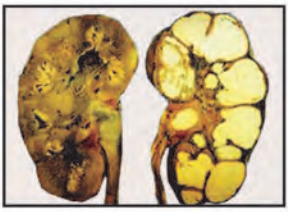
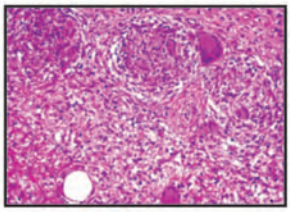
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Genitourinary Tuberculosis



Ganesh Gopalakrishnan
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Genitourinary Tuberculosis

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PREFACE

India accounts for 23% of the global burden of tuberculosis. In 2014 of a total of 9.6 million cases worldwide, 2.2 million cases of tuberculosis were estimated to have occurred in India. Renal tuberculosis is the most common site of extrapulmonary genitourinary tuberculosis (GUTB) comprising of 20% of all extrapulmonary tuberculosis (EPTB).

In 2014, the Central TB Division and Directorate General of Health Services of the Ministry of Health and Family Welfare, Government of India, recognized the need to develop evidence-informed guidelines for EPTB. This was aimed to run concurrently with those for pulmonary tuberculosis from the Revised National TB Control Programme (RNTCP). Unfortunately, evidence-based guidelines for treatment of GUTB are lacking. Should a 6-month regimen be sufficient or should it be 9 months.

While there are individual chapters in various textbooks relating to different aspects of GUTB, a single book devoted to renal tuberculosis is lacking. We, the editors felt that the vast experience in our country by individual physicians should be collated in a comprehensive book which would help urologists enhance their knowledge and also serve to manage our patients effectively.

This has been possible only because of the commitment of the authors who themselves have felt such a need and the untiring efforts of Drs Umesh Shelke and Yash Pamecha both ex-residents of the Urology Department, KEM Hospital, Mumbai.

Ganesh Gopalakrishnan

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ABBREVIATIONS

AKT	Anti-Kock treatment
BDQ	Bedaquiline
C-DST	Culture and drug susceptibility testing
c/o	Complaint of
CAT 1	Category 1
CBNAAT	Cartridges based nucleic acid amplification test
CSIC	Clean self intermittent catheterization
CT	Computed tomography
DDR-TBC	District Drug Resistant Tuberculosis Centre
DMC	Designated Microscopy Centre
DM	Diabetes mellitus
DR-TB	Drug-resistant tuberculosis
DST	Drug Susceptibility Testing
DVDMS	Drug Vaccine Distribution Management System
e/o	Evidence of
EPDR-TB	Extrapulmonary drug-resistant tuberculosis
EP	Extrapulmonary
EPTB	Extrapulmonary tuberculosis
ESRD	End-stage renal disease
FL-LPA	First line probe assay
GUTB	Genitourinary tuberculosis
h/o	History of
HIV	Human immunodeficiency syndrome
IVP	Intravenous pyelography
k/c/o	Known complaint of
LPA	Line probe assay
LUTS	Lower urinary tract symptoms
MDR-TB	Multidrug resistant tuberculosis
MRI	Magnetic resonance imaging
MR-TB	Mono-resistant tuberculosis
PDR-TB	Poly-drug resistant tuberculosis
PMDT	Programmatic management of drug-resistant tuberculosis
PTB	Pulmonary tuberculosis
r/o	Resident of
RNTCP	Revised National Tuberculosis Control Program
RRTB	Rifampicin-resistant tuberculosis
s/o	suggestive of
TBC	Tuberculosis contact
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

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CHAPTER 2

Excerpts from Guidelines on Management of Drug-resistant Tuberculosis

Sujata Patwardhan, Narendra Sutar

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"Taken from the Revised National Tuberculosis Control Programme, Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Nirman Bhavan, New Delhi."

These national guidelines are available on the internet; however, they pertain to pulmonary tuberculosis (TB).[1-5]

Not every consultant or student have time to access to this guidelines and hence certain sections relevant to genitourinary TB (GUTB) and important parts of these guidelines are included in this chapter to help in understanding of our national program and be a part of it by following the guidelines.

The salient topics covered are:

1. Definitions and classification of drug-resistant TB (DR-TB) patients
2. State-level structure and responsibilities
3. Methods for drug-susceptibility testing (DST)
4. Choice of diagnostic technology
5. Specimen collection and transportation to culture and drug-susceptibility testing (C-DST) laboratories
6. Integrated DR-TB diagnostic algorithm
7. Treatment of drug-resistant TB
8. Newer anti-TB drugs
9. Regulatory approvals for bedaquiline in India
10. Integrated DR-TB algorithm
11. Management of DR-TB in extrapulmonary TB patients
12. Management of contacts of DR-TB
13. RNTCP laboratory register for culture, CBNAAT, and DST
14. RNTCP PMDT referral for treatment form
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16. Infection control measures
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DEFINITIONS AND CLASSIFICATION OF DRUG-RESISTANT TUBERCULOSIS PATIENTS

The following are the definitions and classification for DR-TB patients:
Presumptive DR-TB:
It refers to the following patients in order of their risk:

- TB patients found positive on any follow-up sputum smear examination during treatment with first-line drugs including treatment failures.
- Pediatric TB nonresponders
- TB patients who are contacts of DR-TB
- Previously treated TB patients
- New TB patients with HIV co-infection
- All notified new TB patients

A patient is confirmed to have DR-TB only when the results are from a Revised National Tuberculosis Control Programme (RNTCP) quality-assured C-DST laboratory and by a RNTCP-endorsed testing method. Such patients are classified according to the following definitions:

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

Although new TB patients from above-mentioned categories are at the lower risk of drug resistance, testing them further for presence of drug resistance at the time of diagnosis is a necessary standard of care.

- *Rifampicin resistance* (RR): 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 MR, poly-resistance, MDR, or XDR.
- *Multidrug resistance* (MDR): 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 also have additional resistance to any/all FQ OR any/all second-line injectable (SLI) anti-TB drugs.
- *Extensive drug resistance* (XDR): A MDR-TB patient whose biological specimen is additionally resistant to at least a FQ (Ofx, Lfx, Mfx) and a SLI anti-TB drug (Km, Am, and Cm).

It is to be noted that R resistance is quite rare without H resistance. Majority of DST results with R resistance will also be H resistant, i.e., MDR-TB. This has been substantiated in the National Drug Resistance Survey (2014–16).[6] Therefore, RNTCP has taken the programmatic decision that patients, who have any R resistance, should be managed as if they are an MDR-TB patient and this is in line with the World Health Organization (WHO) global guidelines for the programmatic management of drug-resistant TB (PMDT).

