Reply to Wilson *et al.*: The 4-Month Isoniazid, Rifapentine, Moxifloxacin, and Pyrazinamide Treatment Regimen for Drug-Susceptible Pulmonary Tuberculosis: A Word of Caution

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From the Authors:

We acknowledge the valid issues raised by Dr. Wilson and colleagues regarding operationalizing the rifapentine-moxifloxacin (isoniazid, rifapentine, moxifloxacin, and pyrazinamide; HPMZ) regimen recommended in the American Thoracic Society/CDC/Infectious Diseases Society of America/European Respiratory Society 2025 "Updates to the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis" (1). The authors comment on a higher pill burden with the 4-month HPMZ regimen compared with the 6-month isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE or RIPE) regimen, rifapentine supply issues, the availability of drug susceptibility testing (DST) for moxifloxacin, and the cost of HPMZ relative to HRZE. The Joint Panel spent time specifically weighing possible implementation issues and presented these in the Discussion and the extensive Guideline Supplement (1). The Joint Panel made a conditional recommendation for the new regimen but also indicated that for some patients the older regimens could remain better options. The conditional recommendation, as indicated in Table 3 of the Guideline, means that "Different choices will be appropriate for different patients, and you must help each patient arrive at a management decision consistent with her or his values and preferences" (1).

At the time of review, there was limited evidence regarding the issues above. The issue of cost-effectiveness is complex, including different durations of the compared regimens, cost of each drug, cost of directly observed therapy, cost of DST, and other aspects, as well as variations in each of these across different regions and countries, as discussed in the Guideline Supplement (1). A recent study, published after the Joint Panel review, found similar total direct costs between the 4- and 6-month regimens (2). At the time of the Joint Panel review, there was a paucity of evidence regarding the acceptability of more pills in a shorter duration regimen. The We Are TB patient representative to the Joint Panel expressed a preference for the shorter regimen, despite the pill burden. There may be differences in acceptability regarding pill burden versus duration of treatment for some patients. A new 300-mg formulation of rifapentine is under development, and new coformulated tablets with the other components of the regimen in the future can also reduce pill burden. DST is needed for both regimens, for rifampin and for moxifloxacin, potentially affecting the feasibility of using the shorter regimen.

We expected that there would be publications after the Joint Panel's review of available evidence that would address implementation issues. In particular, evidence is needed to recognize which of the implementation issues are actual significant problems to overcome. We note the retrospective review by Louie and colleagues (3) that identified adherence issues with even low-grade adverse events, highlighting differences between clinical trial conditions and medical practice. We look forward to emerging and future publications that will provide evidence regarding the implementation challenges of the new regimens and for steps to lift barriers to short-regimen implementation.

Just as we have several options for treatment of latent tuberculosis infection, it is desirable to have several options for treating tuberculosis, which may be tailored to the patient and the resources of the tuberculosis program. ■

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

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References

1. Saukkonen JJ, Duarte R, Munsiff SS, Winston CA, Mammen MJ, Abubakar I, *et al.* Updates on the treatment of drug-susceptible and drug-resistant tuberculosis: an official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med* 2025;211:15–33.
2. Winston CA, Marks SM, Carr W. Estimated costs of 4-month pulmonary tuberculosis treatment regimen, United States. *Emerg Infect Dis* 2023; 29:2102–2104.
3. Louie JK, Agraz-Lara R, Velásquez GE, Phillips A, Szumowski JD. Experience with four-month rifapentine and moxifloxacin-based tuberculosis treatment in San Francisco. *Open Forum Infect Dis* 2024; 11:ofae178.

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