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Review Article

DRUG-RESISTANT TUBERCULOSIS CONTROL IN INDIA – RECENT UPDATES

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Abstract

India bears 27% of the global burden of MDR TB. The emergence of drug-resistant TB can be controlled by early diagnosis and well-timed initiation of appropriate &effective treatment regimens guided by newer diagnostic tools. Patient compliance to treatment through effective patient support system and social awareness on the disease is very essential. To counter DR TB in India, PMDT services were introduced in the year 2007 and nationwide coverage was achieved in the year 2013**.** Recently in March 2021, guidelines for Management of DR TB patients in the country under PMDT have been revised and being implemented under the programme. Upmost emphasis is given for prevention, detection and appropriate treatment by building the quality standards. This article briefly surmises about the burden, programme performance, diagnosis and treatment facets in management of DR TB. Additionally, information about patient support mechanism and ongoing research & clinical trials in this domain are highlighted.

Keywords: NTEP, PMDT, Drug Resistant TB, MDR, XDR, Diagnosis, Treatment.; **Key Message**: PMDT in India

INTRODUCTION

The burden of drug resistant TB in India

Tuberculosis (TB) is a disease that has relentlessly affected communities and nations since times immemorial. India is ranked at number one among the eight countries that accounted for 66% of new TB cases in the year 2019.[1] About 40% of the Indian population is infected with TB bacillus.[2] The disease incidence rates (per 100,000 population) as estimated by World Health Organization (WHO) for the year 2019 for total TB is193 *(132-266),* Human Immunodeficiency Virus (HIV) prevalence among incident TB cases is 2.7% (2.7-2.7%) and Multi Drug Resistant (MDR)/Rifampicin Resistant (RR)-TB is 9.1 (5.3-14).[1]The findings of National Drug Resistance Surveillance (2014–2016) revealed that 28% of TB patients were resistant to any drugs (22% among new and 36.82% among previously treated) and proportion of total MDR TB in India was at 6.19% (5.5-6.9) i.e. 2.84% (2.28-3.5) among new cases and 11.62% (10.21-13.15) among previously treated pulmonary TB cases[3].However, in the year 2019, WHO estimated proportions of TB cases with MDR/RRTB at 2.8% (2.3-3.5) among new cases and 14% (14-14) among the previously treated cases in India.[1] India bears 27% of the global burden of MDRTB, with an estimated 124,000 people developed MDR/RR-TB disease in the country in the year 2019.[1]The evolution of drug-resistant TB can be controlled by ensuring rapid and timely TB diagnosis, adequate infection control in TB treatment facilities, judicious and correct use of drugs for therapy, patient compliance to drug regimen and social awareness on TB control and drug regimen.[4]However, the emergence of drug resistant tuberculosis has become a significant public health problem interfering in effective TB control programmes, additionally it also reflects on the effectiveness in management of drug-sensitive TB cases under the National TB control/elimination programme.

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Programmatic management of drug resistant tuberculosis (PMDT)

WHO's End TB Strategy aims to reduce TB deaths by 90% and reduce incidence by 80% between 2015 and 2030; and ensure that no family is burdened with catastrophic health expenditure due to TB. The National Tuberculosis Elimination Programme (NTEP) erstwhile known as Revised National Tuberculosis Control Programme (RNTCP) has committed to eliminate TB in India by the year 2025, five years ahead of WHO's Sustainable Development Goals' targets aiming at ending TB in the world by 2030.[5] To achieve this desired outcome, NTEP has developed an ambitious National Strategic Plan (NSP-: 2017-2025) in line with the National Health Policy, 2017 with the following strategies for DR TB Management**:**[5]

- Prevention of DR TB
- Strengthening procurement and Supply Chain Management (SCM) of Second-Line anti-TB Drug (SLD)
- Nutritional assessment and support
- Improving adherence through counselling support
- Treatment Regimen containing newer drugs
- Drug Resistance Surveillance
- Drug Sensitivity Testing (DST) guided treatment for all types of TB

In the year 2018, NTEP under Programmatic Management of Drug Resistant Tuberculosis (PMDT) rolled out the Shorter MDR treatment Regimens with nationwide Bedaquiline (Bdq) access and introduction of Delamanid (Dlm) in 7 states across the country. Nationwide expansion of Delamanid access for TB cases aged 6 to 17 years was also introduced. Recently in March 2021, guidelines for Management of DR TB patients in the country under PMDT have been revised. Emphasis is given to decentralize DR TB services by improving access to quality care services to:

- **Prevent:** Warranting airborne infection control at all health care facilities, households & community levels and access to effective TB Preventive Treatment (TPT) and

programmatic management of TPT is part of the strategy to prevent DR-TB.

