Reply to Alffenaar et al

TO THE EDITOR—We thank Alffenaar and colleagues for their thoughtful review of the therapeutic drug monitoring (TDM) portion of the newly released tuberculosis treatment guidelines [1–3]. We agree that there are strong data to support concentration-response relationships for many tuberculosis drugs, ranging from in vitro data to animal model data to clinical trial data [4–6]. Furthermore, we agree that for most tuberculosis drugs, this concentration response currently is best described by the relationship between the free drug (not protein bound) area under the concentration-time curve divided by the minimum inhibitory concentration [7, 8]. This is described in greater detail in Appendix C to the new guidelines, and readers are encouraged to review this document (http://cid.oxfordjournals.org/content/suppl/2016/07/20/ciw376.DC1/ciw376supp_file3.pdf). Recent studies on high-dose rifampin and high-dose rifapentine not only demonstrate that these drug exposure-response
relationships exist in patients with tuberculosis, but suggest that controlling these exposures could improve treatment outcomes [6, 9]. Many clinical factors affect treatment outcome (eg, extent of disease, cavitation, individual metabolism, adherence, frequency of dosing, comorbid disease); unlike many of these factors, drug exposure can be directly influenced by the clinician.

There is wide variety in the application of TDM across US, Canadian, and European tuberculosis centers, ranging from very frequent usage to virtually no usage. These differences reflect varying opinions about the costs and benefits of TDM, and the level of proof needed to adopt the technology routinely. Such differences in opinion existed among the authors of the new tuberculosis treatment guidelines; hence, the guidelines reflect a compromise [1]. Alffenaar and colleagues correctly point out that a prospective, randomized study of TDM could be highly informative, but we agree that it would incur considerable expense in the context of already constrained tuberculosis research and tuberculosis program budgets. Thankfully, many clinicians in the United States, Canada, and Europe have begun publishing their experiences with TDM, and at a minimum, the data show that one can control drug exposure [7, 8, 10]. The debate continues about what optimal exposures might be.

Alffenaar and colleagues further point out the potential utility of dried blood spot (DBS) technology to eliminate the freezing requirement for samples, easing the collection and shipping challenges. This would be particularly advantageous in high-burden countries with limited access to freezers and dry ice for shipping. Some drugs (eg, isoniazid, ethionamide, and cycloserine) are less stable than others (eg, rifamycins [moderate stability], pyrazinamide, or fluoroquinolones [high stability]). Thus, DBS technology also has limitations. Discussion continues on the cost efficiency of these different approaches (serum/plasma vs DBS). Greater utilization will likely depend on greater success in lowering costs for shipping and assay.

TDM is one important tool that can be used to optimize drug exposure, and thus to increase efficacy or potentially to shorten treatment duration. Shorter durations could produce cost savings that more than offset assay costs. Additional research on this topic is encouraged.

Note
Potential conflicts of interest. C. A. P. has received research support from Jacobus Pharmaceuticals. He is the Director of the Infectious Disease Pharmacokinetics Lab at the University of Florida, but this clinical laboratory does not pay any of his salary. A. V. has served as the chief of a Centers for Disease Control and Prevention (CDC) clinical research branch doing clinical trials in tuberculosis, which receives institutional support through pharmaceutical company support to the CDC Foundation. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

Correspondence: C. A. Peloquin, Infectious Disease Pharmacokinetics Lab, College of Pharmacy, and Emerging Pathogens Institute, University of Florida, 1600 SW Archer Rd, Rm P4-33, PO Box 100486, Gainesville, FL 32610-0486 (panahid@ufl.edu).

Clinical Infectious Diseases® 2017;64(1):105–6
© The Author 2016. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail journals.permissions@oup.com. DOI: 10.1093/cid/ciw679