We read with interest the paper by Narendran and colleagues [1]. The authors suggest that human immunodeficiency virus (HIV)-infected patients who receive thrice-weekly antituberculosis therapy are at higher risk of acquired rifampicin resistance compared with HIV-uninfected patients, despite the use of combination antiretroviral therapy. We emphasize the need for studies that investigate the possible effects of HIV on antituberculosis therapy, particularly in light of the emergence of drug resistance that results in difficult-to-treat multidrug-resistant and extensively drug-resistant cases. Both in vitro and clinical data show that low area under the concentration-time curve and maximum plasma concentration of rifampicin in relation to minimum inhibitory concentration were associated with the occurrence of resistance [2, 3]. Therefore, it seems relevant to collect pharmacokinetic data in clinical studies.

The pharmacokinetics of rifampicin are highly variable; especially in case of tuberculosis–HIV coinfection, reduced rifampicin exposure is not uncommon [4]. It can be expected that low drug exposure, after thrice-weekly dosing, is likely to have a higher impact on clinical outcome than after daily dosing. The World Health Organization therefore now discourages thrice-weekly antituberculosis therapy in cases of tuberculosis–HIV coinfection.

We have demonstrated that therapeutic drug monitoring (TDM) in combination with drug susceptibility testing may help to optimize treatment in individual patients [5]. Since low rifampicin plasma concentrations are so strikingly common [6], we argue in favor of routine TDM in tuberculosis–HIV coinfected patients. We recognize that obtaining full pharmacokinetic curves is not feasible in most routine settings. However, optimal sampling strategies to estimate drug exposure in combination with dried blood spot analysis may provide a feasible alternative [7, 8]. Dried blood spot analysis provides sample stability and easy logistics at low cost per sample, making TDM available in low- and middle-income countries [7].

Further, we speculate that the rifampicin resistance in the study by Narendran and colleagues could be influenced by cotrimoxazol use. Earlier data showed that cotrimoxazole was active against tuberculosis [9] and increased efficacy of rifampicin treatment [10]. In their study, HIV-infected patients with a CD4 count <350 cells/µL were given cotrimoxazol. The median CD4 count in the HIV+–highly active antiretroviral therapy (HAART) group was...
lower than in the HIV+–non-HAART group, which may have resulted in fewer participants in the HIV+–non-HAART group receiving cotrimoxazol, with subsequent effect on the development of drug resistance.

To conclude, we recognize that TDM data from randomized clinical trials to support a routine TDM program are currently lacking. However, the data from in vitro pharmacokinetic and pharmacodynamic modeling and data from a single prospective study [2] support the strategy to evaluate drug exposure and use this knowledge in clinical decision-making.

**Note**

_Potential conflicts of interest._ All authors: No potential conflicts of interest.

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