- **Detect:** Early identification and diagnosis by highly sensitive diagnostic tools for TB & DR-TB are key strategies to detect DRTB.
- **Treat:** Expanded treatment and management of DRTB in line with guidelines of shorter oral Bedaquiline-containing MDR/RR-TB regimen.
- **Build:** Ensuring adequate human resources, funding, community engagement, use of Information Communication Technology (ICT) for treatment support, promoting TB research, strengthening drug logistic management are some of the important components of National Strategic Plan (NSP) to build systems for PMDT.

Achievements and Milestones of PMDT activities: In India, PMDT services were introduced in the year 2007 and the countrywide coverage was achieved by the year 2013.[3] As on March 2021, PMDT Services have been expanded and facilitating a vast network of diagnostic laboratories [C&DST -81, CBNAAT-1268, Truenat - 1879 and LPA (FL-67, SL-57], provision/supply of drugs, Bedaquiline & delamanid containing shorter regimen and decentralized treatment care services through 173 Nodal DR TB Centres pan India.[6] The programme has achieved greater milestones post implementation and periodical revisions in the management guidelines of PMDT in India (*Figure 1 & 2*).[6]

Despite of the disruptions caused to the TB care services by the ongoing COVID 19 Pandemic, the programme managed to cater diagnostics and treatment care services for >50000 MDR/XDR/HrTB cases in the year 2020. The successful treatment outcome rates for MDR TB patients through conventional regimen varied from 44% to 52% during the period 2007 to 2016 (***Figure 3***). However, higher Success rate of 60% was observed among patients put on treatment using shorter MDRTB regimen with inject able in the year 2018.[6] During the period 2012 to 2016, treatment outcomes as cure for XDRTB patients through conventional regimen varied from 17% to 23% (***Figure 4***). However, this was increased to 34% in the year 2017.[7,1,3] Patients put on shorter MDR regimens in 2nd and 3rd quarter 2018 showed improved treatment outcomes in terms of cure and treatment completed of about 60% (***Figure 5***).

Diagnosis of drug resistant TB

The NTEP has consistently advocated the implementation of its guidelines for the diagnosis and treatment of TB in both the public and private sectors. Patients at risk of DR TB as defined by the programme are diagnosed by using WHO endorsed rapid diagnostics (WRD) like Cartridge Based Nucleic Acid Amplification Test (CBNAAT) / chip based molecular test-TruNAAT / Line Probe Assay (LPA).