STATE-LEVEL STRUCTURE AND RESPONSIBILITIES

The National Expert Technical Working Group has developed national policies, and technical and operational guidelines. The state level is where the majority of planning

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activities, implementation, and monitoring occur. The State PMDT Committee is responsible for developing the plan of action for implementation, expansion, maintenance, and supervision, monitoring and quality enhancement of PMDT services in the respective state.

Drug-resistant Tuberculosis Center

Treatment of DR-TB is not completely based on centralized and institutionalized care for the entire duration. In fact, clinical care needs the presence of a clinical and patient support expert resource center. This is the DRTBC which is a 20–30-bedded tertiary care facility established to serve a population of approximately 10 million, with an airborne infection.

Overall PMDT structures and roles are:

- Diagnose rifampicin-resistant patients at district level
- Receive diagnostic/follow-up specimens
- Provide rapid results to district field and DR-TB center
- Maintain records and NIKSHAY
- Quality assurance of results
- Maintain ward and airborne infection control (AIC) measures
- Pretreatment evaluation
- Start MDR/XDR-TB treatment
- Consult for complications
- Clinical expert resource
- Maintain records and NIKSHAY
- Identify suspects and refer specimens
- Coordinate for test results
- Refer patients to N/DDR-TBC (nodal/district DR-TB center)
- Coordinate care and drug flow from district drug store to field level
- Maintain records, NIKSHAY, monitor, and supervise
- Prepare and ship drug boxes to district level
- Manage supply chain for diagnostics and drugs
- Maintain records, NIKSHAY, and DVDMS (Drug vaccine distribution management system)
- Initiate patient on standard DRTB regimen (MDR/RR-TB, H mono-/poly-DR-TB patients)
- Manage adverse drug reaction (ADR)
- Maintain records and NIKSHAY
- Identify presumptive case and refer specimens
- Support, supervise, and manage DR-TB patients
- Communicate results to patients
- Manage minor adverse effects
- Refer patient for the treatment initiation
- Collect and refer follow-up specimens.

METHODS FOR DRUG SUSCEPTIBILITY TESTING

Presently, drug resistance detection using the following technologies is available for diagnosis of DR-TB through rapid molecular diagnostic testing:

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Line probe assay (LPA) for detection of *Mycobacterium tuberculosis* (MTB) complex and resistance to first-line drugs R, H and second-line drugs class FQ and class SLI drugs[7,8] and cartridge-based nucleic acid amplification test (CBNAAT) Xpert MTB/rifampicin testing using the GeneXpert platform for now.[8]

Growth-based phenotypic drug susceptibility testing: Culture, though a highly sensitive and specific method for TB diagnosis, requires 2–8 weeks to yield results and hence does not help in early detection. However, culture will be used for long-term follow-up of patients on DR-TB treatment and help detect early recurrence in both drug-sensitive and DR-TB. The growth-based phenotypic culture methods include automated liquid culture (LC) systems, e.g., BACTEC MGIT 960, BacT/Alert or VersaTREK, and solid [Löwenstein–Jensen (LJ)] media.

Rapid molecular drug resistance testing: LPA provides rapid diagnosis of R and H resistance as well as resistance to class FQ and class SLI drugs. LPA can yield results in 72 hours.

Nucleic acid amplification test (NAAT) provides accurate and rapid diagnosis of TB by detecting MTB and R resistance conferring mutations.[8] The test can be performed on both respiratory and nonrespiratory specimens and yield results in 2 hours. Presently, under RNTCP, its use is recommended for diagnosis of DR-TB in presumptive DR-TB patients and TB in children, extrapulmonary TB (EPTB) and in key population such as people living with HIV (PLHIV), socially and clinically vulnerable groups and for active case finding efforts.

Drug resistance status is determined by either of the following methods:

- *Drug resistance tests (DRTs) using molecular methods*: This can be performed on sputum specimen (direct) or on culture isolates (indirect) for diagnostic purpose. The methods are PCR-based and cannot be used for determining response to treatment. The tests that belong to this group include:
  - *CBNAAT*: It can be performed on smear-positive, smear-negative and EP specimens. The test detects TB and resistance to R LPA is performed on smear-positive specimen. The test detects TB and resistance to R and H [first-line LPA (FL-LPA)] as well as class FQ and class SLI [second-line LPA (SL-LPA)].
- *Drug susceptibility test*: These are growth based tests and can be performed on LJ culture isolates or in LC system mycobacteria growth indicator tube (MGIT) for both pulmonary and EP specimen. Most commonly used method for testing is the economic variant of the proportion sensitivity. MGIT is preferred method for DST and both first- and second-line anti-TB drugs can be tested. Following drugs can be tested for susceptibility by LC:
  - *First-line drugs*: R, H, Z*
  - *Second-line drugs*: Lfx, Mfx, Km, Cm, Am -
  - *Other drugs*: Lzd, Cfz*, Bdq*, Dlm*, etc.

  *When standardized, the WHO endorsed and approved for use in program.

CHOICE OF DIAGNOSTIC TECHNOLOGY

The program has substantially scaled up the laboratory capacity of various C-DST laboratories. The choice of technology to be used for diagnosis of DR-TB has been determined as per recommendations of the National Laboratory Committee. The choice of technologies is given in the following text.

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Drug Resistance Diagnostic Technology Choice

Following are the choices for drug resistance diagnostic technology:

- *First*: CBNAAT/LPA
- *Second*: LC isolation and LPA DST
- *Third*: LC isolation and liquid DST

All the follow-up cultures will be done through the LC. If the state is facing challenges, with respect to follow-up culture by LC, this may be communicated to the Central TB Division for facilitation.

Specimen Collection and Transportation to C-DST Laboratories

Obtaining good quality specimens of adequate volume is critical to ensuring correct diagnosis. Though the guidelines are specifically mentioned only sputum, the same are applicable to a collected specimen. The Laboratory technician needs to explain the process of collecting "a good-quality sputum specimen" while adhering to AIC measures. The program recommends collection of sputa one spot and one morning, OR two spot specimens collected within a gap of at least 1 hour (if the patient is coming from a long distance OR she/he is unlikely to return to give the second specimen). Ideally, a sputum specimen should have a volume of 2–5 mL and preferably be mucopurulent. Care should be taken to ensure that specimens sent for molecular testing are not heavily blood stained or contaminated. It is advisable to let the hemoptysis subside before collecting the specimen. The patient must be advised to collect the specimen in a sterile container (50-mL conical tube) after thorough rinsing of the mouth with clean water. Specimens should be transported to the laboratory as soon as possible after collection. In case of leakage or spillage of specimen during transportation leading to nontesting of specimen, special care should be taken to ensure recollection of specimen.

