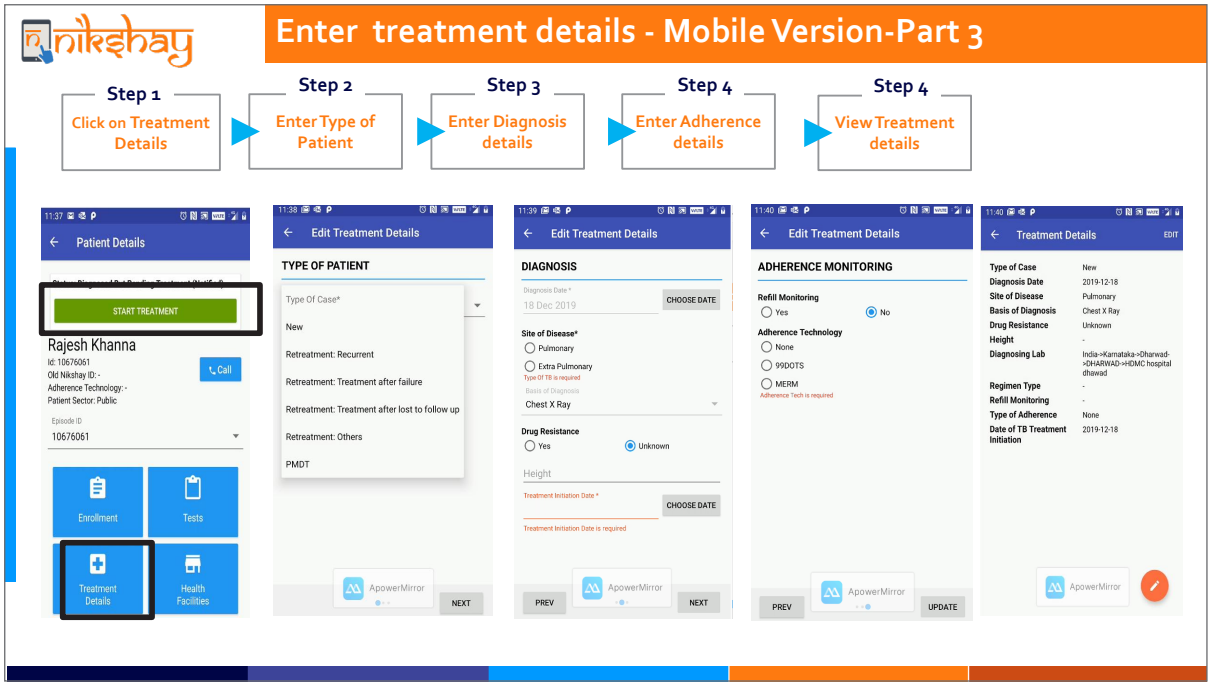


Figure 9.14 Treatment details - Mobile Version - Part 3

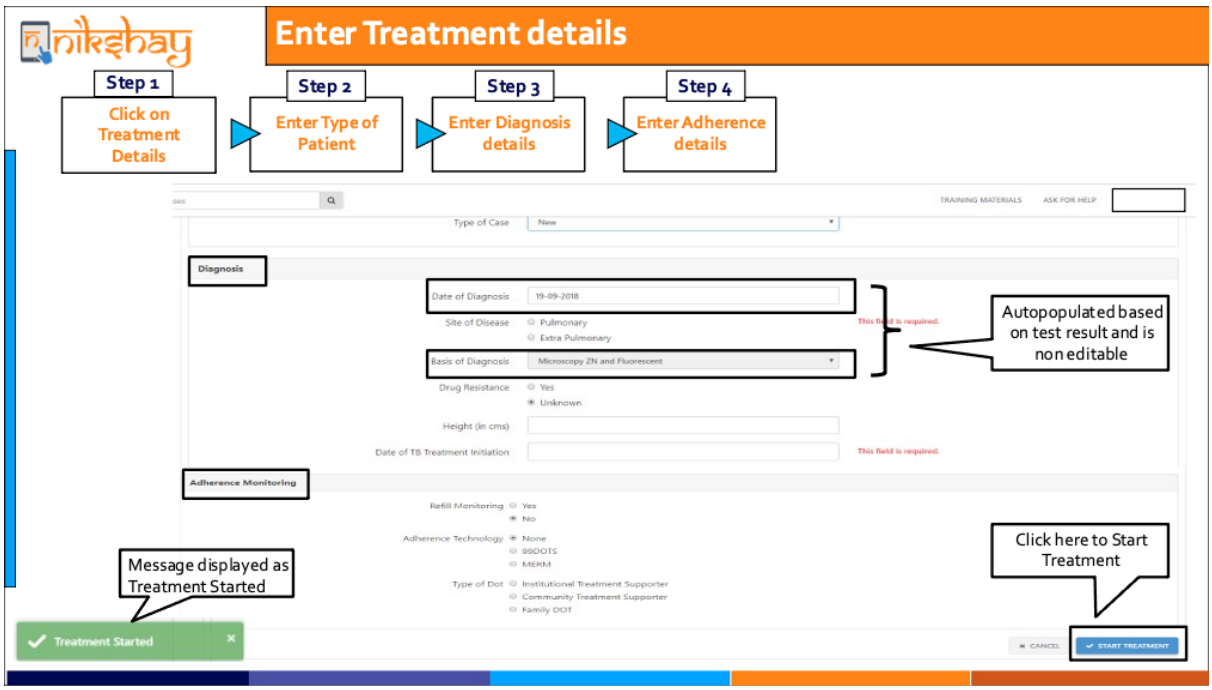


Figure 9.15: Treatment Details Dialog Box-Web-Part 4

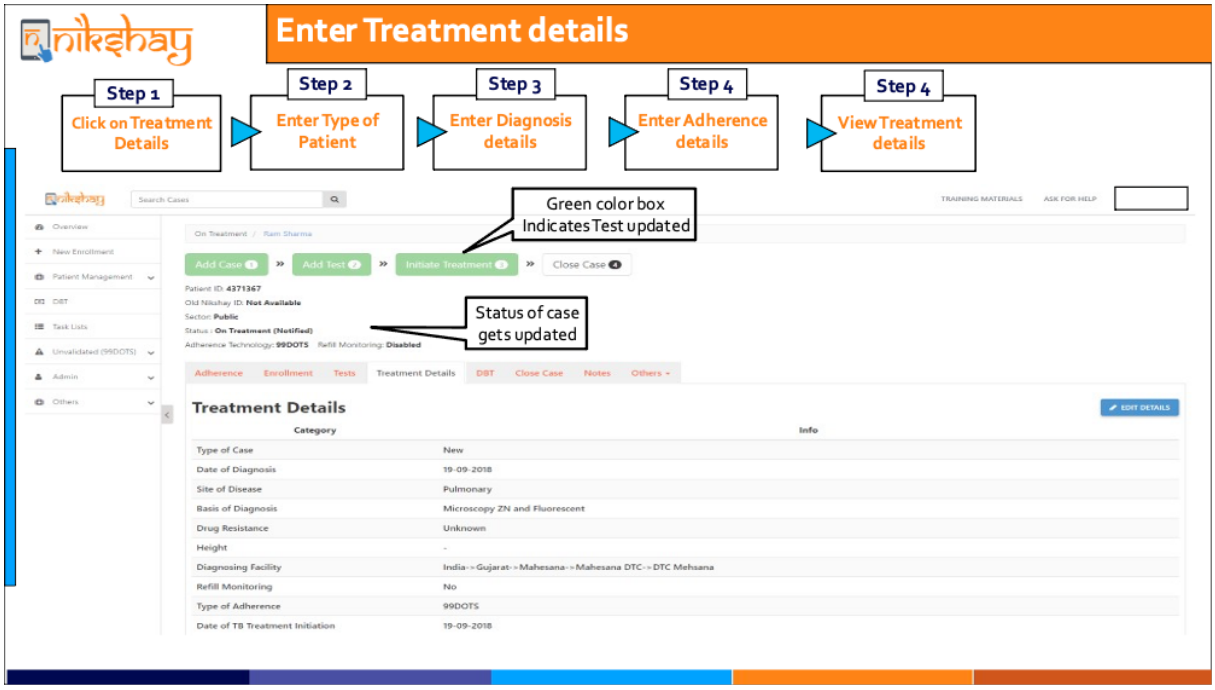


Figure: 9.16 Treatment details dialogue box-web-Part 5

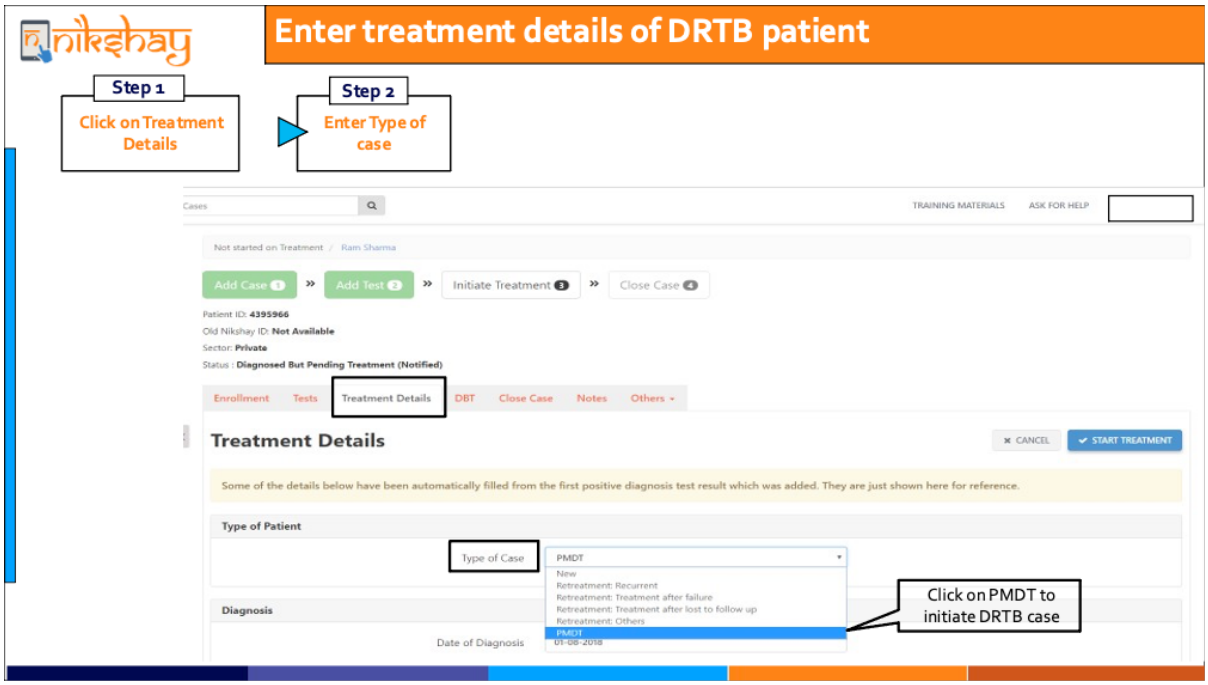


Figure 9.17: Treatment details dialogue box-web-Part 6

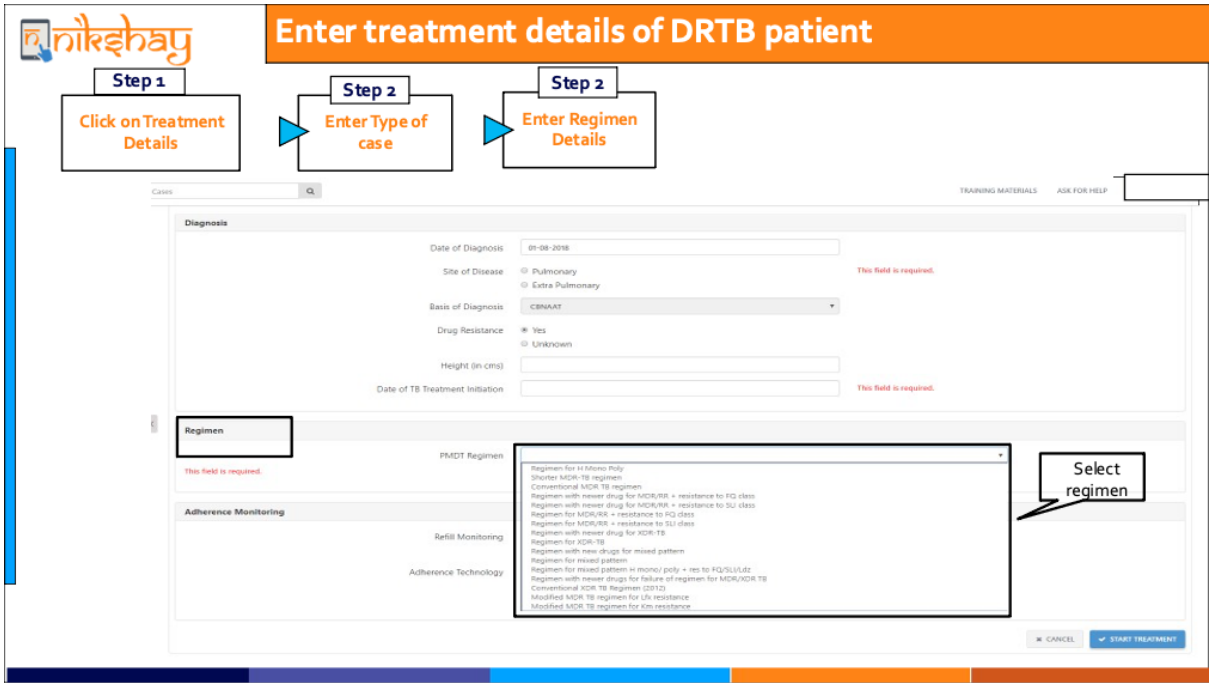


Figure 9.18 Treatment details dialogue box-web-Part 7

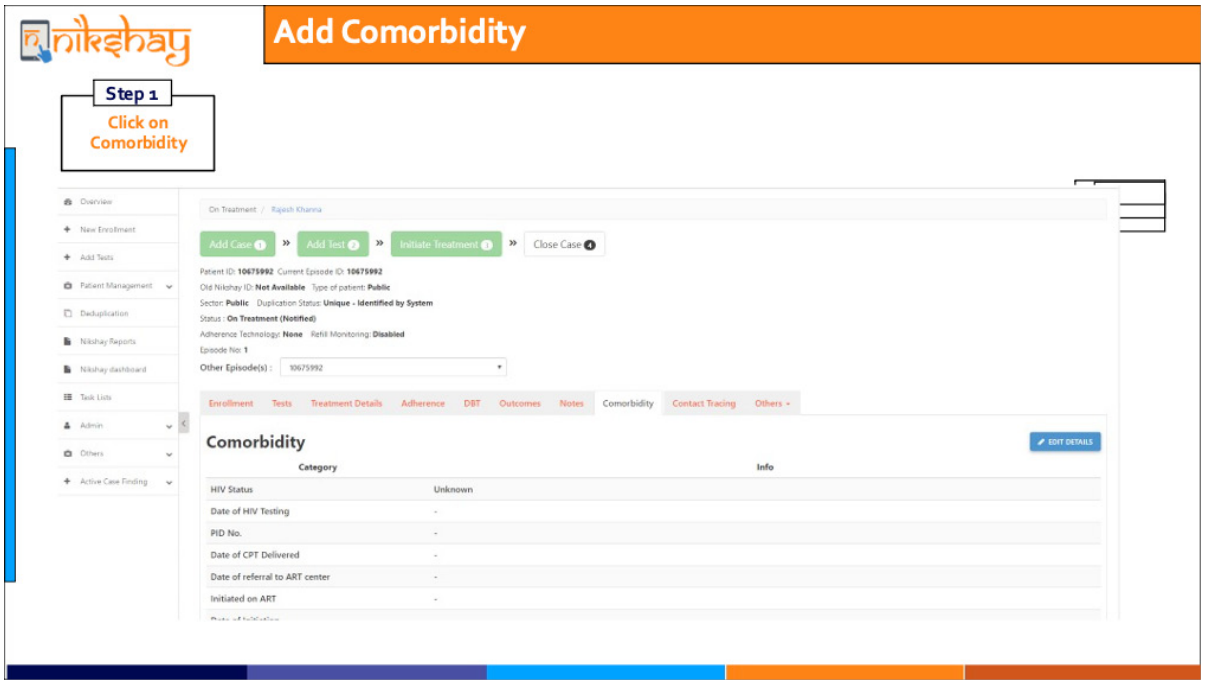


Figure 9.19 Co-morbidity details dialogue box-web-Part 1

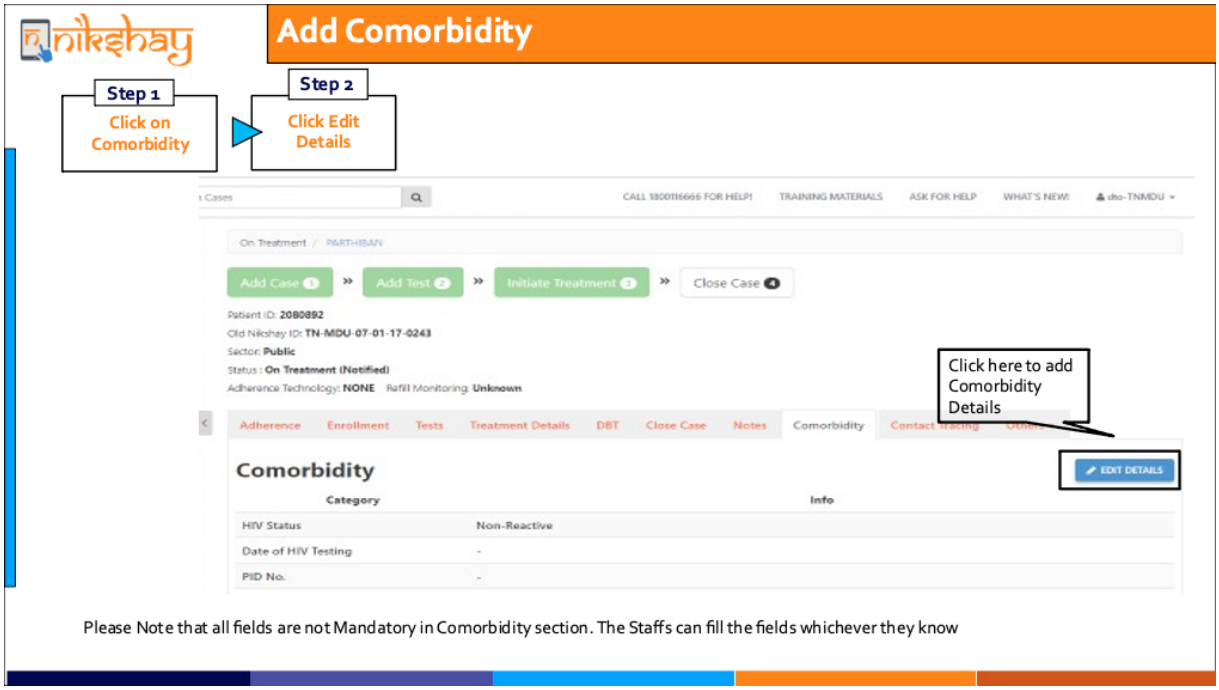


Figure 9.20 Co-morbidity details dialogue box-web-Part 2

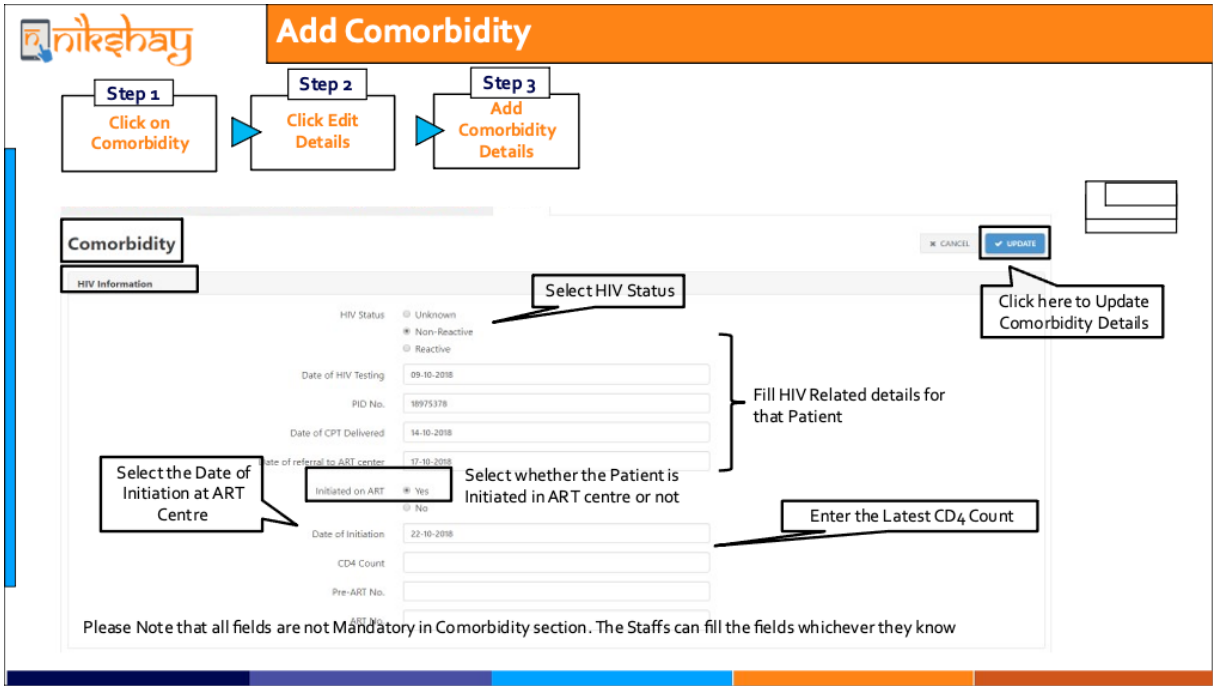


Figure 9.21 Co-morbidity details dialogue box-web-Part 3

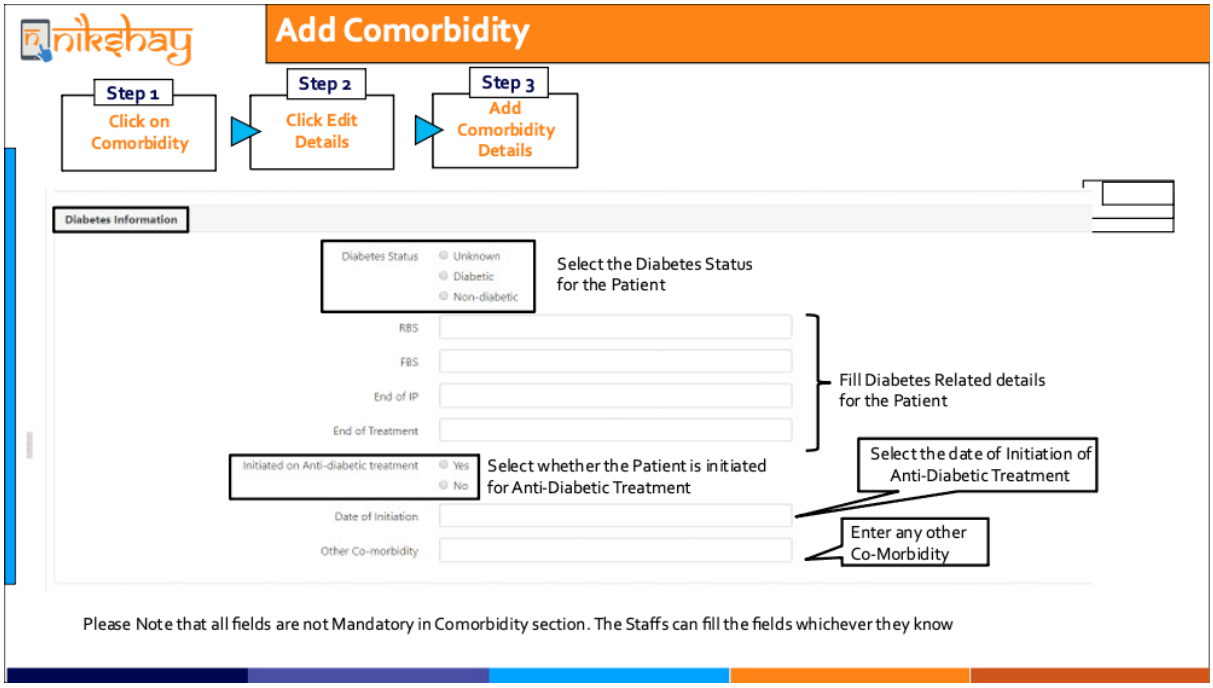


Figure 9.22 Co-morbidity details dialogue box-web-Part 4

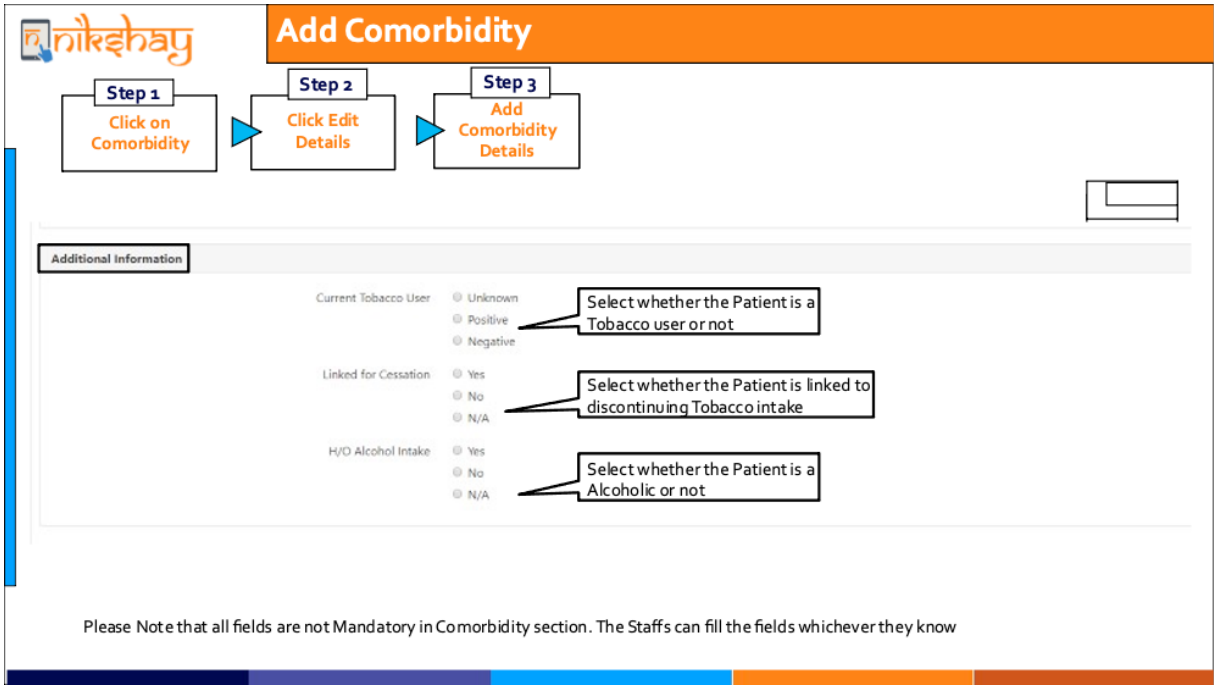


Figure 9.23 Co-morbidity details dialogue box-web-Part 5

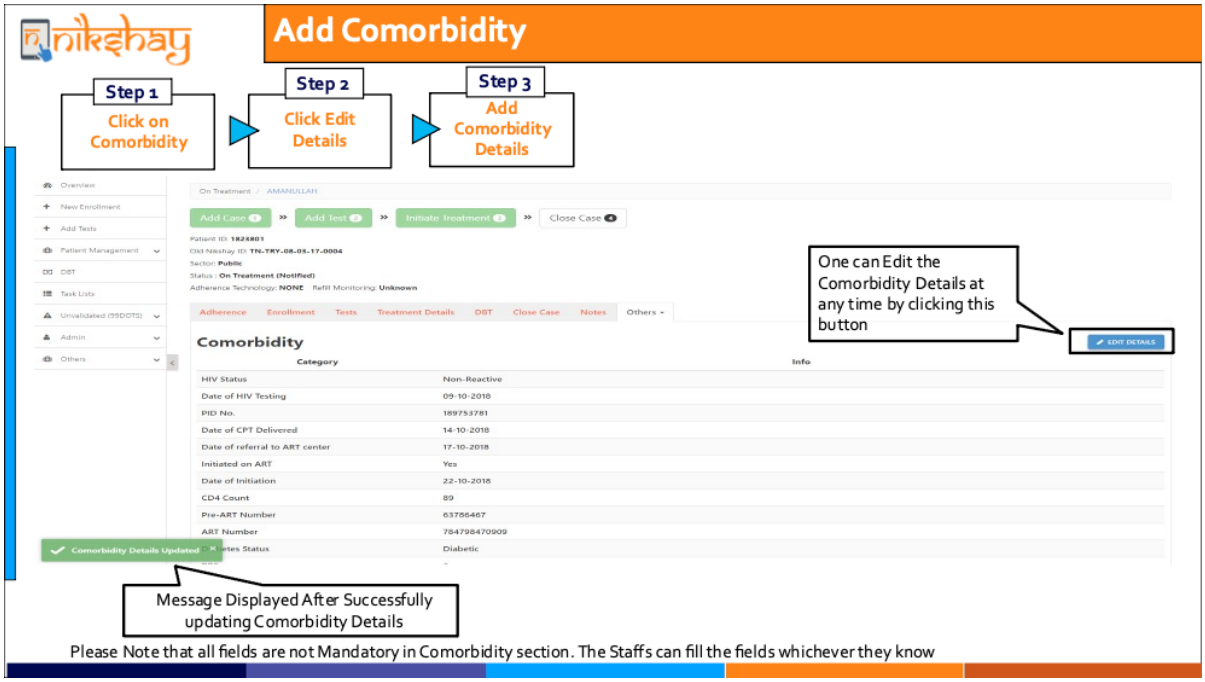


Figure 9.24 Co-morbidity details dialogue box-web-Part 6

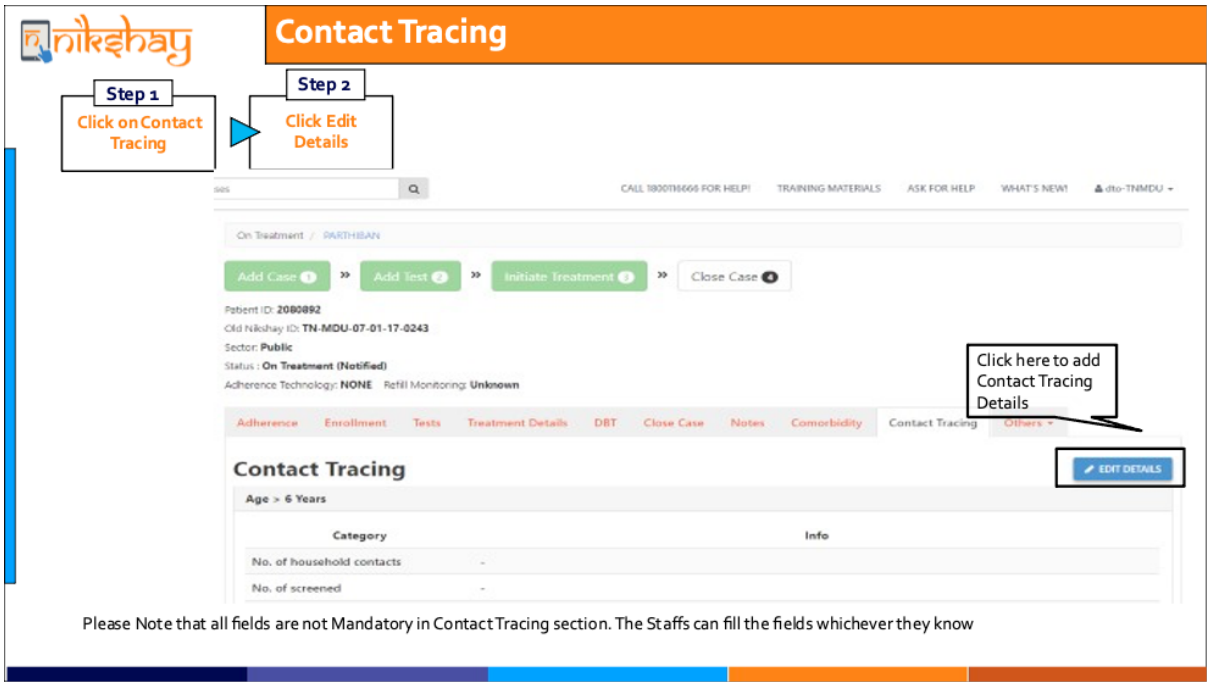


Figure 9.25 Contact tracing details dialogue box-web-Part 1

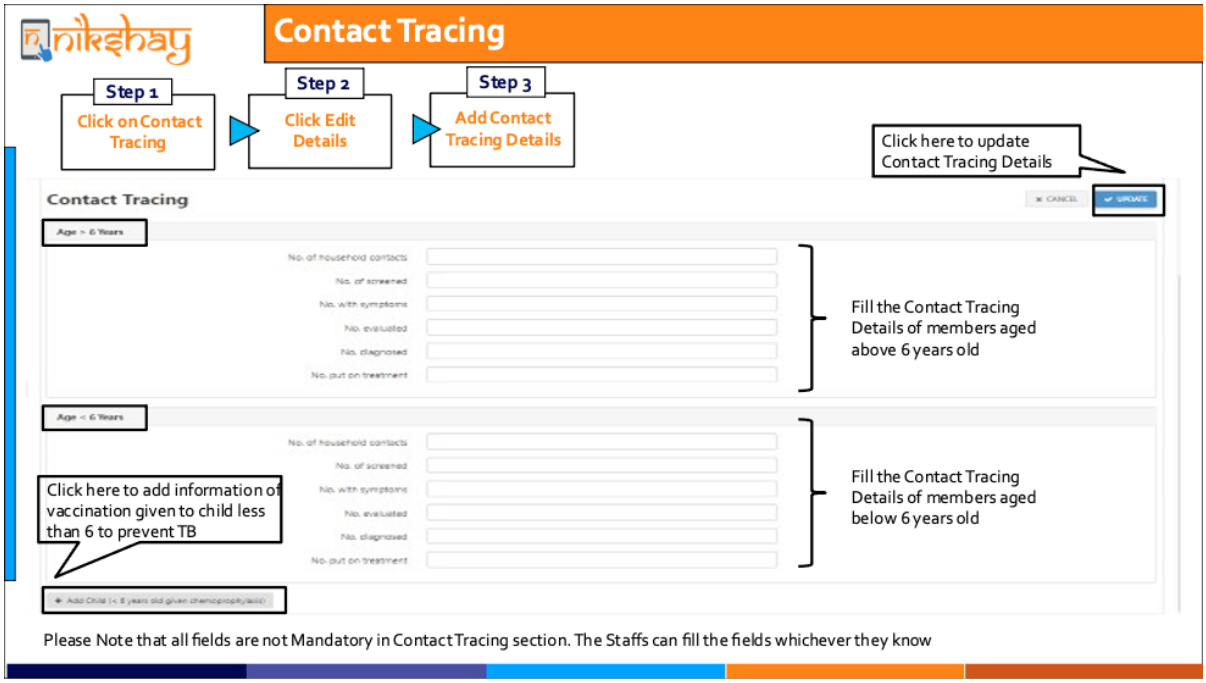


Figure 9.26 Contact tracing details dialogue box-web-Part 2

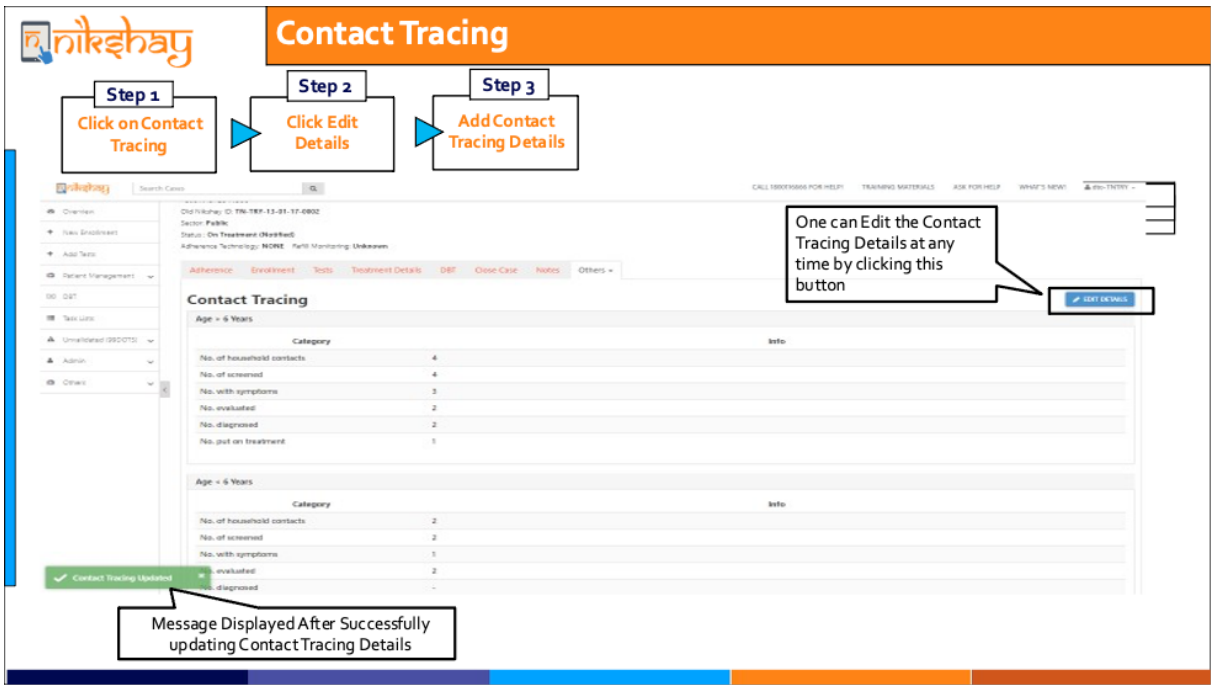


Figure 9.27 Contact tracing details dialogue box-web-Part 3

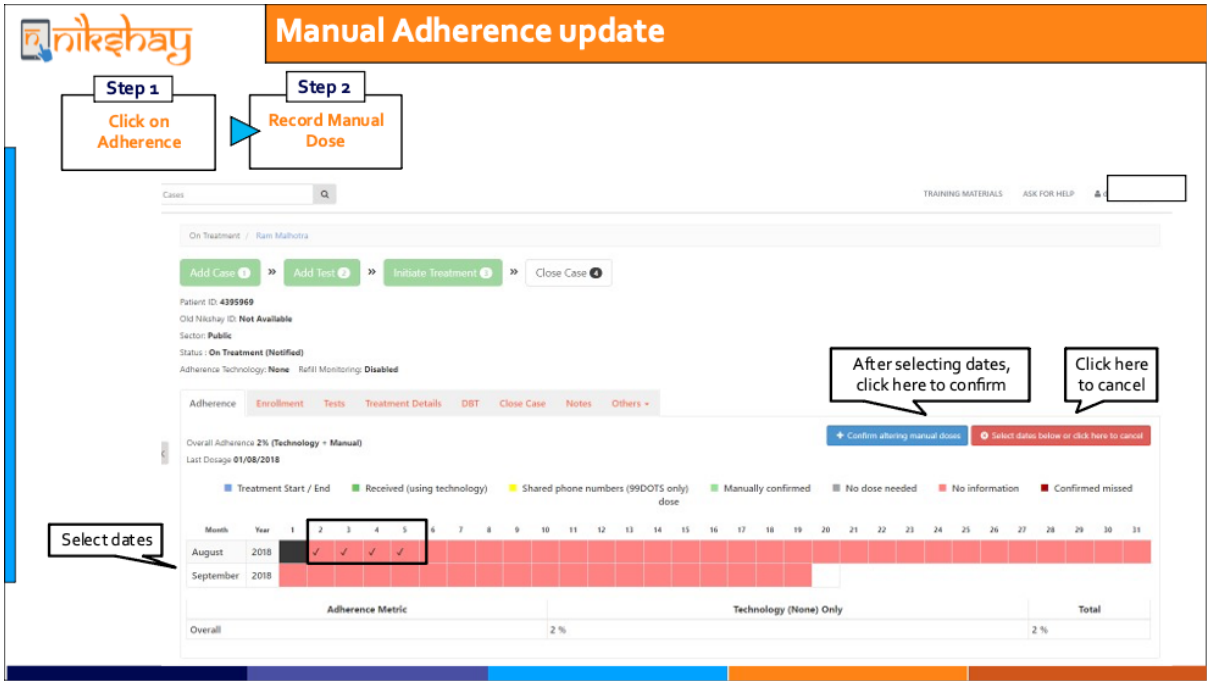


Figure 9.28 Adherence details dialogue box-web-Part 1

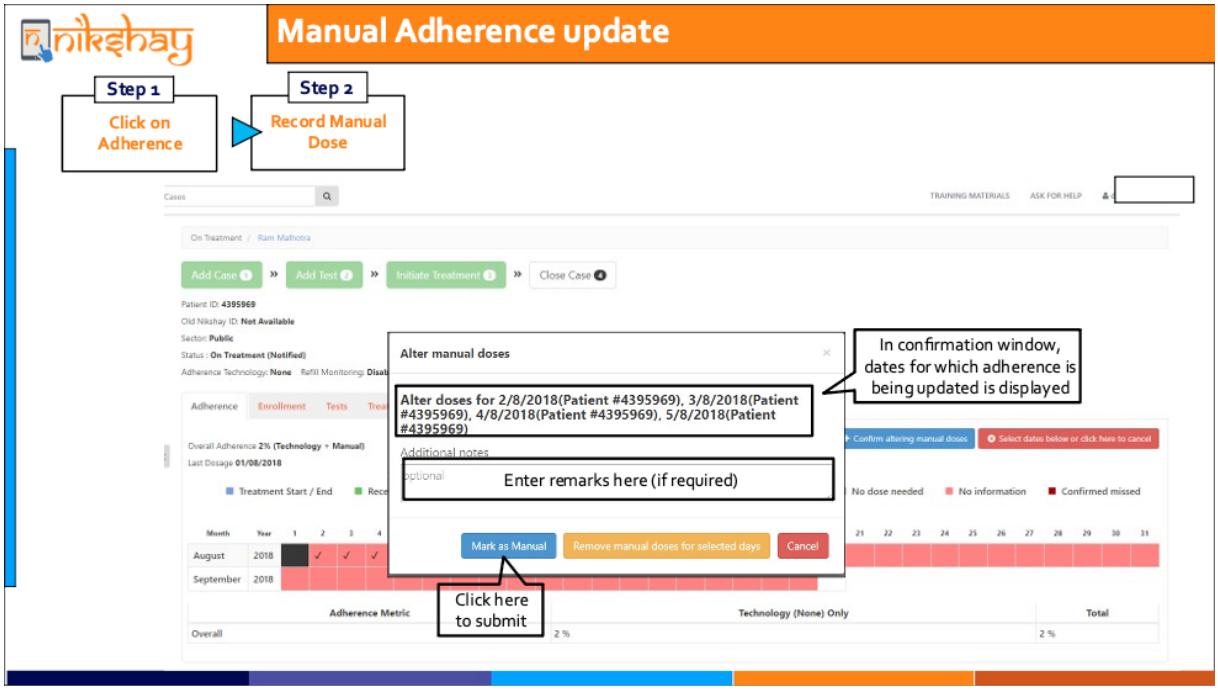


Figure 9.29 Adherence details dialogue box-web-Part 2

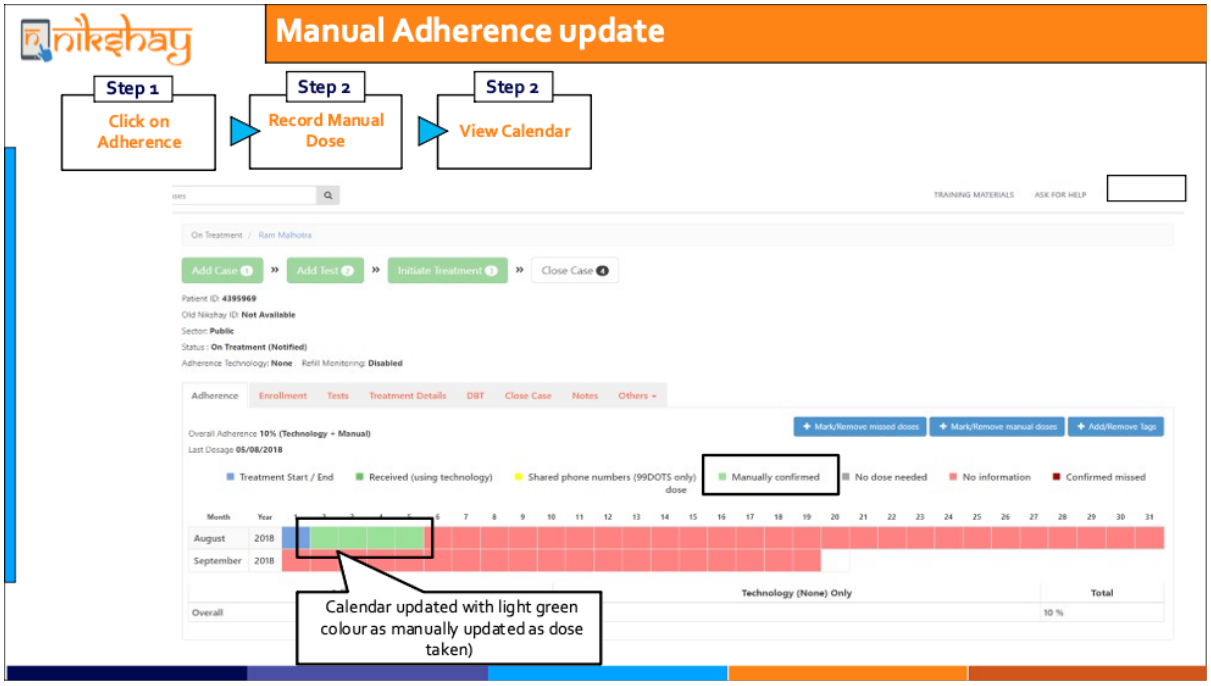


Figure 9.30 Adherence details dialogue box-web-Part 3

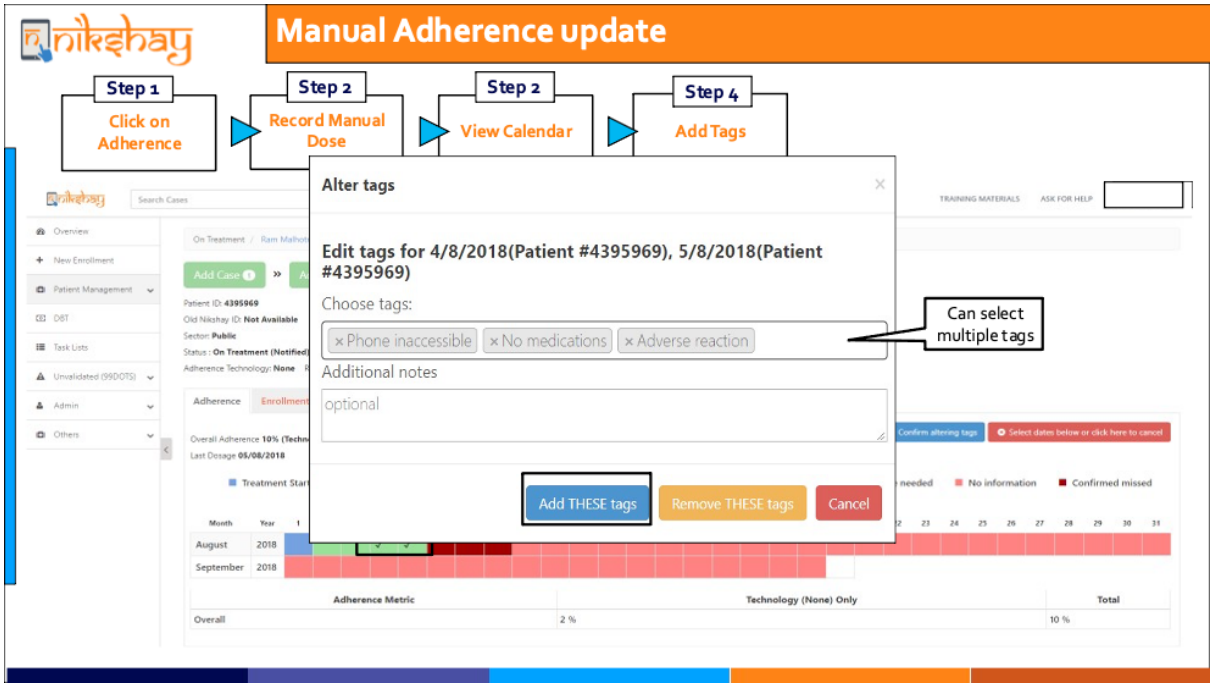


Figure 9.31 Adherence details dialogue box-web-Part 4

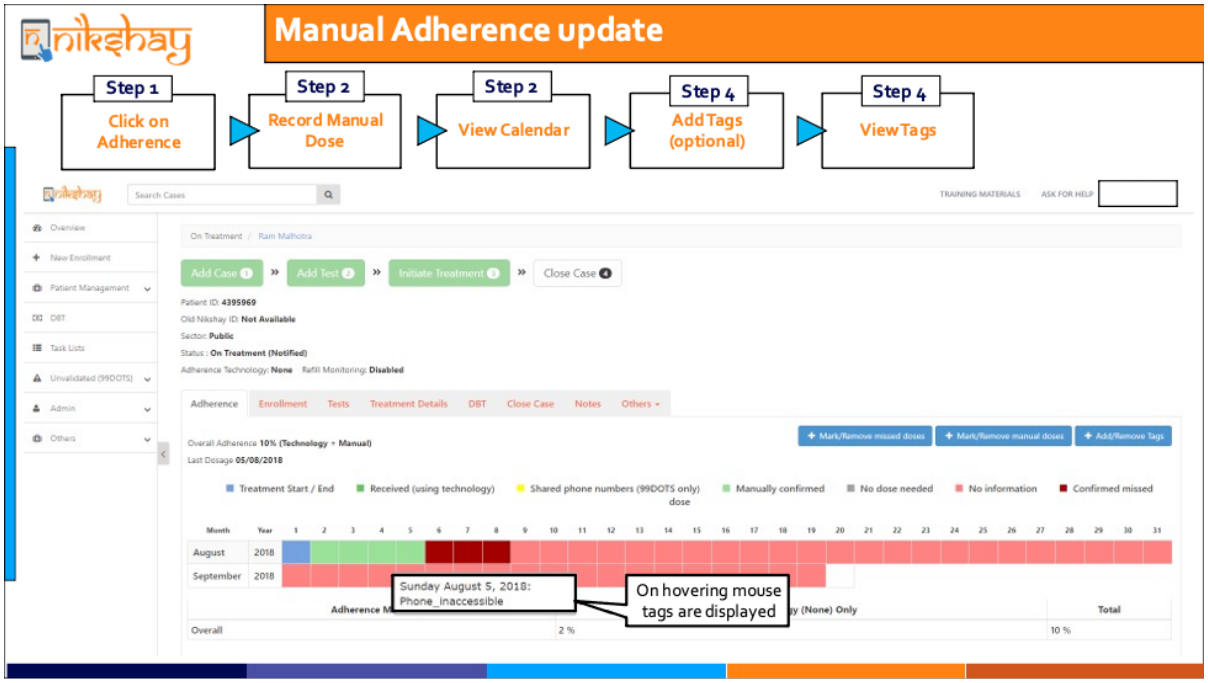


Figure 9.32 Adherence details dialogue box-web-Part 5

9.2.4. Transfer module in Nikshay

Transfer module in Nikshay facilitates access to patient information through episode ID. Provision of shifting of patient from one HF to another is possible if the patient has changed his/her residence for the purpose of treatment. However, it may not be required if patient is referred for consultation only and expected to return to his/her original HF. In Nikshay, the referring health facility must update details from the current HF of patient to the HF where patient is being transferred. The receiving health facility gets the intimation about the transfer even before the patient reaches.

In addition to this, patient transfer module also provides the provision to pull the patient belonging to another HF to the recipient HF. The accountability of transferred patient is now with the receiving health facility and the treatment initiating facility. A separate transfer register is also available to get details about various transfers from and to a given district, which can be downloaded from Nikshay reports as described in the section on Monitoring below. Should exceptionally be required, a feature to print transfer requests from Nikshay shall also be made available.

9.2.5. NTEP PMDT digital treatment card from Nikshay

Going forward with the emphasis on digital record management in PMDT, there may not be a need to maintain a physical copy of the treatment card usually. The same is available online via Nikshay with all the pertinent details about the patient. However, should such a copy be required in selected circumstances, Nikshay also has the feature to print these treatment cards for individual patients as the need may be. Should any record under exceptional circumstances be maintained tentatively on the physical treatment card then the concerned staff should take prompt action to digitise the same by updating it in Nikshay. The digital treatment card shall have all the pertinent details about the patient care cascade in real-time including contact tracing information, co-morbidity information, patient regimen details including drugs prescribed, doses prescribed, etc.

Episode ID (previously known as Nikshay ID for patient). The Episode ID refers to the unique identification number generated for each episode of TB for the person. Each episode is linked to the patient through the Patient ID and is able to track individual episodes from the presumptive stage to long term outcomes for that episode. The first episode ID is generated at the time of enrolling patient for the first time, which is also known as Patient ID. A different episode ID will be generated for each subsequent treatment episode linked to the same Patient ID. New episodes can only be created once the outcome for the current episode is entered. A patient may be searched in the system through either the episode or the patient ID and the latest episode can be traced for that patient.

As per the NTEP TOG, all TB patients are to be notified at the time of diagnosis. For documentation and monitoring purposes, each event of detection of additional resistant for which the patient is expected to be treated with different regimen is counted as a separate episode. For example, if the DS-TB patient is diagnosed with H mono/poly DR-TB, a new episode should be created in system. Similarly, if patient on shorter oral Bedaquiline-containing MDR/RR-TB regimen, need a regimen change to start the longer oral M/XDR-TB regimen, subsequent episode needs to be created.