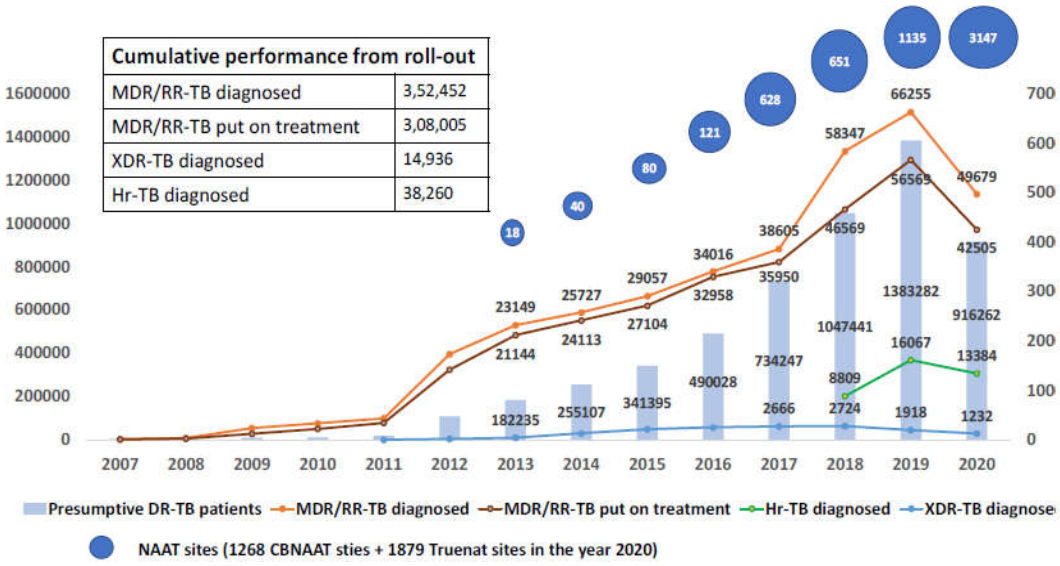

Figure 1. Year wise expansion of PMDT with performance in India (Original Source PMDT Guidelines 2021)

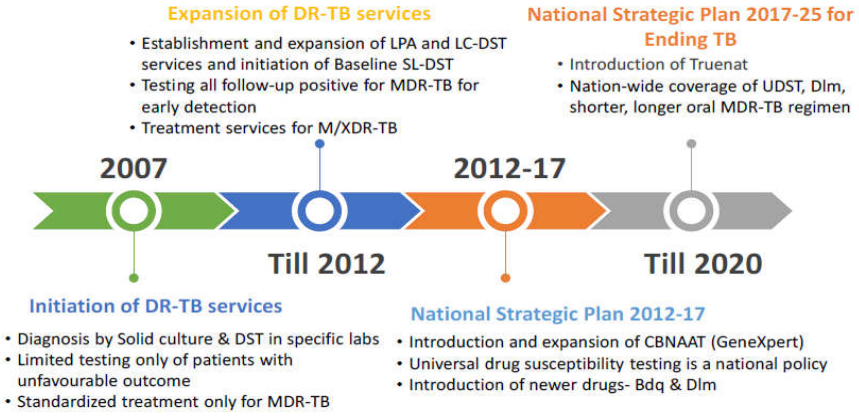

Figure 2. Milestones in evolution of PMDT in India (Original Source PMDT Guidelines 2021)

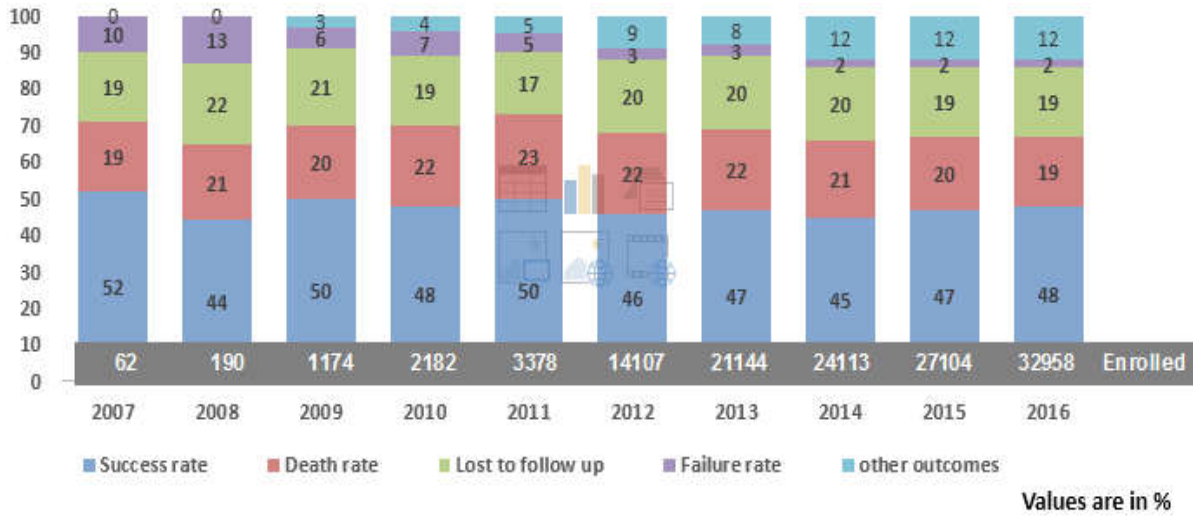

Figure 3. Treatment outcomes for MDR-TB -Conventional Regimen: 2007-16 (source NIKSHAY)

