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## Optimal management of drug-resistant tuberculosis : Can India Lead the Way?

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1 **Optimal Management of Drug-Resistant Tuberculosis: Can India Lead the Way?**

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23

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27 (endTB & endTB-Q) sponsored by MSF, testing shorter MDR-TB regimens. J Furin has  
28 received funding from the Stop TB Partnership's Global Drug Facility to support the roll out of  
29 pediatric formulations of second-line drugs.

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## 31 **Optimal Management of Drug-Resistant Tuberculosis: Can India Lead the Way?**

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33 The past decades have witnessed a revolution in the diagnosis and treatment of rifampicin-  
34 resistant/multidrug-resistant tuberculosis (RR/MDR-TB). Rapid molecular diagnostic tests can  
35 confirm a bacteriologic diagnosis of TB and determine resistance to key medications within  
36 hours of specimen submission. Once diagnosed, the vast majority of people living with  
37 RR/MDR-TB can be successfully treated using all-oral regimens in as little as six months. In  
38 spite of the tremendous setbacks experienced in the global management of TB caused by the  
39 COVID-19 pandemic, the future holds great promise for innovative management of RR/MDR-  
40 TB. More and more evidence is being generated by researchers on new drugs and regimens and  
41 is being reviewed by WHO in a timely manner to inform evidence-based guideline updates.  
42 Globally, countries have shown the ability to efficiently adopt and adapt such guidelines to their  
43 local settings.

44 In India, TB remains a major health problem: India is among the eight countries that accounted  
45 for more than two thirds of the global TB cases occurred in 2020. And the majority of the  
46 world's drug-resistant TB cases reside in India: in 2021, 1 of every 4 MDR-TB cases globally  
47 was Indian. Thus, in 2021 there were an estimated 119,000 (93,000 to 145,000) MDR-TB cases  
48 in India, though these figures are considerably underestimated as only 76% of new TB cases and  
49 73% of previously treated Indian TB patients were even tested for rifampicin resistance.[1] The  
50 estimated number of MDR- and extensively drug-resistant (XDR)-TB patients who were started  
51 on treatment in India was a paltry 4 per 100,000 and 1 per 100,000 population respectively, with  
52 sub-optimal overall success rates of 57% in 2019.[1]

53 Several challenges still persist in the country in terms of the optimal management of RR/MDR-  
54 TB: increasing levels of resistance to WHO-recommended Group A and B drugs;[2, 3]  
55 substantial rates of catastrophic costs being faced by people with RR/MDR-TB in the country;  
56 marked heterogeneity in the roles of private providers in TB management and, more in general,  
57 lack of a strong engagement with the private sector. These obstacles are exacerbated by the lack  
58 of adequate investment in health at the national level.[4] Indeed, on any given day, far more  
59 Indian TB patients are still treated in the private sector than the public sector. Even in India's  
60 poorest state, Bihar, the private sector treats three times as many patients as the public sector.[5]  
61 The abysmal quality of prescriptions of Mumbai's private practitioners has long been known.  
62 When the prescriptions of 106 private practitioners in Dharavi, a vast, overcrowded slum in the  
63 center of Mumbai, were audited, only 3 of 106 were found to be appropriate.[6] Despite this,  
64 reporting of data is very poor in the private sector. There is also limited access to counseling and  
65 support services for people living with the disease. In addition, as in many other countries across  
66 the globe, the COVID-19 pandemic further exacerbated some of these issues, reversing years of  
67 progress in the management of TB in the country. During the pandemic, a significant reduction  
68 was observed in the number of DR-TB patients in India started on treatment. As compared to  
69 2019, there was a 14% reduction in in the numbers of MDR-TB patients commenced on  
70 treatment.[7] While these issues could be seen as being insurmountable barriers to the optimal

71 care of people living with RR/MDR-TB, facing them head-on also provides multiple  
72 opportunities for innovation which India is poised to embrace.