As per the diagnostic algorithm, two fresh specimens need to be collected at designated collection centers [designated microscopy center (DMC) or peripheral health institute (PHI) level] by trained laboratory technician (LT) and transported in a cool chain on the same day to the nearest CBNAAT laboratory for all eligible patients. At the CBNAAT site, the test is performed. For all results reported as TB [rifampicin-susceptible (RS) and RR], the second specimen needs to be repacked by the CBNAAT LT and transported to the RNTCP C-DST laboratory on the same day in cool chain. The request form (RNTCP request form for examination of biological specimen for TB) updated with the CBNAAT result should be sent along with the transported specimen. Simultaneously, the result of CBNAAT test is to be communicated to the patient and provider. At the C-DST laboratory, SL-LPA is performed for RR-TB and FL-LPA for RS-TB. All specimens need to be delivered to the RNTCP C-DST laboratory within 48–72 hours of collection. Ideally, an agency (courier/speed post) should be identified for this purpose by the concerned district TB officer (DTO). NGOs may be engaged as per partnership guidelines for specimen transportation in cool chain. If none is available, transporter need to be identified from the health system/community to transport the specimen in biosafe conditions with appropriate enablers. Models for packaging specimens are given in **Figure 2.1**. The following points are critical for the collection of fresh sputum specimens at designated collection points:

- 50-mL conical bottom tubes (made of polypropylene material) and the three-layer packing materials such as thermocol box, ice gel pack (pre-freezed at –20°C for 48 hours), request form for examination of biological specimen for TB, polythene bags, tissue paper roll as absorbent, parafilm tapes, brown tape for packaging box,

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FIG. 1: Technical specifications of transport box for sputum specimen transportation in cool chain.

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permanent marker pen, labels, BIOHAZARD sticker, scissors, and spirit swab should be supplied to the DMCs for collection of sputum through the DTO.

- About 50-mL conical tubes should carry a label indicating the date of collection of the specimens along with patient's details such as name, date of specimen collection, name of DMC/District Tuberculosis Center (DTC), Lab. No:- XYZ, and specimen A or B.
- Laboratory technician at DMCs should be trained to carefully to pack the sputum specimens in the cool box to avoid spillage of the specimens.
- Laboratory technician of DMC issuing the conical tubes to the patients should give clear instructions to the patients on correct technique of collection of the sputum. Also the date of issue of the conical tubes to the patient should be recorded.
- Laboratory technician of DMC should ensure that the request form for examination of biological specimen for TB is packed in a separate plastic zip pouch and placed in the cool box before sealing the lid of the box. Also, the BIOHAZARD symbol should be pasted on the external side of the cool box along with the label indicating the postal address of the C-DST laboratory assigned.
- Laboratory technician of DMC should promptly inform the specimen transport agency such as a courier/speed post service to collect and transport the specimens.
- As per national guidelines on biomedical waste management the containers used for transporting sputum specimens to the C-DST laboratory should be labeled with a "BIOHAZARD" sticker.

INTEGRATED DR-TB DIAGNOSTIC ALGORITHM

The vision of the program is to offer DST to TB patients at the earliest time in their diagnostic process. The integrated diagnostic algorithm starts with two groups of patients who are either presumptive TB or diagnosed TB. The main objective of this algorithm is to segregate people based on risk assessment for DR-TB and offer DST-guided treatment based on drug-resistance status at least for R resistance at the time of diagnosis of TB, i.e., Universal DST. The subsequent time points when DST is offered if any of the following events occur during the course of a TB treatment schedule:

- Bacteriologically positive after intensive phase of a course of TB/DR-TB treatment
- Failure to respond to treatment as per RNTCP definitions
- Recurrence of TB diagnosed after a course of TB treatment
- For patients who are retrieved after lost to follow-up
- For patients found to be HIV positive before or anytime during the course of TB treatment
- Any other reason as per treating physicians' advice.

Two diagnostic specimens would be collected from the patients one early morning and one spot specimen wherever possible, but if there is a likelihood of the patient not returning for the second collection or traveling from long distance then two spot specimens may be collected with a gap of at least 1 hour. The DR-TB diagnostic algorithm is as given in **Flowchart 2.1**.

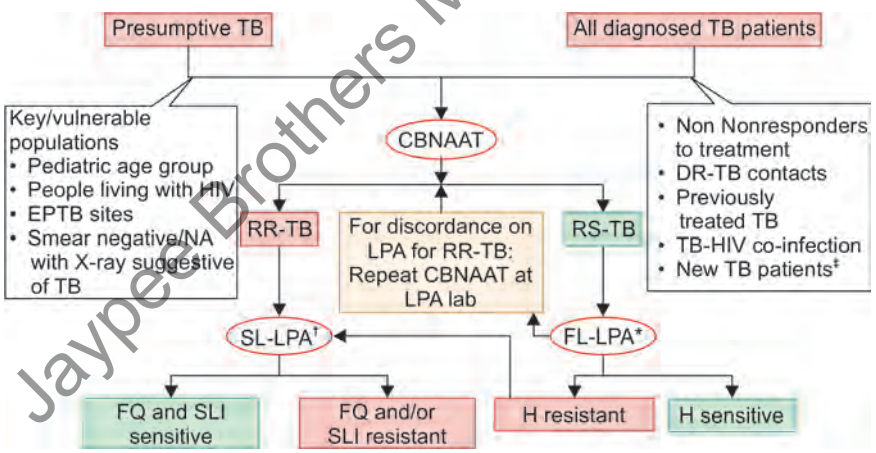
Persons presumed to have TB are:

- From this group those belonging to the pediatric age group
- PLHIV
- EP group or with a smear-negative chest X-ray suggestive of TB will be offered CBNAAT test.

By virtue of using CBNAAT as the TB diagnostic test, the R status is also available simultaneously along with TB detection.

The integrated DR-TB diagnostic algorithm 2020 guidelines has been shown in **Flowchart 2.2**.