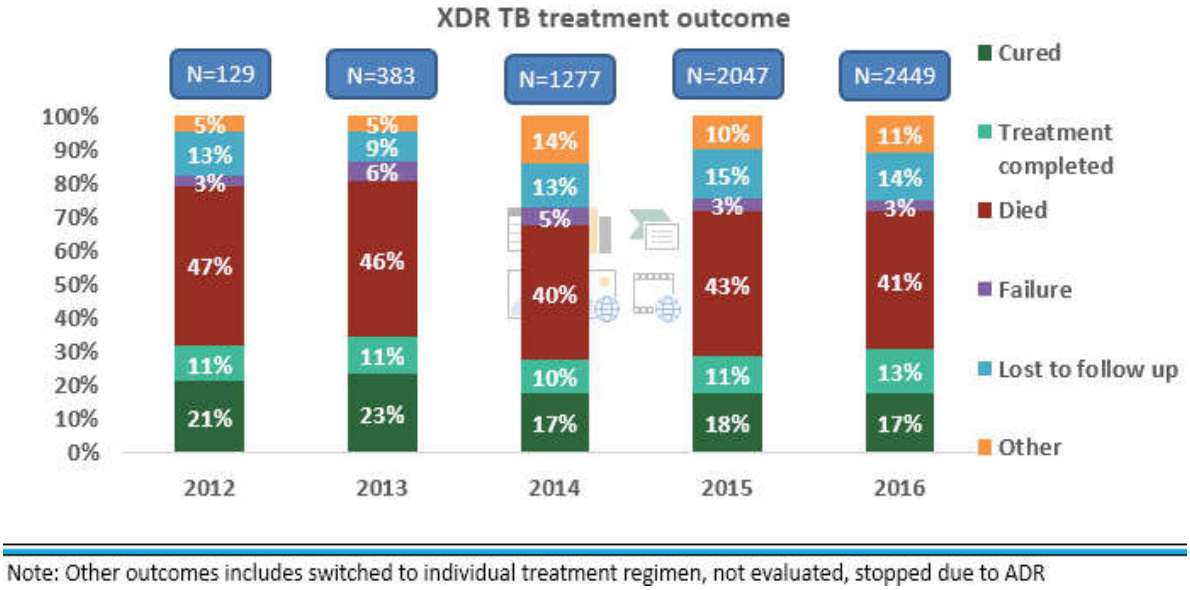

Figure 4. Treatment outcomes for XDR-TB : 2012-16 (source NIKSHAY)

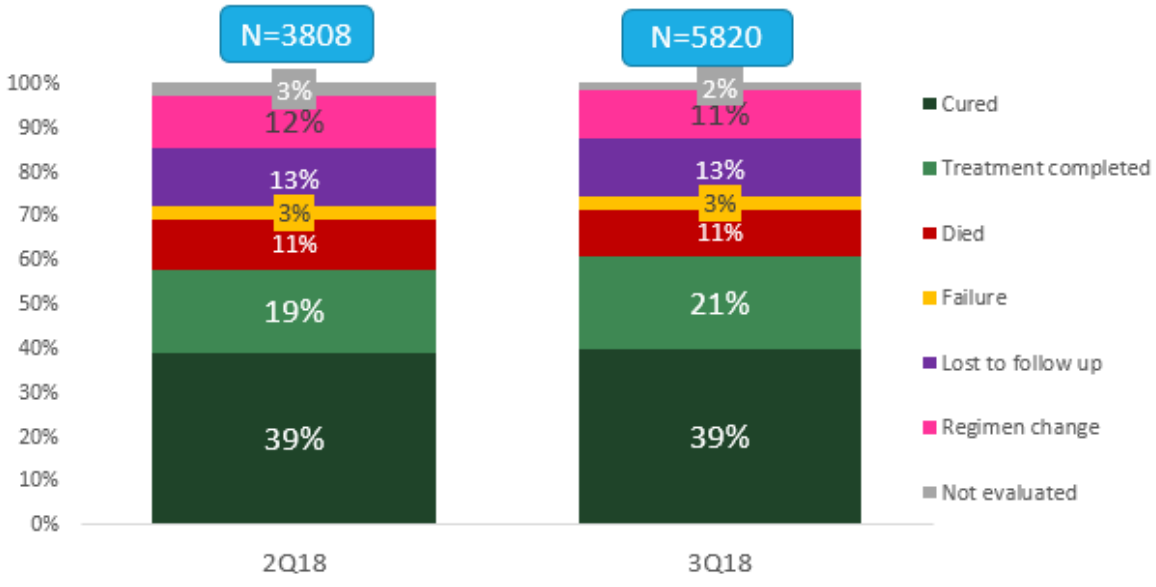

Figure 5. Treatment outcomes for shorter MDR TB regimen: 2018 (source NIKSHAY)

