# A quest to optimize the clinical pharmacology of tuberculosis and human immunodeficiency virus drug treatment

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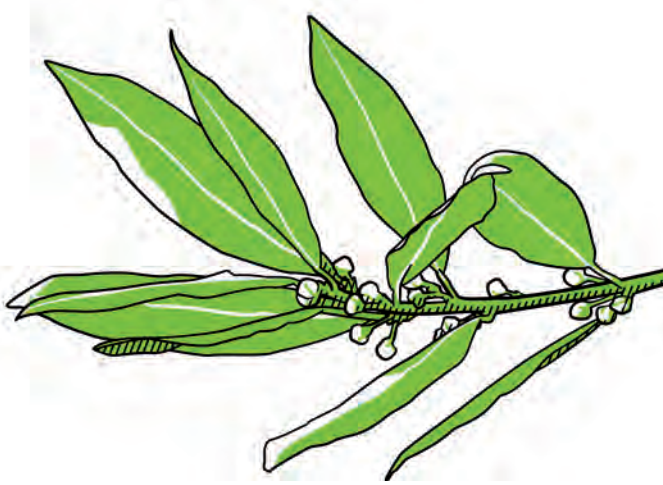
# Letters to the editor and case-report



# The never ending struggle against development of drug resistance

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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 [8]. Further, we speculate that the rifampicin resistance in the study by Narendran and colleagues could be influenced by co-trimoxazole use. Earlier data showed that co-trimoxazole was active against tuberculosis and increased efficacy of rifampicin treatment [9]. In their study, HIV-infected patients with a CD4 count <350 cells/μL were given co-trimoxazole. 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 co-trimoxazole, 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 pharmacodynamics modelling and data from a single prospective study [2] support the strategy to evaluate drug exposure and use this knowledge in clinical decision-making.

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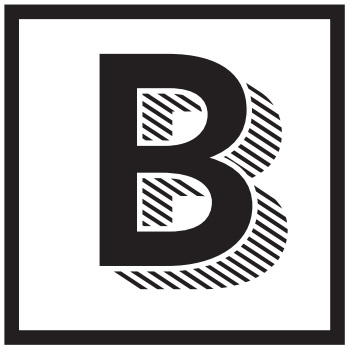

# The role of therapeutic drug monitoring in individualised drug dosage and exposure measurement in tuberculosis and HIV co-infection

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We read with interest the paper by Esposito *et al.* [1] reporting a difficult-to-treat extensively drug-resistant tuberculosis (TB) case. TB treatment in HIV-positive individuals can also be particularly challenging. An HIV-positive 26-year-old male showing excessive weight loss (body mass index 17.5 $kg \cdot m^{-2}$) and clinical deterioration was admitted to the Beatrixoord Tuberculosis Centre (University Medical Center Groningen, Haren, the Netherlands) for the treatment of pulmonary TB. *Mycobacterium tuberculosis* isolated from sputum appeared susceptible to all first-line drugs tested. The patient received rifampicin (RIF) (600 mg), isoniazid (300 mg), pyrazinamide (1500 mg) and ethambutol (1200 mg) under directly observed therapy. He started with emtricitabine (200 mg), tenofovir (245 mg) and raltegravir (800 mg twice daily) 2 weeks later as combination antiretroviral therapy. Therapeutic drug monitoring (TDM) was performed to evaluate the extent of the effect of RIF on raltegravir. Multiple blood samples were drawn over a period of 12 h to evaluate RIF exposure. Although raltegravir concentrations were adequate, strikingly low RIF concentrations were measured [2]. Unfortunately, RIF concentrations were not measured in an earlier stage of the treatment. Newly obtained plasma samples confirmed the low RIF concentration. To detect a potential decreased absorption, the same dosage of RIF was administered intravenously, which resulted in an acceptable RIF exposure (figure 1).

Drug–drug interactions influencing the absorption of RIF were not expected based on the concomitantly administered medication. The patient had no gastro-intestinal complaints and the faeces showed no presence of Giardia lamblia, Entamoeba histolytica and Cryptosporidium spp. Between the start of the TB treatment and the TDM day he had gained 11.2 kg. No obvious signs were present that could account for the remarkably low drug exposure after oral administration. However, despite the decreased bioavailability of RIF, the patient responded well to therapy. Because a decreased bioavailability was noticed in a late phase of treatment and considering the positive treatment outcome, it was decided not to change treatment. The patient has remained clinically well and free of relapse 2 years after completion of TB treatment.