The pool of all DR-TB patients (MDR/RR-TB, H mono/poly DR-TB or XDR-TB) diagnosed either at NAAT labs or C&DST labs in public/private labs will be updated digitally. The episode ID will capture all subsequent events that are taking place for that episode. For every change in diagnosis or regimen, a new episode ID will be created. This creates a lifecycle-based model where multiple events of single patient, pertaining to diagnosis and treatment, are linked together as shown in **Figure 9.1**. All relevant information of a particular patient would be available with the episode ID accessible to all user levels.

A new episode should be created when the patient is no longer eligible for current regimen and the current regimen needs to be stopped. There is no need to create a new episode in situations when the current episode is continued with just modification in the regimen composition. However, the change in composition of regimen should be documented in the dispensation module for that patient. This will help track the patient for its regimen within Nikshay.

9.2.6. NTEP PMDT treatment book

NTEP PMDT treatment book **(Annexure 31)** is the document that must always be available with the patient. When a patient is diagnosed as having DR-TB and is placed on a regimen for DR-TB, NTEP PMDT treatment book should be filled out by the health-care provider. This treatment book will be kept by the patient and should be brought whenever s/he comes to DR-TBC or DTC or HF for clinical follow-up or for ADR management. The treatment book contains the following sections:

- name, sex, age, complete address, marital status, contact number and Aadhaar no. of the patient;
- name & designation and contact number of treatment supporter;
- name of TB unit, HF, DR-TBC, district and state;
- information about initial home visit, by whom it has been done and on what date;
- information about Nikshay ID and PMDT TB numbers;
- essential information about reason for testing, which are as follows:
  - whether new or previously treated patient;

  - whether presumptive TB, private referral or presumptive NTM;
  - whether presumptive DR-TB at diagnosis or due to contact of DR-TB patients or follow-up smear positive at end of IP or it is a private referral;
  - whether presumptive H mono/poly DR-TB resistant; and
  - whether presumptive XDR-TB patient due to MDR/RR-TB at diagnosis or four months culture positive or culture reversion or failure of MDR/RR-TB regimen or recurrent patient of second-line treatment.
- information about DST results for different anti-TB drugs;
- information about contact investigation (number of members screened, out of it number of presumptive TB identified, out of which number of presumptive TB patients evaluated, and out of which number of TB patients & DR-TB patient diagnosed);
- information about DR-TB committee meetings with dates and decisions;
- information about TB site (whether pulmonary or extra-pulmonary) and the different types of treatment regimen under which patient has been provided the treatment, with date of initiation of treatment and date of registration;
- information about weight (in kg) and height (in cms) of the patient;
- information about different weight-bands for DR-TB regimen;
- information about different types of anti-TB drugs prescribed to patients and its dosages;
- information about eligibility and consent of patient if a new drug has been prescribed;
- information about culture results and other investigations (serum creatinine, liver function tests, ECG, complete blood count, serum electrolytes, urine test for pregnancy) done at different interval of continuation of treatment till the end of treatment;
- information about DST results for different first and second-line anti-TB drugs done in different months [with date of specimen collection & type of DST (L J/LC/LPA/NAAT);]
- information about blood sugar testing (random blood sugar and fasting blood sugar) with date and initiation of anti-diabetic treatment;
- information about thyroid function test done at initiation of treatment and at end of six months of treatment;
- information about X-ray test done at different interval;
- information about dates of starting intensive and continuation phase;
- information about change of regimen and reason for the same;
- information about monthly administration of drugs with weight of patient for full duration of treatment;
- information about retrieval action taken for a patient who has missed his doses;
- information in detail about any adverse drug reaction taken place and action taken for its remedy
- clinical notes made by physicians during visit by DR-TB patient for any complaint, which includes the following:
  - date of visit
  - chief complaints made by the patient
  - major findings of clinical examination
  - different types of investigations done
  - what treatment providedcounselling notes.
- information about the disease, its mode of transmission, treatment, drugs in the regimen,

side effects of drugs, and other information for the patient;

- information about treatment outcome of the patient with date;
- information about post-treatment follow-up clinical & sputum examination (result with date) done at interval of 6, 12, 18 and 24 months after end of treatment; and
- few important do's and don'ts for the patient.

