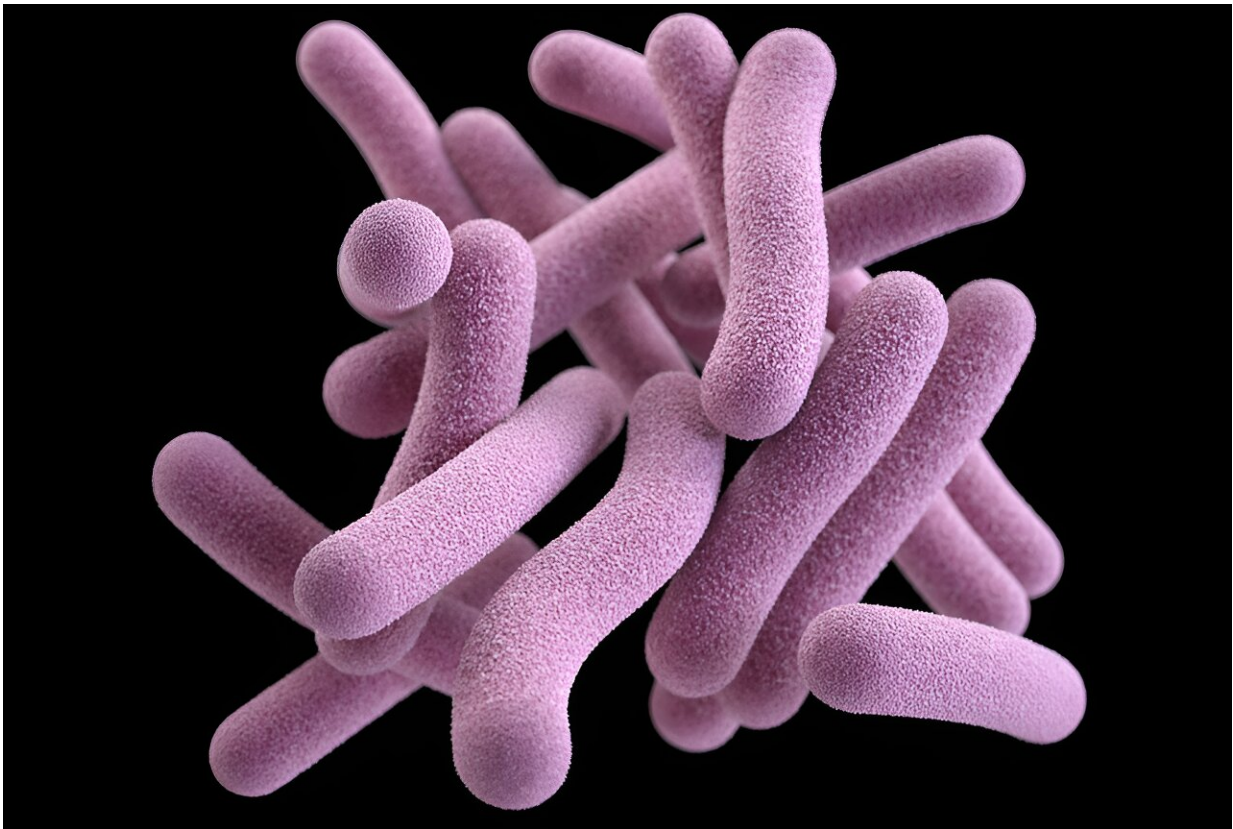


Drug-resistant tuberculosis responds rapidly to bedaquiline-based second-line therapy

February 27 2024



Mycobacterium tuberculosis. Credit: United States Centers for Disease Control and Prevention

Patients who have drug-resistant tuberculosis (TB) have a similar microbiological response to bedaquiline-based second-line medications

as patients with drug-sensitive TB taking first-line regimens, according to researchers at Weill Cornell Medicine in New York and GHESKIO Centers in Haiti.

Second-line medications are those that are given when one or more of the drugs given first for the disease are not effective. The research could have implications for shortening the duration of treatment for drug-resistant TB, which currently requires medications for up to 2 years, while those with drug-sensitive TB complete treatment in about 6 months.

The [study](#), published in *The Journal of Infectious Diseases*, "is thought to be the first to address the knowledge gap surrounding the microbiological response of patients receiving these two therapies," said the paper's lead author Dr. Kayvan Zainabadi, assistant professor of molecular microbiology at Weill Cornell Medicine.

"We found that the [new drugs](#) we use to treat the drug-resistant form of the disease are as effective as our first-line medicines," said study co-author Dr. Daniel W. Fitzgerald, director of the Center for Global Health at Weill Cornell Medicine. "Historically, they were much worse."