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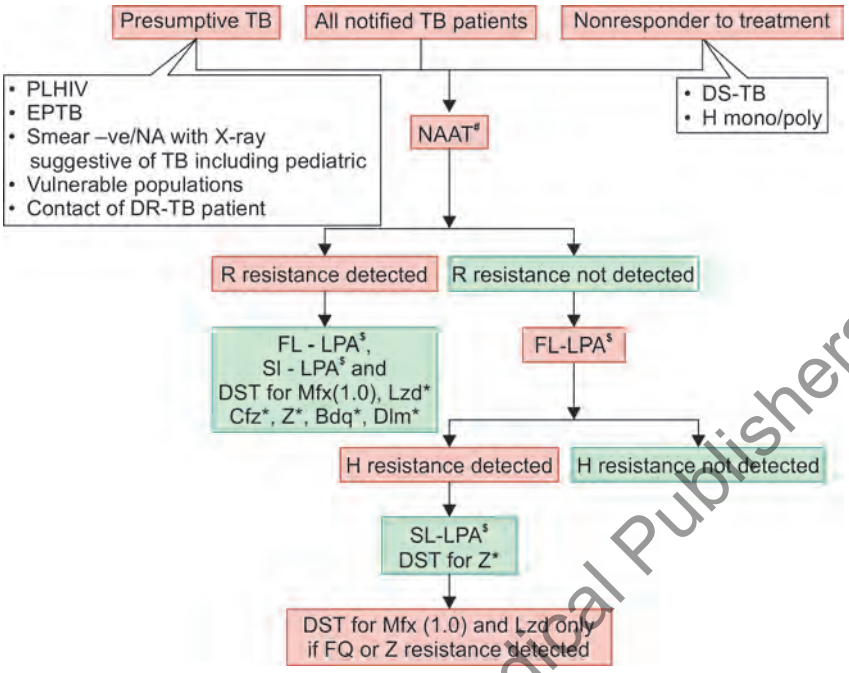
* Offer molecular testing for H mono/poly resistance to TB patients prioritized by risk as per the available lab capacity

† LC DST (Mfx 2.0, Km, Cm, Lzd) will be done only for patients with any resistance on baseline Sl-LPA. DST to Z, Cfz, BDQ and DLM would be considered for policy in future, whenever available, standardized and WHO endorsed.

‡ States to advance in phased manner as per PMDT Scale up plan for universal DST based on lab capacity and policy on use of diagnostics.

(CBNAAT: cartridge-based nucleic acid amplification test; DR-TB: drug-resistant TB; DST: drug-susceptibility testing; EPTB: extrapulmonary TB; FL-LPA: first-line line probe assay; FQ: fluoroquinolone; LC: liquid culture; NA: not available; PMDT: programmatic management of drug-resistant TB; RR-TB: rifampicin-resistant TB; RS: rifampicin-susceptible TB; SL-LPA: second-line line probe assay; SLI: second-line injectable; TB: tuberculosis)

FLOWCHART 2.1: Drug-resistant tuberculosis diagnostic algorithm guidelines 2019.



NAAT include CBNAAT and TruNAAT
* Whenever available
$ Culture isolated to be subjected to LPA for smear negative specimens

FLOWCHART 2.2: The integrated DR-TB diagnostic algorithm guidelines 2020.

TREATMENT OF DRUG-RESISTANT TUBERCULSOSIS

This section provides guidance on the treatment of all forms of DR-TB patients.

Classes of Anti-TB Drugs Recommended for Treatment of DR-TB Patients

The anti-TB drugs recommended for treatment of MDR/RR-TB patients are grouped based on efficacy, experience of use, and drug class and aligned with revised classification as per the WHO PMDT Guidelines 2016. The same is explained in **Table 2.1**.[9]

Newer Anti-TB Drugs

After almost five decades of discovery of rifampicin, the first new drug named bedaquiline (Bdq) with anti-TB effect was approved for treatment of MDR-TB by the US Food and Drug Administration (FDA) in late 2012.[10] This was followed by the approval of another new drug delamanid (DLM) by the stringent regulatory authority of various countries.[11] The drug development pipeline of new and repurposed drug has gained momentum in the recent past and more new molecules are expected to be approved in the future.

Bedaquiline is a new class of drug, diarylquinoline, that specifically targets mycobacterial ATP synthase, an enzyme essential for the supply of energy to MTB. Strong bactericidal and sterilizing activities against MTB have been shown in preclinical,

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TABLE 2.1: Recommended anti-TB drugs for treat of MDR-/RR-TB patients.[3]

New grouping of drugs		
A. Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)	Am Cm Km (S)
C. Other second-line agents	Ethionamide/Prothionamide Cycloserine/Terizidone Linezolid Clofazimine	Eto/Pto Cs/Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	D1 Pyrazinamide Ethambutol High-dose isoniazid	Z E H^{h}
	D2 Bedaquiline Delamanid	Bdq Dim
	D3 p-aminosalicylic acid Imipenem-cilastatin Meropenem Amoxicillin-clavulanate (Thioacetazone)	PAS Ipm/Cls Mpm Amx-Clv (T)

(MDR-TB: multidrug-resistant tuberculosis; RR-TB: rifampicin-resistant TB)

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laboratory, and animal experiments. The drug has a high volume of distribution, with extensive tissue distribution, highly bound to plasma proteins and is hepatically metabolized. The drug has an extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping Bdq. The dosing schedule has been established after extensive pharmacokinetic/pharmacodynamic (PK/PD) studies in animals and humans and hence needs to be administered as per the manufacturer's advice. Bdq has shown significant benefits in improving the time to culture conversion in MDR-TB patients.[10]

Delamanid, as per an interim policy guidance document released by the WHO in 2014, may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB.[11] The process for introduction of DLM under RNTCP is ongoing and guidance for the same will be released subsequently as an addendum to these guidelines.

Regulatory Approvals for Bedaquiline in India

On December 24, 2014, the Apex Committee under the Ministry of Health and Family Welfare, Government of India for supervising clinical trials on new chemical entities in the light of directions of the Supreme Court of India approved the use of Bdq (100 mg) in adults aged 18 years and above as part of a combination therapy of pulmonary TB due to MDR-TB.

Considering MDR-TB as a serious condition with high mortality and a disease of special relevance in the Indian health scenario, the committee recommended waiver of local

clinical trials at this stage and approved Bdq with restriction that it shall be used under the RNTCP framework for conditional access through the PMDT program for treatment of MDR-TB patients only.

Criteria for Patients to Receive Bedaquiline

Inclusion criteria: The criterion for patients to receive Bdq as approved by the Apex Committee is—adults aged >18 years having pulmonary MDR-TB.

Additional requirements:

- Nonpregnant females or females not on hormonal birth control methods are eligible. They should be willing to continue practicing birth control methods throughout the treatment period or have been postmenopausal for past 2 years.
- Patients with controlled stable arrhythmia can be considered after obtaining cardiac consultation.