9.2.7. Workflow related to follow-up and outcomes

In this activity (swim-lane) the person would be assessed for TB follow-up criteria and if feasible conduct follow-up for the person who would be re-entering the screening activity. On follow-up screening the person would be assessed for any relapse. If there is no relapse and the follow-up duration is over then an outcome would be assigned. If follow-up duration is not over then the person again enters the screening process. If a relapse is noted then follow-up may not be conducted and an outcome would be assigned. In all cases where a relapse is noted as per the workflow for an outcome, a new episode would be generated. If no relapse is noted then the person would be of no interest to the TB workflow.

Outcome for a person/patient can be captured in Nikshay at various levels as described in the swim-lane diagram above. The various outcomes captured are as under:

- Cured
- Treatment complete
- Treatment failure
- Died
- Lost-to-follow-up
- Mark as duplicate
- Treatment regimen changed

9.2.8. Patient counselling register

The DR-TB counsellor is supposed to update and maintain this register on a regular basis **(Annexure 11**). The counselling session carried out with the patient and family members from the time of pre-treatment evaluation to long-term follow-up are expected to be captured in this register. Priority should be given for counselling of the DR-TB patient, however, counselling services utilized for the DS-TB patient needs to be captured in the same register.

9.2.9. Active drug safety management and monitoring (aDSM) form

The standard formats for active drug safety management and monitoring (aDSM) forms **(Annexure 32, 33)** would be used at all the sites for aDSM. Patient initiated on any DR-TB regimen must be covered under aDSM mechanism from the time of initiation of treatment. Treatment review form should be filled for any SAE reported during the course of treatment. The review form of aDSM is filled by the health facility managing SAE. Going forward in Nikshay aDSM module is under development. The standard **Annexure 32 and 33** for recording aDSM would be available at the very minimum in Nikshay. It is also envisaged to have the various questionnaires pertaining to ADRs as well as aDSM be available at multi-levels of hierarchy including self-reporting for persons/patients which would enable better tracking of diversity and quantum of such events. Ability to add tests which might be indicated in the case of these ADRs/aDSM monitoring events would also be added in Nikshay and the system is envisaged to be intelligent enough to pose questions based on the plausibility of availability

of information from that staff/person/patient. Any of the following 6 SAEs needs to be promptly reported by the concerned health facility to NTEP using the aDSM review form on a real-time case-to-case basis in Nikshay once the SAE is clinically managed.

1. Death
2. Any hospitalization
3. Any permanent disability
4. Congenital anomaly
5. Any other life-threatening conditions
6. Any conditions where the intervention is required to prevent permanent impairment/ damage.

Hard copies of the aDSM forms need to be maintained at the respective health facility. If the patient's treatment regimen is changed due to any reason, irrespective of duration of treatment, a new aDSM - treatment initiation form is filled by the treatment initiating health facility for each new treatment episode the patient is initiated on.

9.2.10. Supply chain and logistics management: Drug dispensation module-Nikshay

The dispensation module within Nikshay has been revamped to capture details of drugs being dispensed to TB patients on a real-time basis. This includes 3 sections, namely:

1. Dispensation details that capture basic information related to dispensation like date of prescription, dispensation, weight band, current weight etc;
2. Product details that capture the source, product name and quantity issued; and
3. Refill details which capture the start date, number of days and refill due date for the dispensation.

In addition, ability for correlation of adherence and prescription functionality would be available to the user, through which they can record adherence only if there are corresponding dispensation details available. The outcome validations have been inbuilt according to which the required numbers of doses as per different regimen and the follow up test status would be considered prior to declaration of outcome. The flow of information in the Dispensation Module of Nikshay has been depicted in the figure 9.33 below:

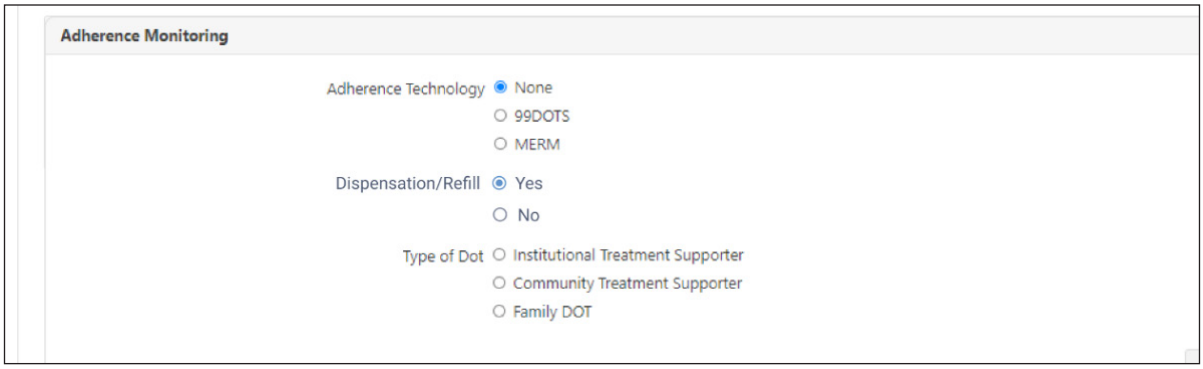


Figure 9.33 Adherence details dialogue box

Dispensation module in Nikshay is under development and would be made live soon. The mock-ups for the same are as under:

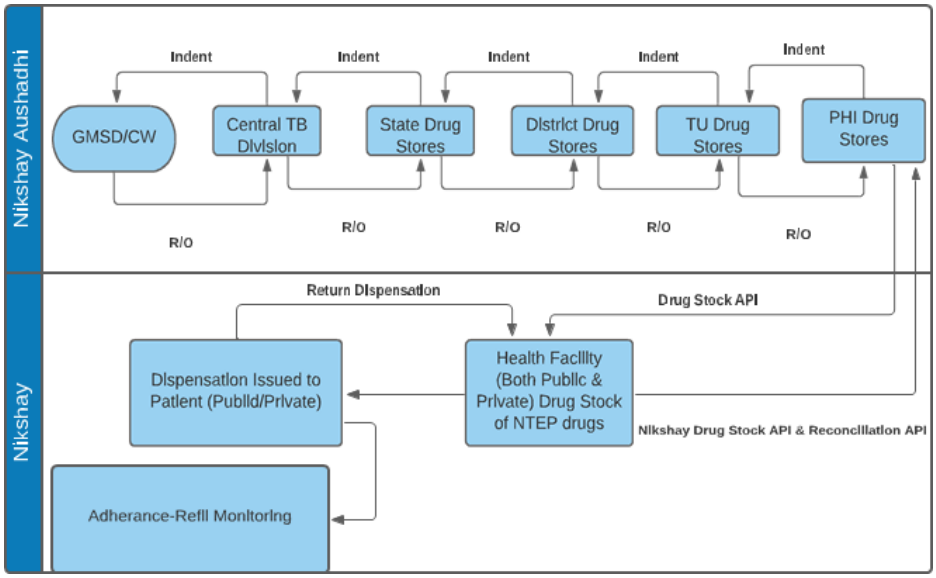


Figure 9.34 Swim-lane diagram for dispensation module

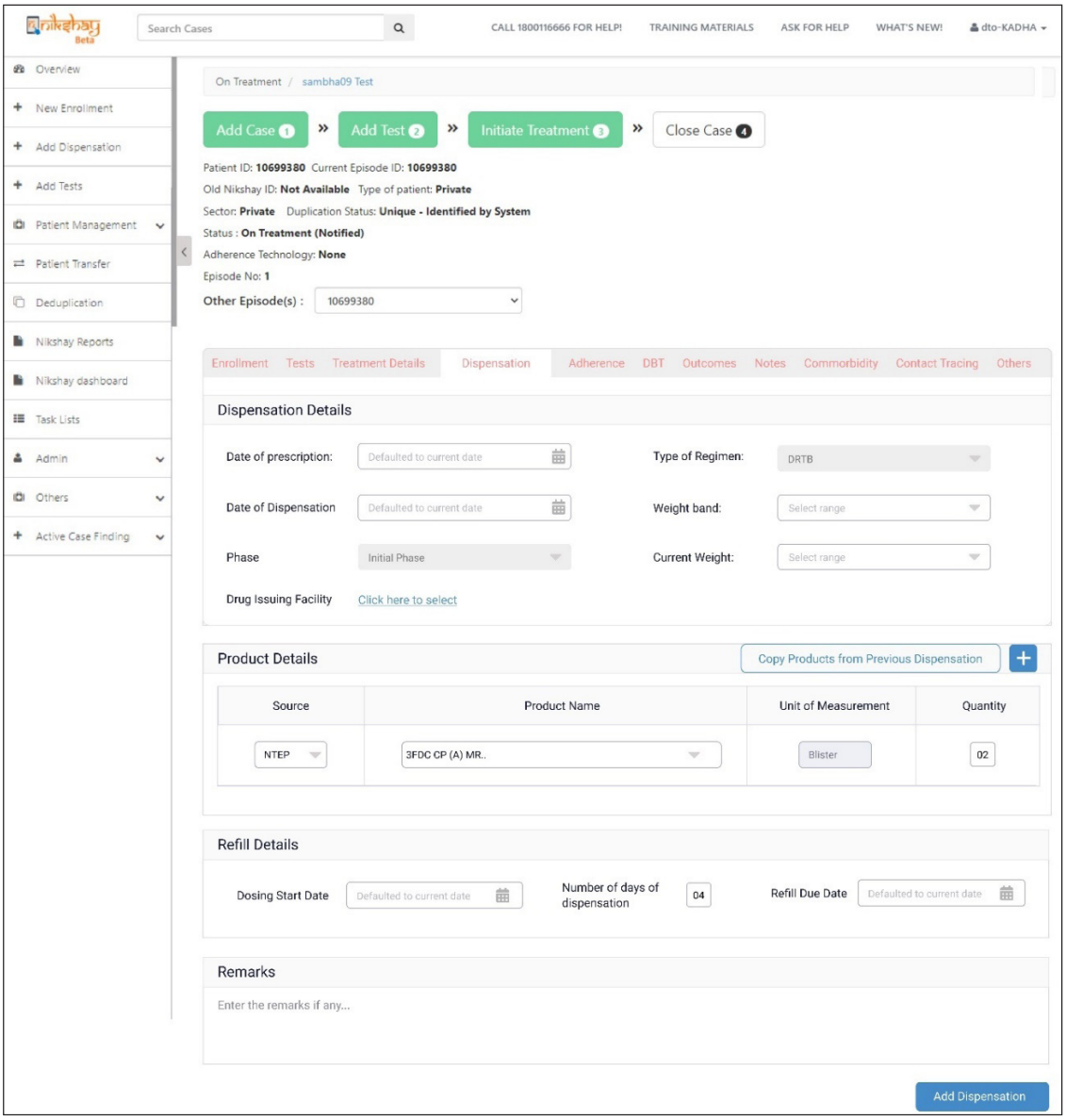


Figure 9.35 Mock-up for dispensation module-Part 2

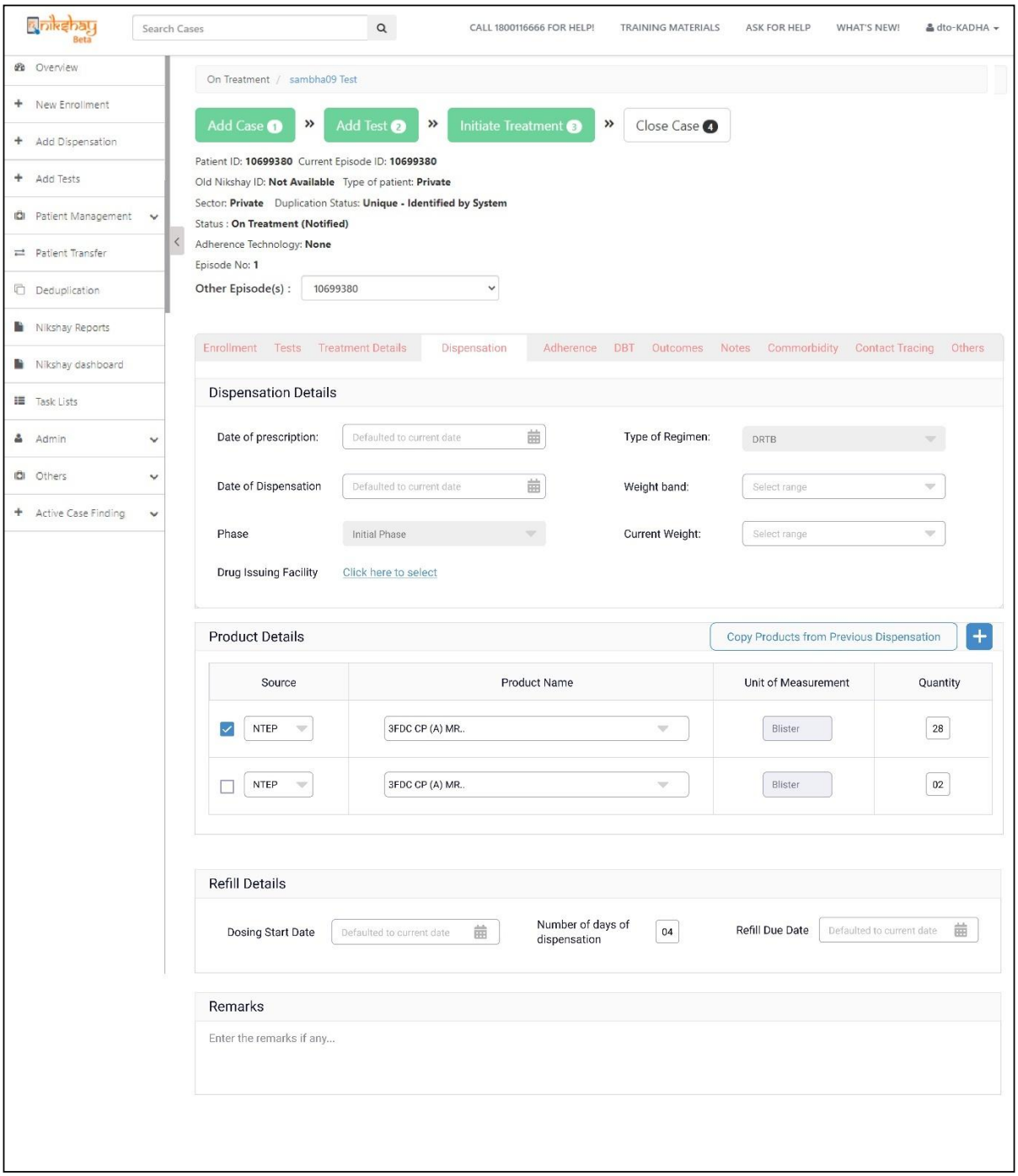


Figure 9.36 Mock-up for dispensation module-Part 3

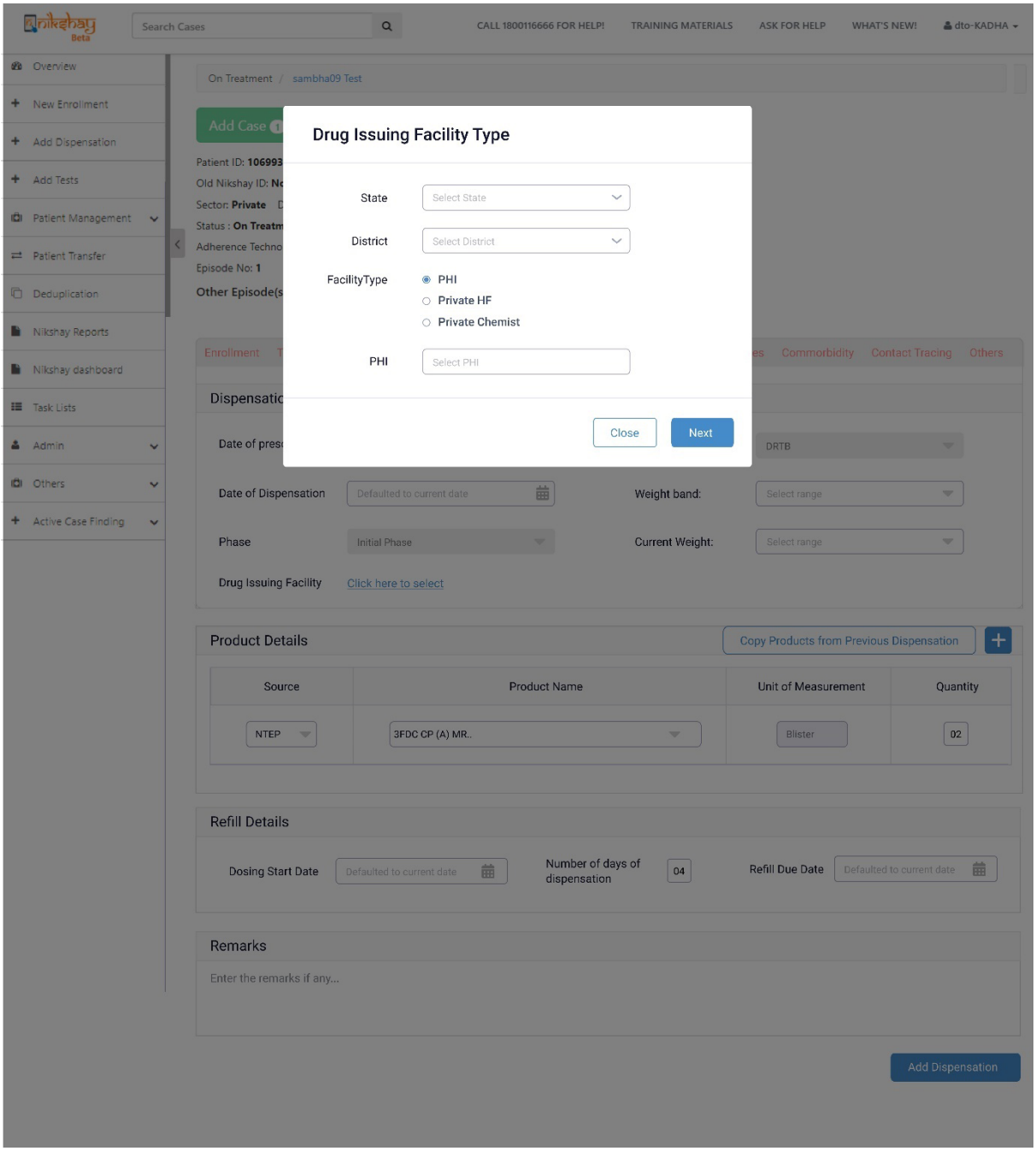


Figure 9.37 Mock-up for dispensation module-Part 4

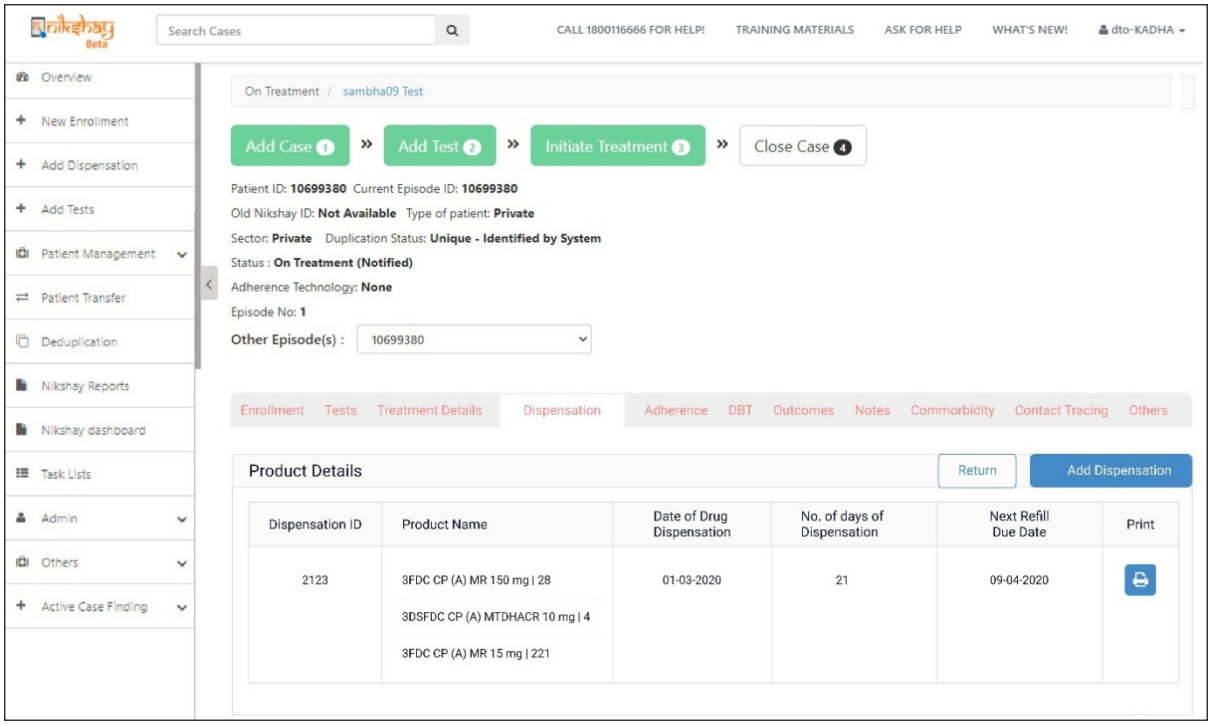


Figure 9.38 Mock-up for dispensation module-Part 5

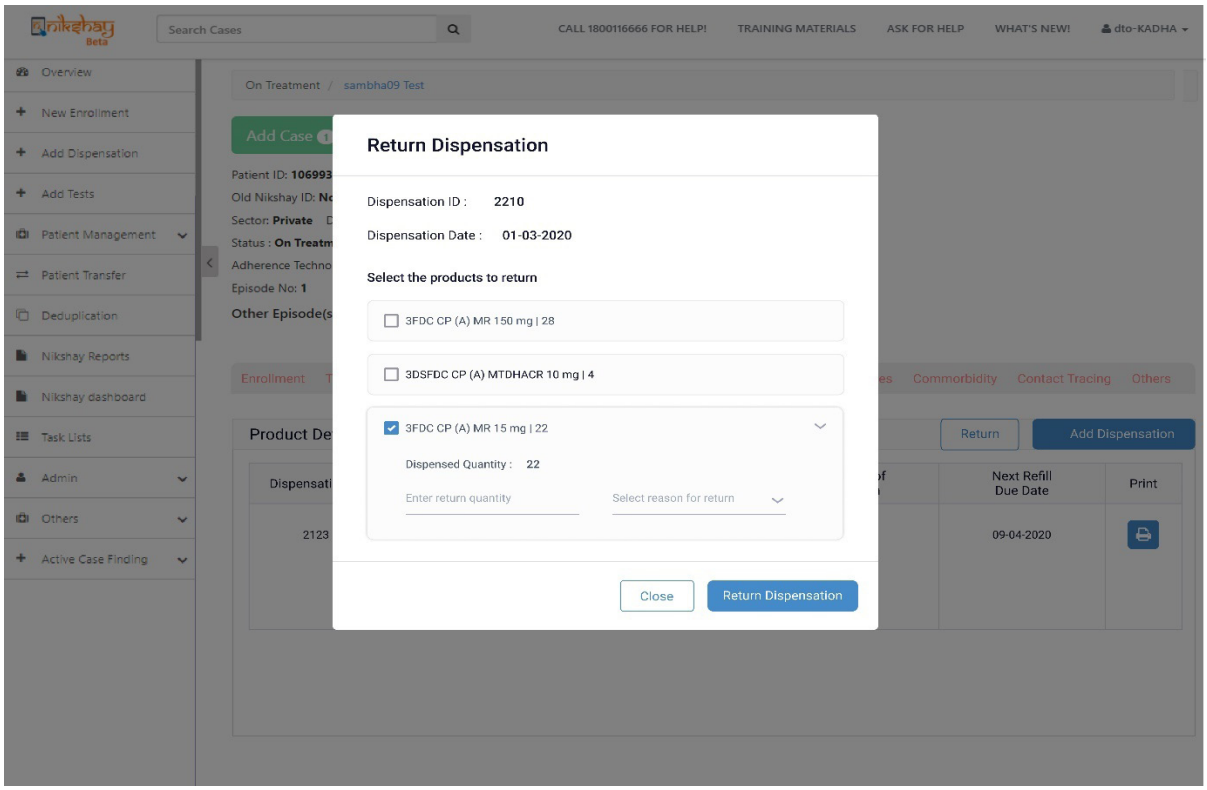


Figure 9.39 Mock-up for dispensation module-Part 6

9.2.11. Line-lists (online registers) available in Nikshay for monitoring:

Nikshay is a person-based reporting system. In the above sections the points of data entry have been elaborately described. Unlike the physical registers, digital information management system brings uniformity of data and mitigates redundancy of data entry. Also, for the sake of visualisation, Nikshay provides access to variety of downloadable line-lists akin to physical registers including but not limited to the digital copies of the physical forms and registers maintained erstwhile.

These line-lists can be downloaded through https://reports.nikshay.in/ as per the screenshot below. Should hard copies of any line-lists be required to comply with the regulatory requirements, these line-lists (registers) can be downloaded from Nikshay and be time stamped and maintained as per requirement. While downloading these line-lists(registers) one needs to be meticulous in selecting the appropriate period of report which usually refers to notification date as the type of date to be selected, though these can be modified as per need. Also, the cohort based on diagnosing facility or current facility should be diligently specified to get accurate data. Human error due to erroneous interpretation of data terminology is the most common reason worth avoiding in the interest of accuracy and precision.

The following registers are available on Nikshay for downloading:

1. Adherence register
2. C&DST test register
3. MERM patient register
4. Patients not-offered UDST list
5. Patients not offered F line LPA list
6. Patients not offered S LPA list
7. DR-TB notification register
8. DR-TB follow-up register
9. Co-morbidity register
10. Contact tracing register

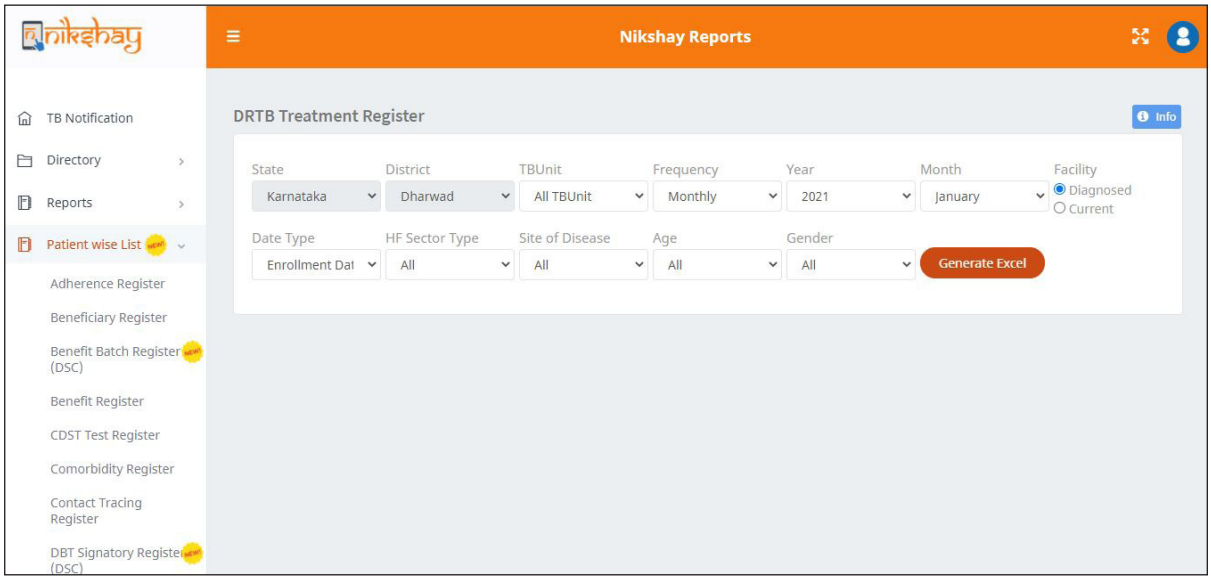


Figure 9.40 Registers as patient-wise list available for download from Nikshay

The section below summarises the various line-lists (registers) available in Nikshay pertinent to PMDT monitoring along with the list of variables available.

1. **Adherence register.** Adherence information of selected patient cohort initiated on treatment either technology-based or manually updated.

Table 9.4 Variables of adherence register

Variables of adherence register-Set 1	Variables of adherence register-Set 2	Variables of adherence register-Set 3	Variables of adherence register-Set 4
Patient ID	Current facility - TU	District (Residence)	MERM last seen
Episode ID	Current facility - HF	TU (Residence)	MERM last used
Patient's name	Health facility Sector Type	Total number of doses missed	MERM start date
Phone	Type of Case (New/ Re-Treatment/ PMDT)	Total number of doses taken	MERM end date
Age	Patient status (Treatment not started/On treatment)	Average adherence (Tech)	MERM last battery voltage (mV)
Gender	Treatment initiation date	Average adherence (Tech + Manual)	MERM refill date
Address	Adherence (Tech)	Doses taken last 3 days(Tech + Manual)	MERM refill date enabled
Current facility - State	Treatment outcome	Doses taken last 7 days(Tech + Manual)	MERM RT hours
Current facility - District	Treatment outcome date	Doses taken last 30 days (Tech + Manual)	Adherence string (day-wise data)
	State (Residence)	MERM IMEI	

2. **C&DST test register.** List of patients offered NAAT, culture, DST, FL LPA, SL LPA, Truenat MTB and Truenat MTB-RIF

Table 9.5 Variables of C&DST test register

Variables Set 1	Variables Set 2	Variables Set 3	Variables Set 4	Variables Set 5	Variables Set 6
Test Id	HF name lab	Residential district	Current facility HF Type	Z	Bdq
Date of test Updated in Nikshay	Lab type	Type of test	Predominant symptom	Km	Dlm
Date tested	Patient ID	Reason for testing	Predominant symptom duration	Cm	MFX1
Date reported	Episode ID	Treatment status	History ATT	MFX5	Final interpretation
Test status	Name	Diagnosis date	No of HCP visited before diagnosis of current episode	MFX2	

Variables Set 1	Variables Set 2	Variables Set 3	Variables Set 4	Variables Set 5	Variables Set 6
Type of specimen	Gender	TB treatment start date	Visual appearance of sputum	LFX	
Date of specimen collection	Age	Current facility state	Culture type	LZD	
State name	Primary phone	Current facility district	h	CFZ	
District name	Address	Current facility TU	r	ETO	
TB unit	Residential state	Current facility HF	e	PAS	

3. **MERM patient register.** Details of patient adherence and battery status, refill details, etc. MERM device related information available in this report.

