EDITORIAL

# To End Tuberculosis, India must Embrace Innovation: Lessons from the ZeNix Trial Results

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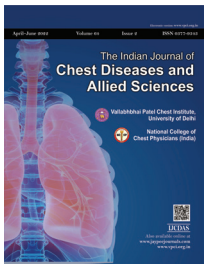


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## Abbreviations used in this Article

COVID-19 = Coronavirus diseases-2019; NTEP = National Tuberculosis Elimination Program; US-FDA = United States Food and Drug Administration; WHO = World Health Organization; DCGI = Drug Controller General of India; MDR-TB = multidrug-resistant TB; ITRC = Indian TB Research Consortium; ICMR = Indian Council of Medical Research

At the beginning of the COVID-19 pandemic, the crisis in India required a diversion of human resources and diagnostic facilities. The resources of the National Tuberculosis Elimination Program (NTEP) proved extremely helpful; thanks to its understanding and expertise in managing infectious diseases, including its experience in contact tracing and nationwide diagnostic testing services network. The health-care infrastructure in India was hardly capable of handling the existing disease burden, and without reallocating these resources, the government could not have been as successful as it was in limiting COVID-19 casualties. India has the highest burden of TB in the world, and repurposing TB care resources led to a 25% decrease in TB notification (signaling less surveillance, monitoring, and evaluation of TB cases) in 2020 as compared to 2019.[1]

## An Age-old Threat

Limiting the potential damage of COVID-19 can be credited to the collaborative efforts in innovation, production and technology sharing of diagnostics, treatments, and other tools. Therefore, the fact that TB has remained one of the top causes of death from an infectious disease demonstrates that there is a lack of political will and funding needed to deploy and scale-up new tools to adequately fight this age-old pandemic.

Tuberculosis can be cured with antibiotics, especially with newer medicines that have been developed recently with little underlying resistance. However, the challenge is the speed at which the adoption of new treatments happens both globally and in major countries. As an example, the drug bedaquiline was first approved in December 2012 by the United States Food and Drug Administration (US-FDA). However, it was only in 2018 that the World Health Organization (WHO) recommended it as a core drug for treating multidrug-resistant TB (MDR-TB). Until 2018, only about 25,000 people received bedaquiline to treat their TB, most of them in South Africa. This was despite the fact that the pharmaceutical company behind bedaquiline (Johnson and Johnson) agreed to donate supplies for about 20,000 patients. Following the WHO recommendation for bedaquiline in 2018, usage has increased, but that did not change matters much. While about 169,000 patients were treated for MDR-TB in 2020, only about 52,000 of those received bedaquiline. That is roughly 30% of all who could have benefitted.

In India only 10,140 patients were provided treatment with bedaquiline out of the more than 56,000 who received MDR-TB treatment overall, this is about 18%, well below the global average. In contrast, South Africa had nearly 100% of MDR-TB patients using bedaquiline in 2020, which underscores how policy decisions can delay access to innovative treatments.

## Providing Access

We are now faced with a new opportunity to embrace a TB treatment innovation. A regimen for highly drug-resistant forms of TB has been developed by the non-profit TB Alliance — a three-drug, all-oral, six-month BPaL regimen consisting of bedaquiline (B), pretomanid (Pa), and linezolid (L). It was first approved by US FDA in August 2019 and recommended for use under operational research conditions by the WHO in June 2020. Several high burden countries including Ukraine, South Africa, Philippines, and Nigeria have begun implementing this regimen under WHO guidelines, starting as early as October 2020. Ukraine presented its experience from the regimen at the Union TB conference recently and they have been able to closely mirror the results from clinical trials in their settings. Despite India having the highest burden of MDR-TB cases in the world and the Drug Controller General of India (DCGI) also issuing approval for the drug in July 2020, the first patient in the country received BPaL only in October 2021.

The results of the Nix-TB study, a pivotal Phase-3 clinical trial of the BPaL regimen, showed a treatment success rate of approximately 90%.[2] The treatment continues to be studied in clinical trials, including the ZeNix trial, which is a four-arm study evaluating

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whether the efficacy of the BPaL regimen can be maintained using lower doses and shorter durations of the drug linezolid to reduce its known adverse reactions, including peripheral neuropathy and myelosuppression. The results of ZeNix were presented in July 2021 at the International AIDS Society Conference on HIV science and showed that the same high efficacy can be achieved by using a shorter duration or smaller dose of linezolid.[3]

This is fantastic news for patients, and, as India has already approved pretomanid as part of the BPaL regimen, the country should explore providing access to TB patients in the country. A regimen like this could lift India's drug-resistant TB success rate, which ranges between 36 and 46%, well below its peers and global average. A six-month regimen could also simplify TB treatment delivery as the current treatments that last 18–24 months involving follow-up throughout will be untenable in a healthcare system that has been battered by COVID-19. More than one in four cases of drug-resistant TB worldwide in 2019 were recorded in India.[2] Hence, finding newer and better treatments for drug-resistant forms of TB is extremely important and can meaningfully contribute to fulfilling India's ambitious goal of TB eradication in India by 2025, ahead of the 2030 target of the Sustainable Development Goals set by the United Nations.