73 India is also home to cadres of high-quality researchers, research institutions and health care  
74 providers who have the potential to propel the country forward in the struggle to solve the  
75 country's RR/MDR-TB crisis. And there are glimmers pointing to cause for optimism in the  
76 country, including: the effective implementation of a national RR/MDR-TB registry (Nikshay);  
77 the availability of a nutritional support program for all RR/MDR-TB patients (Nikshay Poshan  
78 Yojana); the access to whole genome sequencing / next generation sequencing of *Mycobacterium*  
79 *tuberculosis* strains in selected sites; and the growing implication in both national and  
80 international clinical trials testing new regimens for RR/MDR-TB (including BEAT-TB,[8]  
81 endTB,[9] endTB-Q, STREAM 2[10]). Compassionate use is an early access channel allowed by  
82 the Indian Drug Law (which is referred to as "patient name based importation" in the national  
83 drug law) and can potentially facilitate the availability of new drugs, as they successfully  
84 complete Phase II trials.[11–13] Such mechanisms have been used to enable early access to  
85 bedaquiline and delamanid.[14] Having such a mechanism in place is particularly important, as  
86 the TB pipeline has never been richer and many new compounds with new mechanisms of action  
87 are being evaluated in Phase II.

88 Civil society actors in India have also emerged as key players in the country's efforts to tackle  
89 RR/MDR-TB. India is one of the first countries to have developed a strategy to end stigma and  
90 discrimination associated with TB.[15] In 2019, two DR-TB survivors in India – who have lost  
91 their hearing because of the toxicity of older treatment and lack of access to better-tolerated  
92 drugs like bedaquiline - have challenged the patent application on the fumarate salt of  
93 bedaquiline, which would prevent the development of generic versions of this key medicine, in  
94 turn delaying the scale-up of more affordable bedaquiline-containing regimens.

95 When looking at how India has managed innovation in recent years, however, there is also cause  
96 for concern. First, the update and revision of national guidelines has often not kept pace with  
97 new evidence-based recommendations published by WHO. In a landscape in continuous and  
98 vertiginous evolution, this poses unacceptable hurdles to practitioners struggling to offer optimal  
99 care to RR/MDR-TB patients. This issue is particularly relevant in view of the major changes  
100 introduced by the latest WHO recommendation on the treatment of RR/MDR-TB.[16] The  
101 gradual introduction of new regimens, through pilot studies in a few selected centers in India, has  
102 led to delays in access to optimal care. This strategy would not be adequate for newly approved  
103 shorter treatment regimens that have proven to be effective in randomized controlled clinical  
104 trials (ie. TB-PRACTECAL) and that are expected to be rolled out following recent WHO  
105 endorsement. Second, specific populations have not received the attention they need. For  
106 instance, pediatric RR/MDR-TB is still severely underdiagnosed. Furthermore, children with  
107 RR/MDR-TB are often receiving second-line injectable agents as part of their treatment, while  
108 all-oral regimens are now the WHO standard of care and even newer drugs like bedaquiline and  
109 delamanid can be given to children irrespective of age, with formulations that are suitable for  
110 them. Third, the concerning high rates of resistance to key second-line drugs in the country  
111 have not been addressed by sufficient efforts to improve diagnostic resources. Access to rapid

112 molecular testing for second-line drugs including fluoroquinolones, including the new Xpert  
113 XDR assay, and the capacity for detection of resistance to key new drugs like bedaquiline,  
114 clofazimine, linezolid and nitroimidazoles (delamanid and pretomanid) are still not universally  
115 available in the country. While there has been progress on the availability of bedaquiline across  
116 the country, RR/MDR-TB patients with higher-level resistance to WHO Group A and B drugs  
117 have still limited access to salvage treatment regimens, including delamanid and carbapenems  
118 that represent their only hope of achieving cure.[17]

119 What would it take for India to pivot toward a more leading role in the global approach to  
120 RR/MDR-TB and become a driver of innovation as opposed to a late adopter? A revised, more  
121 agile process for guideline revision is needed to prompt timely implementation of new all-oral  
122 regimens, as additional evidence is being generated on shorter, safer treatment. Advances in  
123 RR/MDR-TB treatment, including new drugs belonging to new chemical classes or with new  
124 mechanisms of action, should be accompanied by universal roll out of drug susceptibility testing  
125 for new drugs, including, when available, rapid molecular tests.[18] Establishing targeted plans  
126 for vulnerable patient populations, such as children, and implementing differentiated models of  
127 care that place people at the center of the care they are provided should be a priority.[19] Finally,  
128 more attempts should be made to include and educate private practitioners. Far more Public  
129 Private Mix (PPM) partnerships need to be established than the few pilot sites currently  
130 available. This is also key to increase notifications and ensure that accurate estimates on TB  
131 cases are available to develop strategies and allocate funding and resources. Establishing  
132 partnerships with impacted communities will also be instrumental to develop comprehensive  
133 strategies to tackle TB in the country. All these activities will urgently need to be supported with  
134 adequate, dedicated funding.

