

Cross national collaborative efavirenz studies in Uganda: Reflections on challenges and opportunities

Presenters

1. Dr. Sarah Nanzigu (MakCHS)
2. Prof. Lars L Gustafsson (KI)

Collaborating Institutions

1. Karolinska Institute (SE)
2. Makerere University College of Healthy Sciences (Ug)
3. Baylor College of Medicine (Ug/Tx)
4. Mbarara University (Ug)

Collaborating Researchers

Karolinska Insitutet

- Prof. Lars Naver (Co-principle Investigator)
- Prof. Lars Gustafsson (Co-sponsor)
- Dr. Jaran Eriksen (Co-Investigator)
- Dr. Sandra Soeria-Atmadja (Co-Investigator/ PhD)
- Dr. Johanna Rubin (Co-Investigator)

Makerere University

- Dr. Sarah Nanzigu (Principle Site Coordinator)
- Bernad Oyang
- **Prof. Celestino Obua (Was site PI, now VC at Mbarara University)**

Baylor College of Medicine

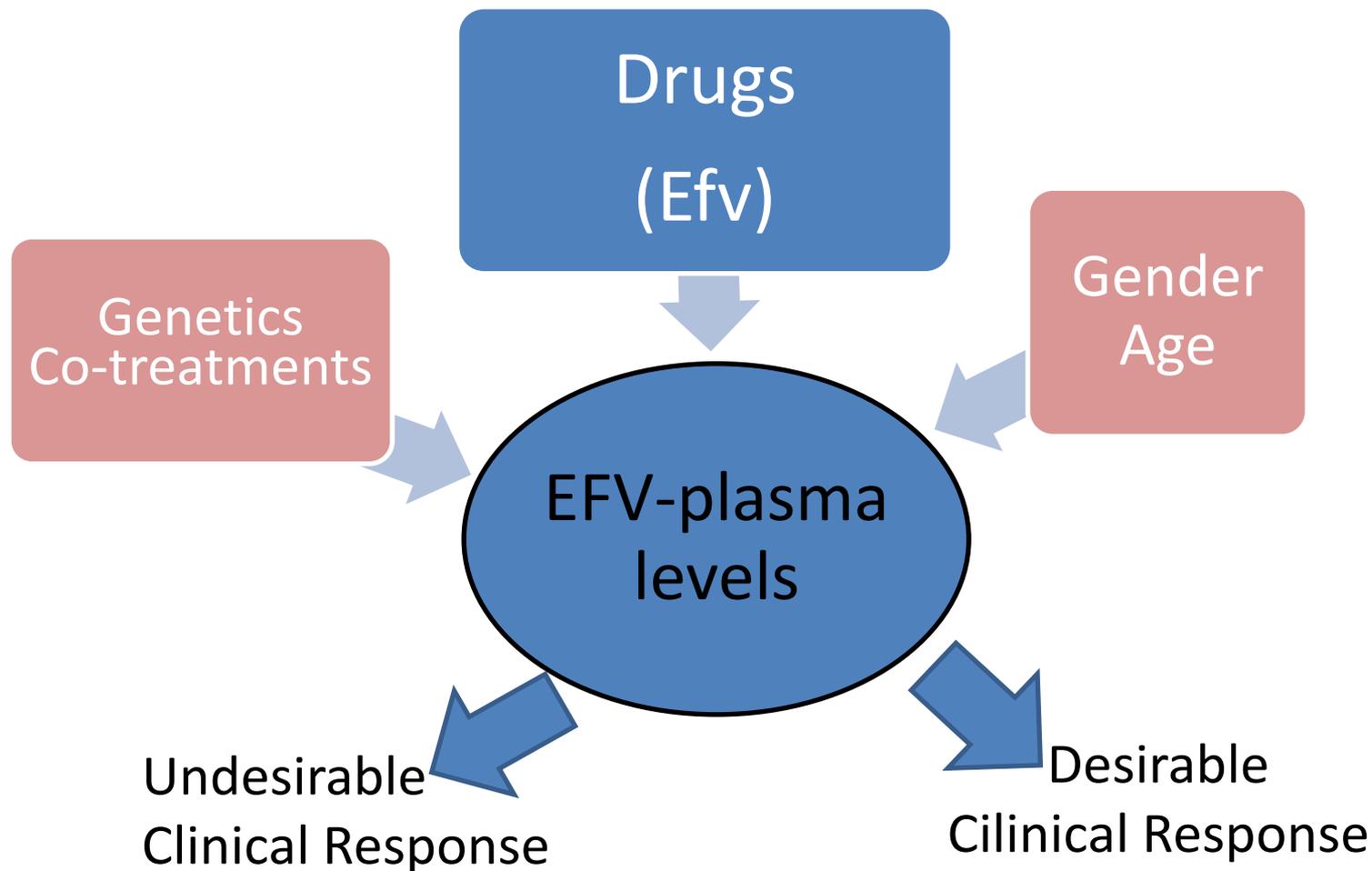
- Asoc. Prof. Adeodata Kekitinwa (Co-sponsor)
- Dr. Grace Kisitu (Co-Investigator/ Study Manager)
- Dr. Pauline Amuge

