GenoType MTBDR*plus*. *rpoB* mutations outside the 81-bp rifampicin resistance determining region are not covered by these commercial assays. Another, not unusual cause of missed rifampicin resistance is heteroresistance resulting from a mixed population of both susceptible and resistant TB bacilli (3). If patients with resistance to isoniazid and missed rifampicin resistance were treated with the World Health Organization levofloxacin-strengthened first-line regimen, resistance to fluoroquinolone would emerge rapidly. Because the efficacy of second-line TB treatment relies on a fluoroquinolone as a core drug, treatment options would be dramatically reduced. Finally, as shown by Dooley and colleagues, as well as by previous studies (4), high-dose isoniazid may overcome mutations that confer resistance to isoniazid and render normal doses ineffective (4). Excluding isoniazid, which has the highest early bactericidal activity of all first-line drugs, increases the risk of acquiring rifampicin resistance, as mutant bacilli may survive the early phase of TB treatment.

Moreover, Boeree and colleagues showed that high-dose rifampicin (35 mg/kg) was safe and reduced time to culture conversion when compared with normal-dose rifampicin (10 mg/kg) (5). Although isoniazid is used for its bactericidal activity against actively replicating bacilli, rifampicin has both a bactericidal effect against rapidly replicating bacilli and a sterilizing effect against dormant bacilli. Both types of action are needed to ensure a relapse-free cure (6).

Globally, about 11.6% of patients with recurrent TB have rifampicin-susceptible/isoniazid-resistant TB. Studies should compare high-dose first-line regimens with normal-dose regimens in terms of safety, treatment success, and acquired rifampicin resistance in patients with rifampicin-susceptible/isoniazid-resistant TB. If it is shown to be safe and efficacious, high-dose first-line treatment could be used in all patients with recurrent rifampicin-susceptible TB, regardless of initial isoniazid resistance, thus avoiding delays in retreatment. Such an improved use of first-line anti-TB drugs would have major advantages. No additional susceptibility testing beyond rifampicin testing would be required and there would be no delay between a diagnosis of rifampicin-susceptible recurrent TB and initiation of treatment. If first-line treatment could rely on first-line drugs only, second-line treatment options would be maximally safeguarded. ■

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Reply to Decroo *et al.*

From the Authors:

We read with interest the letter from Decroo and colleagues referencing our INHindsight clinical trial, in which we show that 7 days of high-dose isoniazid (HD-INH) is active against pulmonary tuberculosis, with INH resistance mediated by *inhA* mutations (1).

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We agree that in addition to its utility as an agent against multidrug-resistant tuberculosis (MDR TB), HD-INH, as part of a regimen using optimally dosed first-line drugs, could play a role in the treatment of INH-resistant, rifampicin-susceptible (INH-R) TB. We acknowledge that INH has some advantages over levofloxacin, the currently recommended drug for INH-R TB, in general—it is more readily available and narrow-spectrum—and drug susceptibility testing may be more commonplace for INH than for levofloxacin (now or in the future). Certainly, higher doses of rifampicin are also needed for drug-susceptible and INH-R TB, as current doses result in suboptimal efficacy—especially in patients who are underweight or have advanced disease, meningitis, or HIV—and allow no forgiveness for missed doses (2).

Although we share Decroo and colleagues's enthusiasm, in our opinion, more needs to be done before HD-INH can be generally recommended. A one-dose-fits-all dosing approach must be carefully weighed against the risk of toxicity in patients with slow NAT2 (*N*-acetyltransferase 2) metabolizer status, whose INH concentrations can be up to threefold higher than those in fast acetylators, and the consequences of potential differences in efficacy related to mutation type. Accumulating indirect evidence that HD-INH has activity against strains with *katG* mutations (which tend to produce higher minimum inhibitory concentrations *in vitro*) needs confirmation (3–5). In the next phase of INHindsight, we will measure the early bactericidal activity of HD-INH (15–20 mg/kg) in patients with pulmonary TB caused by *Mycobacterium tuberculosis* strains with *katG* mutations. Eventually, simple and low-cost tests to determine host and bacterial genetic characteristics (NAT2 status and INH resistance mutation type) may be of great help for selecting patients who would benefit from HD-INH, and the dose that would provide the strongest microbiologic activity for a given patient with INH-R or MDR TB. It is important to appreciate that safety data for HD-INH (especially doses of ⩾15 mg/kg) given for prolonged periods of time are still limited. However, with a broader roll-out of the "short-course" MDR TB regimen, information about the safety and tolerability of the 10-mg/kg dose across multiple geographic populations should soon be available. ■

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