Table 1. Changes in the revised guidelines of DR TB

2017	2019
• **Base line DST for MDR/RR TB Patients** - SL LPA at base line - Mfx (2.0), Km, Cm - SL LPA for follow up culture +ve at end of IP and culture +ve 12 month onwards • **Base line DST for H mono/poly DR TB Patients** - SL LPA - CBNAAT and SL LPA for follow up positive at 3rd, 6th and 9 month	• **Base line DST for MDR/RR TB patients** - FL LPA & SL LPA at base line - LC DST (Mfx 1.0, Lzd & Z) - SL LPA for follow up culture +ve at 3rd& 6th months onwards • **Base line DST for H mono/poly DR TB Patients** - SL LPA - DST for Z - DST for Mfx (1.0) & Lzd only if FQ or Z resistance detected - CBNAAT and SL LPA for follow up positive at 3rd, 6th and 9 month

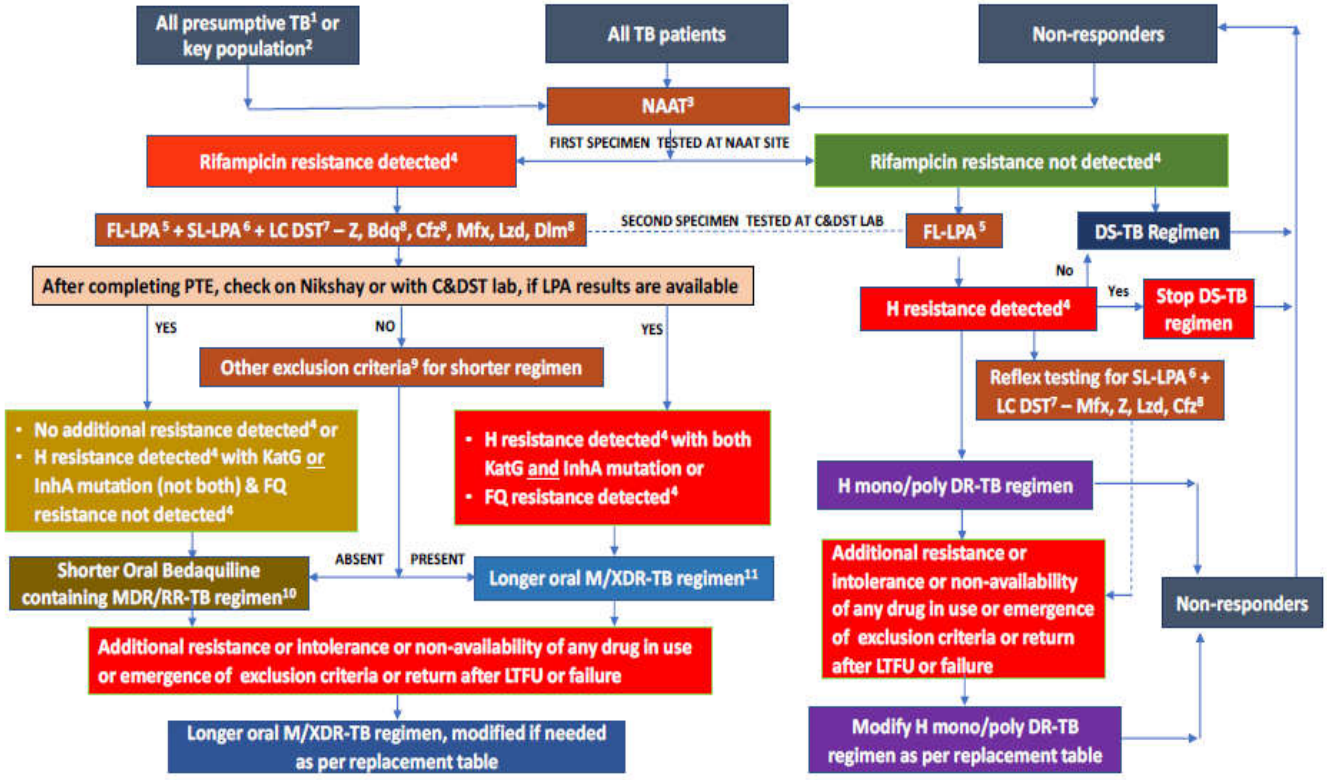

Figure 6. The revised integrated diagnostic& treatment algorithm for drug resistant TB(Original Source PMDT Guidelines 2021)

