

Trial signals major milestone in hunt for new TB drugs

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Singapore: A novel approach to discover the first new tuberculosis (TB) combination drug regimen cleared a major hurdle when phase II clinical trial results found it could kill more than 99 percent of patients' TB bacteria within two weeks and could be more effective than existing treatments, according to a study published in the *Lancet*. These results add to a growing body of evidence that the new regimen could reduce treatment by more than a year for some patients.

The findings from researchers and the non-profit TB Alliance raise hope for a treatment breakthrough amid the growing and dangerous epidemic of drug-resistant forms of TB that, in some cases, are becoming untreatable. The results, presented at the 2012 International AIDS Conference, also reveal progress in the pursuit of an antiretroviral-compatible TB treatment, which is critical to treating the millions of people with TB/HIV co-infection. Today, TB remains the largest killer of people with AIDS, but very often, TB and HIV treatments cannot be given together because of drug-drug interactions and side effects.

The clinical trial tested a combination of one completely novel drug candidate, a new TB drug candidate already approved to treat other infectious diseases, and one existing TB drug. These results, along with pre-clinical data, suggest that this novel combination could treat both drug-susceptible and some forms of drug-resistant TB in only four months. Currently, people with multi-drug resistant TB (MDR-TB) require 18 to 24 months of treatment. Even those with ordinary TB need six months of taking drugs every day.

"These findings confirm the promise of novel TB regimens to be shorter, simpler, safer, and, compared with today's MDR-TB drugs, much less expensive," said Dr Mel Spigelman, CEO and president of TB Alliance. "The next trial to advance this regimen is already underway. We now have real momentum toward bringing to market treatments that will ultimately help save millions of lives."

TB Alliance's push to test new drugs in combination has been done to produce a regimen that not only would be faster and easier for patients, but also would tackle two other challenges as a major step in stopping the spread of drug-resistant TB - the complexity and high cost of treatment. This promising regimen eliminates the use of injectables and projects to reduce the

cost of MDR-TB therapy by as much as 90 percent.

TB is one of the world's most ancient and deadly infectious diseases, dating back thousands of years and found in remains of Egyptian mummies. When HIV/AIDS exploded in the 1980s and 1990s, especially in sub-Saharan Africa, that epidemic triggered a historic jump in the number of TB deaths. An estimated 1.4 million people die from TB, and roughly 9 million people develop the disease, each year. One-third of all people on earth-nearly 2.5 billion people-have a latent form of TB.

The study, NC-001, or New Combination 1, was a two-week trial successfully completed at two centers in South Africa. It involved the new combination therapy called PaMZ, consisting of the novel TB drug candidate, PA-824; moxifloxacin, an established antibiotic not yet approved for use in first-line TB therapy and being developed in partnership with Bayer Healthcare AG; and pyrazinamide, an existing TB drug. NC-001 was funded by the Bill & Melinda Gates Foundation, the United States Agency for International Development, UK Aid, and Irish Aid.

"Treating drug-sensitive and drug-resistant TB with the same regimen can simplify the delivery of TB treatment worldwide," said Dr Andreas Diacon, the trial's principal investigator and lead author of the *Lancet* study. "The results of this study give healthcare providers on the front lines of the TB epidemic hope for better, faster tools needed to stop this disease."

A second trial called New Combination 2 (NC-002) was launched earlier this year to test the PaMZ combination over two months in patients, further advancing it through clinical development. NC-002 is currently enrolling patients and will be conducted at eight sites in South Africa, Tanzania and Brazil, and will build global capacity for TB trials.

In addition to these results, pharmaceutical companies are seeking regulatory approval for individual TB drug candidates-advances made possible by the existence of the most promising research pipeline for TB drugs in history. TB experts say any new drugs for tuberculosis would be an extraordinary development, but that new TB drug combinations are potential game-changers due to their expected impact.

The NC-001 trial also validated the approach to development of novel regimens. Dr Mario Raviglione, director of the Stop TB Department at the World Health Organization, said testing multiple new TB drug candidates simultaneously has already proven to be a major advance.

"Because of testing drugs in combination, we have already saved several years in the research process to find new, effective regimens to treat TB," Raviglione said. "The results look strongly promising from this early trial. If further testing holds up these results and the regimen is affordable in poor countries, it is huge progress. We could shorten drug regimens substantially for everyone, regardless of whether the form of TB is sensitive or multi-drug resistant. That would be a dramatic step forward."