

# A New FDA-approved Antibiotic for Drug-resistant Tuberculosis Treatment

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Tuberculosis (TB) is one of the most primitive diseases known to mankind and yet it continues to be a public health challenge and one of the leading infectious causes of death worldwide.<sup>1</sup> About one fourth of the world's population is infected with *Mycobacterium tuberculosis* (M. tb), the bacteria that causes TB.<sup>2</sup> Despite availability of effective chemotherapy regimen to cure TB, global eradication seems to be a challenge due to ability of *tubercle bacilli* to survive as latent infection within the human body. The first reported case of TB was in 1882; however, an antibiotic wasn't available to the general public until 1940s.<sup>3</sup> The discovery of rifampicin in 1963 was a game-changer and it facilitated subsequent development of short course chemotherapy regimen for management of TB. In the last few decades, no new antimicrobial surfaced for TB treatment despite growing incidence of TB and emergence of multi drug-resistant TB. Subsequently, bedaquiline was licensed in 2018, followed by delamanid in 2019 for the treatment of drug resistant TB.<sup>4</sup>

According to the World Health Organization (WHO), TB continues to be a global disease involving every country of the world.<sup>4</sup> Emergence of drug resistance to first line anti-tubercular drug is making this disease more deadly and difficult to treat. HIV and TB co-existence is another problem area, which undermines the efforts of disease control significantly.<sup>5</sup> In HIV patients, chances of treatment failure is quite high due to weakened immune system and increasing drug resistance, thus making them difficult to treat, let alone cure.

The drugs used to treat multi drug-resistant (MDR) TB have been designed to either treat the infected immune system, destroy the bacteria or provide treatment for both in a synergistic manner.<sup>3</sup> However, treatment failure rates for MDR-TB and extensively drug-resistant (XDR) TB are significantly high due to prolonged treatment regimen, high associated financial burden, and drug-related adverse effects. There have been global efforts to find out shorter regimens of MDR-TB treatment and to improve treatment outcomes.

Gler<sup>3</sup> et al. conducted a trial with addition of delamanid to MDR-TB drug regimen and found better outcomes. However, there were concerns about drug interactions and potential to cause QT-prolongation.

TB Alliance, a non-profit organization, developed the latest drug in market called Pretomanid, for MDR-TB and XDR-TB.<sup>6,7</sup> This new antibiotic, previously known as 'PA-824', was approved by the USA Food & Drug Administration (FDA) on August 14<sup>th</sup>, 2019 and has been used to design newer and shorter regimen for drug-resistant TB.<sup>7,8</sup> Pretomanid, a nitroimidazooxazine compound, has bacteriostatic as well as bactericidal capabilities in treating TB.<sup>9</sup> This new agent was used in combination with bedaquiline and linezolid (BPaL regimen) and was shown to be successful in treating MDR-TB. A study using the BPaL regimen was performed in South Africa, which showed that 89% of the trial participants had a favourable outcome with their clinical infection resolved and sputum cultures negative for TB after six months of treatment and six months of post-treatment follow-up.<sup>7</sup> Moreover, this combination therapy was so successful that WHO estimated success rates for populations in need of treatment for extensive drug-resistant (XDR-TB) and non-responsive or intolerant MDR-TB to be 34 and 55%, respectively.

Despite the reported positive outcome, adverse effects were noticed such as hepatic adverse effects, QT prolongation and myelosuppression. Further studies are needed to study the tolerability and efficacy of this drug combination in patient subgroups with extra pulmonary TB or associated significant cardiac, hepatic, or renal impairment.<sup>7</sup>

In conclusion, pretomanid containing newer anti-tubercular drug regimens, has shown promising results to treat drug-resistant TB. Pretomanid is only the third drug in last four decades to be discovered for the treatment of MDR/XDR tuberculosis.<sup>9,10</sup> Such strides are still met with disparaging challenges, so it is crucial that future TB drugs are designed with shorter therapeutic regimes, improved efficacy, and safety profiles in order to address the high global burden of drug-resistant TB.

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