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The new look of MDR and XDR-TB treatment: the times they are a-changing

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When a 50-year drought without a single new tuberculosis drug ended in 2012 with the approval of two new medicines, delamanid and bedaquiline, the tuberculosis community was poised for fast improvements to multidrug resistant (MDR) tuberculosis care and cure rates. Yet, 5 years later, the new medications are still not used widely enough in the areas most affected by MDR tuberculosis. Will recent evidence of their safety and effectiveness finally tip the scale and substantially improve MDR tuberculosis care?

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In 2016 alone, there were 600 000 new cases of the multidrug resistant (MDR) forms of tuberculosis. Only 54% of them were cured using older, challenging-to-take conventional treatments that have devastating side-effects (including psychosis, renal and liver damage, nausea, or permanent deafness) and can require over 14 000 pills and injections for up to 2 years. The potential for quicker, less toxic, and more effective treatments have made many in the tuberculosis community impatient to see new drugs like delamanid and bedaquiline used on a wide scale as fast as possible.

Yet the road to new and effective medical treatments is long. In low-income and middle-income countries (LMICs), where 95% of tuberculosis-related deaths occur, uptake of the new drugs has been slow. This is partly due to clinicians' hesitancy to use the new medications, usually rooted in outdated or very conservative WHO and national tuberculosis guidelines, as well as administrative hurdles related to drug registration and importation. Unresolved questions also demand clinical research that few low-resource health systems have the money or capacity to answer: how safe and effective are delamanid and bedaquiline compared to older regimens, especially in specific subgroups like those with HIV or children?

Recent research is answering these and other questions. Even before South Africa's bold expansion of bedaquiline, which a retrospective study published this week showed has had a substantial mortality benefit, in France and in LMIC settings in Georgia, Armenia, and elsewhere, the drug had already been shown to be fast and effective. Delamanid has been used less widely, despite evidence of its success (one previous trial showed promise and the other was inconclusive). Yet interim findings from the endTB observational study, one of the largest studies of the new drugs to date, suggest that drug regimens containing delamanid achieved excellent results even among patients with extensively drug-resistant (XDR) tuberculosis. Reporting 6 months after more than 1200 study patients had started

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treatment, the endTB study also confirms the substantial side-effects of older injectable medications (36% experienced hearing loss, acute renal failure, or electrolyte imbalances) and other key drugs (11% of linezolid patients experienced peripheral neuropathy, optic neuritis, or myelosuppression). Side-effects (such as QT prolongation) that were initially a concern for patients receiving new tuberculosis drugs occurred at clinically relevant levels in only 3% of those receiving delamanid- or bedaquiline-containing drug regimens. The final results will be published later this year.

As this and other studies emerge, policy and guidelines must evolve. The upcoming WHO Guideline Development Group meeting in Geneva on July 16–20 and the UN General Assembly High-Level Meeting on Ending TB in New York in September provide opportunities to put the newest evidence into policy and practice in 2018. The evidence is increasingly clear: delamanid and bedaquiline are safe, successful alternatives to more toxic tuberculosis treatments, and both drugs merit being elevated in the WHO hierarchy of drugs for resistant tuberculosis. Additionally, the era of prioritising injectable drugs should end. Although appropriate in some cases, injectables are almost always more toxic (and painful). Their use should be guided by the availability of alternatives, the capacity to monitor for side-effects, and the ability to quickly discontinue their use at the first sign of trouble. A patient-centred approach is paramount.

Studies like endTB and others show that, with focused effort, the hurdles that imperil tuberculosis treatment innovations can be overcome. Improving guidance will accelerate the integration of these new drugs, ultimately achieving better patient outcomes. In this case, new research is providing a roadmap for policymakers who want to cure more drug-resistant tuberculosis, more quickly, easily, and safely. Let's hope that, for tuberculosis patients, the times really are a-changing.

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This blog was corrected on July 14, 2018. An earlier version stated that the endTB study is a clinical trial. It is in fact an observational study.