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Revolutionary new treatment regimens for multidrug-resistant tuberculosis

Multidrug-resistant tuberculosis continues to be a major global public health crisis. WHO estimated that, in 2017, there were 458 000 cases of multidrug-resistant tuberculosis, defined as resistance to the two frontline drugs for tuberculosis, rifampicin and isoniazid.[1] A huge global burden of multidrug-resistant tuberculosis remains undiagnosed and untreated, with only one in four cases detected. Furthermore, just over half of those patients who are diagnosed with multidrug-resistant tuberculosis are being cured using WHO-approved treatment regimens.

Apart from inadequate facilities to diagnose multidrug-resistant tuberculosis, health services and patients in areas highly endemic for multidrug-resistant tuberculosis face major challenges. The treatment regimens are lengthy and involve expensive injectable agents, with considerable adverse effects, that require substantial patient support and follow-up to minimise toxicity, ensure cure, and reduce further emergence of resistance. The relative contributions of new and well established drugs to treat multidrug-resistant tuberculosis have informed the design of optimal multidrug-resistant tuberculosis regimens and their duration of treatment, and they serve as the basis for development of WHO multidrug-resistant tuberculosis therapeutic guidelines. In 2011, treatment for multidrug-resistant tuberculosis constituted 20 months, requiring an injectable drug for 8 months and inclusion of a fluoroquinolone. The pressure to reduce the long duration and high cost of treatment for multidrug-resistant tuberculosis led to shorter regimens being used under programmatic and trial conditions. In 2016 WHO endorsed, in select cases, on the basis of very low certainty in the evidence, a conditional recommendation for a shorter 9–12-month regimen that included injectables to treat multidrug-resistant tuberculosis.[2] Although intuitively appealing, the stringent criteria for its use meant that it was applicable to only a small proportion of individuals requiring treatment.[3]

A rapid WHO communication[4] published in August, 2018, made key changes to the recommended treatment for multidrug-resistant tuberculosis, prioritising oral drugs over injectables. For the first time ever, a new all-oral 20-month treatment regimen is now proposed, which is anticipated to be less toxic and more efficacious and to reduce hospitalisation rates.[5] The regimen recommends bedaquiline and linezolid together with levofloxacin or moxifloxacin and cycloserine or clofazimine. Injectable kanamycin and capreomycin are no longer required. Full WHO guidelines will follow soon. This revolutionary all oral regimen has the potential to radically change treatment delivery for multidrug-resistant tuberculosis.

The success of this WHO recommendation will depend on political and donor momentum, which needs to accelerate if the global multidrug-resistant tuberculosis crisis is to be curtailed and controlled. At the current slow rate of investment and progress this acceleration remains unrealistic. Implementation of the new recommendations must happen quickly with minimal disruption to health systems and

tuberculosis services.[4,5] This major change will have important operational implications for all tuberculosis stakeholders. It is reassuring, therefore, that WHO is creating a multi-partner task force to assist countries with large multidrug-resistant tuberculosis burdens in preparing for the implementation of the new recommendations. However, there are concerns that the WHO-recommended oral regimen might not be translated effectively in all geographical settings. Immediate priorities include the improvement of rapid diagnostic facilities for multidrug-resistant tuberculosis, enhanced drug procurement strategies, and revision of national tuberculosis programme policy guidelines. Adequate health-care worker training must be provided before these changes are adopted and implemented.

Crucial to improving access to new drugs for all multidrug-resistant tuberculosis patients will be the availability of resources and budgets. These new all-oral regimens are about two to three times costlier than the previously recommended regimens for multidrug-resistant tuberculosis. Using the Global Drug Facility[6] negotiated prices, estimated costs will be US$1600 to use bedaquiline and linezolid for 6 months with levofloxacin as the fluoroquinolone, and $2100 for linezolid for 12 months with moxifloxacin as the fluoroquinolone. The new regimen might consolidate a fragmented market, bring down drug prices, and stimulate competition from generic manufacturers. Through use of this regimen, success rates of treatment for multidrug-resistant tuberculosis are anticipated to increase, with the potential to substantially slow down, halt, and reverse the progression of the multidrug-resistant tuberculosis epidemic.[7] However, success will depend on the regimen's long-term efficacy and cure rates and its ability to expand treatment access and improve patient adherence and follow-up.[8] Evidence-based treatment recommendations remain a priority for global guidelines, and operational and scientific research should be aligned to the roll-out of the all-oral WHO recommendation. These should include the effects of the regimen on the host microbiome and its consequences.[9]

Several new combinations of treatment-shortening and efficacy trials are underway,[10] providing hope that evidence-based treatment recommendations are still a priority for improved management and treatment outcomes for multidrug-resistant tuberculosis. Studies in progress that will inform the adoption of shortened regimens in the context the new drugs include NiX and ZeNiX, PRACTECAL, Stream-2, NeXT, and END-TB.[10] The results of these trials are eagerly awaited. Given that many patients with multidrug-resistant tuberculosis generate aberrant host immune responses to *Mycobacterium tuberculosis*, which result in lung damage and long-term functional disability, the development of adjunct host-directed therapies is important.[11] Thus, the quest to find an ideal treatment regimen to further revolutionise tuberculosis treatment, that is all-oral, low-cost, non-toxic, short-course, simple, and applicable to all forms of tuberculosis needs to continue.

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