Exclusion criteria:

- Currently having uncontrolled cardiac arrhythmia that requires medication
- Having any of the following QT/QTc interval characteristics at screening—marked prolongation of QT/QTc interval, e.g., repeated demonstration of QTcF (Fredericia correction) interval >450 ms; and history of additional risk factors for Torsade de Pointes, e.g., heart failure, hypokalemia, family history of long QT syndrome.

Bedaquiline is provided along with a background regimen based on DST results. Certain conditions as listed below should be taken into consideration while choosing the drugs for the background regimen in patients who:

- Have evidence of chorioretinitis, optic neuritis, or uveitis at screening which precludes long-term Lzd therapy.
- Have the following laboratory abnormalities (DAIDS grading of adverse events):
  - Creatinine grade 2 or greater, i.e., >1.5 times the upper limit of normal (ULN);
  - Hemoglobin grade 4 (<6.5 g/dL)
  - Platelet count grade 3 or greater (≤49,999/mm^3);
  - Absolute neutrophils count grade 3 or greater (≤749/mm^3);
  - Aspartate aminotransferase (AST) grade 2 or greater (>2.5 times ULN)
  - Alanine aminotransferase (ALT) grade 2 or greater (>2.5 times ULN)
  - Total bilirubin grade 2 or greater (>1.6 times ULN)
  - Lipase grade 2 (with no signs or symptoms of pancreatitis) or greater (>1.5 times ULN).

  Note: If results of the serum chemistry panel, hematology or urinalysis are outside the normal reference range (including above-listed parameters), the patient may still be considered if the physician judges abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable. Hypokalemia, hypomagnesaemia, and hypocalcaemia should be corrected prior to a patient receiving Bdq.

Patients who are not found to be eligible for a Bdq-containing regimen would have DST results for the key first-line and second-line drugs and managed with DST-guided regimens.

Bedaquiline is indicated in adult MDR-TB patients not eligible for the newly WHO-recommended shorter regimen.[12]

These may include:

- MDR-/RR-TB patients with resistance to any/all FQ *OR* to any/all SLI
- XDR-TB patients

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- Mixed pattern-resistant TB patients
- Treatment failures of MDR-TB + FQ/SLI resistance *OR* XDR-TB
- MDR-/RR-TB patients with extensive pulmonary lesions, advanced disease and others deemed at higher baseline risk for poor outcomes.[12]

Caution must be exercised that Bdq is not added to a failing regimen in any patient already on DR-TB treatment.

Integrated Drug-resistant Tuberculosis Algorithm

The integrated DR-TB algorithm (**Flowchart 2.1**) clearly indicates the management strategies to be followed right from the day the results of CBNAAT test are available. These management strategies are described in subsequent sections of this document. The program is improving laboratory capacity to offer DST for all TB patients (Universal DST). An integrated algorithm offers FL-LPA for the presumptive DR-TB found R sensitive on CBNAAT. The LPA will be primarily utilized to do DST for second-line drugs and to test FL-LPA to detect H mono-resistance as per the available laboratory capacity. The program would continue building capacity of the laboratories to eventually test all R-sensitive patients on LPA to detect H mono-resistance that would serve as a surrogate for poly-drug resistance. These patients would be managed as per the algorithm. Within the first 2–3 months, patients would receive the LC-DST results, reach their final classification, and treated with the appropriate regimen.

MANAGEMENT OF DR-TB IN EXTRAPULMONARY TB PATIENTS

Management of bacteriologically confirmed EP DR-TB patients will be considered by the program provided the diagnosis is made by an RNTCP C-DST laboratory. **Treatment regimen and schedule for EP DR-TB patients will remain the same as for pulmonary DR-TB**. Patients must be registered in the PMDT register and the treatment outcome of treatment completed will be considered.

Investigations and Pretreatment Evaluation

Patients would be sent to the DR-TBC for pretreatment evaluation and treatment initiation. EP DR-TB patients will undergo all those pretreatment investigations as done for pulmonary DR-TB patients as part of pretreatment evaluation prior to initiating regimen for DR-TB.

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

Initiation of Treatment

After pretreatment evaluation, treatment for EP DR-TB should be initiated based on weight of the patient. Treatment regimen, weight band, and schedule for EP DR-TB patients will remain the same as for pulmonary DR-TB.

Monitoring Progress During Treatment and Follow-up

Post treatment monitoring and follow up recommended for MDR/RR-TB patients both pulmonary and extra pulmonary as well as for paediatric TB cases are based on classification as per the WHO PMDT guidelines 2016. The same is explained in **Table 2.2**.

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TABLE 2.2: Follow-up schedule.

Type of cases	Follow-up schedule	Extension of treatment	Action on follow-up positive	Long-term follow-up
Drug-sensitive pulmonary TB (New and Previously treated TB)	• Microbiological: One specimen at the time of completion of the intensive phase of treatment • Weight: Monthly • Chest X-ray: If required • Physician evaluation: Whenever required	Extension of IP is not required	If the sputum smear is positive in follow-up at any time during treatment, DST should be done as per presumptive DR-TB case	After completion of treatment the patients should be followed up with clinical and/or sputum examination at the end of 6, 12, 18, and 24 months
Multidrug-resistant pulmonary TB (with or without additional drug resistance)	• Microbiological: One sputum specimen will be collected and examined by culture at least 30 days apart from the 3rd to 7th month of treatment (i.e., at the end of the months 3, 4, 5, 6, and 7) and at 3-monthly intervals from the 9th month onwards till the completion of treatment (i.e., at the end of the months 9, 12, 15, 18, 21, and 24). If any culture during CP or end of treatment is positive then it should be followed by monthly culture for 3 months • Weight: Monthly • Chest X-ray: At the end of IP, end of treatment and whenever clinically indicated • Physician evaluation including adverse drug reaction monitoring every month for 6 months, then every 3 months for 2 years	• In MDR-TB cases IP can be extended for maximum 3 months (maximum duration of IP: 9 months). • In all MDR-TB with additional drug resistant cases (including XDR-TB) patients, IP can be extended for maximum 6 months (maximum duration of IP: 12 months)	On follow-up, if sputum culture is found to be positive at 6 months or later, repeat DST for second-line drugs to decide on further course of action. DST to other additional second line drugs may also be done if laboratory facilities are available to guide treatment	