Drug exposure of first-line anti-TB drugs has gained renewed interest after the hollow-fibre infection model showed that the effectiveness of these drugs is driven by the ratio of area under the curve (AUC) of concentration–time to minimum inhibitory concentration (MIC) [3]. In addition, evidence is accumulating that sub-therapeutic concentrations may contribute to acquired drug resistance and treatment failure [4]. A reduction of anti-TB drug exposure, in particular RIF, in HIV patients was reported earlier [5], but not in all studies [6]. Enteropathy caused by parasitic infections or by HIV itself (enterocyte apoptosis) and diarrhoea can often explain the reduced drug absorption in HIV patients. In our patient, the AUC from time zero to 24 h after dosing ($AUC_{0-24}$) was 2.43 $mg \cdot h \cdot L^{-1}$ after oral administration and 29.92 $mg \cdot h \cdot L^{-1}$ after *i.v.* administration, resulting in an estimated bioavailability of 8.12%. For this specific case we speculate that the exposures of concomitantly administered anti-TB drugs

were sufficient and contributed to the microbial killing and hence the favourable treatment outcome. Furthermore, an additional susceptibility test revealed that the MIC for RIF was <0.0625 mg·L$^{-1}$, which translates to an $AUC_{0-24}$/MIC ratio of 38.88. The hollow-fibre infection model showed that maximal microbial killing was achieved by a RIF daily $AUC_{0-24}$/MIC ratio of 24.14 [3]. It would seem conceivable in the case of our patient that, despite the low RIF exposure after oral administration, a positive treatment outcome was achieved due to the remarkably low MIC for RIF.

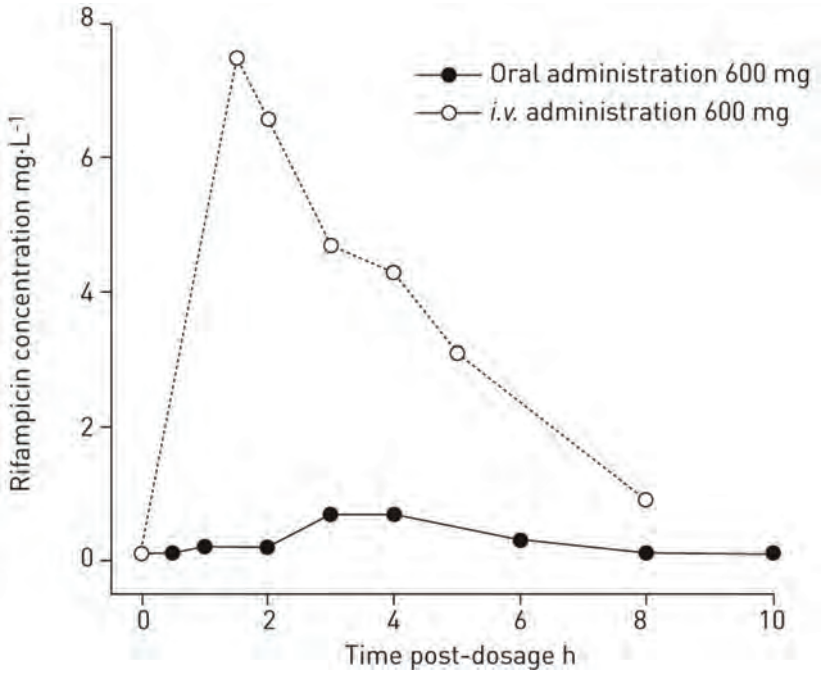


**Figure 1.** Serum rifampicin concentrations over time, when administered either orally or intravenously.

Our case strengthens the suggestion that RIF absorption from the digestive tract may be severely impaired in TB and HIV co-infected patients. Especially in the continuation phase of TB treatment, variability in drug exposure may result in virtual monotherapy if the exposure of one of the two given drugs is very low. Although the World Health Organization treatment guidelines for TB [7] make no mention of it, TDM has the potential to optimise treatment and to prevent extremely low anti-TB drug exposure in TB and HIV co-infected patients, as suggested earlier for multidrug-resistant (MDR)-TB treatment [8]. A recent consensus statement on MDR-TB treatment has already anticipated that TDM will be part of future guidelines [9]. In general, TDM may show its added value in patients who do not respond to treatment because of malabsorption, drug–drug interactions, increased drug metabolism, diabetes or TB infection in sanctuary sites. Early detection of low drug exposure may help to improve treatment response and prevent development of further drug resistance [8].

Our observation emphasises not only that drug concentrations should be measured but also that drug susceptibility should be evaluated by determining a MIC value. TDM and drug susceptibility testing should go hand in hand because, when combined, these tools help tailor the AUC/MIC ratio and thereby optimise therapy. This reduces the risk of treatment failure due to low drug exposure [4]. At present, TDM of anti-TB drugs can be advocated in case of toxicity or failing treatment response, but data from randomised clinical trials to support a routine TDM programme for all TB and HIV co-infected patients is lacking. As obtaining a full pharmacokinetic curve is not feasible in most routine settings, limited sampling strategies to estimate drug exposure in combination with dried blood spot analysis may provide an alternative [10]. In addition, the number of patients needed for screening may be reduced if it becomes clear which target populations are at increased risk of sub-therapeutic exposure. Cost/benefit ratios for TDM might be variable across subpopulations. Whether low drug exposure is relatively common in patients with TB and HIV co-infection is currently unknown. Only an adequately designed study can help clarify a possible role for routine TDM for subpopulations of TB patients.

