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Closing the book on Category II: time for individualized regimens for patients with recurrent tuberculosis

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FOLLOWING THE CLINICAL TRIALS by the Singapore Tuberculosis Service and the British Medical Research Council in the 1970s, the 6-month 'short-course' tuberculosis (TB) regimen, based on isoniazid, rifampicin, and pyrazinamide, was widely adopted in the 1980s.[1,2] However, for patients undergoing retreatment for TB disease, there was no clear evidence-based treatment regimen. In an effort to fill this gap, in 1991 the World Health Organization (WHO) endorsed the 'Category II' regimen, an 8-month regimen with the addition of streptomycin, as a retreatment regimen for patients with TB disease relapse, treatment failure, or treatment after an interruption of at least 2 months.[3] Despite this endorsement, it was already recognized that the addition of a single drug to a failing regimen set the stage for the amplification of drug resistance and poor clinical outcomes.[4–6] Nearly two decades later, in the face of mounting data pointing to its ineffectiveness, in 2010 the WHO recommended against using the Category II regimen.[7] This reversal remains highly relevant for the 19% of retreatment cases estimated to have drug resistance in the context of relapsed or recurrent disease in 2016.[8]

In this issue of the *Journal*, Cohen et al. have conducted a systematic review of the published literature examining treatment outcomes for patients who received Category II treatment.[9] They identified 39 studies published after 1991 with treatment outcome data. Despite heterogeneity between studies, their review confirmed poor outcomes for patients treated with a Category II regimen, with nearly all studies reporting treatment success rates below the global target of 85%. Patients undergoing treatment for relapse had slightly better outcomes as compared to those returning to treatment after interruption, treatment failure, or other, yet their treatment outcomes were still consistently below global targets.

The findings of this review reinforce and provide further momentum for TB clinicians and program managers to 'close the book' on the Category II regimen. The authors state that their review supports the current recommendations, 'that in settings where rapid DST [drug susceptibility testing] is not routinely available, patients who have failed treatment should be

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started on an empirical MDR-TB [multidrug-resistant TB] regimen unless it is known that drug resistance rates are low in that population.' While we agree with the authors, we would also emphasize more strongly the need for universal access to comprehensive DST, an intervention that is both cost-effective and improves patient outcomes.[10–12] Countries that are still employing a Category II regimen despite the 2010 WHO recommendation should revise their approach to managing patients with recurrent disease. There are published examples to navigate this process, including from Georgia, where local stakeholders were engaged in the design of new guidelines for retreatment regimens.[13]

The average time from research findings being published to changes being seen in clinical practice has been estimated at 17 years,[14] an interval that is far too long for the many patients exposed to an inadequate retreatment regimen each year. As articulated by Marcos Espinal of the WHO Stop TB Program in 2003—nearly 17 years ago—'It is time, therefore, to close the chapter on cases who fail the treatment regimen with first-line drugs and receive poor retreatment regimens based on the same drugs that, of note, are not used in high-income countries. It is neither biomedically correct nor programmatically, ethically or financially appropriate to perpetuate a policy when new evidence speaks clearly againstit.'[15]This exhortation continues to ringtrue.Itis time to stop administering the Category II regimen and design individualized regimens based on DST for patients with recurrent TB disease.

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