Continued

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Continued

Type of cases	Follow-up schedule	Extension of treatment	Action on follow-up positive	Long-term follow-up
	• S. creatinine monthly for first 3 months then every 3 months during the injectable phase • Thyroid function test during pretreatment evaluation and whenever indicated • For additional drug resistance: ECG once a month in IP whenever moxifloxacin is used • Complete blood count with platelets count: Weekly in first month, then monthly to rule out bone marrow suppression and anemia as a side effect of Linezolid • Renal function test: Monthly creatinine and addition on monthly serum electrolytes to the monthly creatinine during the period then injection capreomycin is being administered • Liver function tests: Monthly in IP and 3 monthly during CP • Chest X-ray: Every 6 months in XDR-TB patients			
Mono- /Poly-drug resistant Pulmonary TB	Microbiological: One sputum specimen is collected and examined with smear and culture at 2nd and 3rd months and then culture examination at 3 monthly intervals till completion of treatment	IP can be extended for maximum 3 months (maximum duration of IP: 6 months)	If the sputum/ culture is positive in follow up at any time during treatment, DST should be done as per presumptive DR-TB case	After completion of treatment the patients should be followed up with clinical and/or sputum examination at the end of 6, 12, 18, and 24 months

Continued

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Type of cases	Follow-up schedule	Extension of treatment	Action on follow-up positive	Long-term follow-up
Extrapulmonary TB	• Weight: Monthly • Chest X-ray: If required • Physician evaluation: Whenever required • In patients with extrapulmonary tuberculosis, the treatment response is best assessed clinically. The help of radiological and other relevant investigations may also be taken as above	• Extension of IP or and/or CP in DS-EPTB may be required in consultation with the specialist concerned • Extension of IP DR-TB EPTB may be required in consultation with the specialist concerned • Refer to guidelines for EPTB duration of treatment		
Pediatric TB	• In children, who are unable to produce sputum, the response to treatment may be assessed clinically. The help if radiological and other relevant investigations may also be taken	Same as above		

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Clinical monitoring is the most important criteria for the follow-up of patients with EP DR-TB. Regular patient monitoring and periodic follow-up of nodes and other EP symptoms with culture from the discharging node/sinus are the key in monitoring of treatment in EP lymph nodal DR-TB.

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

Clinical monitoring: This is important in case of EP DR-TB. Monitoring and follow-up can be done clinically based on the following:

- Weight gain
- Decrease or increase in symptoms (healing of ulcer/scrofuloderma)
- Increase or regression in size of nodes [possibility of Immune Reconstitution Inflammatory Syndrome (IRIS) to be considered and differentiated from disease progression].
- Appearance of new nodes

- If chest symptomatic, monthly sputum for AFB and chest X-ray (to rule out pulmonary involvement).
- Other EP sites to be monitored (USG abdomen, if necessary)
- Serum creatinine—monthly for first three months of treatment and then quarterly till the patient receives Km and further when clinically indicated.
- Liver function test, as clinically indicated
- Monitoring for drug adverse reactions

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

Management of Contacts of Drug-resistant Tuberculosis

"Close contacts" of DR-TB patients are defined as people living in the same household as the index patient, or spending many hours a day together with the patient in the same indoor space. Contact tracing is an underutilized strategy that can stop the transmission of multidrug-resistant strains. Studies have shown that contact investigation is a high-yield strategy that, in many high-burden TB countries, probably merits more resources even for regular, drug-susceptible TB patients.[13]

All close contacts of DR-TB patients should be identified through contact tracing and evaluated for active TB disease as per RNTCP guidelines.

If the contact is found to be suffering from pulmonary TB disease, irrespective of the smear-based microbiological confirmation, she/he will be identified as a "Presumptive DR-TB." The patient will be initiated on regimen for new or previously treated patient based on their history of previous anti-TB treatment. Simultaneously, two sputum specimens will be transported for culture and DST to an RNTCP-certified C-DST laboratory where she/he will be evaluated as per DR-TB diagnostic algorithm.

If the patient is confirmed as having DR-TB, appropriate DR-TB treatment must be initiated. Further, the patient will be sent to the DDR-TBC ward for pretreatment assessment and initiation of appropriate regimen. Among asymptomatic contacts of patients with DR-TB, it would be important to rule out active TB by appropriate clinical examination and investigation. Although alternative prophylaxis treatments have been suggested, there is no consensus regarding the choice of drug(s) and the duration of treatment. Prompt treatment of DR-TB in index case is the most effective way of preventing the spread of infection to others. There are multiple opportunities to investigate contacts of DR-TB patients, namely:

- *Patient:* Contact investigation starts with education of the DR-TB patient. Patients should be educated about the infectiousness of their disease and the high-risk of transmission to contacts who share the same living space. While they should not be unduly alarmed, they should be informed that their family members are likely already infected with DR-TB, so the most important intervention is to monitor them closely for symptoms of active TB.
- *Family*: One of the most important reasons to do a home visit for every DR-TB patient at the initiation of DR-TB treatment is to do contact investigation. A community nurse or healthcare provider should educate the family that they are all likely already infected with DR-TB, and explain the importance of notifying the community or clinical team quickly about family members who develop symptoms of active TB.
- *Clinical team*: The clinical team has multiple opportunities to inquire about the health of the DR-TB patient's family contacts. At every clinical evaluation, doctors and nurses should ask the patient whether any family member has developed TB symptoms.

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- *Community nurses or healthcare providers educated on DR-TB*: During home visits to check adherence or assess the social situation, the community nurse should enquire if there are any family members who have developed symptoms of active TB. The community nurse may directly interview family members at their home as they are best suited to address fears or doubts about the health system or other social barriers to treatment for DR-TB contacts.
- *Community health workers*: In community-based programs that incorporate home-based treatment support, community health workers are the closest to the family and are most likely to identify family members with TB symptoms. This is particularly true for members of the extended family who visit periodically. The following measures should be taken to prevent spread of DR-TB infection:
  - Early diagnosis and appropriate treatment of DR-TB patients.
  - Counseling patient and family on infection control measures such as cough etiquette and sputum disposal.
  - Screening of contacts as per RNTCP guidelines.
  - Further research into effective and nontoxic chemoprophylaxis in areas of high DR-TB prevalence.

Management of Contacts of Drug-resistant Tuberculosis

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 comprehensive request form for examination of biological specimen for TB is to be used for requesting for microscopy, CBNAAT or culture DST, or chest X-ray or TST, or any other tests. It is essential to record patient details, reason for testing, and type of tests requested. The front page of the form is for recording patient details, reason for testing (diagnosis or follow-up), test requested, result of sputum smear microscopy and NIKSHAY ID (expected in case of notified TB patient subjected for DR-TB screening). This form should be filled by the staff of the health facility that is sending the specimen with a request for examination and expected to be transported along with specimen to the concerned laboratory or health facility for the requested test. Back page is to report the results of CBNAAT, LPA, DST, and any other tests requested.

