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Reply to "Breakpoints and Drug Exposure Are Inevitably Closely Linked"

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We thank Alffenaar and colleagues on their very insightful comments regarding the new breakpoints for multidrug-resistant tuberculosis (MDR TB) (1). We agree that the impact of the definition goes beyond statistical increases in the prevalence of MDR TB and has a direct impact on who should be treated with first-line regimens. Revision of breakpoints implies changing the regimens on which patients are started. Patients may be started on less effective second-line drugs with more toxicity. However, a preferred solution is exactly what Alffenaar and colleagues suggest, i.e., to use pharmacokinetics/pharmacodynamics (PK/PD) to define the drug doses necessary to overcome the high MICs.

In the early PK/PD work on rifampin and isoniazid, the efficacies of these drugs were found to be area under the concentration-time curve (AUC)/MIC driven, while resistance suppression and postantibiotic effect were found to be related to the peak concentrations/MIC (2–5). This implies that if the MIC rises, the effect can be compensated for by increased doses. The dependence of sterilizing effect and resistance suppression on peak drug concentration and AUC, and indeed on AUC/MIC and peak concentration/MIC, has recently been demonstrated in patients for all the first-line antituberculosis drugs (6, 7). Both AUC and peak concentration are increased by higher doses. Thus, as Alffenaar et al. suggest, increased doses will lower the breakpoints. In the original PK/PD-based derivation of the new breakpoints 5 years ago and in the clinical validation of these breakpoints, we emphasized that breakpoints are dependent on the dose being administered (8–10). Thus, for those drugs, such as rifampin, isoniazid, pyrazinamide, and ethambutol (and quinolones), for which the maximum tolerated doses are far above what we currently administer, it is a good solution indeed to increase the dose. Higher doses of these compounds are likely to be well tolerated based on current clinical trials (as Alffenaar et al. point out) and also based on our reanalysis of earlier clinical trials. Increasing the AUC/MIC and peak/MIC ratios will extend the efficacy of the regimen against organisms with a wider range of MICs and the number of patients with favorable responses, thereby changing the breakpoint MIC, as we have pointed out especially for rifampin and pyrazinamide (4, 9). Therefore, we agree that increasing the dose may obviate the need to change the regimen to a second-line regimen.

On the other hand, clinicians are often reluctant to increase doses. Where there is concern that doses high enough to be effective may be toxic, replacement of the drug deemed to have an MIC indicative of drug resistance with a fluoroquinolone, such as moxifloxacin, gatifloxacin, or levofloxacin, at the correct dose may be a good solution. An alternative solution would also be to measure the drug concentrations achieved in patients and, if these are low, to increase the dose of the particular drug by using a Bayesian approach. The last approach has the virtue of allaying the fears of those who worry about concentration-driven toxicity, since the concentration of the drug to be dosed higher is low to begin with. Individual dose adjustment based on drug concentration measurement and MIC determination may even reduce toxicity.

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