Patients' response to treatment is monitored by follow up culture on Liquid Culture Mycobacteria Growth Indicator Tube (MGIT) system (for critical follow-ups requiring clinical response) and Lowenstein-Jensen medium for non-crucial follow-ups. Universal drug susceptibility testing (UDST) is to be provided for rapid detection of Rifampicin resistance and further detection of FQ resistance among RR-TB. Identification of Mycobacterial species is performed bycommercial Immunochromatic test (ICT)**.**[8] MDR-TB diagnosis is offered to all patients as well as patients who remain smear positive on any follow up during treatment, failures of first line treatment and those at high risk such as contacts of MDRTB cases. Since there is no separate regimen for previously treated cases, all such cases are offered LPA for diagnosis of Isoniazid (H) resistance in addition to Rifampicin (Rif) resistance.[9] The changes in the revised guidelines and revised integrated diagnostic algorithm of DRTB are presented in *Table -1 & Figure-6*. The integrated diagnostic algorithm provides an opportunity for performing upfront NAAT testing for certain types of presumptive TB (*Viz.PLHIV, presumptive EP-TB cases, presumptive paediatric TB, contacts, sputum smear negative X-ray suggestive of TB and other vulnerable groups*).

Global Laboratory Initiative (GLI – a Working Group of the Stop TB Partnership) has developed and published a document titled " Line probe assays for drug-resistant tuberculosis detection, Interpretation and reporting guide for laboratory staff and clinicians" to provide practical guidance for the interpretation of the most commonly used first line and second line probe assays. Few important revisions to manufacturer interpretations have been made in the document such as using of the term "Resistance not detected" instead of "Susceptible" to define the bacteria resistance profile; differentiation of resistance into "Resistance inferred" and "Resistance detected"; stratification of resistance mutations for Isoniazid (H) and Moxifloxacin (Mfx) into mutations associated with a "low-level increase in minimum inhibitory concentration (MIC)" and "high-level increase in MIC".[10] The stratification of resistance has important implications for the inclusion of H and Mfx in the treatment regimen since resistance due to mutations associated with low-level increases in MICs for H or Mfx may be overcome by increasing the drug dose.[10] For instance, as in case of H where presence of mutation only in inhA gene and not in katG gene is to be associated with low level increase in MIC and suggests that increasing the drug dose to maximum of 15mg/kg may be effective; and also if

mutations in inhA gene is detected, it is associated with cross-resistance to ethionamide (Eto) and prothionamide (Pto). [10] Therefore, if mutations in inhA are detected by LPA, resistance to Eto and Pto should be reported and these medicines not used in the treatment regimen. For Mfx, if mutations associated with low level increase in MIC is detected or when resistance to Mfx is inferred, high dose Mfx (up to 800 mg daily to adults) can be used in the treatment. However, it is recommended to perform DST for Mfx at the Clinical Breakpoint (CB). If the MTBC strain is resistant to Mfx at the CB or if presence of mutations associated with high-level increase in MIC is detected, the drug cannot be considered as an effective medicine. A technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis was published by WHOin the year 2018. The critical concentrations (CC) and clinical breakpoints for medicines recommended for the treatment of RR TB and MDRTB is given in the document. The document also describes CC and method of DST for newer drugs like Bedaquiline, Delamanid, Clofazamine, and Linezolid and for Pyrazinamide.

WHO has also published Technical guide on next-generation sequencing technologies for the detection of mutations associated with drug resistance in *Mycobacterium tuberculosis* complex (2018) which signifies Next-generation sequencing (NGS) as great potential method for rapidly diagnosing DRTB in diverse clinical reference laboratory settings worldwide. The guide provides a comprehensive review of the recent data supporting the characterization of MTBC resistance mutations as predictors of phenotypic drug resistance to the major anti-TB drug compounds to help support NGS data analysis and results interpretation.