Table 9.5 Variables of MERM patient register

PatientId	Patient_Status	Allocated_to_ Patient	Average_ Adherence_Total
Patient's name	Type of patient	Mermstartdate	Doses taken last 3 days
State current	Outcomeassigned date	Mermstopdate	Doses taken last 7 days
District current	Treatmentoutcome	RefillaAlarm En	Doses taken last 30 days
TBUccurrent	Typeofcase	RT hours	
HF current	Merm_ID	Alarm enabled	
HFtype	IMEI	Alarm_Time	
HFcode	Last seen	Total_Doses_Taken	
Diagnosis date	Last opened	Total_Doses_Missed	
Treatment initiation date	Last battery	Average_Adherence_ Tech	

4. **Patients not-offered UDST list, patients not offered FL LPA list and patients not offered SL LPA list**: List of patients not offered UDST, where UDST is defined as having offered a rapid molecular test knowing the resistance status for at least rifampicin and FQ (upcoming as per revised UDST definition), List of bacteriologically confirmed Patients not offered FL LPA and SL LPA is generated through Nikshay. Sample variables available for List of patients not offered FL LPA are as under. Similar set of variables are also populated for other two line-lists as well.

Table 9.6 Variables of UDST, FL LPA and SL LPA not offered

Variables-Set1	Variables-Set2	Variables-Set3
Patient Id	Diagnosing facility district	UDST test details
Episode Id	Diagnosing facility TBU	UDST test date
Patient's name	Diagnosing facility HF	FLPA test request generated
Age	Diagnosis Date	Date of TB treatment initiation
Gender	HIVstatus	Current facility state
P address	Type of patient	Current facility district
Pincode	Type of case	Current facility TBU
Primary phone	Site of disease	Current facility HF
Emergencycontact	Basis of diagnosis	
Diagnosing facility state	Bacteriologically confirmed	

5. **DR-TB notification register.** List of total notified DR-TB patients will be generated soon. Currently, patient initiated on DR-TB treatment is being populated in DR-TB treatment register along with their treatment outcome details. With digital data entry, this register can be simultaneously and in real-time viewed at all levels required. Nikshay now has the ability to link patients with respective NDR-TBC/DDR-TBC without changing the current health facility in Nikshay (i.e. without transferring the patient). This feature enables multi-centric patient management while also reducing redundancy of data entry and improving data accuracy and consistency.

Table 9.7 Variables of DR-TB notification register

Variables Set1	Variables Set2	Variables Set3	Variables Set4	Variables Set5	Variables Set6	Variables Set7
Diagnosing facility state	Patient ID	Landmark	Enrolment facility HF	Microbiologically confirmed	Site of disease	End of CP SM date of report
Diagnosing facility district	Patient status	Pincode	Enrolment facility HF type	Date of TB treatment initiation	EP site	End of CP lab ID
Diagnosing facility TBU	Patient name	Residential state	Enrolment facility HF type	Current facility state	Treatment outcome	End of CP final interpretation
Diagnosing facility HF	Age	Residential district	Enrolment facility HF ID	Current facility district	Treatment outcome date	
Diagnosing facility HF type	Gender	Residential TU	User ID enrolment	Current facility TBU	Bank details added	

Variables Set1	Variables Set2	Variables Set3	Variables Set4	Variables Set5	Variables Set6	Variables Set7
Diagnosing facility HF ID	Weight	Primary phone	HIV status	Current facility HF	Follow-up done count	
Diagnosis date	Patient Address	Key population	Diabetes status	Current facility HF type	UDST done	
Enrolment date	Taluka	Enrolment facility state	Basis of diagnosis test name	Current facility HF ID	End of IP SM Date of Report	
Episode ID	Town	Enrolment facility district	Basis of diagnosis lab serial no.	Type of case	End of IP lab ID	
Old Nikshay ID	Ward	Enrolment facility TBU	Basis of diagnosis final inter-pretation	PMDT regimen type	End of IP final inter-pretation	

6. **DR-TB follow-up register.** DR-TB patient-wise list contains specimen collection date; test report date and result of all follow-up culture & smear; date of entry in Nikshay for patients initiated on treatment during specified period. Timeliness of follow-up culture/smear and its entry can be monitored through this report

Table 9.8 Variables of DR-TB follow-up register

Variables-Set1	Variables-Set2	Variables-Set3	Variables-Set4	Variables-Set5	Variables-Set6
Patient ID	Current health facility TBU	Culture follow-up of DR-TB 4M final interpretation	Micro follow-up of DR-TB 6M final interpretation	Culture follow-up of DR-TB 12M final interpretation	Culture follow-up of DR-TB 27M final interpretation
Episode ID	Current health facility HF	Culture follow-up of DR-TB 4M date reported	Micro follow-up of DR-TB 6M date reported	Culture follow up of DR-TB 12M date reported	Culture follow-up of DR-TB 27M date reported
Patient's name	Current health facility HF type	Micro follow-up of DR-TB 4M final interpretation	Culture follow-up of DR-TB 7M final interpretation	Culture follow-up of DR-TB 15M final interpretation	Culture follow-up of DR-TB post6M final interpretation
Diagnosis date	Current health facility HF ID	Micro follow-up of DR-TB 4M date reported	Culture follow-up of DR-TB 7M date reported	Culture follow-up of DR-TB 15M date reported	Culture follow-up of DR-TB post6M date reported

Variables-Set1	Variables-Set2	Variables-Set3	Variables-Set4	Variables-Set5	Variables-Set6
Date of TB treatment initiation	Treatment outcome	Culture follow-up of DR-TB 5M final interpretation	Micro follow-up of DR-TB 7M final interpretation	Culture follow-up of DR-TB 18M final interpretation	Culture follow-up of DR-TB post12M final interpretation
Regimen type	Treatment outcome date	Culture follow-up of DR-TB 5M date reported	Micro follow-up of DR-TB 7M date reported	Culture follow-up of DR-TB 18M date reported	Culture follow-up of DR-TB post12M date reported
Current health facility sector	Culture follow-up of DR-TB 3M final interpretation	Micro follow-up of DR-TB 5M final interpretation	Culture follow-up of DR-TB 9M final interpretation	Culture follow-up of DR-TB 21M final interpretation	Culture follow-up of DR-TB post18M final interpretation
Site of disease	Culture follow-up of DR-TB 3M date reported	Micro follow-up of DR-TB 5M date reported	Culture follow-up of DR-TB 9M date reported	Culture follow-up of DR-TB 21M date reported	Culture follow-up of DR-TB post18M date reported
Current health facility state	Micro follow-up of DR-TB 3M final interpretation	Culture follow-up of DR-TB 6M final Interpretation	Micro follow-up of DR-TB 9M final interpretation	Culture follow-up of DR-TB 24M final interpretation	Culture follow-up of DR-TB Post24M final interpretation
Current health facility district	Micro follow-up of DR-TB 3M date reported	Culture follow-up of DR-TB 6M date reported	Micro follow-up of DR-TB 9M date reported	Culture follow-up of DR-TB 24M date reported	Culture follow-up of DR-TB post24M date reported

At each user level, task lists would be generated in Nikshay providing the line-list of patients for the pending actions to ensure timely intervention by field-level health workers. Event based SMS as information to the concerned field staff as well as Programme Managers would also be enabled in Nikshay in the near future.

9.2.12. Nikshay PMDT dashboards for monitoring

Nikshay dashboards for PMDT (upcoming) will provide a visual representation of various PMDT indicators in aggregate format to users across all levels of hierarchy i.e. National → State → District→ TU → Health facility (HF or private sector HF). This includes various types of graphs, tables and geographic views. The ability for users to monitor the indicators across the entire care cascade, over time, across sectors and drill down up to the HF level is available. The dashboards are accessible via a web browser, and can be viewed using both, desktop, and mobile devices. It is aimed to enable programme managers and staff across all levels to monitor and review performance against the selected indicators. The tentative list of indicators which would be available in the PMDT dashboard is listed below:

1. Coverage of Universal Drug Susceptibility Testing (UDST) along with turnaround time
2. Profile of resistance pattern for patients
3. Case finding, case holding including adherence, treatment outcomes etc.
4. Disaggregation of data by age and gender across all indicators

9.3. Implementation of Nikshay PMDT module

9.3.1. Responsibilities of digital recording and monitoring in Nikshay

The processes and decision points as described in the swim-lane diagram have potential data entry points. These along with potentially responsible persons including supervisory staff are as listed in **Table 9.9** below:

Table 9.9 Responsibilities of data entry and monitoring data entry based on activities, workflow, process, decision and level of health system

Activity/ Workflow Swim-lane	Process/ Decision	Point of Contact of the person with the health system	Person Responsible for Data Entry	Person Responsible for ensuring Data Entry
Enrolment/ Screening	• Entering patient demographic details and screening details in Nikshay • Authentication of the person as unique in the system and making a decision if the person enters TPT workflow or TB workflow • The decision regarding the type of test to be conducted which is part of diagnosis workflow swim-lane is practically done simultaneously • Accordingly test request should also be generated in Nikshay	Field	ASHA/ANM/ MPWs	STS/CHO of HWC/MO of PHC/CHC/DTO
		HWC/PHC/CHC	MPWs/General health staff/ TBHV	STS/CHO of HWC/MO of PHC/CHC
		District hospital/ Taluk hospital	General health staff/TBHV	STS/MO/DTO
		Medical college/ DR-TBC/NDR-TBC	General health staff/TBHV/ SA/ senior DR-TB TB-HIV supervisor	STS/MO/DTO
		ART centre	General health staff/ART DEO	STS/MO/DTO
		Private health facility	Private practitioner/ PPSA field coordinator/ DEO	STS/PPSA partner/MO-DTC/DTO

Activity/ Workflow Swim-lane	Process/ Decision	Point of Contact of the person with the health system	Person Responsible for Data Entry	Person Responsible for ensuring Data Entry
Diagnosis/ Tests workflow swim-lane	Decision regarding type of test to be conducted is taken in the first step along with enrolment/ screening. Accordingly, once the person reaches a diagnostic facility the test request should ideally be already generated. Entering test details and updating test results is what is contemplated as data entry points at this stage	TDC/NAAT/ C&DST lab	LT/DEO	STLS/MO-DTC/DTO
Treatment-workflow swim-lane	Taking a decision regarding treatment-start of treatment, type of treatment, etc… and updating the details of treatment	PHC/CHC/ District hospital/ Taluk hospital/ Medical college	TBHV/General health staff/ SA/Senior DR-TB TB-HIV supervisor	STS/MO-DTC/ MO-ART-centre/DTO
Follow-Up & Outcome Workflow Swim-lane	Taking a decision regarding follow-up, updating follow-up details	PHC/CHC/ District Hospital/ Taluk Hospital/ Medical College/N/DDR-TBC	TBHV/General Health Staff/ SA/ Senior DR-TB TB-HIV supervisor	STS/MO-DTC/ MO-ART-centre/DTO

9.3.2. Real-time reporting via Nikshay

There would be real-time reporting of all DR-TB activities in Nikshay as explained above. This can be prepared as an output of the Nikshay, *i.e.* PMDT notification register including follow up, NAAT & C&DST lab register, ADR report (Upcoming in Nikshay), etc. Individual patient wise details like laboratory test report, treatment card, drug dispensation summary and ADR summary (upcoming in Nikshay) for the patient and PMDT treatment card can also be downloaded from Nikshay. This can only be possible, if real-time entries are made by all labs, N/DDR-TBC as well as field staff.

The dashboard in Nikshay will give quick access to the process and output indicators as required. However, if states do not ensure real time data entry on Nikshay for DR-TB patients, there remains a threat that incomplete, incorrect or delayed data entry may not reflect the real performance of the districts and states in PMDT. Hence, the programme will follow a data freezing policy for all DR-TB reporting timelines for consideration of use of data for monitoring and performance review purposes. The data freezing time frame for DR-TB case finding, case holding, interim outcome and treatment outcome report from Nikshay is given in **Table 9.10** below.

Table 9.10 Data freezing time frame for PMDT reporting from NIKSHAY

Sr. No.	Indicator	Time point for CF, CH, Interim and TO reports	Cohort evaluation for reporting and monitoring	For example if reporting is in x= April 2021, following are the corresponding cohort for report evaluation
DR-TB notification and put on treatment				
1	DR-TB notification	Real-time	x-2 month	Cohort ending Feb 2021 and previous
2	Put on treatment	Real-time	x-2 month	Cohort of Feb 2021 and previous
DR-TB Interim report				
3	H mono/poly DR-TB regimen	4th month	x-6 month	Cohort of October 2020 and previous
4	Shorter oral Bedaquiline-containing MDR/RR-TB regimen	4th month	x-6 month	Cohort of October 2020 and previous
5	Longer oral M/XDR-TB regimen	6th month	x-10 month	Cohort of June 2020 and previous
6	BPaL regimen	4th month	x-6 month	Cohort of October 2020 and previous
7	Prior longer M/XDR-TB regimen (DST guided regimen)	6th month	x-10 month	Cohort of June 2020 and previous
DR-TB treatment outcome				
8	H mono/poly DR-TB regimen	9th month	x-12 month	Cohort of April 2020 and previous
9	Shorter oral Bedaquiline-containing MDR/RR-TB regimen	11th month	x-15 month	Cohort of January 2020 and previous
10	Longer oral M/XDR-TB regimen	20th month	x-24 month	Cohort of April 2019 and previous
11	BPaL regimen	9th month	x-12 month	Cohort of April 2020 and previous
12	Prior longer M/XDR-TB regimen (DST guided regimen)	24th month	x-30 month	Cohort of October 2018 and previous
Note: All the data of diagnosis and follow-up test details and treatment outcomes should be expected to be updated real-time in Nikshay				

Erstwhile used quarterly reports in hard copies would become history going forward. Nikshay-based recording and reporting has been underlined as the crux of information flow and management for PMDT. Reports can now be generated via Nikshay either on monthly and/or quarterly basis while adhering to the data freezing policy to provide consistency and accuracy for meaningful and actionable programme management. The figure above refers to

the data filters currently available in Nikshay to produce custom reports as per the needs of the States/Districts. Most of them are self-explanatory, however caution must be exercised in selecting Date Type which could be:

1. Notification date
2. Treatment start date

The usual practice is to select notification date as the date type which may be tweaked to suit preferences.

PMDT reports which are available via Nikshay reports include:

1. Case finding report (upcoming)
2. Case holding report
3. Interim smear/culture conversion report
4. Treatment outcome report

The reports would provide aggregate information on the following:

1. Total treatment episodes diagnosed in a given jurisdiction in a given period (Case finding)
2. Total treatment episodes initiated on different available regimen (Case holding). The report also provides following details
   - No of extra-pulmonary DR-TB episodes
   - No of DR-TB episodes in females
   - No of DR-TB episodes in children less than 15 years
   - No of DR-TB episodes in HIV-+-ve patients.
3. Interim smear/culture conversion as per different available regimen (Interim smear/culture conversion report)
4. Treatment outcome report for different available regimen. (Treatment Outcome Report)

With the dispensation module up and about sooner than later, details on regimen, including any modifications due in part to ADRs would be made available through data populated from each individual dispensation issued to the person/patient.

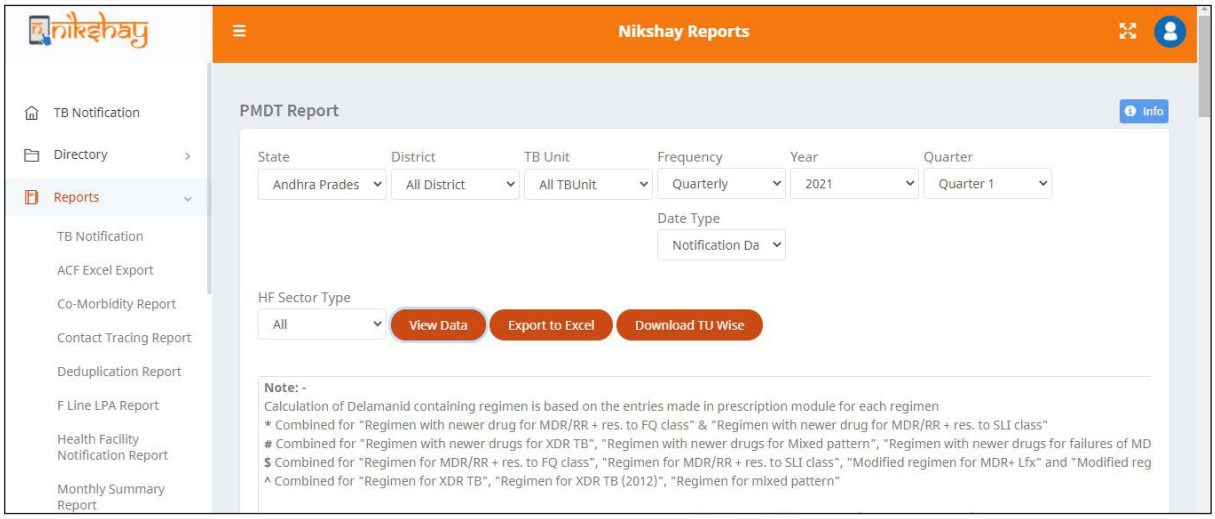


Figure 9.41 Downloading PMDT reports in Nikshay

9.3.3. Principles of data management in Nikshay

Nikshay will meticulously adhere to certain prime principles of data management. Comprehending these would enable users to efficiently and effectively utilize available information. The three cardinal principles in data management through Nikshay are as under:

i. Date of diagnosis as the basis of monitoring patients
ii. Monitoring based on 'Current Health Facility' i.e. after accounting for transfers for all indicators other than 'Notification'
iii. Reports based on count of 'Current Treatment Episodes' rather than 'Diagnostic Episodes'

9.3.4. Training in data management

All information will be available in digital form via Nikshay. To facilitate better quality of information as well as data analysis, Nikshay for real time monitoring of DR-TB patients through dashboards and monitoring indicators will be used. States are expected to monitor all relevant indicators of diagnosis and treatment initiation cohort. All relevant users will be able to monitor auto calculated monitoring indicator from Nikshay.

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

9.3.5. Cohort analysis

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

While referring the patient to N/DDR-TBC, the CHO/HF staff must update the DR-TB facility in Nikshay in Health Facility tab to make the patient details accessible and editable to the N/DDR-TBC. All patients initiated on DR-TB treatment at N/DDR-TBC, should be updated on Nikshay.

A DR-TB treatment cohort is defined as a group of patients diagnosed during a specified time period (e.g., one quarter of the year). The date of DR-TB diagnosis determines what case finding cohort the patient belongs to. However, since it would take around 2-3 months for most DR-TB patients to detect the presence of resistance to other second-line drugs on phenotypic DST, additional detection of resistance wherein the change in treatment

regimen is warranted should be considered as a new treatment episode. The treatment initiation status should be updated against each such treatment episodes. In Nikshay, treatment outcome should be updated for the existing episode of DR-TB patient when the current regimen needs to be permanently changed due to detection of resistant to additional second-line drugs or intolerance or ADR. New episode needs to be created. The relevant test for the episode and treatment initiation details should be updated in Nikshay for the subsequent episode.

For analytical purposes, the cohort definition would be based on the date of diagnosis entered in subsequent episode. For example, RR-TB patient notified during January month would be accounted for the same month irrespective to the date of treatment initiation. If same patient is found to be resistant to FQ on SL LPA during March month later to initiation on shorter oral Bedaquiline-containing MDR/RR-TB regimen, the regimen needs to be changed due to detection of additional resistance. Outcome needs to be updated for the treatment episode where the patient was diagnosed as RR-TB and initiated on shorter oral Bedaquiline-containing MDR/RR-TB regimen. Subsequent episode needs to be created and result of SL LPA should be entered in test module along with treatment initiation details of longer oral M/XDR-TB regimen. In this situation, the patient would not be accounted as RR-TB patient for January cohort but same patient would be accounted in March month for RR + FQ resistant (current) episode. This will enable monitoring of interim and final outcomes of patients stratified by the specific regimen that the patient was eventually put on.

Further, auto-generated indicators and interactive maps would be made available to facilitate supervision, monitoring and evaluation at all levels through Nikshay.

Cohort analysis should be performed on all diagnosed DR-TB patients, using the date of DR-TB diagnosis to define the cohort. Cohort analysis of treatment outcomes should also be performed on all patients who receive DR-TB treatment, regardless of treatment duration.

Patients still on treatment at the end of a designated cohort treatment period must be explicitly identified as such irrespective of whether they were culture-positive or negative at the time of cohort analysis. This is an interim status until a final outcome is available.

POINTS TO REMEMBER

- ✓ The key objectives of the recording and reporting system are to enable real-time access of the patient's details for management of individual patient at all levels and real-time generation of reports to track the progress for the purpose of monitoring. Nikshay is a web-based case-based recording and reporting system under NTEP;
- ✓ The programme is cognizant of the possibility of operational challenges towards real time Nikshay based recording and reporting, which may be variable for different States, Districts and TUs. Accordingly, it is recommended that states, districts and TUs may strategically prioritize complete transition to Nikshay to achieve the goal of Nikshay-based recording and reporting no later than October 2021;
- ✓ aDSM form, PMDT treatment book, counselling register and request form for examination of biological specimen would be considered as exceptions and to be maintained in hardcopies for the time being. However, aDSM forms are also an interim measure awaiting the aDSM module in Nikshay;

- ✓ Print option would be available for test request, treatment card and selected reports particularly to meet the operational requirements;
- ✓ Information flow would be as per the swim-lane diagram consisting of processes across enrolment, diagnosis, treatment, outcome and follow-up; and
- ✓ The suggestive list of potential staff responsible for data entry, data analysis and ensuing action is as per the guidance table on recording and reporting responsibilities.

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Annexures

Annexure 1: Checklist for upgradation of district DR-TB Centre (DDR-TBC) to initiate newer drug containing oral regimens

1	Name of the DDR-TB centre under appraisal	
2	Does the DDR-TB centre have a DDR-TB centre committee constituted as per the requirement?	☐Yes ☐ No
3	If 'No' expected date of constitution of the committee	
4	Specialist from pulmonologist, microbiologist, psychiatrist, cardiologist, ENT and Ob & Gy, surgeon included in the DDR-TBC committee	☐ Available in-house ☐ Outsourced from private provider ☐ Linked with NDR-TBC
5	No. of doctors trained for DR-TB from the district?	
6	What is the number of DR-TB cases anticipated to be eligible Longer oral regimen annually?	
7	What is the number of DR-TB cases anticipated to be eligible for shorter oral Bedaquiline containing regimen annually?	
7	Have 2 separate beds been identified for male and female DR-TB patients and/or out-patient facility with well-ventilated waiting developed?	☐ Yes ☐ No
8	Infection control measures at the DDR-TB centre (Refer to Infection Control Guidelines)	☐ Adequate ☐ Inadequate
9	Does the DDR-TB centre have all the facilities for undertaking pre-treatment evaluation for initiation of all the type of DR-TB regimens?	☐ Yes ☐ No
10	If 'No" have alternative arrangements been made?	☐ Yes ☐ No
11	Are emergency drugs available at the DDR-TBC? Or access to emergency services nearby?	☐ Yes ☐ No
12	Is ECG machine (12 leads with automatic QTc reader available?)	☐ Yes ☐ No
13	Access to latest PMDT guideline is available at site	☐ Yes ☐ No
14	Does the DDR-TBC have a computer with an internet connection	☐ Yes ☐ No
15	Are printed and electronic copies of the following recording and reporting formats available	Printed Nikshay ID & Password
	NTEP PMDT Treatment Book	☐ Yes ☐ No
	aDSM treatment initiation form	☐ Yes ☐ No

	aDSM treatment review form	☐ Yes ☐ No
16	Who is assigned responsibility to maintain data at DDR-TBC and update/monitor in Nikshay?	☐ HF DEO ☐ Senior DR-TB TB-HIV supervisor ☐ Other _____
17	Adequate quantity of SLD stock available as per the anticipated monthly patients enrolled on treatment by regimen	☐ Yes ☐No

Note: This check list should be filled by the evaluator and submitted to the state for further approval at the time of site evaluation for initiating District DR-TB Centre

Additional Remark:

Annexure 2: Composition and ToR of State PMDT Committee, NDR-TBC and DDR-TBC

State PMDT Committee

Composition of State PMDT Committee

Title	Designated officials
Chairperson	Principal Secretary/ Secretary (Health)
Vice chairperson	Director of Health Services
Member	Mission Director (NHM)
Member	Director of Medical Education and Research
Member secretary	State TB Officer
Member	Director STDC
Member	Chairperson State Task Force
Member	Microbiologist-IRL
Members	2 eminent chest physicians (medical colleges/private sector)
Members	Representative of PvPI
Members	Regional Team lead, WHO NTEP TSN
Member	State headquarter medical consultant, WHO NTEP TSN
Member	1 representative each from any 2 NGOs/CBOs working in the TB programme
Member	1 representative from professional bodies like IMA

Terms of reference of State PMDT Committee

1. Develop plan of action for implementation, expansion, and maintenance of PMDT in the respective state.
2. Select, facilitate upgrade and designate institutes to serve as DR-TBC within each state.
3. Periodically review the implementation status of PMDT in the respective state to ensure that NTEP PMDT policies and guidelines are being followed.
4. In coordination with the respective STO, ensure that drug ordering and distribution is managed in a timely and appropriate manner.

Nodal DR-TB Centre Committee

Composition of Nodal DR-TB Centre Committee

Title	Designated officials
Chairperson	Medical superintendent or director of the institute
Vice-chairperson	HoD respiratory medicine or general medicine
Nodal officer	Senior doctor from the department hosting the NDR-TBC
Member secretary	Senior medical officer – DR-TB centre
Member	HoD microbiology or IRL microbiologist
Member	HoD psychiatry*
Member	HoD Ob&Gy*
Member	HoD ENT*
Member	HoD dermatologist*
Member	HoD pharmacology
Member	Cardiologist* or physician
Member	1 eminent pulmonologist from NGO/private sector
Member	WHO NTEP Consultant
Member	DTO of the district where NDR-TBC is located
Special invitees	DTOs of the districts linked (as and when needed)

***** To be consulted physically or virtually as and when required

Note: The chairperson can co-opt other specialists as required. The routine clinical decisions can be taken by the available doctor and informed to the NDR-TBC in subsequent meetings.

Terms of reference of NDR-TBC

1. Periodically review the implementation status of PMDT in the respective nodal DR-TB centre to ensure that NTEP PMDT policies and guidelines are being followed.
2. Coordinate with the IRL/ C&DST labs for DST/DRT results and enter the details in Nikshay.
3. Arrange for examination of DR-TB patients referred for their treatment eligibility, open treatment book and start PMDT regimen for all eligible patients.
4. DR-TB patients who require admission may be admitted in the indoor facilities of the DR-TB centre as needed.
5. Ensure respective DTOs are informed of patients discharge in a timely manner.
6. Submit regularly reports to the state TB cell and state PMDT committee.
7. Arrange tele/ video consultation with relevant specialist on case-to-case basis as well as with linked DDR-TBC to provide required clinical decision support.
8. Empanel the private practitioners of various disciplines if the required specialist is not available in public sector. In coordination with the respective STO and DTOs, ensure that drug ordering and distribution is managed in a timely and appropriate manner.
9. Accountable for review of record, report, Nikshay data entry.
10. Monitoring of performance of DR-TB and PMDT in catchment geography using analysis of data from downloadable Nikshay reports and dashboard.

District DR-TB Centre Committee

The basic minimum requirements for the composition of District DR-TB Centre Committee,

Title	**Designated officials**
Chairperson	Chief Medical Officer
Co-chairperson	Medical Superintendent/ Director/ Head of the institute
Nodal person	Physician in-charge of DDR-TBC
Member Secretary	DTO of the district
Members	Specialists* from pulmonologist, microbiologist, psychiatrist, Ob & Gy, cardiologist, ENT, dermatologist, pharmacologist etc.
Member	MO medical college, If placed
Member	Medical consultant (concerned), WHO NTEP TSN
Member	Any other invited member, if required

** Specialist available in-house, outsourced from private sector or linked with NDR-TBC*

Terms of reference of DDR-TBC

1. Ensure arrangement for patient treatment initiation as per PMDT guidelines.
2. Periodic review of treatment initiation, aDSM and patient monitoring activities carried out at DDR-TBC
3. Coordinate with DTO, TUs, HFs, other department and NGO to ensure patient is linked with all essential services required.
4. Empanel private practitioners of various disciplines which are not available in the committee and required for management of DR-TB.
5. Arrange tele/ video consultation with relevant specialist on case-to-case basis as well as with linked NDR-TBC to seek guidance required for clinical decision support. DDR-TBC should also arrange tele/ video consultation with HFs on case-to-case basis to provide required clinical decision support.
6. Accountable for review of record, report, Nikshay data entry.
7. Monitoring of performance of DR-TB and PMDT in catchment geography using analysis of data from downloadable Nikshay reports and dashboard.

