Aggressive regimen reduces mortality in drug-resistant TB

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An MDR-TB patient receives medication in Lima, Peru. Credit: Partners In Health

(Medical Xpress)—Aggressive drug regimens used to treat multidrug-resistant tuberculosis reduce the risk of death by about 40 percent when they include at least five drugs likely to be effective against a patient's tuberculosis strain, a retrospective study conducted amid an epidemic of multidrug-resistant tuberculosis (MDR-TB) in Peru has found.

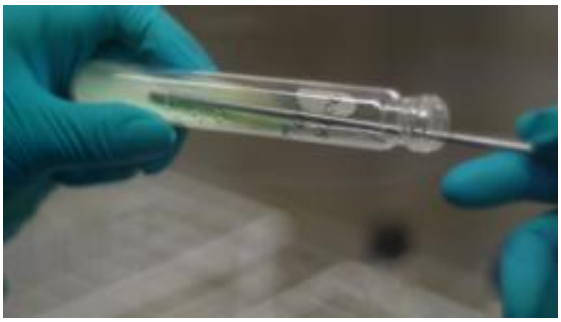
Based on their findings, the researchers concluded that TB policymakers and program directors should consider this aggressive regimen the standard of care as they design and implement treatment programs and regimens, as well as conduct randomized trials, for patients with drug-resistant TB. The results were published March 13 in *PLOS ONE*.

"As scale-up efforts are moving forward in the global fight against MDR-TB, it's important to know that there is a standard, that not just any drug regimen will do," said Carole Mitnick, HMS assistant professor of global health and social medicine, who led the study. "It is important," she notes, "that strategies for introducing new drugs should be informed by these findings in order to optimize the effectiveness of regimens, and prevent resistance to the new drugs."

In the 19th century, TB was responsible for 25 percent of deaths worldwide. Although TB is now largely controlled in the US and Europe, it remains a dangerous disease in poor populations, especially in Africa and Asia and pockets of South and Central America. The curable disease kills some two million people a year, with 500,000 new cases of drug-resistant TB reported annually. The Andean nation of Peru currently faces an epidemic of MDR-TB, with many circulating strains failing to respond to nearly half of the dozen or so antibiotics used to combat the disease, the researchers said.

Evolving resistance

Naturally-occurring drug-resistant mutants appear in large populations of TB bacteria. Treatment regimens that are inadequate through design or delivery select for these drug-resistant mutants and can lead to strains that are no longer susceptible to common drugs. People sick with these TB strains can transmit them to friends and family. If new rounds of treatment do not provide adequate coverage for the drug-resistant microbes, strains resistant to yet more drugs can emerge, the researchers said.



A biologist in Lima, Peru cultivates mycobacterium tuberculosis for drug susceptibility testing. Credit: Joshua Mitnick

The framework for the aggressive regimen was developed during MDR-TB outbreaks in the United States. To plan a particular patient's regimen, clinicians need a laboratory to test the bacteria found in a sample of sputum to learn whether those bacteria are susceptible or resistant to each drug tested. Clinicians also ascertain whether the patient has been previously treated for TB, and, if so, with which drugs. Based on that specific profile, the patient will be treated with at least five drugs likely to be effective.

This approach had never been systematically evaluated in the United States because in that country the priority in the face of this lethal, transmissible disease has been placed on treating all patients with the most potent, rather than lower-cost, regimens. Elsewhere in the world, however, there has been greater emphasis on finding less resource-intensive treatments, without systematically evaluating their effectiveness. One often-sacrificed component of TB treatment delivery is the extent to which laboratory testing is used to provide information about drug effectiveness. Without laboratory analysis of each individual's particular strain of the disease to determine which drugs will be effective, regimen potency is likely to be compromised.

Access to laboratories

The challenge of cost and effectiveness points out the importance of collaboration that seeks to build stronger health systems, the researchers said. While Peru was expanding its own TB laboratory capacity, it established a mutually beneficial exchange program with the Massachusetts State Laboratory Institute in Boston. Clinicians in Peru initially shipped TB samples to Boston for analysis. This enabled the Massachusetts lab technicians to see enough samples to maintain their expert certification in TB strain analysis, and it allowed the Peruvian physicians to create tailored, potent drug regimens for their patients. In subsequent years, Peru has built up its capacity to perform the tests locally.

"Some people want there to be a simple, one-size-fits-all approach to TB, but evolving drug resistance really makes that impossible," said senior author Mercedes Becerra, HMS associate professor of global health and social medicine. "It's vital to have a global network of laboratories equipped for and committed to addressing this problem, so everyone everywhere has access to testing."

Aggressive approach

The drug regimens were adjusted periodically to manage side effects during treatment. To qualify as "aggressive," the regimen needed to include at least five likely effective drugs. If the patient received such a regimen on at least 75 percent of the days in a particular month, the regimen was classified as aggressive. During any month, patients whose treatment qualified as aggressive had their risk of death reduced by about 40 percent. In another recent study, the researchers also showed that, among the MDR-TB patients who were cured, the aggressive regimen reduced recurrence of TB.

Both studies were conducted retrospectively, using data collected from patients who received care between 1999 and 2002 from a consortium, which included Partners In Health, led by the Peruvian National Tuberculosis Program. Peru's program was built on Partners In Health's earlier work treating MDR-TB patients in rural Haiti. That program was adapted for Haiti from the successful approach used to cure MDR-TB patients in the United States.

In the early years of Peru's TB program, the concept of using the aggressive regimen approach was met with some skepticism, the researchers said, noting that there is a lot of debate among global health policymakers about how to use scarce resources in settings with high TB prevalence. Some critics thought that the extra effort of building lab capacity and aiming for aggressive MDR-TB regimens was too much of a luxury. But since the approach had never been evaluated, there was no evidence to judge the value of the work, the researchers said.

"Much of the global policymaking for treating MDR-TB has happened in a kind of data-free zone," said Becerra, who worked with Partners In Health to help implement the program. "Now we can advance this conversation based on evidence about what specific kinds of regimens have the best chance to actually save lives."

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