Treatment of drug-resistant TB

DRTB patients are being managed with the support of a nation-wide network of DRTB centres, NTEP staff, general health system staff, community volunteers and the private health facilities. Importance is given in decentralization of newer drugs containing regimen to district level for indoor/outdoor based treatment initiation. Every patient is clinically evaluated for suitable & eligible treatment regimens prior to the treatment initiation and periodically monitored & evaluated throughout treatment process with Integrated Nikshay module of DR TB. The Drug susceptibility testing (DST) results, history of previous treatment and adverse reaction to drugs are taken into account to further guide the selection of the regimen.[6]

NTEP provides simplified regimen for various types of DRTB including shorter oral Bdq-containing MDR/RRTB regimen and longer oral M/XDRTB regimen based on DST results with scope in difficult patients to extend Bdq beyond 6 months, combined use of Bdq & Dlm and Bdq use in pregnancy.[6]The brief outlines of the regimens of DR TB as per the revised guidelines are presented in *Table 2*.

- Use of Bdq -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.
- Use of Dlm – if available, no history of prior use and no exclusion criteria for its use, Z – if resistance not detected, Eto – If InhA mutation not present, Am – if SL LPA pattern suggests. DST for Lzd, Cfz and Z will be considered whenever it is available under programme.

TB preventive treatment (TPT) is also introduced for household contacts of TB patient in the revised guidelines for preventing transmission of DR-TB in the community as a major policy implication. Under this, the Contacts of TB patients who are considered to be at risk of developing TB disease are also be assessed for sign and symptoms of TB and after ruling out TB in contacts, TPT will be offered as per the guidelines.

Patient support mechanism

- Patient & family counselling for cough etiquette, disease transmission, adherence, AIC.
- Free diagnostic, pre-treatment evaluation tests and drugs.
- Support for travel for sample collection, pre-treatment evaluation, ADR management.
- Nikshay PoshanYojana (NYP): Financial support of Rs. 500/per month till the completion of treatment.
- Call Centre - Nikshay Sampark: 1800 11 6666.
- Assessment of co-morbidities.
- Social support provision and linkage.

Way Forward

The programme is aiming to implement the revised DR TB Guidelines throughout the country with induction of following newer initiatives:

Table 2. Treatment regimens for drug resistant TB

Treatment Category	Duration	Treatment regimens
Shorter oral Bdq-containing MDR/RR TB regimen	9–11 months	**(4-6) -Bdq$_{(6\ m)}$, Lfx, Cfz, Z, E, H^{h}, Eto/(5) Lfx, Cfz, Z, E,** - *From start to end of 4th month – Bdq, Lfx, Cfz, Z, E, Hh, 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, Hh and Eto are stopped together.*
Longer oral M/XDR TB regimen	18-20 months	**(18-20) LfxBdq$_{(6\ month\ or\ longer)}$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 XDR-TB patients the duration of longer oral XDR-TB regimen would be for 20 months*
H mono/poly DR-TB regimen	6 or 9 months	**(6 or 9) Lfx R E Z** - *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.*

- Establishment of DST facilities for Lzd, Z, &Cfz. (DST for Bdq&Dlm)
- Complete the preparatory activities of training and required procurements.
- Strengthening of aDSM
- Introduction of advance features in Nikshay for management, monitoring and evaluation of DR TB cases.
- Strengthening patient support systems within the programme.
- Introduction of child friendly formulations for paediatric DR TB cases.
- Strengthen supervision and monitoring
- Strengthening programme by promoting operational research and clinical trials on newer regimens

Ongoing Global Research on DR/XDR TB

The ongoing global research on DR/XDR TB are summarised and tabulated as under: [9]

