

New generation of drugs show early efficacy against drug-resistant tuberculosis

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Combining care delivery and research leads to better treat for resistant tuberculosis in challenging settings. Credit: Jean-Pierre Amigo / endTB

New treatment regimens for multidrug-resistant tuberculosis (MDR-TB) have shown early effectiveness in 85 percent of patients in a cohort that included many people with serious comorbidities that would have excluded them from clinical trials, according to the results of a new international study.

The results, based on [observational data](#) from a diverse cohort of patients in 17 countries, underscore the need for expanded access to the recently developed TB medicines bedaquiline and delamanid. By contrast, the historical standard of care, still in use in much of the world, has approximately 60 percent treatment efficacy globally.

The study was published July 24, 2020, in the *American Journal of Respiratory and Critical Care Medicine*.

"This is important evidence that these new regimens will work well for the true population suffering from this disease," said lead study author Molly Franke, associate professor of global health and social medicine in the Blavatnik Institute at Harvard Medical School.

The research was conducted as part of endTB, an international partnership with leaders from HMS, Partners In Health, Médecins Sans Frontières, Interactive Research & Development, the Institute of Tropical Medicine in Antwerp and Epicentre.

"Our findings underscore the need for urgent expanded access to these drugs," said Carole Mitnick, associate professor of global health and social medicine in the Blavatnik Institute at HMS and a co-author of the study. While recent announcements of a price reduction for bedaquiline and an expected reduction for delamanid are welcome, the researchers said, more must be done to improve treatment guidelines worldwide and to scale up treatment with these new regimens.

The need for better treatments for MDR-TB is dire. The WHO estimates that there are nearly 500,000 new cases of MDR-TB per year and that nearly 200,000 people die of the disease each year. In 2018, only one out of three patients were given an effective treatment, and only half of these were cured.

In the early 2010s, regulatory agencies approved the first new TB drugs in 50 years, bedaquiline and delamanid, offering hope for more effective and less toxic MDR-TB treatment. With the historical standard of care and some newer regimens, certain subgroups of patients, including those with HIV or hepatitis C or diabetes experience worse treatment outcomes than patients without these conditions. In addition, these conditions preclude patients from participating in clinical trials for these drugs.

It's important to examine whether these subgroups experience any benefit from the new regimens that might be observed in healthier study participants, the researchers said. They noted that only a large cohort study has the statistical power to explore these differences.

The endTB study showed that for the new regimens, early treatment response was similar for patients without serious comorbidities or other complicating factors and for those with diabetes, hepatitis C and severe drug resistance.

Patients with severe TB disease when they started treatment had worse outcomes than patients with less severe disease. Sixty-eight percent of people with severe disease had early favorable responses to the new regimen, compared to 89 percent without severe disease. Among patients with HIV coinfection, early outcomes on the new regimens were favorable in 73 percent, compared to 84 percent in those without HIV.

The results are based on an analysis of early treatment results from more than 1,000 MDR-TB patients who were enrolled in the study between April 2015 and March 2018. The study examines outcomes after 6 months in a treatment that lasts 15 months or longer. Long-term effectiveness will be measured at the end of treatment and during follow-up.

For this study, the researchers counted how many of those patients, within the first six months of treatment with regimens containing bedaquiline, delamanid, or both, experienced culture conversion, a state in which the bacteria that cause TB can no longer be found on a sample. Previous studies have shown this to be a strong predictor of successful treatment outcomes.

Confirmation with end-of-treatment outcomes will be important and more work needs to be done to ensure successful treatment in these populations, the researchers said.

"The early results from these studies offer convincing evidence that these new regimens offer a very promising alternative to the historical regimens that achieve approximately 60 percent success at end of treatment, and to other new treatments that are becoming available," said Mitnick, who is a senior researcher at Partners In Health and co-principal investigator of the clinical trials being conducted by endTB.

"We're eager to follow these patients as they progress through treatment in order to verify the effectiveness of these new regimens," she added.

Observational research makes so many important contributions to improving treatment outcomes for complex illnesses in complicated populations that it is critical to continue research efforts past the stage of [clinical trials](#) in illnesses like tuberculosis, the researchers said.

While tuberculosis has nearly disappeared in wealthier populations, it remains a critical threat in communities with fewer resources. A big part of the challenge of treating MDR-TB is finding regimens that will work in low-resource settings with complex populations that often include great diversity and many people who might be undernourished or sick with other illnesses.

The partnership is also studying the safety of the new regimens. Preliminary results suggest that side effects from the new regimen may be much less severe than those seen with the historical treatment, which has been known to cause deafness and psychosis.

"TB is well-controlled where control is easy," Mitnick said. "We need to find better ways to treat it where it's difficult."

The global reach of endTB has now provided clinicians with invaluable hands-on experience with bedaquiline and delamanid and helped change country guidelines, getting the new drugs registered for use in more than half of the 17 endTB countries, the researchers said. The endTB observational study has contributed to changing global guidelines, including new recommendations for concomitant use of bedaquiline and delamanid and extended use of each drug.

The endTB partnership is using the same model for promoting innovation to prepare for what researchers hope will be the next change on the horizon in care for MDR-TB: all-oral, shortened regimens, which are being studied in the current phase of endTB's clinical trial. While the implementation program continues to roll out and reaches new patients, the endTB trial has enrolled 465 patients with MDR-TB in new all-oral regimens that could transform care for MDR-TB.

The all-oral regimens used in the endTB observational study and the all-oral, shortened regimens studied in the trials would be particularly helpful during international health crises like the coronavirus pandemic, the researchers noted. These all-oral regimens are much easier to deliver in routine times and especially so in times of extreme crisis that burden health systems.

"If the ongoing trials demonstrate reduced toxicity of the all-oral, shortened regimens, this is another huge benefit for their delivery in

good times and bad," Mitnick said.

The project also transformed the landscape for TB trials by running in six countries (Georgia, Kazakhstan, Lesotho, Pakistan, Peru, South Africa) on four continents. This is the first time a clinical trial has taken place in some of these sites, the researchers said.

"In global health we see many vicious cycles, where poverty and lack of access to care combine to make diseases worse," Franke said. "On the other hand, bringing care delivery, training and research together the way we are in the endTB project can be a kind of virtuous cycle, where each turn of the wheel brings better care, improved health and greater well-being."

More information: Molly F Franke et al, Culture Conversion in Patients Treated with Bedaquiline and/or Delamanid: A Prospective Multi-country Study, *American Journal of Respiratory and Critical Care Medicine* (2020). [DOI: 10.1164/rccm.202001-0135OC](https://doi.org/10.1164/rccm.202001-0135OC)

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