Srivastava and Gumbo recently published a very interesting report on the lack of effect of pharmacokinetic (PK) mismatch between isoniazid and rifampin (6). These carefully documented results, involving two short half-life tuberculosis (TB) drugs, can be seen as consistent with previous literature by Dickinson and Mitchison (2). Those earlier studies showed that, under specific experimental conditions, isoniazid’s effects are slow to be detected in vitro, whereas rifampin’s effects are quickly observed. In contrast to in vitro results, it is well described that isoniazid has the “fastest” response clinically, at least as measured by early bacterial activity (EBA) (1, 5).

In the abstract and within the text, the authors conclude that “current efforts aimed at better pharmacokinetic matching to decrease M. tuberculosis resistance emergence are likely futile and counterproductive” (6). This might be interpreted as applying to all drug combinations under all circumstances. While this may not have been the intention of the authors, it is reasonable to point out that the most significant concerns about pharmacokinetic mismatch clinically did not arise from regimens employing isoniazid and rifampin. Those concerns arose from once-weekly regimens of isoniazid (a short half-life drug) and rifapentine (a long half-life rifamycin) (7, 8). Similar concerns have been raised about intermittent regimens, and especially the use of such regimens in immunocompromised patients. Until such combinations are tested in vitro and further evaluated clinically, it seems premature to describe all such efforts to evaluate PK mismatch as “futile and counterproductive.”

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