For all specimens sent from peripheral health institutes, test requests should be initiated from the specimen collecting health facility and entered in NIKSHAY/e-NIKSHAY on the spot in real time. This will enable instant online intimation about the upcoming specimen at the health facility (CBNAAT 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/e-NIKSHAY on real time to save time required to scan results and send it to the concerned health facility. Final report of the test may be printed out through NIKSHAY at any health facility. Real-time data entry helps the program to disseminate information at all levels such as N/DDR-TBC, district, TU, and PHI to initiate reflex actions for further patient management on real-time basis.

RNTCP Laboratory Register for Culture, CBNAAT, and Drug-susceptibility Testing

The RNTCP laboratory register for culture, CBNAAT, and DST is used to record CBNAAT, LPA, and culture and DST examination results. This will be maintained by the concerned laboratory staff. Results of all specimens tested at these sites are expected to be entered in NIKSHAY/e-NIKSHAY. For all presumptive DR-TB patients, test results should be updated

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in existing NIKSHAY ID to maintain continuity while presumptive TB patients tested at these laboratories, NIKSHAY ID may be generated, after ensuring that it is not generated elsewhere. The individual should be notified if diagnosed with TB and NIKSHAY ID should be shared with along with the report. Results of subsequent tests carried out will be entered in the same ID. This gives an opportunity to easily extract the test results of all specimen provided by the patient and thereby track his/her response to the treatment. All the follow-up investigations carried out will be entered periodically using the same NIKSHAY ID.

RNTCP PMDT Referral for Treatment Form

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

Referral module in NIKSHAY facilitates access to patient information through NIKSHAY ID. Provision of shifting of patient from one district to another is possible if the patient has changed his/her residence permanently. In NIKSHAY, the referring health facility must update details under "request for transfer" section to intimate receiving health facility about the transfer even before the patient reaches. In addition to information mentioned in "request for transfer" section, the receiving health facility is able to access all other patient information as well. The accountability of transferred patient is now with the receiving health facility and the treatment initiating facility.

RNTCP PMDT Treatment Card

The RNTCP PMDT treatment card is a key instrument for the treatment supporter administrating drugs daily to the patient. The card will be initiated at D/NDR-TBC when the patient is initiated on treatment either on outpatients or on indoor basis. The original treatment card will be maintained at the respective DR-TBC and copy kept by the treatment supporter. The card should be updated daily, documenting the administration of drugs by the treatment supporter. The card is the source to update periodically the PMDT register and adherence details on NIKSHAY. Accountable systems have to be developed locally for updating cards at all levels. When or if the patient moves from DR-TBC to his/her district of residence a copy of the card, must follow the patient. Once the patient has switched to other regimen at NDR-TBC, a new set of treatment cards along with new treatment booklet should be prepared for the patient and the same shared with the field. A copy of this card may be used as a notification form and to inform final outcome of treatment.

Newer Information and Communication Technology (ICT) solutions [Medication Event Reminder Monitor System (MERM), etc.] to promote information management about the patient's treatment adherence are being tested at field level for DR-TB patients. This will help in autoupdation of treatment adherence details in NIKSHAY/e-NIKSHAY as well as flag patients with frequent treatment interruptions to prompt visits of healthcare providers and supervisors to intervene and retrieve the patient on treatment. If the patient

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is under the ICT monitoring system, treatment card in hard copy should be maintained at the treatment supporter level. A treatment supporter will be relieved from the regular updation of treatment card in NIKSHAY during such condition.

The card contains the following sections:

- *Page 1 of the treatment card*:
  - *Basic demographic information*: Name, sex, age, address, telephone number, state, DR-TBC, district, TU, PHI, and details of the treatment supporter. Some part of this information will be auto populated from available information while other information can be added at district or N/DDR-TBC level which should be supplemented by treating PHI.
- *PMDT TB number*: This is a new unique patient identification number given to the patient at the DR-TBC on initiation of treatment. The PMDT TB number should include S. No/Nodal or District/Name of DR-TBC code/year of initiation of treatment, e.g., PMDT-TB number of first patient started on treatment at Nagpur DDR-TBC during 2017 will be 1/D-NGP/2017. Every year PMDT TB number will be started at 1. The Nodal DR-TB center will maintain its PMDT number separately starting from 1st of every year, e.g., PMDT number of 1st patient initiated at Nodal DR-TBC belong to Nagpur District will be 1/N-NGP/2017. The district where the Nodal DR-TBC is located has to maintain separate District DR-TB PMDT register if center is also functioning as DDR-TBC. This would remain as a transitory system till the time most DR-TB patients are tracked with the help of NIKSHAY. This will be done till it is time to completely transition from paper-based registers to autogeneration of electronic registers from NIKSHAY PMDT modules directly.
- *NIKSHAY ID*: NIKSHAY ID refers to the unique ID which is generated at the time of testing for TB. As per RNTCP Technical and Operational Guidelines (TOG), all TB patients are to be notified at the time of diagnosis. This information is recorded in the TB notification register. Pool of all DR-TB patients (RR/MDR/H Mono/poly, etc.) diagnosed either at CBNAAT laboratory or C-DST laboratories or in private laboratory will be updated digitally. The NIKSHAY ID will capture all subsequent events that are taking place for diagnostic and treatment pathways. This creates a lifecycle approach where multiple events happen for a single patient pertaining to diagnosis and treatment pathways which are captured in a single NIKSHAY ID. All relevant information of a particular patient would be available with the same NIKSHAY ID which can be printed at all accessible users' levels. Once the patient is initiated on treatment, details are captured in PMDT treatment register that is maintained at D/NDR-TBC and PMDT number is assigned. The NIKSHAY ID has a provision to capture more than one PMDT number generated at different D/NDR-TBC while patient transfer is done. This provides a log of patient information that helps in tracking all updates starting from DR-TB diagnosis to long-term treatment outcomes.
- *Reason for testing*: This section lists and describes details of the reason for testing. This includes types of patient that have to be ticked as applicable for new, previously treated, presumptive TB, private referral, presumptive nontuberculous mycobacteria (NTM), criteria for presumptive DR-TB, presumptive H mono/poly and criteria for presumptive XDR-TB.
- *DST results at diagnosis:*
  - Detailed DST information for each patient is captured with date of specimen collection. All DST results for CBNAAT, LPA, and LC-DST are captured here once the result is received. SL-LPA result is available as FQ and/or SLI class resistance.