To date, only few laboratories offer TDM for anti-TB drugs. We encourage laboratories to embrace the opportunity to perform TDM for first-line anti-TB drugs as has been done in the past for drug susceptibility testing. The first steps have been made to develop an international quality assurance system for TDM to support laboratories in the effort to provide a high-quality service to their physicians and patients. Certified reference laboratories may provide the services for second-line TB drugs using dried blood spot analysis [8].

A rational introduction of TDM in national programmes will probably improve adequate therapeutic management and contribute to elimination of TB [11]. TDM may help to prevent the emergence of drug resistance and thereby the spread of MDR-TB. In addition, TDM may help to reduce the time to sputum conversion as it optimises drug exposure, thereby preventing transmission to others. For these reasons, TDM will probably be cost effective.

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# Raltegravir and rifampicin in patients with HIV and tuberculosis

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Beatriz Grinsztejn and colleagues [1] presented data suggesting that a raltegravir dose of 400 mg twice daily is equally effective and better tolerated than the currently recommended dose of 800 mg twice daily in patients with HIV who are receiving rifampicin treatment for tuberculosis.

We agree with the authors that larger, phase 3 trials are needed to establish the efficacy of raltegravir 400 mg twice daily in such patients. However, we believe that elucidation of the factors underlying the recorded variability in raltegravir pharmacokinetics is of equal importance [2], since these factors might have a larger effect on raltegravir plasma concentrations, and thereby on efficacy, than the actual dose.

To further illustrate the inter-individual and intra-individual variability, the table shows the 10-h pharmacokinetics of raltegravir 800 mg twice daily in four patients co-infected with HIV-1 and tuberculosis concurrently receiving rifampicin that were obtained for the purpose of therapeutic drug monitoring. Viral suppression was achieved in all four patients and the drug was well tolerated.

Raltegravir maximum concentrations and area under the curve (AUC) varied substantially between the four patients, with a more than ten-fold difference between the highest and lowest values.

This difference might be attributable to factors such as food intake, drug–drug interactions besides the one with rifampicin, an inter-individual difference in the effect of rifampicin-induced metabolism, and decreased absorption or metabolism as a result of their HIV or tuberculosis. However, at the time of measurement, all patients were in a similar phase of their HIV and tuberculosis treatment.

In one patient, high raltegravir concentrations were recorded because of an interaction with omeprazole (40 mg once daily) [3]. After the omeprazole was discontinued and the raltegravir dose was halved to 400 mg twice daily, the raltegravir AUC dropped by 15-fold, after which the dose was changed back to 800 mg twice daily. The patient did not have any side-effects of raltegravir at any time during treatment, but monitoring of raltegravir drug concentrations and side-effects in patients concurrently receiving omeprazole seems to be warranted. As this example shows, the highly variable pharmacokinetics and potential for drug–drug interactions of raltegravir is of equal importance as the dose. Therefore, we look forward to the publication of the pharmacokinetic sub-study mentioned, and suggest that the authors include factors other than the drug–drug interaction between raltegravir and rifampicin explaining the highly variable pharmacokinetics in patients with HIV and tuberculosis.

**Table 1.** Patient Characteristics and Pharmacokinetic Data for Raltegravir.

| Patient | Gender | Age | BW | BMI | Dosage | AUC | $C_{max}$ | $C_{min}$ | CD4 count | VL |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 27 | 64kg | 20.7 | 800mg | 3.5 | 1.0 | 0.1 | 590 | 113 |
| 2 | F | 48 | 56kg | 16.6 | 800mg | 8.5 | 3.3 | BLQ | 50 | 138 |
| 3 | M | 29 | 62kg | 21.0 | 800mg | 14.3 | 3.6 | 0.1 | 50 | <40 |
| 4-1[a] | M | 33 | 67kg | 20.5 | 800mg | 32.6 | 11.8 | 0.1 | 290 | 12306 |
| 4-2 | | | | 20.5 | 400mg | 2.1 | 0.3 | 0.1 | | 76 |
| 4-3 | | | | 20.5 | 800mg | 3.1 | 0.4 | 0.1 | | <40 |

[a]Patient 4 was sampled on 3 occasions (4-1 with omeprazole, 4-2/3 without omeprazole). BW = Body Weight, BMI = Body Mass Index, AUC = Area under the curve (0-12 hours) in mg*h/L, Cmax = maximum observed concentration in mg/L, Cmin is minimum observed concentration in mg/L, VL = Viral Load (HIV-RNA copies/mL), BLQ = Below Limit of Quantification.



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