Evolving treatments for a devastating disease

Mycobacterium tuberculosis, the bacterium that causes TB, infects the lungs, causing cough, fever, and often death. Worldwide, 10.6 million people developed the condition in 2022, resulting in about 1.3 million deaths, according to the World Health Organization (WHO), making it the top infectious disease killer worldwide. Approximately four percent of new TB infections are drug-resistant, which disproportionately contributes to 12 percent of deaths from the disease.

In 2012, the United States Food and Drug Administration approved

bedaquiline, the first new TB drug in four decades, leading the WHO to update treatment guidelines for drug-resistant TB in 2018. The new guidelines allowed for bedaquiline, an oral drug, to replace the more toxic injectable antibiotics such as streptomycin. These new regimens are also much easier to implement in the resource-limited settings where TB is common.

Together, these factors improve the chances of patients completing treatment, which is important because not doing so results in more drug resistance, Dr. Zainabadi said.

Due to differing drug availabilities across the world, there is no single standard bedaquiline-based second-line regimen for drug-resistant TB. Rather, the WHO recommends using a combination therapy consisting of different classes of antibiotics based on availability and local drug resistance patterns. How these new oral, bedaquiline-based second-line treatments compare to first-line therapies in their ability to kill the bacteria is not well understood and prompted the research team to conduct their research.

For this study, the researchers assessed 31 subjects with drug-sensitive TB who took first-line treatment (rifampin, isoniazid, ethambutol, and pyrazinamide) and 23 subjects with drug-resistant TB who took second-line treatment (bedaquiline, pyrazinamide, levofloxacin, linezolid, and clofazimine). Patients were enrolled through Weill Cornell Medicine's partner in Haiti, the Haitian Study Group on Opportunistic Infections and Kaposi's Sarcoma, or GHESKIO.

The researchers measured the number of bacteria in the patients' sputum using an automated clinical test as well as sophisticated laboratory methods capable of detecting cryptic bacteria that typically go undetected by routine methods. They then looked at the rate of the decrease in bacteria over time with therapy.

"The laboratory work to measure the number of bacteria in sputum is incredibly laborious and requires bio-safety level 3 facilities, so it's not something you can do on a thousand people," said Dr. Fitzgerald, who is also the B.H. Kean is a Professor of Tropical Medicine and a professor of medicine in microbiology and immunology at Weill Cornell Medicine.

"The rate of decline measured at two weeks was comparable in the two groups by all measures," said study statistician Dr. Myung Hee Lee, associate professor of clinical epidemiology in medicine and associate professor of statistics. Just two months after treatment, 77.8 percent of patients from both groups tested negative for the bacterium.

"Patients who have drug-resistant TB tend to have advanced disease, and most have previously been treated with first-line drugs," Dr. Zainabadi said. "Seeing them respond at the same rate as drug-sensitive patients to treatment is encouraging."

The comparable response observed in the study may mean treatment can be shortened in drug-resistant patients. However, he noted that resistance to one of the other drugs in the regimen, pyrazinamide, was associated with slower killing of the bacterium during the first two weeks of therapy. These patients may need to be monitored and treated for an extended time.

These study results also support two [clinical studies](#) from other institutions, not yet published in peer-reviewed journals, that evaluated patient outcomes, Dr. Zainabadi said.

Future research

The Weill Cornell Medicine researchers want to build on prior studies in [Scientific Reports](#) and [mBio](#) investigating better tools for monitoring the

disease, Dr. Zainabadi said. "What we're really missing is a clinical diagnostic that can accurately monitor how patients are responding to therapy, including how well regimens are killing TB, and when cure is achieved."

The researchers are also conducting studies using the newer drugs, including bedaquiline, as an alternative to the first-line regimen in people with drug-sensitive TB, said Dr. Fitzgerald. Some patients can't tolerate the first-line [treatment](#) or are allergic to some of the drugs, he said.

"Overall research is moving in the direction of finding new drug regimens for TB and shorter and shorter treatments," Dr. Fitzgerald said. "We now have options for patients."

More information: Kayvan Zainabadi et al, A Bedaquiline, Pyrazinamide, Levofloxacin, Linezolid, and Clofazimine Second-line Regimen for Tuberculosis Displays Similar Early Bactericidal Activity as the Standard Rifampin-Based First-line Regimen, *The Journal of Infectious Diseases* (2023). [DOI: 10.1093/infdis/jiad564](https://doi.org/10.1093/infdis/jiad564)

Provided by Weill Cornell Medical College

Citation: Drug-resistant tuberculosis responds rapidly to bedaquiline-based second-line therapy (2024, February 27) retrieved 28 April 2024 from <https://medicalxpress.com/news/2024-02-drug-resistant-tuberculosis-rapidly-bedaquiline.html>

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