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Can Shorter Regimens Eliminate Drug-Resistant Tuberculosis?

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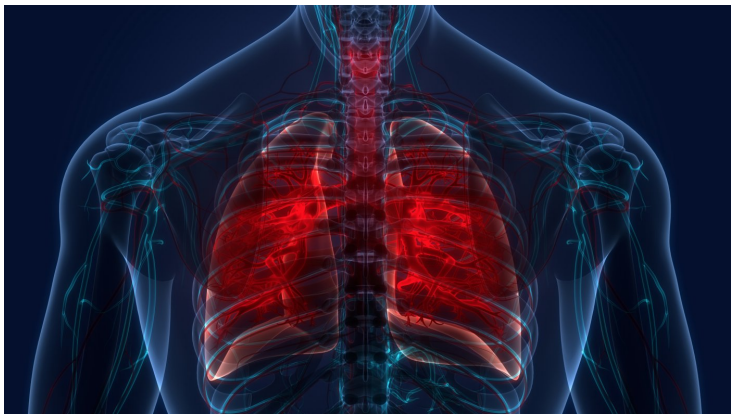
The World Health Organization (WHO) has taken a significant stride in the battle against Tuberculosis (TB) by introducing shorter drug regimens, aiming to curb a disease that claims countless lives globally. This innovative approach addresses the urgent need for more efficient treatments, especially in regions where TB's toll is highest. With traditional therapies often posing risks to liver health, these shortened regimens offer hope, minimising such concerns while enhancing treatment adherence.



Despite countries making bold commitments to end TB by 2030, in the Sustainable Development Goals (SDGs), the WHO End TB Strategy and the 2018 political declaration on the fight against TB, the epidemic shows no sign of slowing down. The deadly disease claimed 1.3 million lives in 2022. Drug-resistant TB is a growing threat – about 410,000 people had multidrug-resistant TB infections in 2022. In response to this pressing crisis, the WHO has been exploring various strategies to combat this deadly disease. Among these efforts is the development of shorter drug regimens, aiming to improve treatment outcomes and reduce the burden on patients.

Pretomanid and the Bedaquiline, Pretomanid, and Linezolid (BPaL) regimen, developed by the non-profit TB Alliance, have transformed the treatment for drug-resistant TB and move us closer to achieving these goals, especially as they relate to the types of TB cases that have traditionally been most difficult and resource-intensive to treat.

“The six-month, all-oral BPaL regimen drastically reduced the time it takes to cure drug-resistant TB, with fewer side effects. Previously, drug-resistant TB treatment lasted up to 18 months or longer, required people to take up to 14,000 pills over the course of treatment, and the success rate barely crept past 50 per cent, depending on the type of TB. With BPaL, the success rate is above 90 per cent, while the pill burden is reduced by roughly 95 per cent,” said **Dr Maria Beumont, Chief Medical Officer at TB Alliance, USA.**

In May 2022, WHO recognised TB Alliance’s advancements and released new guidelines for treating drug-resistant tuberculosis (DR-TB) that relied on BPaL and BPaLM (BPaL + moxifloxacin). A year later, WHO Director-General Dr Tedros Adhanom Ghebreyesus noted that 109 countries have adopted all-oral, six-month, BPaL-based regimens (BPaL with or without moxifloxacin)—in less than four years from the regimen’s first approval (by the United States Food and Drug Administration approval in 2019).

“In total, 70 countries have already procured pretomanid. This is the fastest global roll out of a new TB drug in the modern era, and in many ways outpaced even the global availability of COVID-19 vaccines,” added Dr Maria.

Scaling up shorter drug regimens

The new regimen is shorter, easier on patients, and improves treatment adherence, resulting in better outcomes compared to previous drug regimens.

“The existing regimen is lengthy and includes injectable agents that cause serious adverse effects that often lead to treatment being interrupted and poor treatment outcomes as well as complicate the management of TB in resource-limited settings. Based on the available data, the new regimen containing all oral drugs shortens the duration of treatment with fewer adverse effects and better outcomes, and, therefore improves the quality of life for patients. This is imperative for meeting the WHO’s End TB Strategy and SDGs. The new regimen is shorter and simpler and could be suitable for diverse clinical settings, including both resource-limited and -rich environments,” said **Dr Htin Lin Aung, Rutherford Discovery Fellow and Associate Dean Pacific Research at the University of Otago, New Zealand.**

Several studies have demonstrated the effectiveness of the new regimen. Interim operational research results from five Central and Southeast Asian countries indicate that the BPaL regimen achieved a remarkable 94.5 per cent cure rate in regions burdened by drug-resistant TB (DR-TB). Operational research in these countries was part of the LIFT-TB programme, which provided funding, resources, technical assistance, and wide-ranging expertise from multiple partners for seven countries with high burdens of drug-resistant TB (Indonesia, Kyrgyzstan, Myanmar, Philippines, Ukraine, Uzbekistan, and Vietnam) to advance the implementation and rollout of the BPaL regimen.

All seven countries have established plans to scale up use of the regimen on a national programmatic basis, and programmatic use is underway in four of the seven countries. By the end of 2023, the governments of Kyrgyzstan, Myanmar, Ukraine, and Uzbekistan updated their DR-TB treatment guidelines to enable programmatic use of the BPaL regimen for most forms of DR-TB. India is also likely to roll out the new regimen soon.

“Pretomanid, the BPaL and BPaLM regimens have already made significant impact on the global TB burden. With projections that more than 78 per cent of people with drug-resistant TB will be treated with these regimens by 2026, the impact of these new regimens is only set to grow,” said Dr Maria.

The goal now is to urge high-burden DR-TB countries to update guidelines and offer shorter treatments to all patients in need. Only 40 per cent of the 410,000 people with DR-TB in 2022 had access to the shorter regimen, as per a WHO report. Efforts are underway to boost the adoption of this new regimen.

Viatris, a global healthcare company, MedAccess, and TB Alliance announced a new agreement to reduce the price of pretomanid, a drug used to treat multidrug-resistant tuberculosis and is a part of the new drug regimen, by 34 per cent. The WHO has also issued a call for an action urging countries to accelerate the rollout of new WHO-recommended shorter all-oral treatment regimens for DR-TB, which remains a public health crisis.

Various other studies are underway for even shorter regimens, such as the groundbreaking study spanning Asia and Uganda, researchers from the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), National University Hospital (NUH), and Singapore Clinical Research Institute (SCRI), led by Prof. Nicholas Paton, Department of Medicine and Infectious Diseases Translational Research Programme (NUS Medicine), found a novel TB treatment strategy.

The trial, named TRUNCATE-TB, involved 675 people diagnosed with pulmonary TB. Participants were randomly assigned to either the standard six-month treatment or the TRUNCATE strategy. This approach featured an initial 8-week treatment period, followed by potential extension and early retreatment for non-cured individuals, effectively halving the average treatment duration.

“Pretomanid is now under further investigation, in a trial called NC-009 as part of another new regimen that includes a second generation diarylquinoline (TBAJ-876), which could have favourable efficacy, safety, and resistance profiles compared to bedaquiline. This new regimen may also have the potential to further shorten treatment duration,” said Dr Maria.

UNITE4TB's innovative phase 2B/C trials will test 14 combinations of nine existing drugs, as well as two newly developed candidates (GSK656 and BTZ-043). The ultimate aim is to create shorter regimens that can further improve multidrug-resistant (MDR) treatment, and also be effective for drug-sensitive TB.

Shorter drug regimens are revolutionising the fight against TB, yet efforts are needed to ensure universal accessibility.

Ayesha Siddiqui