Optimization of TB and HIV Co-treatment in Africa: Pharmacokinetic and Pharmacogenetic aspects of drug-drug interactions between Rifampicin and Efavirenz

UNIVERSITY OF HEIDELBERG

Karolinska Institutet

Addis Ababa University

African Institute of Science and Technology

Muhimbili University College of Health Sciences

Background

- TB is the most frequent opportunistic infection in HIV infected individuals.
- Concomitant TB/HIV treatment is recommended in patients with low CD_4 cell counts.
- Concurrent treatment of TB and HIV is complicated due to drug interaction between Rifampicin (RIF) and Efavirenz (EFV)
- EFV is a potent, highly effective and the preferred NNRTI to be used with RIF, is metabolized by the polymorphic CYP2B6 and CYP3A4 / A5 enzyme.
- RIF is a potent inducer of CYP3A4 – reduces the plasma level of EFV. Low exposure for EFV causes increased risk of virological failure and high exposure causes toxicity.
- The appropriate daily dosage of EFV for use in combination with RIF is still unclear.

Rifampicin Interactions: Is EFV dose adjustment required?

Research gaps in the existing knowledge

- The effect of EFV-RIF kinetic interaction and effect of CYP2B6, 3A and MDR-1 genetic polymorphism on EFV-RIF kinetic interaction and ARV treatment outcome is not well investigated.

- The appropriate daily dose of EFV to be used with RIF in treating HIV/TB patients is still unclear.

- **Clinical Trial sites:**
  - Black Lion Medical University Hospital & St. Peter's TB Specialized Hospital, Addis Ababa, Ethiopia.
  - Muhimbili National Hospital, Dar Es Salaam, Tanzania.

Objectives

General objectives:

- To identify optimal dose of EFV to be used with RIF during HIV/TB co-treatment.

Specific objectives

- To determine influence of RIF co administration on plasma and intracellular EFV conc. and ARV treatment outcome by comparing steady state EFV population kinetics and treatment outcome between patients receiving EFV based HAART with or with out RIF.
- To analyze effect of CYP2B6, CYP3A polymorphism on kinetics of EFV alone and on kinetics interaction between EFV and RIF as well as on EFV treatment outcome.
- To assess whether the EFV 600 mg daily dose needs to be increased or not in patients receiving EFV with RIF.
- Capacity building: to support the training of PhD students in clinical research as part of institutional capacity building.

Trial-1

- **Aim:** To determine EFV plasma and intracellular metabolic ratio and population Pharmacokinetics of EFV in patients on ART with or without RIF based anti-TB treatment.

- **Study population**: 200 HIV/non-TB patients receiving 600mg daily dose of EFV based ART (Arm-1) will be recruited in parallel with 200 HIV/TB patients receiving 600mg daily dose of EFV based ART and RIF based anti-TB treatment (Arm-2).
- Patients will be followed-up for 48 weeks prospectively to asses EFV kinetics, phramcogentics, virologic, immunologic, safety/efficacy of 600mg EFV with and without RIF.

Trial-2

- **Aim:** To investigate steady state detailed EFV kinetics (concentration vs. time profile) during and after RIF based TB treatment in the same patient.
- **Study population**: A subpopulation of Arm-2 (n=30) from Trial-1, ARM-2 will be further recruited randomly to participate into intensive EFV pharmacokinetic (AUC 0-24 h) study during and after treatment with RIF.