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Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

TO THE EDITOR: Conradie et al. (March 5 issue)[1] report that in the Nix-TB study, 90% of the patients with drug-resistant tuberculosis had treatment success, although 5.3% of the patients with positive baseline tuberculosis cultures (3 of 57 patients) had bedaquiline resistance, with minimum inhibitory concentrations (MICs) above the critical concentration. In the PRAXIS study involving patients with drug-resistant tuberculosis who were treated with bedaquiline, we found that 5.4% of the patients with positive baseline cultures (5 of 92 patients) had mutations in the bedaquiline resistance gene *Rv0678*, with MICs near the critical concentration.[2] Three of the 5 patients had an unsuccessful outcome. MICs near the critical concentration for other tuberculosis drugs have been associated with treatment failure.[3] The authors of the Nix-TB study do not state whether patients with baseline bedaquiline resistance had worse outcomes than those without bedaquiline resistance at baseline. Complete data on MICs and genome sequencing would help to determine whether an association with treatment failure exists.

Parsimonious regimens such as those evaluated in the Nix-TB study may provide little support when drugs are rendered ineffective by resistance or incomplete adherence. One case (0.9%) of emerging resistance, which was reported in the study, is probably fewer than the number that would occur in the context of routine care in which intense monitoring rarely exists. We identified emerging bedaquiline resistance in 1.7% of the patients in our study (5 of 287 patients),[2] and in 3.3% (4 of 121 patients) in a study conducted in Germany.[4] Resistance testing and enhanced adherence support must be available for all patients.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We concur with Thwaites and Nahid[1] in their editorial that the landmark study by Conradie et al. offers hope for persons with drug-resistant tuberculosis. However, the fact that peripheral neuropathy, albeit mild and manageable, was reported in 81% of the patients shows that toxic effects associated with these high doses of linezolid are problematic.

Of the 77 patients who were receiving linezolid during their stay in our tuberculosis center between 2007 and 2019, a total of 20 (26%) had polyneuropathy. The linezolid dose was adjusted on the basis of the pharmacokinetic profile and drug susceptibility testing. The median final linezolid dose was 600 mg per day (interquartile range, 300 to 600). In some cases, the linezolid dose was reduced to 150 mg daily.[2]

With this clinical experience in mind, we are anxiously awaiting results from the successor of the Nix-TB study (ZeNix; ClinicalTrials.gov number, NCT03086486), in which patients are randomly assigned to receive one of several regimens of linezolid at lower doses. Perhaps therapeutic drug monitoring could be considered for patients who report toxic effects at these lower doses, despite challenges in assessing MICs in low- and middle-income countries. Although linezolid is a powerful treatment for drug-resistant tubercu-

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Table 1. Minimum Inhibitory Concentrations (MICs) of *Mycobacterium tuberculosis* Isolates and Outcomes of the Three Patients.

Patient No.	Bedaquiline MIC	Pretomanid MIC	Linezolid MIC	Week of Culture Conversion	Outcome
		μg/ml			
Patient 1	2	0.12	0.5	No culture conversion	Death at week 11 due to pneumonia and sepsis
Patient 2	4	0.12	0.5	2	Favorable at time of assessment of primary end point
Patient 3	2	0.25	0.5	8	Favorable at time of assessment of primary end point

losis, in the end, we need equally potent but less toxic derivatives, such as sutezolid.[3,4]

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In response to Nimmo and colleagues: Table 1 shows the MICs of *Mycobacterium tuberculosis* isolates and the outcomes in the three patients who had baseline bedaquiline MICs above the critical concentration recommended by the World Health Organization (1 μg per milliliter). All three patients had isolates that were susceptible to linezolid and low MICs for pretomanid.

Whole genome sequencing is in progress to determine mutations that may be associated with these elevated MICs. We agree that emergence of resistance is a concern with a new regimen. Surveillance programs are in place worldwide to evaluate resistance to bedaquiline and linezolid and are planned to be initiated shortly for pretomanid. We encourage the availability of drug susceptibility testing, although whether this testing should be routine for all patients starting a new regimen will need to be determined by individual countries on the basis of resistance rates in their geographic regions. New treatment regimens that are combinations of drugs with low levels of resistance and that are simple, of short duration, and highly effective will enhance adherence.

We join Bolhuis and colleagues in eagerly awaiting the results of the ongoing ZeNix trial, which evaluates lower doses and shorter durations of linezolid treatment as part of the combination regimen of bedaquiline, pretomanid, and linezolid. The results of the trial will help to determine the need for new drugs in the oxazolidinone class that may have fewer adverse effects. Trials are needed to provide data on the value and successful outcomes of therapeutic drug monitoring for linezolid and to determine whether such monitoring is feasible in countries with high tuberculosis burdens.

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Since publication of their article, the authors report no further potential conflict of interest.

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