Annexure 3: Technical specification of ECG machines for PMDT-NTEP

A. Preamble

This guidance is provided in regard to the requirements that should be considered when procuring ECG machines for monitoring of patients being treated either with the shorter MDR-TB regimen or the new drugs for drug-resistant TB treatment, including Bdq and Dlm under PMDT.

The ECG machine can be 1/3/6 channel; however, it should fulfil all the requirements as per technical specifications given below:

B. Technical specifications

S. N.	Features	Technical specifications & operational/functional requirements
1.	Size & weight	• Sturdy & light weight machine <5kg • Should be compact • Should have carry handle for portability
2.	Power supply	• Compatibility with mains 220-240 V (normal), 50/60 Hz power supply • High performance Li-ion rechargeable battery with built-in charger • Equipment should have sufficient battery backup for taking minimum 100 ECGs without AC power • Digital filtering to remove interference from power line, muscle tremor *etc*.,
3.	ECG recording	• ECG recording with 12 leads ▸ Standard leads (the limb leads or bipolar limb leads: I, II & III) ▸ Augmented limb leads- (aVL, aVR and aVF) ▸ Chest leads (unipolar or V leads)- from V1 to V6 • Simultaneous acquisition from 12 leads • Recording speed selection of 25 mm/ sec and 50 mm/ sec with facility for speed selection • Automatic adjustment of baseline for optimal recording • Should have different filters like baseline filter, EMG filter & AC filter • Multiple operating modes -automatic, manual and rhythm • Common mode rejection ratio >90dB
4.	Built-in ECG parametres measurement and interpretation	• Built-in ECG auto-measurement including: HR, P-R interval, P-duration, QRS duration, Q-T interval, Q-TcF (Friedericia), P Axis, QRS Axis, T Axis, R(V5), S(V1), R(V5)+S(V1) • QTcF interval reading/ measurement should also be available with limb leads alone.
5.	Printing and communication	• High-resolution thermal printing array system • Built-in printer should work with standard universal thermal printer paper
6.	Standard accessories	• The machine should be supplied with: • power cord, patient cable, user manual and warranty card, operation manual with user demonstration video CD, interpretation manual & 10 thermal recording paper rolls, 5 bottles of jelly, two sets each of: • patient cable • chest electrodes – both adult and paediatric (2 sets each) • limb electrodes – both adult and paediatric (2 sets each)

S. N.	Features	Technical specifications & operational/functional requirements
7.	Safety profile	• Should be provided with a terminal for good earth connection to preclude electric disturbances while recording • Must have a safety certificate or valid detailed electrical and functional safety test report from a recognized competent authority • Copy of the certificate/ test report shall be produced along with the technical bid
8.	Installation & training	• The firm should install the instrument at the designated location and provide one-day training/ demonstration of operation of ECG machine
9.	Warranty	• Performance warranty of at-least one year from date of installation + additional two-year comprehensive warranty • In case of breakdown of the machine, the supplier shall make the machine functional by repair (including replacement of parts) free of cost at the user site, within 3 days of the receipt of complaint or replace the machine (if necessary)
10.	After sales services	• The suppliers should have adequate after-sales service facilities covering all districts of the country • They should have infrastructure and trained manpower to attend to any complaints within 3 days of receipt of complaints

Annexure 4: Airborne infection control – Recommendations for DR-TB wards & outpatient area

Airborne infection control - recommendation for DR-TB wards

Key recommendations

- Located away from the other wards, with adequate facilities for hand washing and good maintenance and cleaning;
- Adequate ventilation (natural and/or assisted ventilated) to ensure >12 ACH at all times;
- Adequate space between 2 adjacent beds, at least 6-feet;
- Cough hygiene should be promoted through signage, equipment and practice ensured through patients and staff training, ongoing reinforcement by staff;
- Adequate sputum disposal, with individual container with lid, containing 5% phenol, for collection of sputum; and
- All staff should be trained on standard precautions, airborne infection control precautions and the proper use of personal respiratory protection. A selection of different sizes of re-usable N95 particulate respirators should be made available for optional use by staff.

DR-TB wards are inpatient for initiation of treatment and managing clinical complications during treatment. This includes but is not limited to all NTEP DR-TB centres.

Location and design

- The facility should be located away from the other wards with preferably a separate passage for the patients to access the toilets.
- The facility should have adequate ventilation (natural and/or assisted ventilated) to ensure >12 ACH at all times, preferably >15 ACH. This would be possible only if adequate fixed unrestricted openings, e.g. ventilator windows, are open at all times during the day and night in all seasons. Similarly if assisted ventilation is being used (e.g. exhausts) to maintain the adequate ACH, it should ensure that these are kept switched on at all times.
- In case of frequent power cuts in a setting requiring mechanical or UVGI to maintain safety, a power back-up facility (i.e. generator set) is recommended along with adequate provision for fuel and maintenance.
- The distance between 2 adjacent beds should be optimal (at least 6-feet)
- Visitors should be restricted to the greatest extent practical.

General hygiene

- Handwashing facility (universal precaution) shall be in place for doctors, health-care workers and patients.
- Running water, soap and alcohol hand-rub solution shall be provided.
- Frequent wet mopping of the ward shall be undertaken.
- Lavatory shall be kept clean.

Patient education should be conducted on the following at each admission and reinforced frequently by staff

- Cough hygiene
- Cough etiquette
- Sputum disposal
- Proper use of surgical masks
- Restricted visitor entry

Cough hygiene

- Display signboards in the ward demonstrating cough hygiene.
- All patients admitted in the ward should be issued surgical masks.
- Adequate measures shall be taken for safe collection and disposal of sputum.

Sputum disposal

- Patients should be provided individual containers with lid, containing 5% phenol, for collection of sputum;
- Patients should be instructed on spitting the sputum directly in the container or in a tissue paper which is then thrown in the container; and
- The container should be emptied daily and the sputum disposed off as per the infection control guidelines.

Avoid posting of HCW working in MDR-TB wards if they are immuno-compromised or are on immuno-suppressants for any indication.

Training of MDR-TB ward staff

- All the staff of the DR-TB ward shall be trained in Universal Workplace Precautions, waste segregation and disposal and Airborne Infection Control Practices, with special reference to tuberculosis.

Personal respiratory protection

- N95 particulate respirators must be made available for optional use by any staff working in the ward area if the desired ACH cannot be reached through optimized ventilation. Regardless of whether or not staff chooses to use the respirator, all staff should be provided sensitization and appropriate training on how to choose, use and maintain the respirator.

Airborne infection control - recommendation for outpatient area

TB patients like other patients, have to wait for long periods before they are actually examined by the physician at the outpatient facility. During this period, these patients remain a source for spread of disease to others.

Key recommendations

1. Reduce overall duration of stay in outpatient department by screening, separation and fast tracking of coughing patients and other means.
2. Location of OPD area should be properly ventilated. Adequate ventilation (natural and/or assisted ventilated) to ensure >6 ACH at all times.
3. Education on cough etiquette and respiratory hygiene in waiting area; and
4. Training of institute staff to identify symptomatic patients and provide mask and segregate them if fast tracking is not possible.

Reducing the patient's stay in the outdoor department. Reducing the overall stay of such patients in the health-care facility is likely to prove the single-most effective measure of reducing airborne disease transmission in these areas. This can be achieved by fast-tracking these patients, which can be accomplished by several measures that are not mutually exclusive. Fast-tracking will also depend upon the type of health care facility. At a chest centre/hospital, most patients are chest symptomatic where fast-tracking has no real application, but the process will be more useful for general hospitals. Identification of patient coughing in waiting area and providing mask or segregating them in such a situation is possibly a more feasible and effective way. Implementation of key administrative intervention would vary from facility to facility.

Screening. Screening for TB symptoms can be done at the registration counter itself or at designated cough corners within the facility and those suspected of TB can be given priority. This screening can be performed by physicians, nurses, paramedical staff or volunteers specially deputed for this purpose. A simple three-layer surgical mask must be provided to all coughing patients with directions to cover the cough throughout the time they are in the facility and practice the same at home and at the community level.

Education on cough etiquette and respiratory hygiene. This education can easily be imparted to patients through posters and other audio-visual means, as well as by actual discussion by paramedical staff or volunteers in the waiting area. Outpatient setting should make easy availability of tissue papers and bins with disinfectants for sputum disposal.

Patient segregation. Segregation of patients with respiratory symptoms can be achieved by separate waiting areas for chest-symptomatic. Outpatient area should be well ventilated to reduce overall risk of airborne transmission.

Fast tracking. Patients identified at the registration counter or designated cough corners within the institute must be fast-tracked i.e. allowed to jump queues at all levels to minimize the time they spent in the facility and thereby risk of transmission. Mechanisms like stamping the outpatient form for fast-tracking could be instituted with adequate education materials displayed in the facility on airborne infection control.

Location and design

- The outpatient facility with an open shaded waiting area should be located away from the other OPDs of vulnerable immunosuppressed diseases and paediatric OPD with preferably a separate passage for the patients to access the toilets;
- The outpatient facility should have adequate ventilation (natural and/or assisted ventilated) to ensure >12 ACH at all times, preferably >15 ACH. This would be possible only if adequate fixed unrestricted openings, e.g. ventilator windows, are open at all times during the day in all seasons. Similarly if assisted ventilation is being used (e.g. exhausts) to maintain the adequate ACH it should ensure that these are kept switched on at all times;
- In case of frequent power cuts in a setting requiring mechanical or UVGI to maintain safety, a power back-up facility (i.e. generator set) is recommended along with adequate provision for fuel and maintenance.
- The seating between patient and provider must be such that the direction of air is passing between them to create an air curtain between patient and the provider.

Overcrowding should be restricted to the greatest extent practical.

Annexure 5: Guidance for establishment of "State level – Difficult-to-treat TB clinic (S-DT3C)"

Background

As per the National Anti-Tuberculosis Drug Resistance Survey (2014-16), 2.84% and 11.60% among new and previously treated TB patients respectively, are Multi-Drug Resistant-TB (MDR-TB) in India. Among MDR-TB patients, 21.82% had additional resistance to any fluoroquinolones, and 3.58% to any second-line injectable drugs. While treating these patients, there are always instances of complex patients for which the DR-TB centre committee/ physicians at nodal or district DR-TB centres may require expert consultation to support appropriate clinical decision-making. To support them under a systematic framework, the establishment of "State level – Difficult-to-treat TB clinic (S-DT3C)" is being envisaged at the state/ UT level. The national DT3C would continue to provide clinical decision support on virtual platform via the Central TB Division for patients in whom the S-DT3C may still need guidance pertaining to clinical decision-making for regimen designing, adverse drug reaction or co-morbidity management in difficult-to-treat TB patients.

The S-DT3C is intended to serve as a state-level clinical decision support system and an avenue for capacity building of the nodal & district DR-TB centres in the states in good quality management of difficult DR-TB patients as well as experience sharing and learnings through locally available virtual platform. Ultimately, it is expected to improve quality of clinical care provided to DR-TB patients under the programme and eventually improve quality of life with better chances of treatment success and survival.

The operational mechanism for the establishment and functioning of the S-DT3C is detailed below:

- A team of experts from functional DR-TB centres within the state includes eminent private physicians with experience in managing DR-TB patients and microbiologists, need to be identified for forming the State/ UT level expert panel. These experts should be willing to devote time for this important cause. It is recommended to have between 5-12 experts on this panel (based on need, number of experts may be increased). The experts should review and provide clinical/management advice on the difficult-to-treat patients escalated to them from various nodal or district DR-TB centres in line with the latest NTEP guidelines and their clinical experience. It is preferable to have 1-2 paediatricians and other experts experienced in managing DR-TB patients in the panel.
- Designate a nodal person (preferably State DR-TB coordinator or a Medical Officer from State TB Training & Demonstration centre (STDC)/ State TB cell (STC)) for coordinating the S-DT3C for the state/ UT. S/He should be assigned the responsibility of the focal person in the state to i) receive the patients' queries in a structured format from various nodal/district DR-TB centres; ii) allotting patients' queries received to the experts in rotation; iii) tracking resolution of the clinical/ management decision; iv) communicating the decision of the experts back to the referring nodal/district DR-TB centre within 48 hours; and v) preparing a quarterly summary for the STO and state PMDT committee on the S-DT3C activities as well as raise challenges for resolution, if any.
- The patients referred from the DR-TB centres within the state should be allocated to one expert on rotation basis. The nodal person will allocate the patient to an expert and inform him/ her on e-mail.
- Every expert should be paired with another expert as appropriate for detailed consultation and consensus on the clinical/ management decision for the specific patient.

- For the management of paediatric DR-TB patient, a paediatrician can be paired with the chest physicians for decision-making.
- The nodal person will ensure that each patient referred for expert advice should get resolved within 48 hours. Rigorous follow-up is required from nodal person to track the timeline. Sample excel based tracking sheet is enclosed herewith for reference.
- Apart from the Nikshay based patient ID, every patient referred to S-DT3C should be given a unique ID for tracking purpose. Sample ID is mentioned in the attached tracking sheet.
- State can create a dedicated email ID for the S-DT3C in a standard format: (Abbreviation of the State)-dt3c@gmail.com e.g., up-dt3c@gmail.com, mh-dt3c@gmail.com and so on.
- In the event, the S-DT3C still needs guidance pertaining to clinical decision-making for regimen designing, adverse drug reaction or co-morbidity management in any difficult-to-treat TB patient, the specific patient can be escalated to CTD in the standard template on ntepdt3c@gmail.com for advice from the national experts group of DT3C.

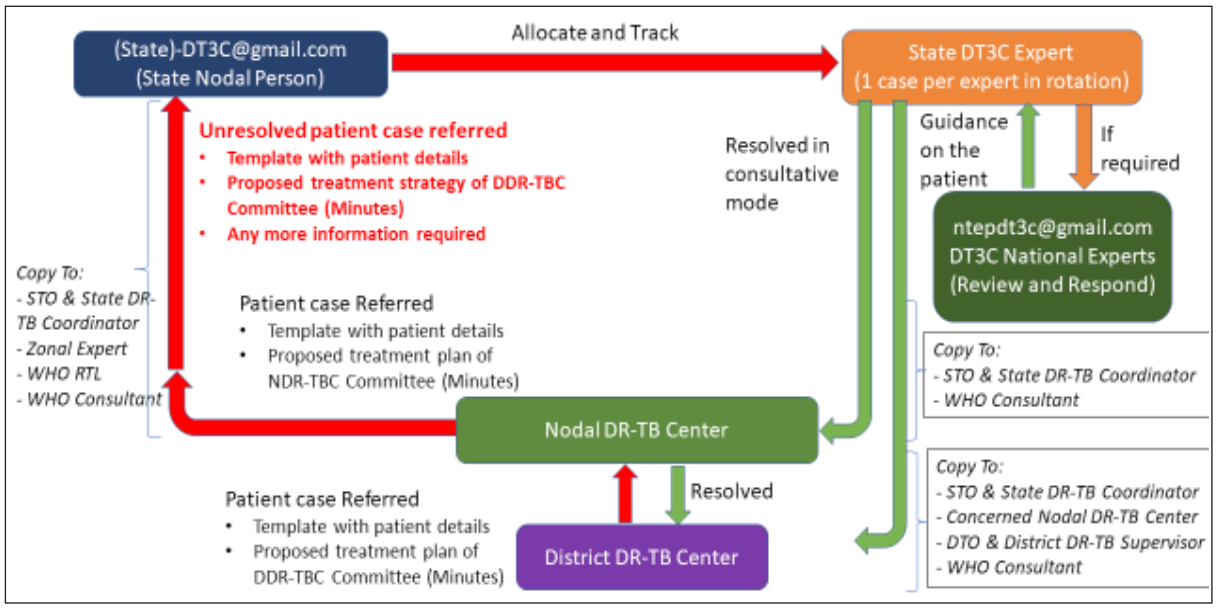


Figure: Stepwise escalation under S-DT3C for resolution

Capacity building under 'State level – Difficult-to-treat TB clinic' Initiative

- In addition to clinical decision support, the state should conduct at least monthly (twice-a-month or more if required) S-DT3C webinars for discussion on the patients resolved during the month to serve as a platform for encouraging capacity building through cross learning.
- S-DT3C webinars should be planned for the benefit of all DR-TB centres and health functionaries.
- Target audience would comprise of members of the nodal & district DR-TB centre committees, state-level experts, faculties and doctors from medical colleges/district/sub-district hospitals, District TB Officers, District Programme Coordinators and Senior DR-TB TB-HIV supervisor WHO NTEP RTL, MO-TC/PHI, STS, STLS, TBHV, CHOs. Additionally, private clinicians/faculties of medical colleges willing to or actively involved in management of drug-resistant TB patients should be invited for participation or facilitation respectively.
- National experts can be invited to observe and facilitate the discussion, whenever required.

Reporting mechanism

States/ UTs will need to submit quarterly report to the CTD in below format by 10th day of subsequent quarter to ddgtb@rntcp.org with copy to ctdpmdt@rntcp.org.

No. of difficult DR TB patients referred to S-DT3C experts in the quarter	Out of A, no. of difficult DR TB patients resolved by S-DT3C	Out of B, responded to within 48 hours of timeline by S-DT3C	No. of S-DT3C webinars held in the quarter
A	B	C	D
XX	XX	XX	XX

Monitoring for actions to improve quality of care

1. State PMDT committee, state TB cell and STDC will review the performance of S-DT3C in each quarter and identify gaps, address challenges in close consultation with experts and higher state officials. It can also be reviewed as part of NTEP quarterly review meeting.
2. As per queries received from the nodal/district DR-TB centres, field level operational issues can be identified and specific corrective actions for clinical or system improvement can be devised for strengthening district or nodal DR-TBC committee/ addressing drug shortages/ filling training gap/ monitoring of loss-to-follow-up and death of DR-TB patients and quality of care etc.

Roles of key players in S-DT3C

1. State S-DT3C experts

Commit time to address patient allocated within 24–48 hours.

- Review patient allocated, consult concerned nodal/district DR-TB centre, if required.
- Decide management strategy and share with S-DT3C nodal person.
- Send the final decision to concerned district/ nodal DR-TB centre with copy to STO, state DR-TB coordinator, DTO, Senior DR-TB TB-HIV supervisor, WHO NTEP RTL and consultant concerned.
- Address additional concerns including ADR management, if any.

If needed, guide the nodal person to raise the query in template with national DT3C with proposed management strategy from S-DT3C experts for national review and inputs with copy to STO, state DR-TB coordinator, WHO RTL and consultants concerned.

2. State TB Officer, state DR-TB coordinator or equivalent staff identified as nodal person

- Establish S-DT3C under information of state PMDT committee.
- Monitor and ensure N/DDR-TBC committee meetings are conducted regularly by all centers in the state.
- Ensure experts under S-DT3C commit time, address the query of N/DDR-TBC provided in template with 24-48 hrs or escalate the query in template from S-DT3C to DT3C with proposed management strategy from S-DT3C experts.
- Provide training to the N/DDR-TBC in completely and correctly filling the template and sharing their treatment strategy proposed by NDR-TBC to S-DT3C.
- Coordinate for any additional information required within shortest possible turnaround time to ensure prompt resolution.

- Address any operational, investigations, drug supply, ancillary drugs and logistic issues; and
- Request techno-managerial support from WHO NTEP RTL consultants in operationalizing and monitoring this from the state level.

3. Nodal DR-TB centre

- Commit time to address query raised by DDR-TBC within 24–48 hours or escalate it to S-DT3C, as needed.
- Conduct NDR-TBC committee meetings regularly.
- Review patients referred by DDR-TBC concerned, suggest treatment strategies and send final replies to concerned DDR-TBC.
- Raise queries with correctly filled template and share treatment strategy proposed by NDR-TBC for difficult-to-treat TB patients from N/DDR-TBC concerned to S-DT3C experts with copy to STO, state DR-TB coordinator and WHO NTEP consultants concerned.
- Respond to any additional request in shortest possible time to resolve the patient or share further concerns/ viewpoints till the management strategy is resolved.
- Implement the management strategy proposed by S/N-DT3C as resolution of the query raised, monitor progress of the patients and revert to S-DT3C for any further challenge during the remaining course of treatment.
- Request techno-managerial support from WHO NTEP consultants concerned in getting the resolution of the patient queries from the S-DT3C, as needed.

4. District DR-TB centre

- Conduct DDR-TBC committee meetings regularly.
- Review patient referred from the field for treatment initiation, decide treatment strategy and monitor progress for every patient enrolled at DDR-TBC.
- Raise query with correctly and completely filled template to the NDR-TBC for the difficult-to-treat patient at their level with copy to the concerned DTO, Senior DR-TB TB-HIV supervisor and WHO NTEP consultant.
- Respond to any additional request in shortest possible time to resolve the patient or share further concerns/ viewpoints till the management strategy is resolved.
- Implement the management strategy proposed by nodal DR-TB centre or S/N-DT3C experts (as the case may be) as resolution of the query raised, monitor progress of the patients and revert back to NDR-TBC for any further challenge during the remaining course of treatment.
- Request techno-managerial support from WHO NTEP consultants concerned in getting the resolution of the patient queries from the NDR-TBC, as needed.

5. District TB officer, Senior DR-TB TB-HIV supervisor, MO-TCs, STS, TBHVs concerned

- Ensure DDR-TBC committee meetings are conducted regularly.
- Provide support to the DDR-TBC in correctly and completely filling the template and sharing the treatment strategy proposed by DDR-TBC to NDR-TBC concerned.
- Coordinate for any additional information required within shortest possible turnaround time to ensure prompt resolution.
- Address any operational, investigations, drug supply, logistic issues.
- Request techno-managerial support from WHO NTEP consultants concerned in getting the resolution of the patients' queries from the NDR-TBC, as needed.

Annexure 6: Diagnosis and management of non-*Mycobacterium Tuberculosis* (NTM)

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

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

Clinical and microbiologic criteria for diagnosis of non-tuberculous mycobacterial pulmonary disease

Clinical	Pulmonary or systemic symptoms
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules and appropriate exclusion of other diagnoses.
Microbiological	1. Positive culture results from at least two separate expectorated sputum samples. If the results are non-diagnostic, consider repeat sputum AFB smears and cultures or 2. Positive culture results from at least one bronchial wash or lavage or 3. Trans-bronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM

Diagnosis of NTM

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

Most frequently isolated non-TB *Mycobacteria* and their sites of infection

Species	Main site of infection	Growth rate
M. avium complex *(M.avium, M. intracellulare, minor species)*	Pulmonary, lymph nodes, disseminated disease	Slow
M. kansasii	Pulmonary, disseminated disease	Slow
M. xenopi	Pulmonary	Slow
M. malmoense (NW Europe)	Pulmonary	Slow
M. ulcerans	Skin	Slow
M. marinum	Skin	Intermediate
M. abscessus	Pulmonary, skin	Rapid
M. chelonae	Skin, soft tissues, disseminated disease	Rapid
M. fortuitum	Skin, soft tissues, pulmonary	Rapid
M. scrofulaceum	Lymph nodes	
M. haemophilum	Disseminated disease	

The minimum evaluation of a patient presenting with features suggestive of non-TB

Mycobacterial (NTM) lung disease should include the following:

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

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

Guidelines for making the diagnosis of NTM-pulmonary disease

- clinical features of an indolent, respiratory disease include cough, expectoration, fever and other constitutional symptoms;
- positive smear for AFB and/or heavy growth of NTM (at least 1+ on solid media) on culture in respiratory specimens with the same species being identified repeatedly;
- NTM can co-exist with M. *tb* and fungal infections;
- histopathological features of *mycobacterial*/granulomatous disease or culture of NTM from biopsy specimens;

- radiological features of nodular infiltrates with or without cavitation and/or bronchiectasis lesions;
- underlying host conditions include immunosuppression, AIDS, alcoholism, COPD, cystic fibrosis, diabetes, malignancies, prior TB, esophageal motility disorders *etc.;*
- absence of other causes of pulmonary lesions, such as TB, aspergillosis, *etc.;*
- persistence of AFB after anti-TB treatment for two weeks or more with NAAT or LPA report not detecting *M. tb*; and
- smear positive, NAAT negative, LPA-TUB band absent with or without R resistance in patients of presumed DR at diagnosis also need to be evaluated.

For more information on NTM including extra-pulmonary NTM, microbiologists are encouraged to refer to the latest British Thoracic Society (BTS) or American Thoracic Society (ATS) guideline.

Treatment of NTM

NTM are uncommonly encountered clinical pathogens; some species, in fact, are much more likely to be isolated as a result of specimen contamination than as a result of disease. It can also be isolated from patients with lower respiratory infections especially from patients who live in areas of higher density of environmental NTM presence. This is a transient carriage and usually does not meet the criteria for NTM disease. However, even these species can, under some circumstances, cause clinical disease. The clinician, therefore, must always know the context in which an NTM isolate was obtained to assess accurately the clinical significance of that isolate. Given these complexities, the treatment of NTM will be the prerogative of the NDR-TBCs. When questions about the clinical significance of an NTM isolate arise, expert consultation is strongly encouraged. For management of NTMs including EP NTMs, the physicians of NDR-TBCs are encouraged to refer to the latest international (American/ British thoracic Society) guidelines.

References

1. Charles L Daley et al., 2020. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline Clinical Infectious Diseases, Volume 71, Issue 4, 15 August 2020, Pages e1–e36. [Internet]. (https://doi.org/10.1093/cid/ciaa241. Accessed March 2021).
2. Charles S Haworth et al., 2017. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). [Internet]. (http://dx.doi.org/10.1136/thoraxjnl-2017-210927. Accessed March 2021).

Annexure 7: TB Bacteriology Request Form

(Required for diagnosis of TB, drug susceptibility testing and follow-up)

Patient information			
Patient's name		Age (in years.):____	Gender:☐ M ☐ F ☐ TG
Patient's mobile no. or other contact no.		Specimen collection date (DD/ MM/YY) _____	☐ Sputum ☐ Other (specify)_____
Aadhaar no.(If available)			
Patient's address with landmark		HIV status: ☐Reactive ☐Non-reactive ☐Unknown	
		Key populations: ☐Contact of known TB patient ☐Diabetes ☐Tobacco ☐Prison ☐Miner ☐Migrant ☐Refugee ☐Urban slum ☐Health-care worker ☐Pregnancy ☐ Lactation ☐Other(specify) _____	

Name and type of referring facility (HF/TDC/TU/ DTC/ ICTC/ART/Medical college/DR-TB centre/private/others, specify): _____ **Health establishment ID (NIKSHAY): _ _ _ _**	Episode ID: _____ Test request ID: _____
State: _____ District: _____ Tuberculosis unit (TU): _____	

Reason for testing

Diagnosis and follow-up of TB		
Diagnosis of TB		Follow-up (Smear and culture)
H/O anti TB Rx for >1 month: ☐ Yes ☐ No		
☐ Presumptive TB ☐ Sm-ve, Chest X-ray suggestive of TB ☐ Repeat exam ☐ Private referral	Predominant symptom _____ Duration _____ days	Reason: ☐ End IP ☐ End CP Post-treatment:☐ 6m ☐ 12m ☐ 18m ☐ 24m

Diagnosis and follow-up drug-resistant TB		
Diagnosis of DR-TB (DRT/ DST)		Follow-up (Smear & culture)
Presumptive MDR-TB	☐ New ☐ Previously treated	Treatment: ☐ H mono/poly DR-TB regimen ☐ Shorter MDR-TB regimen (Inj/Oral) ☐ Longer oral; M/XDR-TB regimen
	☐ At TB diagnosis ☐ Contact of MDR/RR-TB ☐ Follow-up Sm+ve ☐ Private referral ☐ Discordance resolution	
☐ Presumptive H mono/poly		
Presumptive Pre XDR/XDR -TB	☐ MDR/RR-TB at diagnosis ☐ Follow up culture positive _____ months ☐ Failure or recurrent of MDR/RR-TB regimen ☐ Discordance resolution	Treatment follow-up month: _____ Post treatment follow-up month:_____

Test requested:

☐ Microscopy ☐ NAAT ☐ FL -LPA ☐ SL -LPA
☐ Culture ☐DST ☐Gene sequencing ☐ Other (Please specify) _____
Requested by (name, designation and signature): _____
Contact number: _____ Email ID:_____

Annexure 8: Health and safety guidelines for staff/ workers involved in sputum transportation

This document describes the guidelines for transportation of all samples potentially containing bacteria that causes tuberculosis (TB).

Sputum samples have been transported across the country for several years by courier, post or human carrier. There are no recorded cases of illness due to the release/ leakage of bacteria from samples during transport, although there are reported incidents of damage to the outer packaging.

The sputum specimen is packaged in triple layers in such a manner that it arrives at the destination in good condition and presents no hazard to the transporter.

The triple layer packaging contains the following

1. **Primary container.** A watertight, leak-proof, unbreakable tube containing the specimen. The tube is packaged with enough absorbent material to absorb all fluid in case of breakage or leakage.