It is a welcome step that the NTEP and the Central TB Division have already started the trial with BPaL in pre-XDR and XDR-TB cases, and the Indian TB Research Consortium (ITRC) of the Indian Council of Medical Research (ICMR) is in an advanced stage for the preparation for this drug regimen trial in MDR-TB cases. These will obviously be game-changers.

The COVID-19 has helped the delivery of several TB services, like remote advice and support gain prominence. It has also invigorated research on TB. The WHO emphasizes that the TB diagnostic pipeline is robust in terms of the number of tests, products, or methods in development. Now that we have seen innovations in TB over the last few years with three new drugs for drug-resistant TB approved in the last decade, so much more could be achieved if the funding gap for TB research and development was closed — whether it is for drugs, vaccines, or diagnostics. The COVID-19 emergency should teach us a lesson—the importance of adopting and adapting cutting-edge research without delay. By embracing these findings and other potential innovations, India can put an end to the suffering that comes with drug-resistant TB as well as the inadequate treatments that are currently available to patients.

Subsequent to the Nix-TB trial regimen, three new regimens were reported recently and those are the NExT trial by Esmail et al,[4] the ZeNix trial as discussed above,[3] and the TB-PRACTECAL trial, although the latter two are reported in abstract form only.[3,5] These trials are built on the 6-month "NiX-TB" regimen,[2] an all-oral 6-month treatment regimen with bedaquiline, pretomanid, and high-dose linezolid, that achieved a 90% cure rate in a cohort of patients with an advanced spectrum of drug-resistant TB. The problem with the regimen (Nix-TB trial) was that 81% of patients in the trial experienced peripheral neuropathy, and 48% experienced myelosuppression and these toxicities were attributed to the high dose of the 1200 mg of linezolid used in the trial, given for a full 6months. The NExT trial reduced the linezolid dose to 600 mg daily, and ZeNix studied that dose plus two regimens in which linezolid was given for only the first 2months at either 1,200 or 600 mg per day, and TB-PRACTECAL gave linezolid at 600 mg for 4 months followed by 2 months at 300mg daily.[2,4,5] All of these dose reductions decreased toxicity substantially. Although the protocol-defined favorable outcome proportion with the NExT regimen was only 51%, this was largely attributable to the discontinuation of linezolid; overall positive outcomes at 24 months were 75%. In the ZeNix and TB-PRACTECAL trials, where discontinuation of linezolid was not an unfavorable outcome, cure rates were 89–93%. Thus, it appears to be a reasonably well-tolerated,but effective 6-month treatment regimens for MDR/RR-TB with existing medications. Many more regimens (at least) 10 are under trial in various countries with or without bedaquiline containing regimens for shorter periods of tims.[6]

Based on these publications, the WHO has published a rapid communication in early May this year about some new regimens that have not yet been appraised by it and have recently been tested in trials or used programmatically.[7] These regimens include a new 6-month regimen based on bedaquiline, pretomanid and linezolid (BPaL) in combination with moxifloxacin (BPaLM), that was evaluated in the TB-PRACTECAL randomized clinical trial; the 6-month regimens based on the BPaL combination with decreased exposure to linezolid (lower dosing or shorter duration) evaluated in the ZeNix study and the modified all-oral shorter regimens (6–9 months or 9–12 months) containing all three Group A medicines evaluated in the NeXT trial or implemented by the NTP in South Africa.

Although bedaquiline has shown promising results for patients with DR-TB by improving the rate of culture conversion and reducing TB-related mortality, increasing numbers of cases with acquired bedaquiline resistance (ABR) have been reported in recent years.[8] A recent systematic review reported the median (IQR) frequency of phenotypic ABR as 2.2% (1.1–4.6%) and 4.4% (1.8–5.8%) for genotypic ABR. Therefore, treatment regimens should include drugs with high resistance-preventing capacity through high and early bactericidal activity.

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