Name	Description	Phase	Status/DoC
ACTG A5300/IMPAACT P2003B (PHOENIx)	The purpose of this study is to compare the efficacy and safety of 26 weeks of delamanid (DLM) versus 26 weeks of isoniazid (INH) for preventing confirmed or probable active tuberculosis (TB) during 96 weeks of follow-up among high-risk household contacts (HHCs) of adults with multidrug-resistant tuberculosis (MDR-TB) (index cases). High-risk HHCs are those with HIV or non-HIV immunosuppression, latent TB infection, and young children below the age of 5 years.	Phase 3	Ongoing 2025
IMPAACT PK of Bedaquiline in Children	The purpose of this study is to evaluate the pharmacokinetics (PK), safety, and tolerability of an antituberculosis drug, bedaquiline (BDQ), when used to treat multidrug-resistant tuberculosis (MDRTB) in HIV-infected and HIV-uninfected infants, children, and adolescents.	Phase 1-2	Ongoing 2022
STREAM Stage 2	Comparison of a 6 and 9 month bedaquiline-containing regimen against the WHO and Bangladesh regimen	Phase 3	Ongoing 2021
NiX-TB	Study of bedaquiline, pretomanid, and linezolid in patients with XDR-TB and MDR-TB for 6 months with an option of 9 months	Phase 3	Completed
TB-CHAMP	Randomized double blind placebo-controlled, superiority multi-center trial to evaluate the efficacy of levofloxacin vs. placebo for the prevention of MDR-TB in child and adolescent household contacts	Phase 3	Ongoing 2021
TB-PRACTECAL	Multi-centre, open label, multi-arm, randomized, controlled, phase II-III trial evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and re-purposed anti-TB drugs for the treatment of biologically confirmed pulmonary MDR-TB	Phase 2-3	Ongoing 2022
endTB-Q	Phase III, randomized, controlled, open-label, non-inferiority, multicountry trial evaluating the efficacy and safety of new combination regimens for FQ-resistant MDR-TB treatment	Phase 3	Ongoing 2022
ZeNiX	Evaluate the efficacy, safety and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR-TB, or treatment intolerant or non-responsive MDR-TB.	Phase 3	Ongoing 2021
SimpliciTB	DR-TB patients given BPaMZ for 26 weeks (or 6 months)	Phase 2-3	Ongoing 2022
BEAT-TB (India)	Evaluation of the Efficacy and Safety of a Combination regimen of Bedaquiline, Delamanid, Linezolid and Clofazimine in Adults with Pre-extensive (Pre-XDR) and Extensively Drug-resistant Pulmonary Tuberculosis (XDR-TB):Prospective Cohort Study	Phase 4	Ongoing 2023

REFERENCES

1. Global tuberculosis report 2020. Geneva: World Health Organization; 2020. License: CC BY-NC-SA 3.0 IGO
2. Sharma N, Basu S, Chopra KK. Achieving TB elimination in India: The role of latent TB management. *Indian J Tuberc.,* 2019; 66(1): 30-33.
3. Ministry of Health and Family Welfare GoI. Report of the first national anti-TB drug resistance survey: India 2014–16, 2018. https://tbcindia.gov.in/showfile.php?lid=3315
4. Pinto L, Menzies D. Treatment of Drug Resistant Tuberculosis. *Infect Drug Resist* 2011;4: 129-135.
5. Ministry of Health and Family Welfare, New Delhi. National Tuberculosis Elimination Programme. National Strategic Plan to End Tuberculosis in India, 2020. https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=5450&lid=3266
6. National TB Elimination Programme, Central TB Division, Ministry of Health and Family Welfare, Government of India: Guidelines for Management of Programmatic Management of Drug Resistant TB in India, March 2021. https://tbcindia.gov.in/showfile.php?lid=3590
7. World Health Organization: Technical Report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine) 2021. https://www.who.int/publications/i/item/technical-report-on-critical-concentrations-for-drugsusceptibility-testing-of-isoniazid-and-therifamycins-(rifampicin-rifabutin-and-rifapentine)
8. Central TB Division, Ministry of Health and Family Welfare, Nirman Bhavan, New Delhi: India TB Report, 2019.https://tbcindia.gov.in/WriteReadData/India%20TB%20Report%202019.pdf
9. RESIST-TB - Research Excellence to Stop TB Resistance: DR-TB Clinical Trial Progress Report; https://www.resisttb.org/clinical-trials-progress-report
10. Global Laboratory Initiative. Line probe assays for drug resistant tuberculosis detection - Interpretation and reporting guide for laboratory staff and clinicians, 2018. http://www.stoptb.org/wg/gli/assets/documents/LPA_test_web_ready.pdf

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