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Revolutionary New Treatment Regimens for Multidrug Resistant Tuberculosis

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

Apart from inadequate facilities to diagnose MDR-TB, health services and patients in high MDR-TB endemic areas 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 TB drugs to treat MDR-TB have informed the design of optimal MDR-TB regimens, their duration of treatment and serve as the basis for development of WHO MDR-TB therapeutic guidelines. In 2011 treatment for MDR-TB 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 MDR-TB led to shorter regimens being used under programmatic and trial conditions. In 2016, based on 'very low certainty in the evidence' WHO endorsed in select cases a conditional recommendation for a shorter 9 to 12-month regimen that included injectables to treat MDR-TB.² Whilst intuitively appealing, the stringent criteria for its use meant that it was applicable to only a small proportion of those requiring treatment.³

More recently a rapid WHO communication⁴ published in August 2018 made key changes to the recommended treatment for MDR-TB, prioritizing 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, more efficacious, and reduce hospitalization 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 in the New Year. This revolutionary 'all oral' regimen has the potential to radically change treatment delivery for MDR-TB.

The success of this WHO recommendation will depend on political and donor momentum, which needs to accelerate if the global MDR-TB crisis is to be curtailed and controlled. At the current slow rate of investments and progress this remains unrealistic. Implementation of the new recommendation must happen quickly with minimal disruption to health systems and TB services.^{4,5} This major change will have important operational implications for all TB stakeholders. It is reassuring, therefore, that WHO is creating a multi-partner 'Task Force' to assist high MDR-TB burden

countries prepare 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 MDR-TB, enhanced drug procurement strategies, and revision of national TB program policy guidelines. Adequate healthcare worker training must be provided before these are adopted and implemented.

Critical to improving access to new drugs for all MDR-TB patients will be the availability of resources and budgets. These new all-oral regimens are approximately upto 2 to 3-times costlier than the previously recommended regimens for MDR-TB. Using the Global Drug Facility⁶ negotiated prices, estimated costs will be US \$1,600 to use bedaquiline and linezolid for 6 months with levofloxacin as the fluoroquinolone, and US \$2,100 for linezolid for 12 months with moxifloxacin as the fluoroquinolone. The new regimen may consolidate a fragmented market, bring down drug prices and stimulate competition from generic manufacturers. It is anticipated that using this regimen, treatment for MDR-TB success rates will increase and has the potential to substantially slow down, halt and reverse the progression of the MDR-TB epidemic. However, success will depend on the regimen's long-term efficacy and cure rates, its ability to expand treatment access and improve patient adherence and follow-up. Evidence-based treatment recommendations remain a priority for global guidelines, and it is important that operational and scientific research should be aligned to the rollout of the all-oral WHO recommendation. These should include the impact of the regimen on the host microbiome and its consequences.⁹

Currently, there are several new combinations of treatment-shortening and efficacy trials underway¹⁰, providing hope that evidence-based treatment recommendations are still a priority for improved management and treatment outcomes for MDR-TB. Studies in progress that will inform the adoption of shortened regimens in the context the new drugs include NiX and ZeNiX, PRACTECAL as well as Stream-2, NeXT and END-TB.¹⁰ The results of these trials are eagerly awaited. Given that the direct effect of TB drugs on *Mycobacterium tuberculosis* may be limited when there is extensive drug resistance and lung tissue damage with functional impairment, the role of adjunct Host-Directed therapies to improve management outcomes will be important.¹¹ Thus, the quest to find an ideal treatment regimen to further revolutionise TB treatment, that is all oral, of low cost, non-toxic, short course, simple and applicable to all forms of TB needs to continue.

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