Reducing harm in the treatment of multidrug-resistant tuberculosis

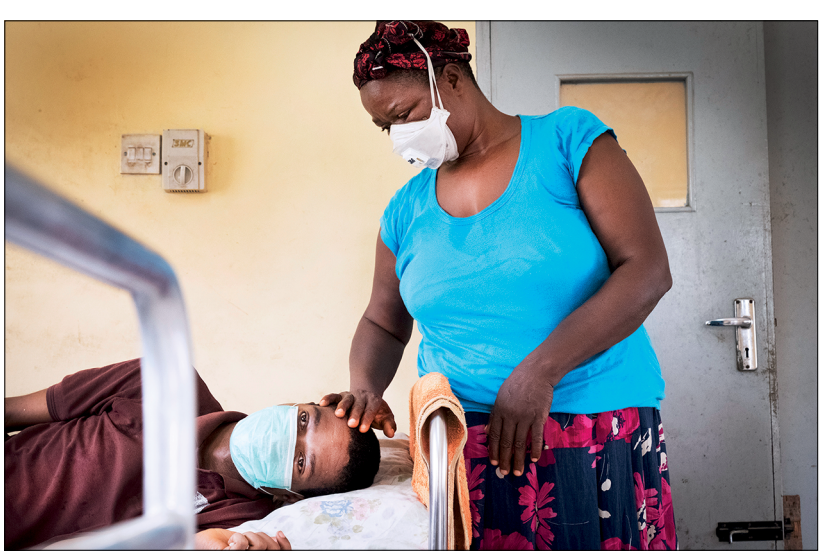
See Articles page 821

When describing the profound hearing loss she suffered as a result of her treatment for multidrug-resistant tuberculosis, the noted advocate Nandita Venkatesan said: "My world fell silent around me. I am in front of people, but I am not here."[1] In the context of India's National Tuberculosis Programme, she seems to be right: 8 years after she was clinically diagnosed, first with abdominal tuberculosis and then multidrug-resistant tuberculosis, Venkatesan was declared to be a treatment success. This outcome is a rarity in multidrug-resistant tuberculosis, for which global success rates are roughly 50%.[2] Yet the bacteriological outcomes by which victories are measured in the battle to end tuberculosis give scant attention to the long-term consequences of treatment, including permanent hearing loss and its attendant unemployment, social isolation, and depression.

Venkatesan's hearing loss was predictable given the prolonged use of injectable drugs, which characterised her treatment. Injectable drugs—including capreomycin and the aminoglycosides kanamycin and amikacin—can cause permanent hearing loss in as many as 60% of people who receive them as part of treatment for multidrug-resistant tuberculosis.[3] Ironically, no injectable drug has been assessed in a randomised controlled trial for multidrug-resistant tuberculosis, and observational studies of their effectiveness show mixed results.[4] Despite this, injectable drugs are still recommended as key drugs for the management of multidrug-resistant tuberculosis.[5] Even more concerning with regard to the routine use of these drugs is that people living with multidrug-resistant tuberculosis are often not informed of the drugs' risks, or are counselled that it is "better to be deaf than dead".[6] However, this callous yet well intentioned advice might be wrong.

In *The Lancet*, investigators from The Collaborative Group for The Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017[7] report findings of their individual patient data meta-analysis of more than 12 000 patients from 25 countries who have been treated for multidrug-resistant tuberculosis—the largest cohort to date. The investigators report an overall treatment success rate of 65% (95% CI 59–70) but found that when it came to the use of the injectable drugs, although amikacin resulted in a modest improvement in treatment success (adjusted risk difference 0·06, 95% CI 0·04 to 0·08), kanamycin was associated with worse treatment outcomes (–0·07, –0·08 to –0·05), and capreomycin was associated with worse treatment outcomes (–0·03, –0·06 to 0·00) and an increased risk of death (0·04, 0·01 to 0·07).[7] These results raise serious concerns about the continued practice of unfettered injectable drug use for people with multidrug-resistant tuberculosis.

Although the study is limited by its retrospective nature, a high degree of heterogeneity, and the presence of potential confounding factors, there are other important findings. The data show that when people receiving treatment for multidrug-resistant tuberculosis are given medications to which their infecting strains have documented resistance, no treatment benefits were seen, including for pyrazinamide. This finding calls into question the common treatment practice for multidrug-resistant tuberculosis of continuing to use therapeutic agents even in the presence of microbiological resistance. The findings also show that use of bedaquiline, linezolid, clofazimine, or later-generation fluoroquinolones was associated with improved treatment outcomes; significant reductions in mortality were associated with the use of bedaquiline, linezolid,



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levofloxacin, or moxifloxacin. These drugs—unlike the other key drugs recommended for the treatment of multidrug-resistant tuberculosis—are also supported by evidence from randomised trials,[8] as is the drug delamanid, which was not included in this meta-analysis because it was only used in a small number of people living with multidrug-resistant tuberculosis.[9]

In July, 2018, the WHO Guidelines Development Group reviewed the evidence from this meta-analysis, which forms the basis for WHO's updated multidrug-resistant tuberculosis treatment guidelines; the top-line recommendations were released on Aug 17, in a welcome and unprecedented move.[10] These recommendations for more effective, all-oral treatment with novel and repurposed drugs are applicable to most people diagnosed with multidrug-resistant tuberculosis, and stand to radically alter the treatment experience for those affected by the disease.

These recommendations must now be rapidly implemented on a global level, with support provided by technical partners and donors so that optimal outcomes can be achieved. A core value in medical practice is to do no harm. Yet each year, tens of thousands of people experience permanent damage from the widespread use of injectable drugs,[4] and there is now evidence that for many people these drugs are not only very toxic but could also be associated with worse treatment outcomes. Delays in providing access to the life-saving drugs bedaquiline, linezolid, and the later-generation fluoroquinolones cannot be tolerated, including for children, pregnant women, and other susceptible populations. The recent activities undertaken by the National Department of Health of South Africa—to replace injectable drugs with bedaquiline in the routine treatment for multidrug-resistant tuberculosis[11]—should serve as a model to improve treatment outcomes, and to spare people with the disease from debilitating adverse events. The data and the WHO recommendations are clear: rapid and concerted action must follow to translate these into treatment changes on the ground to show the men, women, and children who have already lost (or who are at risk of losing) their hearing that although their worlds might have become silent their voices have been heard.

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Better and safer treatment for multidrug-resistant tuberculosis

See **Articles** page 821

From a patient's point of view, treatment of multidrug-resistant tuberculosis has advanced very little in the past 40 years. A long and difficult course of treatment, even when successful, usually means episodes of serious or life-threatening side-effects or disease complications. Patients who push through are not guaranteed a cure. Some who do survive are left with permanent disability.

Throughout the 1990s, clinicians from Partners in Health encountered patients with multidrug-resistant tuberculosis, from Haiti and Peru to Lesotho and Siberia,