2. **Secondary packaging.** A watertight, leak-proof packaging to enclose and protect the primary container. Several primary containers may be placed in one secondary packaging.

3. **Outer packaging.** Secondary packaging is placed in rigid outer packaging to protect the contents from physical damage during transport. Gel packs to maintain temperature along with suitable absorbent/ cushioning material is also placed inside.

The transporter must ensure the following

1. The outer packaging is not damaged and is properly sealed
2. Biohazard label is pasted on the outer packaging
3. “From” and “To” addresses are clearly labeled
4. Contact details (name, phone no.) of receiver is pasted
5. Upright symbol () is pasted appropriately
6. Transport at the earliest (to reach the destination within 72 hours)

Transporter/personnel transporting the sample will be sensitized by the NTEP (DTO/C&DST/IRL) prior to engagement. Sensitization would be provided on the following:

- Symptoms of TB disease and its transmission
- Precautions to be taken to prevent exposure
- Hand hygiene requirements
- Spill management

Steps to be taken in case of accidental damage/ spillage

1. Do not accept if outer packaging is found wet, soiled or broken
2. In case of damage /leakage during transport, the transporter must inform sender/ receiver whoever is nearer.
3. In the event of exposure to any infectious substance, wash hands and affected part with soap and water.
4. In an unlikely event of spillage, do not leave the damaged/broken container unattended. Cover it with cloth/paper and immediately inform the nearest NTEP laboratory for assistance and management.
5. Seek medical advice from medical officer (NTEP)/ District TB Officer (DTO).

Reference

Guidance on regulations for the Transport of Infectious Substances 2017–2018, WHO/WHE/C. [Internet]. (https://apps.who.int/iris/bitstream/handle/10665/254788/WHO-WHE-CPI-2017.8-eng.pdf;jsessionid=1EB462D11A576D7062257585762EA6FD?sequence=1Accessed on 16 March 2021)

Annexure 9: Standard operative procedure for collection, transportation and processing of extra-pulmonary specimens

1. Introduction

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

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

2. Collection of extra-pulmonary specimens

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

2.1 Pleural fluid

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

2.2 Pericardial fluid

Should be collected using ultra sonogram.

2.3 Blood

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

2.4 Tissues

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

2.5 Swabs

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

2.6 Urine

Among specimens expected to be contaminated, urine is the most common. To minimize excessive contamination of urine specimens, special instructions for collecting urine with

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

2.7 Bronchial secretions

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

2.8 Gastric lavage

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

Note:

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

3. Transportation of extra pulmonary specimens

As for pulmonary specimens, extra pulmonary specimens will need to be transported in cool boxes (below 20^0C) to be compatible for liquid culture systems as well as molecular methods. Triple packing system should be used for transportation. All precautions that are followed for transporting pulmonary specimens should be followed for EP specimens too.

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

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

3.1 Specimens and request forms

All specimens transported to the laboratory must be accompanied by the request form. Tests must be performed only upon written request of authorized persons and oral requests without follow up written instructions should not be allowed. It is also important that specimen request forms are kept separate from the specimens themselves. Forms that have been contaminated by specimens should be sterilized by autoclaving. If mistakes in filling request forms and

labelling of specimens are found, reject specimens and mention the reasons for rejection in the register. Document the time of specimen receipt in the laboratory and note any delays in delivery in the remarks column of the register.

4. Registration of samples

4.1 Receipt of incoming specimens

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

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

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

4.2 Decontamination of extra-pulmonary samples

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

Processing of EP specimens for MGIT960

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

Pus and other muco-purulent specimens

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

Gastric aspirates

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

Bronchial washings

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

Laryngeal swabs

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

Tissue

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

Urine

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

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

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

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

Blood

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

Annexure 10: Biomedical waste management

Category	Type of waste	Type of bag or container to be used	Treatment and disposal options
Yellow	(a) Human anatomical waste. Human tissues, organs, body parts and fetus below the viability period	Yellow coloured non-chlorinated plastic bags	Incineration or plasma pyrolysis or deep burial*
	(b)Animal anatomical waste. Experimental animal carcasses, body parts, organs, tissues etc		
	(c) Soiled waste. Items contaminated with blood, body fluids like dressings, plaster casts, cotton swabs, specimen container, packing material and bags containing residual or discarded blood, blood components or body secretions		Incineration or plasma pyrolysis or deep burial*
	(d) Expired or discarded medicines. Pharmaceutical waste like antibiotics, cytotoxic drugs including all items contaminated with cytotoxic drugs along with glass or plastic ampoules, vials etc	Yellow coloured non-chlorinated plastic bags or containers	Expired `cytotoxic drugs and items contaminated with cytotoxic drugs to be returned back to the manufacturer or supplier for incineration at temperature >1200 0C
	(e) Chemical waste. Chemicals used in production of biological and used or discarded disinfectants	Yellow coloured containers or non-chlorinated plastic bags	Disposed off by incineration or plasma pyrolysis or encapsulation in hazardous waste treatment, storage and disposal facility
	(f) Chemical liquid waste. Liquid waste generated due to use of chemicals in production of biological and used or discarded disinfectants, silver X-ray film developing liquid, discarded formalin, infected secretions, aspirated body fluids, liquid from laboratories and floor washings, cleaning, housekeeping and disinfecting activities etc	Separate collection system leading to effluent treatment system	After resource recovery, the chemical liquid waste shall be pre-treated before mixing with other wastewater. The combined discharge shall conform to the discharge norms given in Schedule III
	(g) Discarded linen, mattresses, beddings contaminated with blood or body fluid	Non-chlorinated yellow plastic bags or suitable packing material	Non- chlorinated chemical disinfection followed by incineration or plasma pyrolysis or for energy recovery.
	(h) Microbiology, biotechnology and other clinical laboratory waste. Blood bags, laboratory cultures, stocks or specimens of microorganisms, live or attenuated vaccines, human and animal cell cultures used in research, industrial laboratories, production of biological, residual toxins, dishes and devices used for cultures	Autoclave safe plastic bags or containers	Pre-treat to sterilize with non-chlorinated chemicals on-site as per National AIDS Control Organisation or WHO guidelines thereafter for incineration

Category	Type of waste	Type of bag or container to be used	Treatment and disposal options
Red	Contaminated waste (Recyclable) (a) Wastes generated from disposable items such as tubing, bottles, intravenous tubes and sets, catheters, urine bags, syringes (without needles and fixed needle syringes) and vacutainers with their needles cut) and gloves	Red coloured non-chlorinated plastic bags or containers	Autoclaving or micro-waving/ hydroclaving followed by shredding or mutilation or combination of sterilization and shredding. Treated waste to be sent to authorized recyclers. Plastic waste should not be sent to landfill sites
White (Translucent)	Waste sharps including metals. Needles, syringes with fixed needles, needles from needle tip cutter or burner, scalpels, blades, or any other contaminated sharp object that may cause puncture and cuts This includes both used, discarded and contaminated metal sharps	Puncture-proof, leak-proof, tamper-proof containers	Autoclaving or dry heat sterilization followed by shredding or mutilation or encapsulation in metal container or cement concrete and sent for final disposal to iron foundries or sanitary landfill
Blue	(a) Glassware. Broken or discarded and contaminated glass including medicine vials and ampoules except those contaminated with cytotoxic wastes	Cardboard boxes with blue coloured marking	Disinfection (by soaking the washed glass waste after cleaning with detergent and sodium hypochlorite treatment) or through autoclaving or microwaving or hydroclaving and then sent for recycling
	(b) Metallic body implants	Cardboard boxes with blue coloured marking	

**Disposal by deep burial is permitted only in rural or remote areas where there is no access to common biomedical waste treatment facility. This will be carried out with prior approval from the prescribed authority and as per standards specified in Schedule-III. The deep burial facility shall be located as per provisions and guidelines issued by the Central Pollution Control Board from time-to-time.*

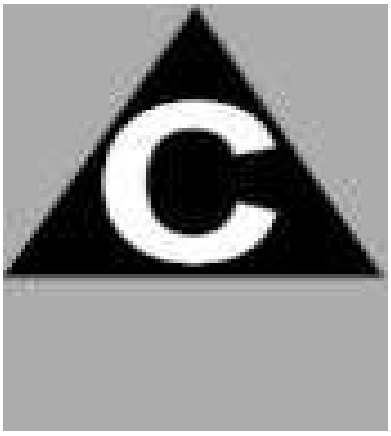
Since there are frequent changes and amendments, BMW guidelines 2016, (amendment 2018) have been adopted and the Feb 2019 amendment included. (Feb 2019 amendment attached).

Schedule IV [See rule 8(3) and (5)] Part A

Label for biomedical waste containers or bags

Cytotoxic hazards symbol

Handle with care



Handle with care

Part B

Label for transporting biomedical waste bags or containers

Day ..... Month .....

Year .....

Date of generation .....

Waste category number .....

Waste quantity……

Sender's name and address

Phone number .....

Receiver's name and address:

Phone number .....

Fax number.....

Fax number .....

Contact person .....

Contact person .....

In case of emergency please contact:

Name and address :

Phone no.

Note: Label shall be non-washable and prominently visible.

Annexure 11: Evidence of efficacy and safety of second-line anti-TB drugs

Source: WHO consolidated guideline on tuberculosis Module 4: Treatment – Drug resistant TB treatment June 2020

Relative risk for (i) treatment failure or relapse and (ii) death (versus treatment success), 2018 IPD-MA for longer MDR-\ TB regimens and Delamanid Trial 213 (intent-to-treat population)

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% confidence limits)	Number treated	Adjusted odds ratio (95% confidence limits)
A	Levofloxacin *OR* moxifloxacin	3 143	0.3 (0.1–0.5)	3 551	0.2 (0.1–0.3)
	Bedaquiline	1 391	0.3 (0.2–0.4)	1 480	0.2 (0.2–0.3)
	Linezolid	1 216	0.3 (0.2–0.5)	1 286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1 096	0.4 (0.3–0.6)
	Cycloserine *OR* terizidone	5 483	0.6 (0.4–0.9)	6 160	0.6 (0.5–0.8)
C	Ethambutol	1 163	0.4 (0.1–1.0)	1 245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)*	290	1.2 (0.5–3.0)*
	Pyrazinamide	1 248	2.7 (0.7–10.9)	1 272	1.2 (0.1–15.7)
	Imipenem–cilastatin *OR* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *OR* prothionamide	2 582	1.6 (0.5–5.5)	2 750	2.0 (0.8–5.3)
	p-aminosalicylic acid	1 564	3.1 (1.1–8.9)	1 609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2 946	1.9 (1.0–3.4)	3 269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

Note: * The values are the unadjusted risk ratios as defined by the study investigators of Trial 213 by month 24.

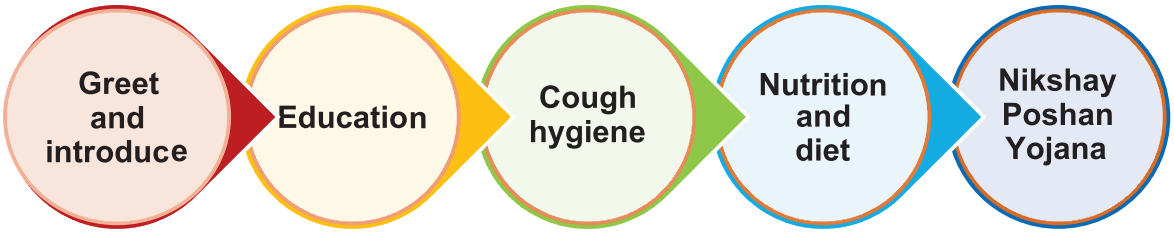
Serious adverse events (SAEs) in patients on longer MDR TB regimens*

Medicine	Absolute risk of SAE	
	Median (%)	95% credible interval
Bedaquiline	2.4	[0.7, 7.6]
Moxifloxacin	2.9	[1.4, 5.6]
Amoxicillin–clavulanic acid	3.0	[1.5, 5.8]
Clofazimine	3.6	[1.3, 8.6]
Ethambutol	4.0	[2.4, 6.8]
Levofloxacin	4.1	[1.9, 8.8]
Streptomycin	4.5	[2.3, 8.8]
Cycloserine/terizidone	7.8	[5.8, 10.9]
Capreomycin	8.4	[5.7, 12.2]
Pyrazinamide	8.8	[5.6, 13.2]
Ethionamide/prothionamide	9.5	[6.5, 14.5]
Amikacin	10.3	[6.6, 17.0]
Kanamycin	10.8	[7.2, 16.1]
p-aminosalicylic acid	14.3	[10.1, 20.7]
Thioacetazone	14.6	[4.9, 37.6]
Linezolid	17.2	[10.1, 27.0]

* From an "arm-based network" meta-analysis of a patient subset from the 2016 IPD for which AEs resulting in permanent discontinuation of a TB medicine (27 studies) or classified as Grade 3–5 (3 studies) were reported. There were insufficient records on delamanid, imipenem–cilastatin and meropenem to estimate risks. Agents that are not in Groups A, B or C are italicized.

Annexure 12: DR-TB counselling tool

DR-TB counselling heads



Greet and Introduce — ***Build rapport in order to establish an effective relationship***

- Greet the patient and introduce yourself; establish boundaries by describing your role clearly
- Collect basic demographic details
- Assure that all the information shared or discussed will be kept confidential
- Free diagnosis and free treatment under NTEP

Education — ***Assess and provide correct and updated information***

- Provide basic information on TB and discuss about symptoms of TB
- Differenciate between DS-TB and DR-TB
- Explain about DR-TB diagnosis
- Explain about DR-TB treatment regimen, duration, side effect and adherence
- Assess and arrange support system available for adherence
- Stigma and discrimination

Cough hygiene — ***Cough hygiene and AIC at home is very important***

- Discuss about contagious nature of TB
- Correct cough hygiene and safe disposal of sputum
- Use of mask / handkerchief
- Wet mopping is advisable

Nutrition and diet — ***Nutritious and high protein diet is important***

- Assess food habits
- Advise based on socio-cultural and economic background
- Consider underlying comorbidities while advise on diet (e.g. Diabetes, Hypertension)

Nikshay Poshan Yojana — ***Inform about social welfare scheme***

- Link the patient with Nikshay Poshan Yojana and other social welfare scheme

Other aspects — ***Important other aspects of counselling***

- De-addiction counselling
- Sexual and reproductive health
- Addressing stigma and discrimination
- Addressing mental health
- Family caregiver counselling

Key messages for TB counselling

1. TB is an airborne infection, caused by the germ *Mycobacterium* tuberculosis.
2. A person contracts TB infection from an open case of TB (usually a sputum smear positive pulmonary TB case). However, infection with TB does not necessarily mean that the infected person would develop TB disease. An infected person develops disease when his/her immunity declines.
3. Prolonged cough, for 2 weeks or more, fever, loss of weight or night sweat can be TB disease and therefore it is essential to consult a doctor and get examined to rule out TB.
4. Sputum microscopy, molecular testing (NAAT test) and treatment for TB (DS-TB or DR-TB) are available free of cost at all the peripheral health institutes under National Tuberculosis Elimination Programme.
5. Diagnosis and treatment services under NTEP are also available to patients seeking care in the private sector.
6. Cure from TB can only be ensured by taking complete and regular treatment. Anti-TB drugs are provided in patient-wise drug boxes, which ensure that the full course of treatment is available.
7. Treatment is provided at a place near the patient's home which is convenient and acceptable to the patient and accountable to the system.
8. Irregular medication or inappropriate regimen are the leading causes of drug-resistant tuberculosis.
9. New drugs (bedaquiline, delamanid and pretomanid) available under NTEP are safe and effective.
10. It is important to maintain cough hygiene and take nutritional food as per custom of the patient.
11. Patient will be linked with Nikshay Poshan Yojana under which TB patient will entitle to direct transfer of benefit of Rs. 500/- per month during entire treatment duration.
12. Contacts of TB patient should also be assessed for sign and symptoms of tuberculosis and after ruling out TB in contacts, TB preventive therapy (TPT) should be offered.
13. In event of adverse drug reaction, patient is advised to seek medical consultation.
14. Patient should follow family planning practice during the entire treatment duration.
15. Pregnant woman with DR-TB and the family should be given thorough understanding regarding the need for MTP if gestation is < 20 weeks (24 weeks when the bill will be passed), risk of delaying treatment, potential effect of newer drugs on the fetus and mother if MTP not opted, and the need for more intense maternal-fetal-neonatal follow-up. The regimen should be individualized in expert consultation, if pregnant woman with tuberculosis is not willing for MTP or gestation is beyond 20 weeks.

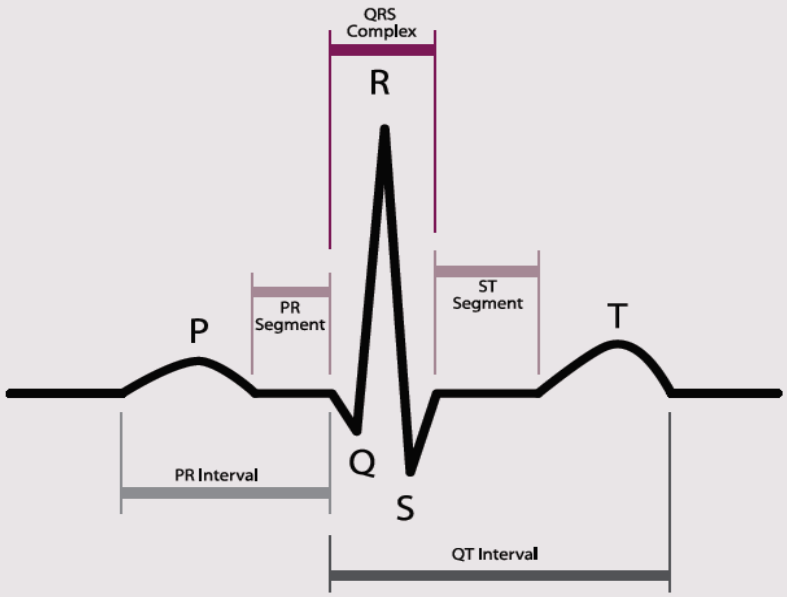
Annexure 13: DR-TB counselling register

Geography					DR-TB Patient Profile						
S. No.	State	District	Block-taluka-TU name	Name of HF	Patient's name	Diagnosis date (DD-MM-YYYY)	Type of DR-TB (MDR / pre-XDR / XDR)	Nikshay ID-Episode ID	Type of DR-TB regimen	Name of treatment supporter	Mobile number of Treatment Supporter

Convergence (Yes-Y / No-N) (Personal-P / Telephone-T)										Interruption and retrieval action				
Pre-treatment counselling	Post-treatment counselling	Initial home visit and counselling of patient	Initial home visit and counselling of caregiver	Follow-up visit-1	Follow-up visit-2	Follow up visit-3	Follow-up visit-4	Follow-up visit-5	Follow-up visit-6	Treatment interruption (no. of times during Rx)	Reason for interruption (ADR /Other)	Retrieved after interruption (no. of times retrieved during treatment)	Lost to follow-up	Retrieved after Lost to follow-up

Annexure 14: Definition of QTc interval

■ The QT interval in an ECG is measured from the start of the Q wave to the end of the T wave (see diagram below).



■ When monitoring the effect of bedaquiline, the QT interval needs to be adjusted (corrected) for the heart rate. Many ECG machines today provide an output of the corrected QT interval (QTc) automatically. If you are using a machine that does not, the following instructions can help you make the necessary correction.

- The preferred way to calculate the QTc is the Fredericia method (QTcF), which is derived by dividing the QT interval by the cubed root of the interval in seconds between the peak of two successive R waves (RR) read from the ECG strip:

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

■ Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.

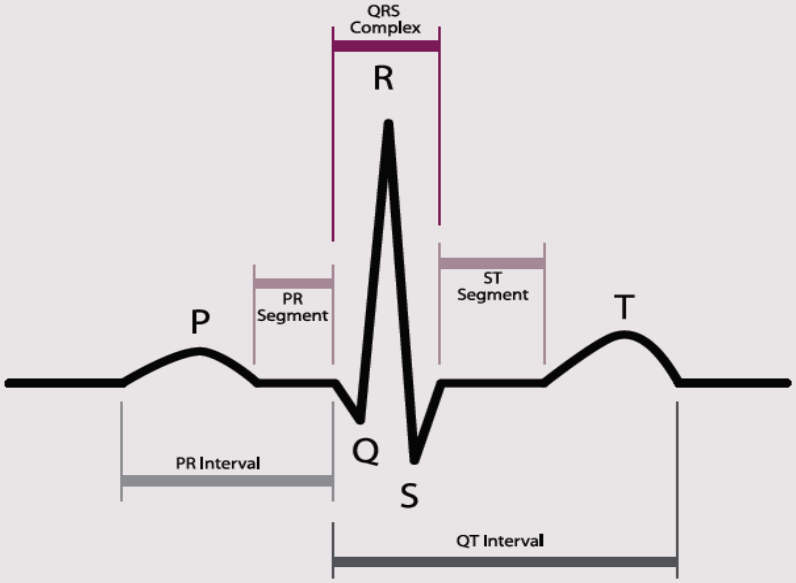
■ A normal value for the corrected QTcF interval is equal to or less than 0.45 seconds (450 ms) in males or 0.47 seconds (470 ms) in females.

QT interval is inversely correlated with heart rate. Generally, QT intervals are corrected for heart rate so that QTc is equal to QT if the heart rate is 60 beats per minute.

Calculation of corrected QTc. There are three different formulas to calculate corrected QTc.

1. Bazzet's formula ($QTcB=QT/RR^{1/2}$)
2. Fredericia's formula ($QTcFri=QT/RR^{1/3}$)
3. Framingham formula ($QTcFra=QT+0.154\ (1-RR)$)

■ The QT interval in an ECG is measured from the start of the Q wave to the end of the T wave (see diagram below).



■ When monitoring the effect of bedaquiline, the QT interval needs to be adjusted (corrected) for the heart rate. Many ECG machines today provide an output of the corrected QT interval (QTc) automatically. If you are using a machine that does not, the following instructions can help you make the necessary correction.

- The preferred way to calculate the QTc is the Fredericia method (QTcF), which is derived by dividing the QT interval by the cubed root of the interval in seconds between the peak of two successive R waves (RR) read from the ECG strip:

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

■ Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.

■ A normal value for the corrected QTcF interval is equal to or less than 0.45 seconds (450 ms) in males or 0.47 seconds (470 ms) in females.

https://play.google.com/store/apps/details?id=com.imedical_apps.ecgcorrectedqt

Use the above link to download mobile app to calculate QTcF or QTcB by entering QT and heart rate.

Annexure 15: Dosing of medicines used in second-line multidrug-resistant TB regimens by weight band (patients under 15 years)

Group	Medicine	Weight-based daily dose	Formulation	Weight bands among patients under 15-years of age							Usual upper daily dose	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
A	Levofloxacin	15–20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g	
			250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)	1.5 g	
	Moxifloxacin	10–15 mg/kg	100 mg dt	0.8	1.5	2	3	4	(>14 y)	(>14 y)	400 mg	Use 10 mg/kg in <6 months.
			400 mg tab	2 mL	3 mL	5 mL	0.5 or 0.75	1	(>14 y)	(>14 y)	400 mg	
	Bedaquiline	-	100 mg tab	-	-	-	2 tabs od for 2 weeks; then 1 tab od M/W/F for 22 weeks		4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks		-	Only in patients aged >5 years (lower dose from 15–29 kg; higher dose from >29 kg)
		-	20 mg dt	-	-	-	10 dts od for 2 weeks; then 5 dts od M/W/F for 22 weeks		20 dts od for 2 weeks; then 10 dts od M/W/F for 22 weeks			
	Linezolid	15 mg/kg od in 1–15 kg	20 mg /mL susp	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	600 mg	
		10–12 mg/kg od in >15 kg	600 mg tab	0.25	0.25	0.25	0.5	0.5	0.5	0.75		

Group	Medicine	Weight-based daily dose	Formulation	Weight bands among patients under 15-years of age							Usual upper daily dose	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
B	Clofazimine	2–5 mg/kg	50 mg cap or tab	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg	Give on alternate days if dose in mg/kg/day is too high
			100 mg cap or tab[e]	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg	
	Cycloserine or terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine)	1	1	2	3	4	(>14 y)	(>14 y)	1 g	
			250 mg cap	4–5 mL	5–6 mL	7–10 mL	2	2	2	(>14 y)	1 g	
C	Ethambutol	15–20 mg/kg	100 mg dt	1	2	3	4	–	–	(>14 y)	-	
			400 mg tab	3 mL	4 mL	6 mL	1	1 or 1.5	2	(>14 y)		
	Delamanid	-	50 mg tab	-	-	-	-	1 bd	1 bd	2 bd	200 mg	Only in patients aged >2 years (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years)
	Pyrazinamide	30-40 mg/kg	150 mg dt	1	2	3	4 or 5	-	-	(>14 y)	-	
			400 mg tab	0.5	0.75	1	1.5 or 2	2.5	3	(>14 y)		
			500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	(>14 y)		

Group	Medicine	Weight-based daily dose	Formulation	Weight bands among patients under 15-years of age							Usual upper daily dose	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
C	Imipenem cilastatin	-	500 mg + 500 mg powder for injection, vial (10 mL)	-	-	-	-	-	-	-	-	Not used in patients aged <15 years (use meropenem)
	Meropenem	20–40 mg/kg iv every 8 hours	1 g powder for injection, vial (20 mL)	2 mL	4 mL	6 mL	8–9 mL	11 mL	(>14 y)	(>14 y)	-	To be used with clavulanic acid
	Amikacin	15–20 mg/kg	500 mg/2 mL solution for injection, ampoule	0.4 mL	0.6 mL	0.8-1.0 mL	1.2-1.5 mL	2.0 mL	(>14 y)	(>14 y)	1 g	
	Streptomycin	20–40 mg/kg	1 g powder for injection, vial	Calculate according to the dilution used					(>14 y)	(>14 y)	1 g	
	Ethionamide or prothionamide	15–20 mg/kg	125 mg dt (ethionamide)	1	1	2	3	4	4	(>14 y)	1 g	
			250 mg tab	0.5	0.5	1	2	2	2	(>14 y)	1 g	
	P-aminosalicylic acid	200–300 mg/kg in 2 divided doses	PAS acid (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)	-	Full dose can be given once daily if tolerated
			PAS sodium salt (equivalent to 4 g P AS acid) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)		
			PAS sodium salt 60% w/w (9.2 g; equivalent to 4 g P AS acid) sachet	1.5 g bd	2–3 g bd	3–4 g bd	4 or 6 g bd	6 or 8 g bd	8–12 g bd	8–12 g bd	-	

Group	Medicine	Weight-based daily dose	Formulation	Weight bands among patients under 15-years of age							Usual upper daily dose	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
Other medicines	Isoniazid	15–20 mg/kg (high dose)	50 mg/5 mL soln	8-10 mL	15 mL	20 mL	-	-	-	-	-	300 mg isoniazid tablet can be used in patients >20 kg. Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in those aged <5 years and 25 mg od in those aged >4 years)
			100 mg tab	1	1.5	2	3	4	4	(>14 y)		
	Clavulanic acid	-	62.5 mg clavulanic acid as amoxicillin/ clavulanate, 250 mg/62.5 mg, powder for oral solution, 5 mL	2 mL bd	3 mL bd	5 mL bd	8 mL bd	10 mL bd	(>14 y)	(>14 y)	-	Only to be used with carbapenems

Annexure 16: Pulmonary rehabilitation

Pulmonary rehabilitation programme

Pulmonary rehabilitation aims to restore patients to an independent, productive and satisfying life and prevent further clinical deterioration to the maximum extent compatible with the stage of the disease. This goal may be accomplished, without materially improving lung function, by helping the patients to become more aware of their disease, more actively involved in their own health care and more independent in performing daily care activities, attempting to reverse the disability from disease.

Aims & objectives

The aims of pulmonary rehabilitation are:

1) Decrease of physical and psychological impairment due to the disease;
2) Increase in physical and mental fitness and performance; and
3) Maximal social reintegration of the patient to lower the handicap.

Expected results of the pulmonary rehabilitation programme

1. A programme of exercise training of the muscles of ambulation is recommended as a mandatory component of pulmonary rehabilitation for patients with COPD.
2. Pulmonary rehabilitation improves the symptom of dyspnea in patients with COPD.
3. Pulmonary rehabilitation improves HRQOL in patients with COPD.
4. Pulmonary rehabilitation reduces the number of hospital days and other measures of health-care utilization in patients with COPD.
5. Pulmonary rehabilitation is cost-effective in patients with COPD.
6. There are psychosocial benefits from comprehensive pulmonary rehabilitation programs in patients with COPD.
7. Six to 12 weeks of pulmonary rehabilitation produces benefits in several outcomes.
8. Longer pulmonary rehabilitation programmes (beyond 12 weeks) produce greater sustained benefits than shorter programmes.

Pulmonary rehabilitation programme components

The goal of PRP is achieved by general conditioning, upper body exercise, lower body exercise and reduction in dyspnoea and meeting educational, psychological and medical needs. Major components of PRP include exercise training, education, psychological and behavioral interventions and outcome assessments. Patient education about the disease and its management is a central feature of PRP but is not effective alone. However, the patient can become more skilled at collaborative self-management and more adherent to the treatment plans. Nutritional supplements can improve fat free mass and muscle strength and nutritional counselling is an integral component of PRP. Psychological intervention may be useful in motivating the patient, since identification of readiness to change may improve compliance with physical training.