135 In conclusion, India has the golden opportunity to take on a key leadership role in the global  
136 fight against RR/MDR-TB. The inspirational goal of making India a “TB-free country” by 2025  
137 - five years ahead of the target set by the UN’s sustainable development goals - is a testimony of  
138 the country’s commitment to tackle TB, a preventable and treatable disease, building on the  
139 plethora of existing actors and initiatives that constitute a unique resource for the country.

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141 **Bibliography:**

142

- 143 1. World Health Organization. Global tuberculosis report 2022. *Geneva. Licence: CC BY-NC-*  
144 *SA 3.0 IGO*. 2022; .
- 145 2. Nambiar R, Tornheim JA, Diricks M, Bruyne KD, Sadani M, Shetty A, Rodrigues C.  
146 Linezolid resistance in Mycobacterium tuberculosis isolates at a tertiary care centre in  
147 Mumbai, India. *Indian J Med Res* 2021; 154: 85–89.
- 148 3. Tornheim JA, Intini E, Gupta A, Udhwadia ZF. Clinical features associated with linezolid  
149 resistance among multidrug resistant tuberculosis patients at a tertiary care hospital in  
150 Mumbai, India. *J Clin Tuberc Other Mycobact Dis* 2020; 20: 100175.
- 151 4. Indian budget 2023: no major announcements on health front. *Financial Express Feb 2nd*  
152 *2023. Accessed 7/2/23. : 2023.*
- 153 5. Arinaminpathy N, Batra D, Khorparde. N, D, S, Vualnam T et al. The number of privately  
154 treated tuberculosis cases in India: an estimation from drug sales data. *Lancet Infect Dis*.  
155 2016;16:1255-1260. .
- 156 6. Udhwadia Z, Pinto LM, Uplekar M. Tuberculosis management by private practitioners in  
157 Mumbai, India: has anything changed in two decades? *PLOS ONE*  
158 <https://doi.org/10.1371/journal.pone.0012023>.
- 159 7. Central TB Division. India TB Report 2022. Available from:  
160 <https://tbcindia.gov.in/WriteReadData/IndiaTBReport2022/TBAnnauReport2022.pdf>;  
161 *accessed on 10/02/2023.*
- 162 8. Padmapriyadarsini C, Vohra V, Bhatnagar A, Solanki R, Sridhar R, Anande L,  
163 Muthuvijayalakshmi M, Bhatia M, Jeyadeepa B, Taneja G, Balaji S, Shah P, Saravanan N,  
164 Chauhan V, Kumar H, Ponnuraja C, Livchits V, Bahl M, Alavadi U, Sachdeva KS,  
165 Swaminathan S, for BEAT India Team. Bedaquiline, Delamanid, Linezolid and Clofazimine  
166 for Treatment of Pre-extensively Drug-Resistant Tuberculosis. *Clinical Infectious Diseases*  
167 2022; : ciac528.
- 168 9. Guglielmetti L, Ardizzoni E, Atger M, Baudin E, Berikova E, Bonnet M, Chang E, Cloez S,  
169 Coit JM, Cox V, de Jong BC, Delifer C, Do JM, Tozzi DDS, Ducher V, Ferlazzo G,  
170 Gouillou M, Khan A, Khan U, Lachenal N, LaHood AN, Lecca L, Mazmanian M, McIlleron  
171 H, Moschioni M, O'Brien K, Okunbor O, Oyewusi L, Panda S, Patil SB, et al. Evaluating  
172 newly approved drugs for multidrug-resistant tuberculosis (endTB): study protocol for an  
173 adaptive, multi-country randomized controlled trial. *Trials* 2021; 22: 651.
- 174 10. Goodall RL, Meredith SK, Nunn AJ, Bayissa A, Bhatnagar AK, Bronson G, Chiang C-Y,  
175 Conradie F, Gurusurthy M, Kirenga B, Kiria N, Meressa D, Moodliar R, Narendran G,  
176 Ngubane N, Rassool M, Sanders K, Solanki R, Squire SB, Torrea G, Tsogt B, Tudor E, Deun  
177 AV, Rusen ID, Adilaa O, Alexandru S, Bellenger K, Bennet J, Bennet D, Bindroo P, et al.

