



**MAKERERE UNIVERSITY**



**Karolinska  
Institutet**

**Laboratory Medicine (Karolinska Institutet), Pharmacology & Therapeutics  
(Makerere University)**

## **PHARMACOGENETIC ASPECTS OF HIV/AIDS, TUBERCULOSIS AND MALARIA: EMPHASIS ON UGANDAN POPULATION**

### **Academic Thesis**

The public defence for the degree of Doctor of Philosophy at Karolinska Institutet and Makerere University will be held at Karolinska Institutet, Alfred Nobel Alle 8, Floor 7, room 7B, Karolinska University Hospital, Huddinge.

**11th November, 2011: 09:30**

by: Jackson Kijumba B. Mukonzo  
B.Pharm, MSc.

*Main Supervisors:*

Assoc. Professor Eleni Aklillu,  
Karolinska Institutet

*Co-Supervisors:*

Professor Lars L. Gustafson  
Karolinska Institutet

Professor Jasper Ogwal-Okeng  
Makerere University

Assoc. Professor Paul Waako  
Makerere University

*Faculty opponent:*

Professor Saye Khoo  
University of Liverpool, UK,  
Department of Pharmacology

*Examination board:*

Professor Håkan Melhus  
Uppsala University,  
Department of Medical Sciences

Assoc. Prof. Moses R. Kamya  
Makerere University,  
College of Health Sciences,  
Department of Internal Medicine

Assoc. Prof. Lars Ståhle  
Karolinska Institutet,  
Department of Laboratory  
Medicine

**Kampala and Stockholm 2011**

# Abstract

Infectious diseases such as HIV, tuberculosis and malaria are endemic in Africa and often require concomitant treatments that may result into subsequent drug–drug interactions. Inter-individual variability in the pharmacokinetics and pharmacodynamics of drugs used in infectious diseases, as a result of genetic polymorphism, has been reported. Pharmacogenetics of HIV, TB and malaria treatments is inadequately described in the African population. This thesis describes the pharmacogenetic aspects of HIV, TB and malaria treatment focusing on the Ugandan population.

Studies were conducted among Ugandan adult health volunteers (n=161) and HIV patients (n = 263), some of whom were co-infected with TB. Health volunteers were examined for the effect of sex and different single nucleotide polymorphisms (SNPs) in ABCB1, CYP2B6 and CYP3A5 genes on single dose pharmacokinetics of efavirenz (n=30) and quinine (n=20). Patients were examined for effects of rifampicin and CYP2B6 (\*6 &\*11), CYP3A5 (\*3,\*5 & \*7) and ABCB1 (c.3435C>T & c.4036A>G) on enzyme induction, efavirenz clearance and efavirenz related CNS toxicities.

Apparent efavirenz oral clearance in subjects homozygous to CYP2B6\*6 and \*11 was 21 and 20% lower than extensive metabolizers respectively, while efavirenz relative bioavailability was 26% higher in subjects homozygous for MDR1 (rs3842). A two-fold increase in apparent peripheral volume of distribution was associated with female sex. Comparisons of efavirenz pharmacokinetics between HIV and healthy volunteers revealed 30% decrease in its bioavailability with HIV/AIDS disease. Long term enzyme induction during efavirenz treatment was greater without rifampicin than during rifampicin co-treatment and it majorly driven by CYP2B6 polymorphism rather than rifampicin treatment. Rifampicin co-treatment influenced neither efavirenz plasma concentrations nor incidence of efavirenz CNS toxicities (p = 0.8). Additionally, efavirenz plasma concentrations dependent CNS side effects are common in HIV/AIDs patients.

Thirty and thirteen fold variations in plasma quinine concentrations and quinine-to-3-hydroxyquinine metabolic ratio respectively, were observed. Plasma quinine concentration was significantly influenced ABCB1 haplotype, CYP3A5 genotype / haplotype as well as sex.

CYP2B6 is the major predictor of efavirenz pharmacokinetics and pharmacodynamics with or without rifampicin co-treatment. CYP3A5 influences quinine but not efavirenz disposition while ABCB1 plays a role in disposition of both drugs. Pharmacogenetics rather than rifampicin co-treatment may determine efavirenz treatment outcomes in TB co-infected HIV patients treated with efavirenz and rifampicin based regimens.