For further details click hyperlink
https://drive.google.com/file/d/1E99Pq_j95XcxuQHplmBlJguQ5YLVla0g/view?usp=sharing

Pulmonary rehabilitation centre for chronic respiratory diseases – The Maharashtra State Anti-TB Association, outside group of TB hospitals, Sewri, Mumbai

Requirements for the PR centre

Space: Around 500 sq. ft.

Equipment:

1. Treadmill
2. Multi-gym
3. Cycle
4. Pulse oxymeters
5. Disposables

Human resources:

1. Two trained physiotherapists (preferable one male and one female)
2. Nurse
3. Attendant

Methods:

- Day 1. Assessment with structured questionnaire – 30 minutes to 1 hour
- Sessions on alternate days lasting 1.5 hours each for 6 to 12 weeks
- Home programme with follow-up assessment every month

Annexure 17: PMDT monitoring indicators

The source of information is Nikshay

Disaggregate by: Types of patients (New/PT); Age; Gender; Site of disease; Public/ Private sector; geography; BMI; Pregnancy status, HIV and other co-morbidities

SN	Indicator	Numerator	Denominator
	Diagnosis		
1	**Coverage of rapid molecular test for TB diagnosis** Number/ Proportion of notified TB patients who were offered a rapid molecular test for bacteriological confirmation of TB Disaggregate by clinically diagnosed and bacteriologically confirmed	No. of notified TB patients who were offered a rapid molecular test for bacteriological confirmation of TB	Total notified TB patients
2	**Coverage of rapid DST for Rifampicin among bacteriologically confirmed TB** Number/ Proportion of bacteriologically confirmed TB patients who were offered a rapid DST for at least Rifampicin	No. of bacteriologically confirmed TB patients who were offered a rapid DST for at least Rifampicin	Total bacteriologically confirmed TB patients
3	**MDR/RR-TB proportion among bacteriologically confirmed TB** Number/ Percentage of patients with at least Rifampicin resistance among all bacteriologically confirmed TB patients offered a rapid DST for at least Rifampicin	No. of patients detected with at least Rifampicin resistance	Total bacteriologically confirmed TB patients offered a rapid DST for at least Rifampicin
4	**MDR/RR-TB notification rate** Number of MDR/RR-TB patients notified per 100 000 population	No. of MDR/RR-TB patients notified in given geography * 100 000	Total population of given geography
5	**Coverage of DST for fluoroquinolones among MDR/RR-TB** Number/ Proportion of MDR/RR-TB patients who were offered a DST for at least fluoroquinolone	No. of Rifampicin resistance TB patients who were offered a DST for at least fluoroquinolone	Total MDR/RR-TB patients
6	**Fluoroquinolone resistant proportion among MDR/RR-TB** Number/ Percentage of patients with fluoroquinolone resistance among all Rifampicin resistant TB patients	No. of patients detected with fluoroquinolone resistance among MDR/ RR-TB	Total MDR/RR-TB patients offered DST for fluoroquinolone
7	**PreXDR-TB notification rate** Number of fluoroquinolone resistant among MDR/RR-TB patients notified per 100 000 population	No. of fluoroquinolone resistant among MDR/ RR-TB patients notified in a given geography* 100 000	Total population of given geography
8	**XDR-TB proportion among MDR/RR-TB** Number/ Percentage of MDR/ RR-TB patients with resistance to fluoroquinolone and at least one of the 2 group A drugs (Bedaquiline/ Linezolid)	No. of MDR/RR-TB patients with resistance to fluoroquinolone and at least one of the 2 group A drugs (Bedaquiline/ Linezolid)	Total MDR/RR-TB patients offered DST for fluoroquinolone and Bedaquiline and/or Linezolid

SN	Indicator	Numerator	Denominator
9	**XDR-TB notification rate** Number of MDR/RR-TB patients with resistance to fluoroquinolone and at least one of the 2 group A drugs (bedaquiline / linezolid) notified per 100 000 population	No. of MDR/RR-TB patients with resistance to fluoroquinolone and at least one of the 2 group A drugs (bedaquiline / linezolid) notified in a given geography* 100 000	Total population of given geography
10	**Coverage of rapid DST for Isoniazid among TB patients with RR-TB not detected** Number/ Proportion of TB patients with RR-TB not detected who were offered a rapid DST for Isoniazid	No. of TB patients with RR-TB not detected who were offered a rapid DST for Isoniazid	Total bacteriologically confirmed TB patients with RR-TB not detected
11	**Isoniazid mono resistant TB (Hr-TB) proportion among TB patients with RR-TB not detected** Number/ Percentage of patients with Isoniazid resistance among TB patients with RR-TB not detected	No. of patients detected with Isoniazid resistant among TB patients with RR-TB not detected	Total bacteriologically confirmed TB patients with RR-TB not detected and offered a rapid DST for Isoniazid
12	**Hr-TB notification rate** Number of Hr-TB patients notified per 100 000 population	No. of Hr-TB patients notified in given geography * 100 000	Total population of given geography
13	**Coverage of DST for fluoroquinolones among Hr-TB** Number/ Proportion of Hr-TB patients who were offered a DST for at least fluoroquinolone	No. of Hr-TB patients who were offered a DST for at least fluoroquinolone	Total Hr-TB patients with RR-TB not detected
14	**Fluoroquinolone resistant rate among Hr-TB** Number/ Percentage of patients with fluoroquinolone resistance among Hr-TB patients	No. of patients detected with fluoroquinolone resistance among Hr-TB	Total Hr-TB patients with RR-TB not detected and offered DST for fluoroquinolone
Process indicators			
1	**Pre-lab patient turnaround-time (TAT)** Disaggregated by testing technology, diagnosis/ follow-up	Average time delay between date of sample collection or Patient notification (whichever is earlier) and date of sample receipt in laboratory	
2	**Lab turnaround-time (TAT)** Disaggregated by testing technology, diagnosis/ follow-up	Average time delay between date of sample receipt in laboratory/NAAT site and date of report	
3	**Post-test patient turn-around-time (TAT)** Disaggregated by testing technology	Average time delay between date of DR report and date of start of treatment	
4	**DR-TB treatment initiation within 7 days of notification** Proportion of DR-TB patients initiated on appropriate regimen within 7 days of notification Disaggregate by DR-TB pattern, regimen	No. of DR-TB patients initiated on appropriate regimen within 7 days of notification	Total no. of DR-TB patients notified

SN	Indicator	Numerator	Denominator
5	**Counselling** Proportion of DR-TB patients offered pre-treatment counselling at N/DDR-TBC Disaggregate by DR-TB pattern	No. of DR-TB patients offered pre-treatment counselling at N/DDR-TBC	Total no. of DR-TB patients notified
5a	**Counselling session per patient** Average no. of counselling sessions per patient by N/DDR-TBC Disaggregate by DR-TB regimen	No. of counselling session conducted by N/DDR-TBC	Total no. of DR-TB patients notified
6	**Preventing LTFU** Proportion of DR-TB patients who interrupted treatment for more than 7 days were retrieved back on treatment before LTFU Disaggregate by DR-TB regimen	No. of DR-TB patients who interrupted treatment for more than 7 days were retrieved back on treatment before LTFU	Total no. of DR-TB patients who interrupted treatment for more than 7 days before LTFU
7	**DR-TB regimen modification** Proportion of DR-TB patients whose regimen was modified based on extended DST results Disaggregate by DR-TB regimen	No. of DR-TB patients whose regimen was modified based on extended DST results	Total no. of DR-TB patients with additional resistant detected based on extended DST while on treatment
8	**Serious adverse events (SAE):** Proportion of DR-TB patients reported serious adverse events (SAE) Disaggregate by DR-TB regimen	No. of DR-TB patients reported serious adverse events (SAE) in respective regimen	Total no. of DR-TB patients put on appropriate treatment
9	**Successful resolution of SAE** Proportion of SAE reported that were resolved successfully	No. of SAE resolved successfully	Total no. of SAE reported
10a	**ICT based treatment adherence of DR-TB** Proportion of DR-TB patients put on ICT based treatment adherence monitoring system (MERM etc.) Disaggregate by DR-TB regimen	No. of DR-TB patients put on ICT based treatment adherence monitoring system (MERM etc.)	Total no. of DR-TB put on treatment
10b	**Treatment adherence rate 1** Proportion of DR-TB patients who missed 7 consecutive dosages while on treatment Disaggregate by type of adherence and by DR-TB regimen	No. of DR-TB patients who missed 7 consecutive dosages while on treatment	Total no. of DR-TB put on treatment
10c	**Treatment adherence rate 2** Proportion of DR-TB patients who consumed at least 80% of total dosages within 120% of total duration of treatment Disaggregate by type of adherence and by DR-TB regimen	No. of DR-TB patients who consumed at least 80% of total dosages within 120% of total duration of treatment	Total no. of DR-TB put on treatment
11	**Follow up cultures** Proportion of DR-TB patients offered follow up culture at critical time points during treatment Disaggregate by DR-TB regimen, 3M / 4M / 6M / 8M / 9M / 11M / 18M / 20M as relevant	No. of DR-TB patients offered follow up culture at critical time points during treatment	Total no. of DR-TB put on treatment

SN	Indicator	Numerator	Denominator
12a	**Weight gain during treatment** Proportion of DR-TB patients who gained weight during the course of treatment as compared to pre-treatment weight Disaggregate by DR-TB regimen	No. of DR-TB patients who gained weight during the course of treatment as compared to pre-treatment weight	Total no. of DR-TB put on treatment
12b	**Average weight gain during treatment** Average weight gain in DR-TB patients Disaggregate by DR-TB regimen	Average weight gain in DR-TB patients between weight at treatment initiation and latest weight recorded during treatment	
	Co-morbidity		
1	**Co-morbidity screening:** Number/ Proportion of DR-TB patients screened for various co-morbidities (HIV, diabetes, alcohol, tobacco) Disaggregate by DR-TB regimen	No. of DR-TB patients screened for various co-morbidities (HIV, diabetes, alcohol, tobacco)	Total no. of DR-TB patients put on treatment
2	**Co-morbidity diagnosed:** Number/ Proportion of DR-TB patients diagnosed for various co-morbidities (HIV, diabetes, alcohol, tobacco) Disaggregate by DR-TB regimen	No. of DR-TB patients diagnosed for various co-morbidities (HIV, diabetes, alcohol, tobacco)	Total no. of DR-TB patients put on treatment
3	**Comorbidity management:** Number/ Proportion of DR-TB patients with various co-morbidities appropriately managed (HIV, diabetes, alcohol, tobacco) Disaggregate by DR-TB pattern	No. of DR-TB patients with various co-morbidities appropriately managed (HIV, diabetes, alcohol, tobacco)	Total no. of DR-TB patients put on treatment
	Contact investigation of DR-TB Index patient and TPT		
1	**Contact investigation coverage** Number/ Proportion of contacts of Index DR-TB patient evaluated for TB disease and TB infection Disaggregate by DR-TB pattern of Index patient (RR-TB with FQ sensitive, Hr-TB with rifampicin sensitive)	No. of contacts of Index DR-TB patient evaluated for TB disease and TB infection	Total number of contacts of Index DR-TB patients
2	**TPT coverage** Proportion of individuals initiated on TPT out of those eligible (if tested – TPT positive or if only screened – ruled out of active TB) Disaggregate by DR-TB pattern of Index patient (RR-TB with FQ sensitive, Hr-TB with rifampicin sensitive)	No. of individuals eligible for TPT who initiated treatment during the specific period	Total number of individuals eligible for TPT during the specific period
3	**TPT completion** Proportion of individuals completing TPT out of those initiating treatment Disaggregate by DR-TB pattern of Index patient (RR-TB with FQ sensitive, Hr-TB with rifampicin sensitive)	No. of individuals who completed a course of TPT of those initiated on TPT during the specific period	Total number of individuals who were initiated on a course of TPT during the specific period

SN	Indicator	Numerator	Denominator
4	**Breakdown rate to TB among all TPT beneficiaries** Proportion of beneficiaries on TPT, diagnosed as TB during the TPT course or during long-term follow-up at 6, 12, 18 & 24 months post-TPT completion Disaggregate by DR-TB pattern of Index patient (RR-TB with FQ sensitive, Hr-TB with rifampicin sensitive)	No. of beneficiaries on TPT diagnosed as TB during the TPT course or during long term follow up at 6, 12, 18 & 24 months post-TPT completion	Total number of beneficiaries who were initiated on TPT during the specific period
Outcome indicators			
1	**Culture negative during treatment** Proportion of DR-TB patients who were follow-up culture negative at critical time points during treatment Disaggregate by DR-TB regimen, 3M/ 4M/ 6M/ 8M/ 9M/ 11M/ 18M/ 20M as relevant	No. of DR-TB patients who were follow up culture negative at critical time points during treatment	Total no. of DR-TB put on treatment
2	**Treatment outcome:** Number/ Proportion of DR-TB patients initiated on treatment with the following reported treatment outcome • Cured • Treatment success • Died • Treatment failed • LTFU • Not evaluated Disaggregate by DR-TB pattern, regimen	No. of DR-TB patients initiated on treatment with the following reported treatment outcome • Cured • Treatment success • Died • Treatment failed • LTFU • Not evaluated	Total No. of DR-TB patients notified / initiated on treatment on respective regimen
3	**Long-term follow-up:** Proportion of DR-TB patients successfully treated who were found to be smear/ culture positive during 6M/ 12M/ 18M/ 24M post treatment follow-up screening disaggregated by DR-TB regimen	No. of DR-TB patients successfully treated who were found to be smear/ culture positive during 6M/12M/18M/24M post treatment follow-up screening	No. of DR-TB patients successfully treated and screened during 6M/12M/18M/24M post treatment follow-up
Direct Benefit Transfer			
1	**Nikshay Poshan Yojana** Proportion of DR-TB patients received all eligible benefits under Nikshay Poshan Yojana according the treatment duration	No. of DR-TB patients received all eligible benefits under Nikshay Poshan Yojana according the treatment duration	Total no. of DR-TB patients notified
2	**Patient travel support** Proportion of DR-TB patients received all travel reimbursement support for all travels as eligible	No. of DR-TB patients received all travel re-imbursement support for all travels as eligible	Total no. of DR-TB patients notified

Annexure 18: PMDT Supervisory checklist- State TB cell

Date of visit: _____ Place: _____ State: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N	Remarks
1	Is the state PMDT nodal officer/coordinator available and trained?		
2	Proportion of STC staff trained on latest PMDT guidelines		
3	No. of PMDT committee meeting conducted in last one year		
4	No. of PMDT review conducted by the state in the last one year? (consider only if minutes of the meeting are available)		
5	No. of meetings chaired by MD (NHM)/PS Health		
6	No. of visits conducted by the STC officials to the nodal DR TB/DR TB centres in the last one year? (visit reports to be considered)		
7	Proportion of blocks having molecular diagnostic facility		
8	Average TAT for NAAT Test (CBNAAT/Truenat) in last quarter (in days) from the date of sample collection		
9	Average TAT for LPA (first-line & second-line LPA) in last quarter (in days) from the date of sample collection		
10	No. of districts without facility for management of DR-TB. Mention names in remarks		
11	Average delay in DR TB treatment iInitiation in last quarter (in days)		
12	Success rate of patients put on Hr-TB regimen reported in last quarter		
13	Success rate of patients put on shorter regimen reported in last quarter		
14	Success rate of the patients put on longer regimen reported in previous quarter		
15	Number of adverse drug reactions reported to the state in last quarter		
16	Is there any district/block that has replaced smear microscopy with molecular testing? (Mention it in the remarks column, if available)		
17	Has the state collaborated with any private facility for PMDT services? (mention it in the remarks column, if available)		
18	Any challenges faced by the state to implement PMDT services? (mention in remarks)		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 19: PMDT supervisory checklist – State TB Training & Demonstration Centre (STDC)

Date of visit: _____ Place: _____ State / District: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N	Remarks
1	Total number of STDCs in the state		
2	Is a full-time Director STDC in place?		
3	Is training coordinator/officer in place?		
4	No. of rooms in STDC with seating capacity for conducting trainings		
5	Is hostel facility available for trainees?		
6	Are adequate number of audio-visual aids like OHP, LED projector, white board & flip chart screens available?		
7	Number of binocular microscopes available for hands on practise during trainings?		
8	Is the annual training calendar prepared and available?		
9	Are printed copies of the latest updated training material available?		
10	Review documentation of trainings conducted in last 6 months at STDC at comment		
11	Is an updated directory of trained manpower maintained?		
12	Number of supervisory visits conducted by STDC in last 6 months		
13	Review the supervisory reports from last 6 months and comment on quality of supervision and documentation		
14	Are the districts being provided regular feedback on programme performance? Check the same for last one year and comment on quality of feedback		
15	Discuss all review and monitoring related activities carried out by the STDC in last one year and comment		
16	Number of research projects carried out in last one year		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 20: PMDT supervisory checklist – IRL/C&DST laboratory facility

Date of visit: _____ State: _____ Name of IRL/C&DST: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N	Remarks
1	Are TB containment & LPA available and functional?		
2	Review functional status of critical equipment and the maintenance arrangements. Are all equipment covered under the annual maintenance contract?		
3	Is continuous supply of electricity and water assured in the C&DST laboratory?		
4	For which technology, the lab received certification?		
5	Are there a dedicated (full time) human resource available for conducting the tests? Are they trained?		
6	Review the availability of consumables for at least 2 months?		
7	What is the average workload? (review at least a quarter data on no. of samples processed for LPA and LC- DST)		
8	Does the lab have a functional refrigerator/cold room to store samples and temp sensitive consumables?		
9	Is there a pending backlog of samples to be tested? (cross-check the storage in refrigerator/ cold room)		
10	Review the TAT from sample collection to reporting of results (including TAT for individual process related to LPA & LC)		
11	Is the C&DST lab register available and updated on Nikshay?		
12	Is there a functional computer with internet connectivity? Review entry in LIMS/ Nikshay		
13	What % of RS and RR cases diagnosed were sent for first-line and second-line DST		
14	What % of H resistant cases diagnosed were subjected to SL LPA		
15	What % of FQ resistant cases diagnosed were subjected to LC&DST		
16	Are biomedical waste management guidelines being followed?		
17	What is the score obtained in the most recent round of EQA?		
18	Number of OSE visits conducted by laboratory in the last 4 quarters. (If applicable)		
19	Action taken on the major observations during OSE visit by NRL		
20	No. of training conducted/ participated [LPA/LCDST/EQA]		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 21: PMDT supervisory checklist – District TB centre (DTC)

Date of visit: _____ District name: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N	Remarks
1	Is the DTO trained in the latest NTEP guidelines?		
2	No. of NAAT sites available in the district		
3	What is the frequency of samples transported for DST to C&DST lab (daily/ weekly/ SOS)		
4	What is the mechanism of specimen transportation: Human carrier/ NGO/ patient referred/ others		
5	No. of TB patients diagnosed in last 3 months		
6	No. of diagnosed pulmonary bacteriologically confirmed patient offered NAAT and results available in last 3 months		
7	No. of diagnosed MDR/RR-TB offered, FL/SL LPA and results available in last 3 months		
8	No. of patients initiated on (shorter/ longer/ H mono/poly DR-TB regimen) in last 3 months		
9	No. & % of DR-TB patients follow-up done amongst eligible in last 3 months		
10	Treatment outcome of various regimen declared in previous 12 months		
11	Are there adequate supplies of all drugs to cater to all the health facilities within the district?		
12	Are there adequate supplies of lab reagents to cater to all the TDCs?		
13	Review the reagent preparation and QC protocols and comment		
14	Is the drug stock register maintained and updated? Has it been cross-checked by the MO-TU?		
15	Randomly cross-check actual physical balance of all drugs and drug boxes – does it match with the closing balance of the stock register?		
16	Is FEFO being followed?		
17	Is Nikshay Aushadhi being used for drug supply management?		
18	Do all the STS/ STLS have functional motorcycles?		
19	Have the salaries and travel related reimbursements (including PoL expenses where applicable) paid to all NTEP staff?		
20	Does the MO-TU conduct monthly and quarterly review of the performance of the TB Unit (say yes only if proceedings are documented)?		
21	Does the MO-TU carry out visits to HFs and patients in his or her TU (~7 days a month)?		
22	Check ATP and tour reports of all concerned staff and comment		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 22: PMDT supervisory checklist – Nodal or district DR-TB centre (N/ DDR-TBC)

Date of visit: _____ NDR-TBC name: _____ Block/ District: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N	Remarks
1	Number of districts (population) catered to by the N/DDR-TBC		
2	Number of beds (Male/ Female)		
	Does the NDR-TB centre have a DDR-TB centre committee constituted as per the requirement?		
3	Date of last meeting (verify the minutes)		
4	Are actions being taken against the resolutions made as per documented proceedings (say Yes only if action taken is documented)?		
5	Does the NDR-TB centre have all the facilities for undertaking pre-treatment evaluation for initiation of all the type of DR-TB regimens? Discuss and comment		
6	Are emergency drugs available at the NDR-TBC? or access to emergency services very nearby?		
7	Is there ECG machine (12 leads with automatic QTc reader) available?		
8	Does the NDR-TB centre have a computer with Internet connection & VC facility?		
9	Are printed (downloaded from Nikshay) and electronic copies of the following recording and reporting formats available: 1. PMDT TB register 2. PMDT treatment card 3. Treatment booklet 4. aDSM treatment initiation and treatment review formats		
10	Is Nikshay Aushadhi being used for drug dispensing?		
11	Are quarterly review meetings with concerned senior DR-TB TB-HIV supervisors being conducted (check proceedings)?		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 23: PMDT supervisory checklist – NAAT facility (for CBNAAT & TRUENAT)

Date of visit: _____ Place: _____ Block / District: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N	Remarks
1	Is a dedicated room available?		
2	Is the NAAT machine functional?		
3	Is the NAAT machine under warranty? If yes, mention dates of last calibration and expiry of warranty in remarks column		
4	In case of a NAAT lab, are other necessary equipment like AC, UPS, hygro-thermometer available and functional?		
5	Is there a dedicated (full-time) lab technician available for conducting the tests?		
6	Is the LT trained?		
7	Are there adequate supply of cartridges/ chips for at least the next one month?		
8	Does the lab have a functional refrigerator to store samples and temp sensitive consumables?		
9	Is there a functional computer with internet connectivity?		
10	Are adequate sample packaging material available?		
11	Is the NAAT lab register available and updated?		
12	What is the average monthly workload (average of at least 6 months)?		
13	What % of RS and RR cases diagnosed were sent for first-line and second-line DST?		
14	What is the average turnaround time from receipt of sample to reporting of results?		
15	Is there a pending backlog of samples to be tested? (cross-check the storage in refrigerator)		
16	Are biomedical waste management guidelines being followed?		
17	What is the score obtained in the most recent round of EQA?		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 24: PMDT supervisory checklist – Visit to private provider

Date of visit: _____ Place: _____ Block/ District: _____

Visit carried out by: _____ Designation: _____

Name of the facility visited: _____

Type of private health establishment *(Clinic with single provider, clinic/nursing home/hospital with multiple provider, laboratory, other)*: _____

Medical speciality served by the health establishment *(M.B.B.S./general medicine/pulmonary medicine/Pediatrics/ENT/general surgery/obstetrics and gynaecology/orthopaedics/pathology / microbiology/other):* _____

Sl.	Observation	Y/N	Remarks
1	Is the facility engaged with NTEP? (mention months in remarks)		
2	When was the latest interaction with the NTEP (CME/personal interaction/ other)?		
3	Total number of patients referred/notified/treatment supported/other etc. since engagement		
4	Are all patients diagnosed by the PP being notified on Nikshay?		
5	What is the primary tool used for diagnosis of TB?		
6	Is the provider receiving the provider incentive on time?		
7	What are the challenges faced by the provider in his or her engagement with the NTEP?		
8	Has the provider been linked to a NAAT lab for testing of samples?		
9	How are samples transported to the NAAT lab?		
10	What is the usual treatment regimen (drugs and duration) prescribed for treatment of drug sensitive TB patient? Give appropriate code number *		
11	What is the usual treatment regimen (drugs and duration) prescribed for treatment of drug resistant TB patient? Give appropriate code number *		
12	What is the frequency of follow-up visits by patients?		
13	What is the frequency of ADRs and how does the PP manage the same – comment		
14	For the provider who is yet to be engaged with the NTEP, what are the major reasons for the non-engagement? Give appropriate code number**		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

* Regimen

1. Commercially available FDC (4 drugs for IP and 2 or more for CP)
2. Commercially available FDC (drug combination other than the above)
3. Commercially available individual drug prescription
4. Referred to NTEP for treatment
5. Any other

* Duration

Drug sensitive TB:

a. Less than 6 months
b. 6 months to 1 year

Drug-resistant TB:

c. Less than 1 year
d. 1–2 years
e. More than 2 years

**

1. PP was not aware of the provisions for engagement with the NTEP
2. No one has approached the PP
3. PP doesn't see any presumptive TB cases
4. PP had been engaged previously but was not satisfied with the engagement (give reasons)
5. Any other reason (specify)

Annexure 25: PMDT supervisory checklist – TB unit (TU)

Date of visit: _____ TU name: _____ Block / District: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N	Remarks
1	Is a designated MO-TU in place?		
2	Is the MO-TU trained in the latest NTEP guidelines?		
3	Name of the linked NAAT site with distance		
4	What is the frequency of samples transported for DST (daily/weekly/SOS)		
5	What is the mechanism of specimen transportation: Human carrier/ NGO/ patient referred/oOthers		
6	Are there adequate supplies of all drugs to cater to all the HFs within the TU?		
7	Are there adequate supplies of lab reagents to cater to all the TDCs (DMCs) HFs within the TU?		
8	Review the reagent preparation and QC protocols and comment		
9	Is the drug stock register maintained and updated? Has it been cross-checked by the MO-TC?		
10	Randomly cross-check actual physical balance of all drugs and drug boxes – does it match with the closing balance of the stock register?		
11	Is FEFO being followed (check expiry and issue dates in the stock register)?		
12	Is Nikshay Aushadhi being used for drug dispensing?		
13	Do the STS / STLS have functional motorcycles?		
14	Have the salaries and travel related reimbursements (including PoL expenses where applicable) paid to all NTEP staff?		
15	Does the MO-TC conduct monthly and quarterly review of the performance of the TB unit (say yes only if proceedings are documented)?		
16	Does the MO-TC carry out visits to PHIs and patients in his or her TU (~7 days a month)?		
17	Check ATP and tour reports of all concerned staff and comment		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 26: PMDT Supervisory checklist – TB diagnostic centre (TDC)

Date of visit: _____ TDC name: _____ Block / District: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N	Remarks
1	Are all medical officers in the TDC trained in NTEP?		
2	Are all MOs identifying chest symptomatic and referring for sputum microscopy?		
3	What is the average % (last 6 months) of new adult OPD being referred for sputum examination?		
4	Is the microscope (BM/FM) functional?		
5	Is the microscope covered under AMC? If yes, mention dates of last preventive maintenance and expiry of warranty in remarks column		
6	Is there a dedicated (full-time) lab technician available for conducting the tests?		
7	Is the LT trained?		
8	Is the lab register maintained and updated?		
9	Are all OSE related documents available for verification?		
10	Are there adequate supply of quality assured reagents for at least the next one month?		
11	Does the lab have a functional refrigerator to store samples and temp. sensitive consumables?		
12	Is there a functional computer, tablet etc with internet connectivity?		
13	Are adequate sample packaging material available?		
14	Is the NAAT lab register available and updated?		
15	What is the average monthly workload (average of at least 6 months)?		
16	Is there a functional X-ray machine (or linkages) available?		
17	What % of diagnosed TB cases have been referred for NAAT testing and subsequently FQ testing?		
18	What is the average turnaround time from receipt of sample to reporting of results in last quarter?		
19	Is there a pending backlog of samples to be tested? (including storage)		
20	Review the system of transportation of drugs, treatment cards etc from the health facility to the treatment support centre and comment. Use the section for observation and recommendations.		
21	Are biomedical waste management guidelines being followed?		
22	Review the sample collection and transport mechanism and comment		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 27: PMDT supervisory checklist – Health & Wellness Centre/ health facility (HWC/HF)

Date of Visit: _____ HWC/HF Name: _____ Block/ District: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	Y/N/No	Remarks
1	Is a designated Community Health Officer (CHO)/ doctor-HF in place?		
2	Is the CHO/ doctor-HF trained in the latest PMDT guidelines?		
3	Name of the linked TB testing centre (distance in km)		
4	Is there a specimen transportation mechanism established?		
5	How many patients are currently receiving PMDT services from the HWC/HF? (P/EP, shorter/longer/ H mono/poly regimen)		
6	No. & % of eligible follow-ups done in last quarter		
7	No. & % of treatment interrupters/ LTFU in previous quarter		
8	No & % of patients retrieved on treatment out of (7)		
9	Are there adequate supplies of all TB drugs in the concerned HWC/HF?		
10	How many presumptive DR-TB cases were referred by the HWC/HF in last quarter?		
11	No. (%) of current DR-TB patients on treatment on ICT based adherence monitoring system (MERM/ VOT/ others)		
12	Assess, whether the CHO/HF is trained and able to manage minor ADRs?		
13	Is the CHO/HF sensitized on Nikshay?		
14	Has the Block Medical Officer/ NTEP officials visited the HWC/HF in last one year?		
15	Has the CHO/ Doctor-HF participated in any TB related meeting in last one year? (check ATP and tour reports of the CHO/ doctor-HF)		

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 28: PMDT supervisory checklist – Visit to treatment supporter

Date of visit: _____ Place: _____ Block / District: _____

Name / designation of treatment supporter: _____/_____

Visit carried out by: _____ Designation: _____

Sl.	Observation	P1	P2	P3	P4	P5
1	Are patient-wise treatment card being maintained for each patient?					
2	Are the facilities (clean water, disposable cups, privacy) for DOT satisfactory?					
3	Are prompt home visits made to bring irregular patients back on treatment? (For patients who have missed doses, check relevant section on treatment card in Nikshay and PMDT treatment booklet for entries)					
4	Are adequate (≥1 month) supply of drugs available for all patients currently on treatment?					
5	Are all available drugs within the date of expiry?					
6	Is the knowledge of the TS adequate? 1. On duration/ frequency/ drug dispensation 2. On frequency of follow-up exams 3. On retrieval of treatment interrupters 4. On correct marking of treatment cards 5. On common ADRs					
7	Is the TS getting the honorarium on time?					