- 178 Evaluation of two short standardised regimens for the treatment of rifampicin-resistant  
179 tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority  
180 trial. *The Lancet Elsevier*; 2022; 400: 1858–1868.
- 181 11. Indian Drug Law, Forms 12A/12B. *available at:*  
182 <https://cdsco.gov.in/opencms/opencms/en/consumer/Drugs-for-Personal-Use/>, accessed  
183 12/02/2023.
- 184 12. Goyal PK, Mathur R, Medhi B. Understanding the challenges and ethical aspects of  
185 compassionate use of drugs in emergency situations. *Indian Journal of Pharmacology* 2020;  
186 52: 163.
- 187 13. Shetty YC, Brahma S, Manjesh PS. Compassionate drug use: Current status in India.  
188 *Perspect Clin Res* 2020; 11: 3–7.
- 189 14. Udwardia ZF, Ganatra S, Mullerpattan JB. Compassionate use of bedaquiline in highly drug-  
190 resistant tuberculosis patients in Mumbai, India. *Eur Respir J* 2017; 49: 1601699.
- 191 15. Central TB Division. Strategy to End Stigma and Discrimination Associated with  
192 Tuberculosis. *Available at*  
193 [https://tbcindia.gov.in/WriteReadData/l892s/2581521802Strategy%20to%20End%20Stigma](https://tbcindia.gov.in/WriteReadData/l892s/2581521802Strategy%20to%20End%20Stigma%20and%20Discrimination%20Associated%20with%20TB%2018032021%20New.pdf)  
194 [%20and%20Discrimination%20Associated%20with%20TB%2018032021%20New.pdf](https://tbcindia.gov.in/WriteReadData/l892s/2581521802Strategy%20to%20End%20Stigma%20and%20Discrimination%20Associated%20with%20TB%2018032021%20New.pdf);  
195 *accessed on 01/02/2023* 2022; .
- 196 16. WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant  
197 tuberculosis treatment, 2022 update. *Geneva. Licence: CC BY-NC-SA 3.0 IGO.* 2022; .
- 198 17. Chavan VV, Dalal A, Nagaraja S, Thekkur P, Mansoor H, Meneguim A, Paryani R, Singh P,  
199 Kalon S, Das M, Ferlazzo G, Isaakidis P. Ambulatory management of pre- and extensively  
200 drug resistant tuberculosis patients with imipenem delivered through port-a-cath: A mixed  
201 methods study on treatment outcomes and challenges. *PLoS One* [Internet] 2020 [cited 2020  
202 Jul 7]; 15 Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7297304/>.
- 203 18. Van Rie A, Walker T, de Jong B, Rupasinghe P, Rivière E, Dartois V, Sonnenkalb L,  
204 Machado D, Gagneux S, Supply P, Dreyer V, Niemann S, Goig G, Meehan C, Tagliani E,  
205 Cirillo DM. Balancing access to BPALM regimens and risk of resistance. *Lancet Infect Dis*  
206 2022; 22: 1411–1412.
- 207 19. Dhakulkar S, Das M, Sutar N, Oswal V, Shah D, Ravi S, Vengurlekar D, Chavan V, Rebello  
208 L, Meneguim AC, Iyer A, Mansoor H, Kalon S, Acharya S, Ferlazzo G, Isaakidis P, Thakur  
209 HP. Treatment outcomes of children and adolescents receiving drug-resistant TB treatment  
210 in a routine TB programme, Mumbai, India. *PLoS One* 2021; 16: e0246639.

211