



**Karolinska
Institutet**

**Division of Clinical Pharmacology, Department of Laboratory
Medicine, Karolinska Institutet**

**Pharmacokinetic and Pharmacogenetic aspects
of drug-drug interactions between antiretroviral
and antituberculosis drugs in Ethiopian
patients: Implication for optimization of TB-HIV
co-treatment.**

Academic Thesis

The public defence for the Degree of Doctor of Philosophy in Medical Sciences at Karolinska Institutet will be held at Karolinska Institutet, Alfred Nobel Allé 8, Floor 4, Lecture room Z, Karolinska University Hospital, Huddinge

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Abstract

TB and HIV are immuno-pathologically interacting epidemic infectious diseases affecting the lives of millions globally & sub-Saharan African region accounts the highest burden of both diseases. Although effective therapies are available for the management of each, TB-HIV co-treatment has faced challenges mainly due to drug-drug interactions & overlapping drug toxicities. To overcome these, efavirenz (EFV) based highly active antiretroviral therapy (HAART) is the preferred regimen while rifampicin (RIF) based anti-TB treatment regimen is a choice to treat TB-HIV co-infection in resource-limited settings. RIF is a known enzyme & drug transporter inducer and/or inhibitor. The dose of EFV to be used in the presence of RIF is, however, controversial. This thesis is primarily carried out to investigate the pharmacogenetic and pharmacokinetic aspect of drug-drug interaction between RIF & EFV aiming to optimize the dose of EFV to be used in TB-HIV co-infected Ethiopian patients.

This study was designed to be carried out in two sub-Saharan African countries (Ethiopia and Tanzania), owing to the heterogeneity of the region genetically and culturally. This thesis focuses on the Ethiopian population. The thesis was conducted by prospectively recruiting cohort of HIV infected individuals without TB (Arm 1; N = 285) in parallel to another cohort of HIV co-infected with active TB (Arm 2; N = 196). All study participants were adults with baseline CD₄ count less than 200 cells per mm³ and were followed for a year. At baseline and follow up periods, clinical chemistry (liver and kidney function tests), hematological parameters (complete and differential blood cell counts) and HAART outcome monitoring (CD₄ counts and HIV RNA viral load) were done. In addition, genotyping for *CYP2B6**6, *CYP3A5* (*3, *6, *7), *UGT2B7**2, *NAT2*, *ABCB1* (3435 C > T & rs3842 A > G) & *SLCO1B1* (*1b & *5) were also done. Pharmacokinetic variables such as plasma/intracellular concentrations of EFV, 8-hydroxy-efavirenz (major metabolite) & metabolic ratio were determined at weeks 4 and/or 16, 16±1h post-dose. Besides, cholesterol, 4β-hydroxy-cholesterol (biomarker for *CYP3A* activity) & metabolic ratio at weeks 0, 4, 16 & 48 were also determined to investigate time-dependent effect of EFV on *CYP3A* enzyme. Socio-demographic factors (Age, sex, baseline body weight and BMI) were also recorded.

This thesis reports paradoxical increase in plasma/intracellular EFV concentrations by RIF co-therapy; coherent to this is improved immunological outcomes among individuals co-treated for TB and HIV with comparable virologic success to HAART than those without RIF co-treatment. The thesis also shows wide between-subject variability in the long-term auto-induction by EFV based on *CYP2B6* genotype. Between & within-subject variability in plasma EFV concentration and immunological outcome are shown to be influenced by RIF co-therapy, *CYP2B6* genotype and baseline body weight. Besides, the thesis demonstrates the influence of *CYP2B6* genotype on *CYP3A* auto-induction by EFV in a gene-dose dependent manner, *CYP2B6* (*6/*6 > *1/*6 > *1/*1). Furthermore, the thesis reveals the importance of differences in ethnicity & environmental factors contributing to wide between-population variability in EFV auto-induction comparing Ethiopian & Tanzanian patients. In addition, associations of *CYP2B6*, *ABCB1* (rs3842 A > G), slow *NAT2* metabolizing genotypes & plasma concentration of EFV with increased incidences of drug-induced liver injury (DILI) and correlation of plasma and intracellular concentrations of EFV are reported in the thesis. The thesis also shows the long-term but not short-term effects of sex and *UGT2B7* genotype in predicting auto-induction as well as plasma concentration of EFV.

In conclusion, EFV dose-escalation from 600mg to 800mg is not required during TB-HIV co-treatment in Ethiopian patients. *CYP2B6**6 genotype is not only a strong predictor for EFV pharmacokinetics but also could predict EFV-based HAART outcomes, DILI & *CYP3A* auto-induction by EFV. In addition to pharmacogenetic variability, the importance of differences in ethnicity & environmental factors are highlighted to optimize HIV treatment across sub-Saharan Africa.