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 29: PMDT supervisory checklist – Visit to DR-TB patient

Date of visit: _____ Place: _____ Block / District: _____

Visit carried out by: _____ Designation: _____

Sl.	Observation	P1	P2	P3	P4	P5
1						
2	Is the patient aware of duration of treatment?					
3	Are Family members/Guardians /inmates etc counselled by NTEP key staff					
4	Has the patient / family members paid for diagnosis, pre trt evaluation or treatment of DR-TB?					
5	Days between diagnosis of DR-TB and Initiation of treatment					
6	Has patient travel cost to the DR-TB Centre (for PTE / ASR etc) been reimbursed?					
7	Is the patient aware of frequency of FU exams and are these taking place as per guidelines					
8	Is the treatment centre accessible and acceptable?					
9	No of doses patient has missed during IP & CP					
10	Are ADRs being managed satisfactorily? (NA/Y/N)					
11	Is the patient receiving DBT payments timely?					
12	Does the patient report home visits by NTEP staff?					
13	Is the patient aware of his/her HIV status?					
14	Has the patient been screened for other co-morbidities (DM, HTN, etc)?					

Major observation

Major recommendations with responsible official/s and timelines

Signature: _____

Annexure 30: NTEP verbal autopsy form

PMDT Number: PMDT NIKSHAY ID: YEAR:

Name of the head of household :

Full Name of the deceased:

Section 1: Details for respondent and deceased

Details of respondent

1. Name of respondent

2. Relationship of respondent with deceased

- ☐ 1. Wife/Husband
- ☐ 2. Brother/Sister
- ☐ 3. Son/Daughter
- ☐ 4. Mother/Father
- ☐ 5. Grandchild
- ☐ 6. Son-in-law/ Daughter-in-law
- ☐ 7. Brother-in-law/ Sister-in-law
- ☐ 8. Parent-in-law
- ☐ 9. Grandfather/Grandmother
- ☐ 10. Other relative
- ☐ 11. Neighbour/No relation
- ☐ 99. Unknown

3. Did the respondent live with the deceased during the events that led to death?

☐ 1. Yes ☐ 2. No ☐ 99. Unknown

4. Respondent's age in completed years

5. Respondent's sex ☐ 1. Male ☐ 2. Female

6. What is the highest standard of education the respondent has completed?

- ☐ 0. Illiterate and literate with no formal education
- ☐ 1. Literate, Primary or below
- ☐ 2. Literate, Middle
- ☐ 3. Literate, Matric Class-X
- ☐ 4. Literate, Class XII
- ☐ 5. Graduate and above
- ☐ 99. Unknown

7. Religion of the head of the household

- ☐ 1. Hindu
- ☐ 2. Muslim
- ☐ 3. Christian
- ☐ 4. Sikh
- ☐ 5. Buddhist
- ☐ 6. Jain
- ☐ 7. No religion
- ☐ 8. Other
- ☐ 99. Unknown

Details of deceased

8. Deceased's Sex ☐ 1. Male ☐ 2. Female

9. Age of Deceased Years: ☐☐

10. Relationship of the deceased with the head of the household

- ☐ 1. Wife/Husband
- ☐ 2. Brother/Sister
- ☐ 3. Son/Daughter
- ☐ 4. Mother/Father
- ☐ 5. Grandchild
- ☐ 6. Son-in-law/ Daughter-in-law
- ☐ 7. Brother-in-law/ Sister-in-law
- ☐ 8. Parent-in-law
- ☐ 9. Grandfather/Grandmother
- ☐ 10. Other relative
- ☐ 11. Neighbour/No relation
- ☐ 12. Self ☐ 99. Unknown

11. What is the highest standard of education the deceased had completed?

- ☐ 0. Illiterate and literate with no formal education
- ☐ 1. Literate, Primary or below
- ☐ 2. Literate, Middle
- ☐ 3. Literate, Matric Class-X
- ☐ 4. Literate, Class XII
- ☐ 5. Graduate and above
- ☐ 99. Unknown

12. What was the occupation of the deceased?

- ☐ 1. Non-worker
- ☐ 2. Salaried
- ☐ 3. Wage earner
- ☐ 4. Profession/Business
- ☐ 5. Cultivator/farmer
- ☐ 6. Agricultural wage labour
- ☐ 7. Non agricultural wage labour
- ☐ 8.. Student
- ☐ 9. Other
- ☐ 99. Unknown

13. Date of death D D / M M / Y Y ☐☐

14. How many years did the deceased live at this address?

15. Place of death?

- ☐ 1. Home
- ☐ 2. On way to health facility
- ☐ 3. PHC/CHC/Rural Hospital
- ☐ 4. District Hospital
- ☐ 5. Private Hospital
- ☐ 6. Other place
- ☐ 99. Unknown

16A. House address of the deceased

16B. PIN ☐☐☐ ☐☐☐

17. What did the respondent think that this person died of?
(Allow the respondent to tell the illness in his or her own words)

Section 2: Past History

Had a doctor EVER stated that the deceased had the following diseases?

	1. Yes	2. No	99. Unknown
18. Hypertension	☐	☐	☐
19. Heart disease	☐	☐	☐
20. Stroke	☐	☐	☐
21. Cholesterol problem	☐	☐	☐
22. Diabetes	☐	☐	☐
23. Tuberculosis	☐	☐	☐
24. HIV/AIDS	☐	☐	☐
25. Cancer (write site in narrative)	☐	☐	☐
26. Asthma	☐	☐	☐
27. Other chronic illness (specify in narrative)	☐	☐	☐

28. Was the deceased taking any medications regularly during the last five years? (Record up to three in Hindi or English only).

1. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
2. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
3. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

First, ask the following questions for the deceased (First Column), and then ask them for the main respondent (second column)

Tobacco, alcohol and diet	Deceased (Ask first)	Respondent (Ask second)
29A. Did s/he smoke tobacco within the last 5 years?	1. Definite Yes **2. Definite No** 99. Unknown	1. Definite Yes **2. Definite No** 99. Unknown
29B. If yes, how many bidis per day?		
29C. If yes, how many cigarettes per day?		
29D. Any other tobacco smoked?	1. Definite Yes **2. Definite No** 99. Unknown	1. Definite Yes **2. Definite No** 99. Unknown
30A. Did s/he chew tobacco within the last 5 years?	1. Definite Yes **2. Definite No** 99. Unknown	1. Definite Yes **2. Definite No** 99. Unknown
30B. Did s/he apply tobacco within the last 5 years?	1. Definite Yes **2. Definite No** 99. Unknown	1. Definite Yes **2. Definite No** 99. Unknown
31A. Did s/he normally drink alcohol (use local term) at least once a week during most weeks in the last 5 years?	1. Definite Yes **2. Definite No** 99. Unknown	1. Definite Yes **2. Definite No** 99. Unknown
31B. If yes, what was the average no. of days per week s/he drank?	_____days OR Unknown	_____days OR Unknown
31C. If yes, what type of alcohol was most commonly consumed?	1. Country liquor **3. Indian made foreign liquor** 2. Toddy **4. Beer** 5. Other	1. Country liquor **3. Indian made foreign liquor** 2. Toddy **4. Beer** 5. Other
32. Was s/he a pure vegetarian (consumed no egg, meat or fish) for the last 5 years?	1. Definite Yes **2. Definite No** 99. Unknown	1. Definite Yes **2. Definite No** 99. Unknown

For female deaths aged 15-49 ask:

33. Was she either known or suspected to be pregnant or within 42 days of delivery or abortion?

1. Yes **2. Definite No** *If YES to question Q33 then DO NOT complete narrative below. Instead complete Form 10D and copy the Form 10D number here*

34. Key symptoms preceding death (check all that apply, and then use symptom list for narrative)

1. Coughing of blood	2. Severe shortness of breath	3. Fainting or giddiness
4. Vomitting, loss of appetite, pain in abdomen	5. Yellowish discolouration of eyes and urine	6. Sudden chest pain
7. Irrelevant behavior or talk	8. Palpitations	9. Seizures/fits
10. Fever	11. Weight loss	12. Paralysis/stroke
13. Urinary problems	14. Diarrhoea/dysentery	15. Odeme (swelling)
16. Severe Weakness		

35. Narrative language code

Section 3: Written narrative in local language

Please describe the symptoms in order of appearance, doctor consulted or hospitalization, history of similar episodes, enter the results from reports of the investigations if available.

Respondent's cooperation: 1. Good 2. Poor

Interviewer name: Desig:

Date: D D / M M / Y Y

Signature/Impresion

Respondent

Interviewer

Annexure 31: NTEP PMDT treatment book

Patient's name: _____

Address: _____

_____

Contact no: _____

Episode ID:_____

Type of case: _____
(Hr-TB, MDR/RR-TB , Pre-XDR-TB , XDR-TB)

Treatment initiation date_____

NTEP PMDT Treatment book

DR-TB centre:_____

District _____

State _____

Patient's name: _____

Age: _____years Gender: ☐ Male ☐ Female ☐ Transgender

Address: _____

_____

Marital status: _____ Occupation: _____

Contact no: _____

Aadhaar no. _____

Name, designation of treatment supporter:_____

_____

_____ Contact no:_____

State:_____ District: _____

TB unit: _____ HF:_____

HWC: _____ Name of CHO-HWC: _____

Initial home visit: Date _____ By:_____

DR-TB centre:_____ District _____ State _____

Reason for testing	
☐ New ☐ Previously treated	
☐ Presumptive TB ☐ Private referral ☐ Presumptive NTM	
Presumptive MDR-TB	☐ At diagnosis ☐ Contact of MDR/RR-TB ☐ Follow-up Sm+ve ☐ Private referral ☐ Discordance resolution
☐ Presumptive H mono/poly	
Presumptive XDR-TB	☐ MDR/RR-TB at diagnosis ☐ follow-up culture positive_____month ☐ Failure or recurrent case of MDR/RR-TB regimen ☐ Discordance resolution

Drug susceptibility test (DST) results																								
Date of sample collection	R	H (inhA)	H (katG)	Z	E	S	Km	Cm	Am	Lfx	Mfx (0.5)	Mfx (1)	FQ class	SLID class	SLID (eis)	Eto*	PAS*	Lzd	Cfz*	Clr*	Azi*	Bdq*	Dlm*
Name of the lab														Date of report										
*R: Resistant; S: Susceptible; C: Contaminated; -- Not done *whenever available*																								

Contact investigation	**<5yrs**	**>5yrs**
No. of members screened		
No. of presumptive TB cases identified		
No. of presumptive TB cases evaluated		
No. diagnosed with TB		
No. of DR-TB diagnosed		
No. Eligible on TPT		
No. Initiated on TPT		

HIV testing:

Date:_____

Result:_____

PID number:_____

CPT start date:_____

ART start date:_____

Blood sugar testing:

Date:_____

RBS:_____

FBS:_____

ADT*

(*write date of starting)

Pregnancy: 1st/ 2nd / 3rd trimester / NA

Lactating: Yes / No / NA

TB Site: ☐ Pulmonary ☐ Extra pulmonary

If extra pulmonary, please specify _____

Type of case

☐ H mono/poly DR-TB

☐ MDR/RR-TB

☐ Pre XDR-TB

☐ XDR-TB

Treatment regimen:

☐ H mono/poly regimen

☐ Shorter Oral Bedaquiline-containing MDR/RR-TB regimen

☐ Longer oral M/XDR-TB regimen

☐ BPaL regimen

Initiation date: _____ Registration date: _____

DR-TB centre committee meetings – dates and decisions		
Date	**Decision**	**Duration of indoor stay**

Pre-treatment investigation					
Test	**Date**	**Result (units)**	**Test**	**Date**	**Result (units)**
ALT (SGPT)			Chest X-Ray findings Cavities (Y/N)		
AST (SGOT)					
Bilirubin- Direct -Indirect					
Albumin					
WBC (TC/DC)			ECG (QTc & other findings)		
Haemoglobin			Creatinine		
ESR			Creatinine clearance		
Platelet count			Blood urea		
Lactic acid			Visual acuity		
RBS			Audiogram		
CD4 count			Psychiatric evaluation		Yes/ No
Hepatitis markers			Surgical evaluation		Yes/ No
TSH			Ophthalmic evaluation		Yes/ No
Urine (R/M)					
UPT					
Potassium					
Magnesium					
Calcium					

Initial weight: _____kgs Height:_____cms BMI:

Weight band:

☐ <16 kg ☐ 16-29 kg ☐ 30-45 kg ☐ 46-70 kg ☐ >70 kg

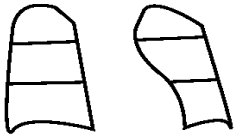
Drug and dosages		
Drugs	**Dose during IP (mg)**	**Dose during CP (mg)**
H		
R		
E		
Z		
Km		
Am		
Cm		
Lfx		
Mfx		
Cs		
Eto		
PAS		
Lzd		
Cfz		
Amx Clv		
Clr		
Bdq		
Dlm		
Name & signature of treating physician: _____		

Month of treat-ment	Smear/Culture results				Other investigations						
	Date	Lab no	Smear	Culture	S. Cr	LFT	ECG*-QTcF	CBC/ platelets	Electrolyte (K, Mg, Ca)	RBS	TSH, T3,T4
2 weeks											
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											
19											
20											
21											

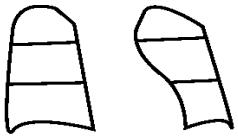
** If baseline ECG is normal, repeat to be done after two weeks, then monthly in IP, and when clinically indicated.*

DST result during course of treatment (LJ/LC/LPA/CBNAAT)				
Specimen collection date				
Drug	Month___	Month___	Month___	Month___
Type of test				
R				
H (inhA)				
H (katG)				
S				
E				
Z				
Lfx				
Mfx (1.0)				
Mfx (0.5)				
Lzd				
Cfz				
Km				
Cm				
Am				
FQ				
SLI				
SLI (eis)				
Eto				
PAS				
Bdq*				
Dlm*				
**Whenever available*				

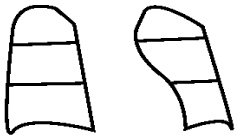
Patient's name:_____



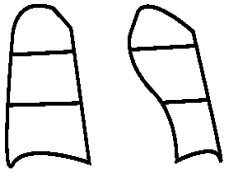
Date :_____
Finding: _____



Date :_____
Finding: _____



Date :_____
Finding: _____



Date :_____
Finding: _____

Date of starting intensive phase: _____

Date of starting continuation phase:_____

Thyroid Function Test		
Month	Zero	Six
Date		
T3		
T4		
TSH		

Details of change in regimen composition during treatment		
Date	**Changed regimen drugs**	**Reason for change**

Administration of drugs (one line per month)

Month & Yr	Day																													Wt in 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	

Month & Yr	Day																														Wt in 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	

Month & Yr	Day																													Wt in 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	

Mark in the boxes: ✓= directly observed; ⓥ Unsupervised; ⓥ = drugs not taken; X = initiation of new box;
Recording of CP should start from fresh line.

Date of retrieval action	By whom	Who contacted	Reason for missed doses	Outcome of retrieval action

Date of adverse drug reaction	Details of symptoms	Action taken

Clinical notes	
Date of visit: Chief complaints: Clinical examination (major findings): Counselling notes: Weight	Investigations Treatment

Clinical notes	
Date of visit: Chief complaints: Clinical examination (major findings): Counselling notes: Weight	Investigations Treatment

Clinical notes	
Date of visit: Chief complaints: Clinical examination (major findings): Counselling notes: Weight	Investigations Treatment

Clinical notes	
Date of visit: Chief complaints: Clinical examination (major findings): Counselling notes: Weight	Investigations Treatment

Clinical notes	
Date of visit: Chief complaints: Clinical examination (major findings): Counselling notes: Weight	Investigations Treatment

Date of clinical follow-up visits		
1st visit: _____	6th visit: _____	11th visit:_____
2nd visit: _____	7th visit: _____	12th visit: _____
3rd visit: _____	8th visit: _____	13th visit:_____
4th visit: _____	9th visit: _____	14th visit:_____
5th visit: _____	10th visit: _____	15th visit: _____
Treatment outcome (cured, treatment completed, died, treatment failed, lost-to-follow-up, not-evaluated)	Date	**Remarks (**provide cause of death, reason for lost to follow-up/failure (culture non-conversion, reversion, ADR, additional drug resistance), latest TB no. in case of failure and put on treatment further)

Post-treatment follow-up clinical & sputum (Result with date)					
Follow-up	**Clinical**	**Smear**	**Culture**	**CXR**	**Impression**
6 months of Rx					
12 months of Rx					
18 months of Rx					
24 months of RX					

General information about disease – patient information booklet (two pages)

Do's and Don'ts for patient
Infection Control
Do's • Cover your mouth with a tissue, handkerchief or upper sleeves of your clothing while coughing. • Wash your hands with soap and water or an alcohol based handwash. • The room where the patient stays for a considerable time should be well ventilated and with proper sunlight. • Any family member who develops cough should also follow similar cough etiquette.
Don'ts • Do not cough and spit in the open. • Do not close or obstruct your windows to ensure proper ventilation.
Nutrition
Do's • Take complete meals inclusive of rice/roti, dal, vegetables, eggs, fish, meat (if available). • At the start of the treatment, there may be some nausea and stomach upset. Kindly consult your doctor for the same.
Don'ts • Do not stop or skip any meal.
Side effects
Do's • If you have any side effects or discomfort on taking treatment, report to your doctor or treatment provider immediately. • For any other illness developed during treatment, report to your doctor or treatment provider immediately.
Don'ts • Be complacent about side effects or discomfort. • Do not try to take medications for side effects on your own.
Carry your treatment booklet whenever you visit any doctor. Take your medicines regularly and complete the full course of treatment as prescribed by your doctor.

Advice on family planning
Infection Control
• All the DR-TB patients are advised to use contraception during treatment period. • If pregnant DR-TB patient, seek expert consultation for advise on medical termination of pregnancy (MTP) and appropriate treatment regimen.

List of drugs that can be used safely or avoided along with Bedaquiline

Group	Safe to use	Drugs to be avoided
Anti-emetics	Metoclopramide	Domperidone, Ondansetron
Analgesics	NSAIDs, Paracetamol	Tramadol
Antacids	Ranitidine, Milk of Magnesia	Pantoprazole, Omeprazole
Anti-histaminics	Pheniramine, Fexofenadine, Cetirizine	Diphenhydramine, Loratadine
Anti-malarials	Artesunate	Chloroquine
Antibiotics	Penicillins, Cephalosporins, Tinidazole	Ciprofloxacin, Norfloxacin, Cotrimoxazole, Metronidazole
Anti-fungals	Terbinafine	Fluconazole, Ketoconazole, Itraconazole
Anti-epileptics	Sodium Valproate	Phenytoin, Carbamazepine, Phenobarbital
Anti-diabetics	Mostly safe	
Anti-hypertensives	Safe (except Diuretics)	Diuretics
Lipid lowering agents		Statins Best to avoid
Antiarrhythmics	Diltiazem, Lignocaine	Amiodarone, Procainamide, Digoxin
Other cardiac drugs	Nitroglycerine, Sorbitrate	Sotalol
Anti-retrovirals	Tenofovir, Zidovudine, Nevirapine, Dolutegravir	Efavirenz, Lopinavir, Ritonavir
Anxiolytics	Benzodiazepines (Alprazolam)	Avoid other sedatives
Anti-psychotics	Risperidone, Lurasidone	Haloperidol, Clozapine, Quetiapine, Olanzapine
Anti-depressants	Best to be avoided, give only if essential with ECG monitoring	Citalopram, Fluoxetine, Sertraline

Annexure 32: aDSM Treatment initiation form

Patient details				Interview Date: _____(DD/MM/YYYY)			
Patient Name ……..		Age:	PMDT No./ File No:_____	Nikshay ID:			
Medical Details							
Type of TB ☐ Pulmonary ☐ Extra-pulmonary TB site/s: _____		Type of drug resistance ☐ H mono/ poly ☐ Pre XDR-TB ☐ XDR-TB					
Pregnancy status (UPT)	☐ Yes ☐ No ☐ Unknown	Date of LMP: DD/MM/YYYY		or estimated current gestation (weeks):			
		If PREGNANT record patient details for follow –up					
Breastfeeding an infant		☐ Yes ☐ No ☐ Unknown					
Addiction or substance abuse							
Injectable Drug abuse Within Past Year	☐ Yes ☐ No ☐ Unknown	Excessive alcohol use in the past year		☐ Yes ☐ No ☐ Unknown			
Tobacco Use Within Past Year	☐ Yes ☐ No ☐ Unknown						
Prior exposure to anti-TB medicines		☐ Yes ☐ No ☐ Unknown					
List the current and past medical conditions & Events (Diabetes, Hypertension, QT prolongation, LFT deranged, Hepatitis, Hypo/hyper thyroidism, Rash, allergic reaction, anaphylaxis, nausea, vomiting, gastritis, diarrhoea, arthralgia, nephrotoxicity, depression, psychotic syndrome, seizures, gynecomastia etc)				Date of Onset	Date of recovery	Still Continue	
						Yes/No	
						Yes/No	
						Yes/No	
						Yes/No	
						Yes/No	
						Yes/No	
Medicines							
Prior exposure to anti-TB medicines	☐ Yes ☐ No ☐ Unknown						
Medicines & traditional medicines taken at any time in PAST 30 DAYS	Indication	Dosage (µ/ mg/g/ ml)	Frequency (OD/BD/ TID)	Route (Oral/IV/ IM/Topical/ other)	Start Date	Stop date	Continues (tick appropriate)
							☐
							☐
							☐
							☐
							☐
							☐
							☐
							☐
							☐
							☐

Any medicines other than anti-TB drugs prescribed at this interview	Indication	Dosage (µ/ mg/g/ ml)	Frequency (OD/BD/ TID)	Route (Oral/IV/ IM/Topical/ other)	Start Date	Anticipated Stop date
Health facility and Reporter information						
Name of treatment initiating health facility: Name of treating clinician/ team: Name of the Reporter: Signature: Date:						

Annexure 33: aDSM Treatment review form

(to be filled when any adverse event reported by the patient on any DR-TB regimen when DAIDS grade 3 or 4-serious adverse event is reported)

<table>
<tr><td colspan="5">PATIENT DETAILS Interview Date: _____(DD/MM/YYYY)</td></tr>
<tr><td colspan="2">Patient Name ……..</td><td>Age: .....</td><td>PMDT No./ File No:_____</td><td>Nikshay ID:</td></tr>
<tr><td colspan="3" rowspan="2">Patient Address:</td><td>Weight (kg):……</td><td rowspan="2">Sex: ☐ Male
☐ Female
☐ Others</td></tr>
<tr><td>Height (cm):……...</td></tr>
<tr><td colspan="5">MEDICAL DETAILS</td></tr>
<tr><td colspan="2">Type of TB
☐ Pulmonary TB
☐ Extra-pulmonary TB site/s: _____</td><td colspan="2">Type of drug resistance
☐ H mono/ poly
☐ RR/MDR-TB</td><td>☐ RR/MDR-TB+ any FQ/SLI
☐ XDR-TB</td></tr>
<tr><td colspan="5">Prior exposure to anti-TB medicines ☐ Yes ☐ No ☐ Unknown</td></tr>
<tr><td rowspan="2">Pregnancy status (UPT)</td><td rowspan="2">☐ Yes ☐ No
☐ Unknown</td><td>Date of LMP: DD/MM/YYYY</td><td colspan="2">or estimated current gestation (weeks):</td></tr>
<tr><td colspan="3">If PREGNANT record patient details</td></tr>
<tr><td colspan="2">Breastfeeding an infant</td><td colspan="3">☐ Yes ☐ No ☐ Unknown</td></tr>
<tr><td colspan="5">ADR description: Reporter's Narrative (Describe the course of events, timing and suspected causes of ADR):</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td colspan="5">For patient under CAP during follow up visit (Fill the details of any event happened since the last follow up visit)
(eg. Minor ADR, Accident, travel, other medication etc)</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td colspan="5">DAIDS grading (Tick appropriate checkbox)
☐ GRADE 1: Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
☐ GRADE 2: Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
☐ GRADE 3: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated
☐ GRADE 4: Potentially life threatening symptoms causing inability to perform basic self-care functions with interventions indicated to prevent permanent impairment, persistent disability or death</td></tr>
<tr><td colspan="2">Date of Onset</td><td colspan="3">DD/MM/YY</td></tr>
<tr><td colspan="2">Date Resolved</td><td colspan="3">DD/MM/YY</td></tr>
<tr><td colspan="2">ADR/SAE Seriousness</td><td colspan="3">☐ Death
☐ Hospitalization required
☐ Life threatening
☐ Prolonged hospitalization
☐ Permanent disability
☐ Congenital anomaly/ birth defect
☐ Other medically important condition
☐ Required intervention to prevent permanent impairment/ damage</td></tr>
</table>

Outcome	☐ Recovered/ resolved ☐ Recovered/resolved with sequel **Recovery date……** ☐ Fatal ☐ Recovering/resolving ☐ Not recovering/ not resolved ☐ Unknown
For Death/SAE	Date of Death……. Primary cause of death (if known): …… Was autopsy performed? ☐ No ☐ Yes (If yes, attach copy of report if available) Hospital Admission Date …… Hospital Discharge Date……

Causality / Relation to medicine	Assign Causality with following grading for suspected drug

Certain	Probable	Possible	Doubtful or Unlikely	Conditional or Unclassified	Un-assessable
H					
R					
E					
Z					
Km					
Am					
Cm					
Lfx					
Mfx					
Cs					
Eto					
PAS					
Lzd					
Cfz					
Amx-Clv					
Clr					
Bdq					
Dlm					
Other					

Dechallenge	☐ No Dechallenge ☐ Reaction Abated ☐ Dose Reduced ☐ Result unknown
Rechallenge	☐ No Rechallenge ☐ Recurrence of event ☐ No recurrence ☐ Result unknown

Expectedness	☐ Expected ☐ Unexpected
If newer drugs (Bdq or Dlm) is suspected ☐ Bdq ☐ Dlm	Start Date of newer drug…… Stop Date of newer drug …… Action taken for suspected drug ☐ No adjustment ☐ Dose Adjusted ☐ Temporary Stop ☐ Permanent Stop If permanent stop, it was provider decision ☐ please specify reason _____ or it was patient decision ☐ please specify reason _____) Batch/Lot No/ Expiry……. Dose…….Frequency…… Route……

LABORATORY & OTHER TESTS					
Test	**Date**	**Result (units)**	**Test**	**Date**	**Result (units)**
Sputum smear			ALT (SGPT)		
Sputum Culture			AST (SGOT)		
Line probe assay			Lactic acid		
Nucleic acid testing			Lipase		
Tuberculin Test			Chest X-Ray		Cavities (Y/N) PI specify Xray findings_____
HIV Antibody			ECG		QTc Any other changes
CD4 Count			Audiometry		
ESR			Visual acuity		
Total WBC			Bilirubin-Direct -Indirect		
Haemoglobin			Hepatitis markers		
Creatinine			TSH		
Creatinine Clearance			Other		
Glucose					
Drug susceptibility					

Medicines								
Anti-TB medicines taken since last interview	**Dosage**	**Frequency**	**Route**	**Start Date**	**Continues**	**If No, Stop date**	**Reason (s) for stopping #**	**Action****
					Yes/ No			
					Yes/ No			
					Yes/ No			
					Yes/ No			
					Yes/ No			
					Yes/ No			
					Yes/ No			
					Yes/ No			
					Yes/ No			
Other medicines & traditional medicines taken since last interview	**Dosage**	**Frequency**	**Route**	**Start Date**	**Continues**	**Stop date**	**Reason (s) for stopping#**	**Action****
					Yes/ No			
					Yes/ No			
					Yes/ No			
					Yes/ No			
					Yes/ No			

All NEW medicines (anti-TB & other) prescribed at this interview	**Dosage**	**Frequency**	**Route**	**Start Date**	**Expected Stop date**	**Indication**

Any other relevant clinical information

REPORTERS INFORMATION
Name of the Reporter: Signature: Date:

** Action taken by clinician in case of suspected adverse event linked to a drug

Dose not changed

Drug withdrawn

Not applicable

Dose reduced

Drug interrupted

Central TB Division
Ministry of Health and Family Welfare
Nirman Bhawan, New Delhi 110011
http://wwwtbcindia.gov.in