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

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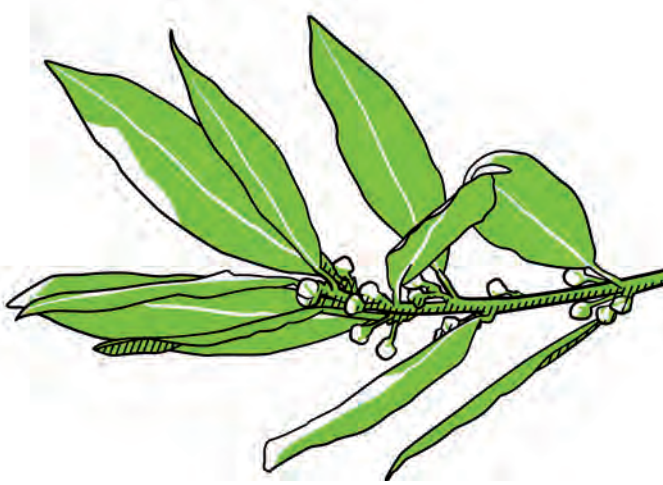
Summary



TB currently is the number one killer among infectious diseases, with a sad record of 1.7 million deaths in 2016 alone. TB control is being burdened by poverty in highly endemic areas and to patient related contributors such as: diabetes, malnutrition, drug abuse, smoking and co-infection with human immunodeficiency virus (HIV). HIV co-infection is the most important predisposing factor for TB. HIV infection increases the risk of latent TB reactivation markedly. The probability of developing TB is 17 – 22-fold higher for people living with HIV compared to those without HIV infection. Patients burdened with both HIV and TB infections suffer from potential drug-drug interactions, the high pill burden, the profound life style adjustments required for the cure or inhibition of their infection and from potential inadequate drug treatment due to pharmacokinetic variability. Therefore, we aimed to provide insight in the treatment of drug-susceptible TB in TB/HIV co-infected patients on the one hand and to provide tools for a tailor-made antiretroviral treatment, particularly for darunavir on the other.

In **chapter 2**, we investigated the effect of HIV-infection on the pharmacokinetics of first-line tuberculosis drugs by assessing published literature. The included studies were assessed for bias, pharmacokinetic data was extracted and clinical relevance was assessed. We found that the available studies provided a heterogeneous dataset from which consistent results could not be obtained. Therefore, we could not make any recommendation with respect of dosing of TB drugs in HIV co-infected patients. We postulate that HIV infection may pose additional risk for low drug exposure, with potential detrimental consequences to treatment outcomes. However, a prospective study with both an HIV-positive- and HIV-negative TB group including data on treatment outcome is needed to confirm our premise. There is a need for a uniform quality assessment tool for PK studies to enable the comparison of findings. Our systematic review revealed knowledge gaps and therefore could be used for designing follow-up studies investigating the effect of HIV infection on the PK of the first-line TB drugs.

In **chapter 3**, we conducted a retrospective study to determine the prevalence of extended TB treatment to assess the risk factors associated with it. We found that treatment was extended to ≥ 200 days in 51% of the patients. Extended TB treatment was associated with a higher frequency of symptoms, presumed to be due to adverse drug reactions (ADR; OR 2.39 95% CI: 1.01-5.69), drug-induced liver injury (DILI) (OR: 13.51; 95% CI: 1.66-109.82) and longer than 2 month smear and culture conversion rate (OR: 11.00; 95% CI: 1.24-97.96 and OR: 8.56; 95% CI: 1.53-47.96). In the multivariable logistic analysis, development of DILI emerged as the single statistically strong risk factor necessitating extension of TB treatment. A prospective study exploring the possible mutual role of pharmacokinetic and pharmacogenetic determinants of DILI among TB patients should be performed.

In **chapter 4a**, we wrote a comment on a study suggesting that 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 suggested that the rifampicin resistance in the study by Narendran and colleagues could be influenced by co-trimoxazole use and we support the strategy to evaluate drug exposure and use this knowledge in clinical decision-making. In **chapter 4b**, we presented a case demonstrating the challenges of TB treatment in a TB/HIV co-infected patients. Despite the low rifampicin exposure in our patient after oral administration, a positive treatment outcome was achieved due to the remarkably low MIC for rifampicin. 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 PK/PD ratio and thereby optimise therapy. In **chapter 4c**, we commented on a study 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 TB. We proposed that elucidation of the factors underlying the recorded variability in raltegravir PK is of equal importance, since these factors might have a larger effect on raltegravir plasma concentrations, and thereby on efficacy, than the actual dose.

In **chapter 5**, we developed and validated a bioanalytical assay which enables the simultaneous determination of fourteen antiretrovirals used in standard care and in resource-limited settings with a simple sample preparation and using stable isotope internal standards followed by LC-MS/MS analysis in human plasma. The selectivity, sensitivity, linearity, accuracy, precision, recovery, matrix effect, stability and dilution integrity and carry-over were validated according to EMA and FDA standards. The bioanalytical method was in accordance with EMA and FDA guidelines. The bioanalytical method was simple, specific, robust and reproducible and demonstrated a high sensitivity for all components making it suitable for both TDM in standard care and for clinical studies.

In **chapter 6**, we developed and validated a darunavir population pharmacokinetic model based on data from daily practice. A one-compartment model with first-order absorption and elimination, resulted in the best model. The Passing-Bablok analysis demonstrated a linear correlation between measured concentration and predicted concentration of r2 = 0.97 ($p<0.05$). The predicted values correlated well with the measured values as determined by a Bland-Altman analysis and were overestimated by a mean value of 0.12 mg/L (range -0.23 – 0.94 mg/L). 98.2% of the predicted values were within the limits of agreement. The population pharmacokinetic model developed was robust and can facilitate TDM of darunavir in a daily outpatient setting.

In **chapter 7**, we prospectively evaluated the food intake and the darunavir concentrations in people living with HIV in an outpatient setting. We found that concomitant food intake in a real life outpatient setting varied greatly and was often unnecessarily high and that a high number of people using darunavir take their drug with an in-between meal or with a snack. Health care providers and patient brochures should ensure their advice on concomitant food intake does not contribute to an unhealthy diet. We advocated that clear advice on the optimal caloric intake is needed to avoid high caloric intake in patients who already have an increased risk of cardiovascular disease due to their HIV infection.

In **chapter 8**, we evaluated predisposing factors for low darunavir plasma concentrations in patients starting the once- or twice-daily dosage. A dichotomal logistic regression analysis was conducted to select the set of variables best predicting a darunavir concentration below median population pharmacokinetic curve. The combination of tenofovir and darunavir potentially leads to decreased estimated glomerular filtration rate and increased darunavir exposure and merits further investigation. The variables best predicting a darunavir concentration besides food intake included age together with estimated glomerular filtration rate (Hosmer and Lemeshow Test p=0.945, Nagelkerke R Square 0.284). Systematic use of TDM may help to identify patients at risk for low drug exposure.

In **chapter 9**, the final chapter of this thesis, we briefly elaborate on the clinical impact of this thesis and we address several issues in both TB and HIV research and drug development. Partly due to the varying results published earlier and partly due to lack of funding and political will, to date still no thorough research has been conducted investigating whether HIV infection leads to reduces first-line TB drug exposures and its impact to clinical outcomes. Therapeutic drug monitoring and drug susceptibility testing should go hand in hand in order to help tailor the AUC/MIC ratio and thereby optimise therapy in each individual patient. In addition, we discuss the utilization of tools such as therapeutic drug monitoring and pharmacokinetic assessment in the treatment of HIV and the importance of making these tools generally available in resource-limited setting.