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Resistance is captured as R against all drugs that belong to that group. Once LC-DST result is available, it is mentioned in lower section of DST preferably.

- *HIV testing*: This section lists the date of testing, PID number, date of starting CPT, and ART (wherever applicable). As per the national policy, information sharing on HIV status of patients should be restricted within healthcare facilities based on the concept of "shared confidentiality." Hence, this information must not be written on the copy of the card held by the treatment supporter and patient booklet.
- *Contact tracing*: This section details number of household contacts screened, number of presumptive TB patients identified, number of presumptive TB patients evaluated, number diagnosed with TB, and number of DR-TB diagnosed. First contact screening should be carried out at the time of treatment initiation, however, this should be a continuous process during the course of treatment as any close contact may present with TB symptoms at any point of time during the course of treatment for index patients. In pediatric DR-TB patients, reverse contact tracing to search for an adult index patient in the household must be considered by healthcare workers.

NIKSHAY

NIKSHAY is the platform for the National Tuberculosis Programme Surveillance System. It envisages establishing ICT-enabled state-of-art surveillance system with system utilization by 100% stakeholders, ensuring 100% notification of TB patients at diagnosis (microbiologically confirmed and clinically diagnosed). The program envisions continuous monitoring and treatment adherence for all TB patients registered with e-NIKSHAY, enabling tracking of all registered TB patients across TB elimination life cycle, geographies, transfers, and referrals.

The first step is to ensure complete entry in all formats. Dashboard functions to track activities and online monitoring indicators with graphical and geomapping displays in NIKSHAY/e-NIKSHAY is helpful in program monitoring provided completeness of data entered is ascertained. Primarily, the source of information for all monitoring indicators will be NIKSHAY. Thus validation of actual report and the entered report should be done at each level to sustain quality of information available digitally. Patient-wise details and aggregated monitoring indicators for specified period is available within NIKSHAY.

e-NIKSHAY

In an attempt to reduce the TB burden in the country, it is envisaged that an ICT system such as e-NIKSHAY could help with coordinated planning and action that is required at various levels. This would be from improving patient awareness and ease of access to TB care to time-bound and effective diagnosis and treatment by the service providers. The goal would be to develop a common integrated platform as an open system to engage ecosystem stakeholders toward effective, timely, and quality assured diagnosis and effective treatment of TB. It would essentially use a case-based approach to the TB lifecycle, enabling patient-based tracking and monitoring allowing for stakeholder integration, as well as timely and accurate reporting and real-time decision support.

The RNTCP shall roll out e-NIKSHAY with support to states on logistics and trainings. This platform will serve as a web-based, case-based recording and reporting system which will also feed into routine surveillance of DR-TB in the country. e-NIKSHAY will be rolled out initially in the states of Gujarat and Maharashtra and gradually scaled up nationally by end of 2018.

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Role of e-NIKSHAY in Recording, Reporting, and SME (Supervision, Monitoring, and Evaluation)

- e-NIKSHAY will gradually replace the cumbersome paper-based system of recording and reporting. Options shall be provided to capture the event at origin through provision of mobile/web applications, tablets, and call centers on real-time basis. This will change and improve reporting structures for more agility and efficiency by providing relevant reports at relevant levels without delay due to paper-based collection, collation, and compilation of reports.
- e-NIKSHAY will generate user-specific task lists on real-time basis according to their job responsibilities aiding staff to prioritize tasks at various levels. ICT-enabled adherence mechanisms [99 Directly observed treatment, short-course (DOTS), MERM, etc.] will feed treatment-related information from patients and providers into e-NIKSHAY enriching it as a patient care and support platform to prioritize patients for differential care.
- e-NIKSHAY will aid the referral and feedback mechanism under the program by providing real-time information on referral of patients for treatment initiation and ADR management. This will aid the program to manage referral and provide feedbacks thereby decreasing lost to follow-up and improved tracking of patients nationally.
- e-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, categories of staff, and geographies. This will aid supervisors and program managers in identifying areas, both thematic and functional for intensive supervision.
- e-NIKSHAY shall generate interactive tables of real-time monitoring indicators to aid review at various levels. The platform will generate alerts in the form of SMS, e-mails, and call from call centers for patients, providers, and supervisors for actions to promote favorable outcomes and improve program management efficiency. The indicators shall be projected as interactive tables/maps to promote information-driven monitoring at all levels.

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INFECTION CONTROL MEASURES

Evidence indicates that DR-TB is similar in transmissibility to DS-TB. Thus, infection control policies and strategies are not much different for DR-TB. All facilities treating DR-TB patients must comply with adequate infection control measures. Ensuring implementation of infection control policy in all healthcare facilities, at public/private/household level and in congregate settings (correctional facilities, military barracks, homeless shelters, refugee camps, student dormitories and nursing homes, among others) is essential. This will help prevent transmission before diagnosis up to initial stages of treatment till the patient has culture converted and turned noninfectious. Actions are required at national and subnational levels to provide managerial direction and at health facility level to implement AIC measures.

Objectives of Revised National Tuberculosis Control Programme

- Achievement of at least 85% cure rate of infectious cases of TB through DOTS involving peripheral health functionaries Augmentation of case-finding activities through quality sputum microscopy to detect at least 70% of estimated cases

The vision of RNTCP is that the people suffering from TB receive the highest standards of care and support from all healthcare providers of their choice. It is spelt out in the National Strategic Plan (2012-17) to extend the umbrella of quality TB care and control to include those provided by the private sector.

Revised National Tuberculosis Control Programme-endorsed Tuberculosis diagnostics

- Smear microscopy for acid-fast bacilli
  - Sputum smear stained with Ziehl–Neelsen staining or
  - Fluorescence stains and examined under direct or indirect microscopy with or without LED.
- Culture
  - Solid (LJ) media or
  - Liquid media (Middlebrook) using manual semiautomatic or automatic machines, e.g., Bactec, MGIT
- Rapid diagnostic molecular test
  - Conventional PCR-based LPA for MTB complex
  - Real-time PCR-based Nu NAAT for MTB complex e.g., GeneXpert
- Radiography where available
- Tuberculin skin test

Ban on TB serology: The serological tests are based on antibody response, which is highly variable in TB and may reflect remote infection rather than active disease. Currently available serological tests are having poor specificity and should not be used for the diagnosis of pulmonary or extra pulmonary TB. Their import, manufacturing, sale, distribution, and use is banned by the Government of India.

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