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High-Dose First-Line Treatment Regimen for Recurrent Rifampicin-Susceptible Tuberculosis

To the Editor:

We read with interest the article by Dooley and colleagues, which showed that high-dose isoniazid (10–15 mg/kg) had early bactericidal activity for *Mycobacterium tuberculosis* (MTB) strains with *inhA* mutations similar to that observed with normal-dose isoniazid (5 mg/kg) for susceptible strains (1). The authors concluded that high-dose isoniazid represents a useful addition to second-line tuberculosis (TB) treatment regimens for patients with rifampicin-resistant TB and isolated *inhA* mutations.

We believe that high-dose isoniazid may also play an important role in first-line TB treatment. At present, the World Health Organization recommends adding a second-line TB drug (levofloxacin) to three first-line drugs (rifampicin, ethambutol, and pyrazinamide) in patients with TB resistant to isoniazid without concurrent rifampicin resistance. Isoniazid would not be included in this levofloxacin-strengthened first-line regimen (2). This recommendation has several major implications.

To implement this recommendation, rifampicin and isoniazid susceptibility testing should be performed, particularly in previously treated patients, who are at risk of initial resistance. Before prescribing levofloxacin for patients with rifampicin-susceptible/isoniazid-resistant TB, additional fluoroquinolone susceptibility testing is recommended (2). Access to rifampicin susceptibility testing has increased substantially, but access to isoniazid and fluoroquinolone susceptibility testing is still poor in most high-TB-burden countries, where samples still have to be transported to referral laboratories. Although novel diagnostic tools, such as Xpert MTB/XDR, are on the horizon, their widespread implementation will still take years. This will cause treatment delays of several months and result in losses to follow-up between the time of TB diagnosis and treatment initiation. In addition, not all rifampicin resistance is detected by frequently used rapid tests, such as Xpert MTB/RIF and

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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. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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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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