Background

Indications for EFV have expanded in the recent past

- Previously; Recommended for 1st line in adolescents & adults
- Changes
 - To include children from 3 years
- Further considerations
 - Children below 3 years
 - Pregnancy including 1st Trimester

Challenges with Efavirenz use



We aim at providing evidence-based recommendations for better utilization of efavirenz in HIV-infected Africans (young & adult), including those with relevant drug-interactions and genetics

Collaboration Background

Pre-Efv study Era: SIDA Phase1 (2001-2007)

3 PhDs including current VC at MUST

Initial equiping in PK lab



Initiation of Efavirenz studies

PhD project: 2 Mak Students (2007-2014)

Aim

Studying pharmacokinetics and genetics of efavirenz in adult Ugandans, including those cotreated for TB

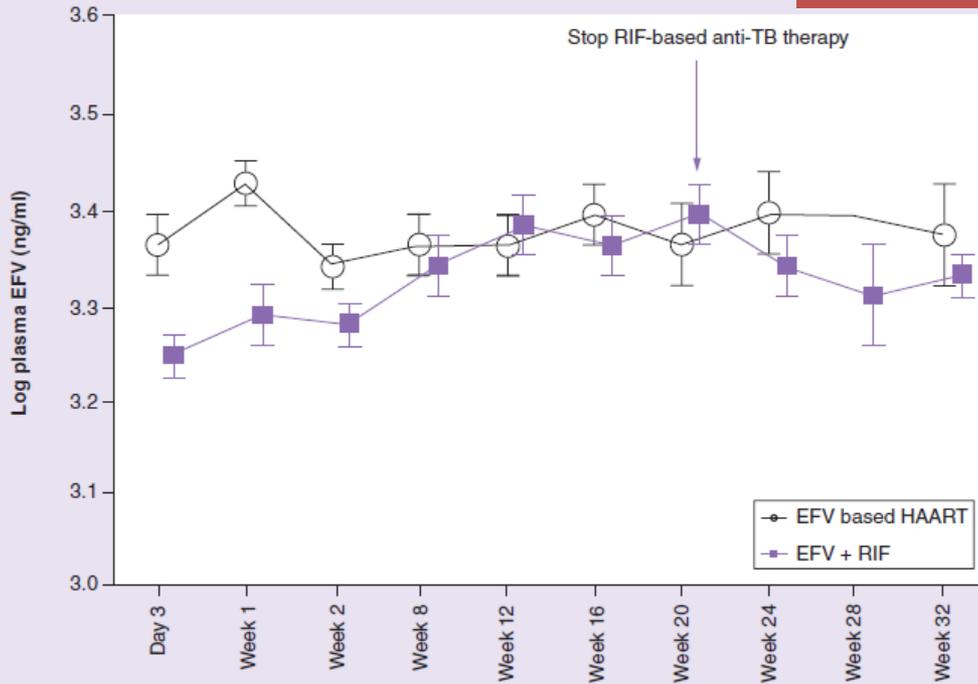
Results

Great variation in efavirenz plasma levels

Efavirenz plasma levels averagely high

CYP2B6*6 playing major role

Effect of Rifampicin

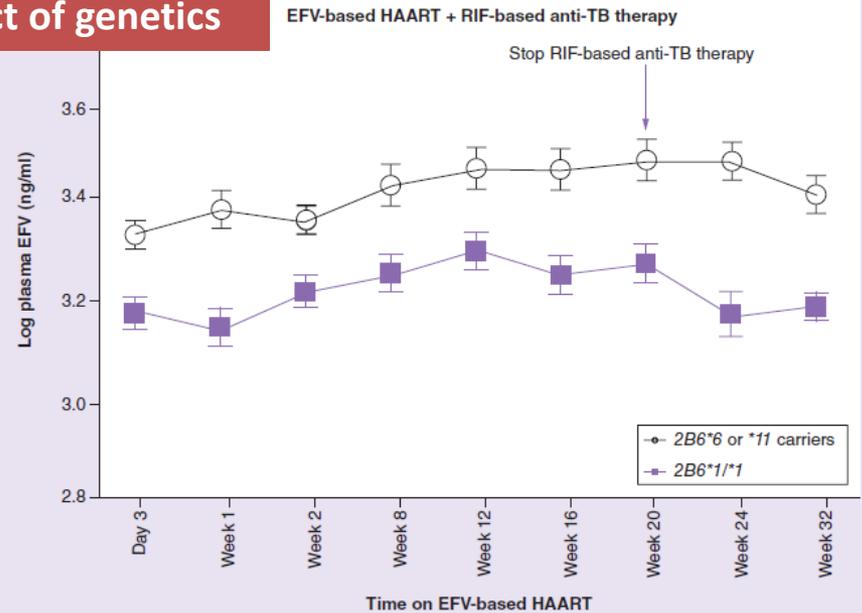
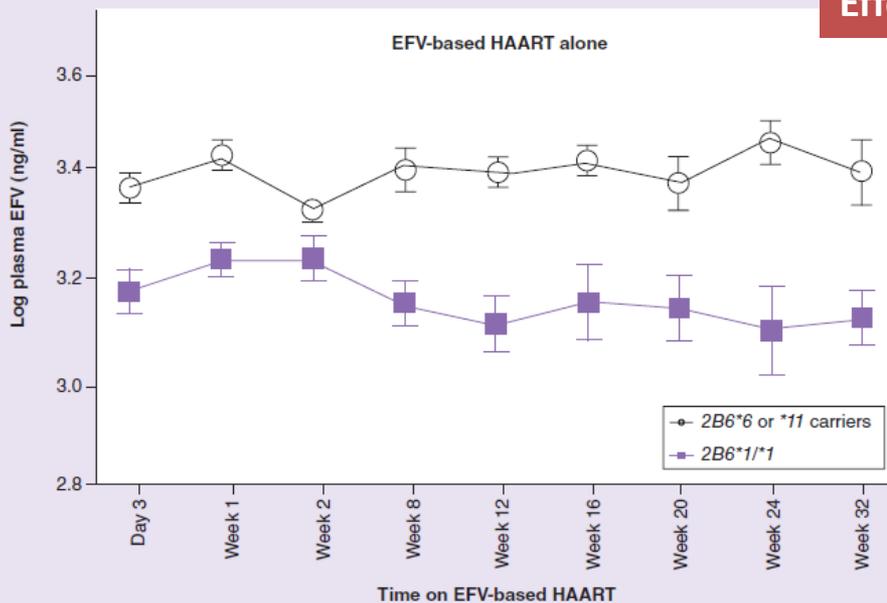


Reports

Minimal difference between HAART and HAART+RIF over 2 wks

CYB2B*6 *1/*1 showed persistently lower efv levels

Effect of genetics

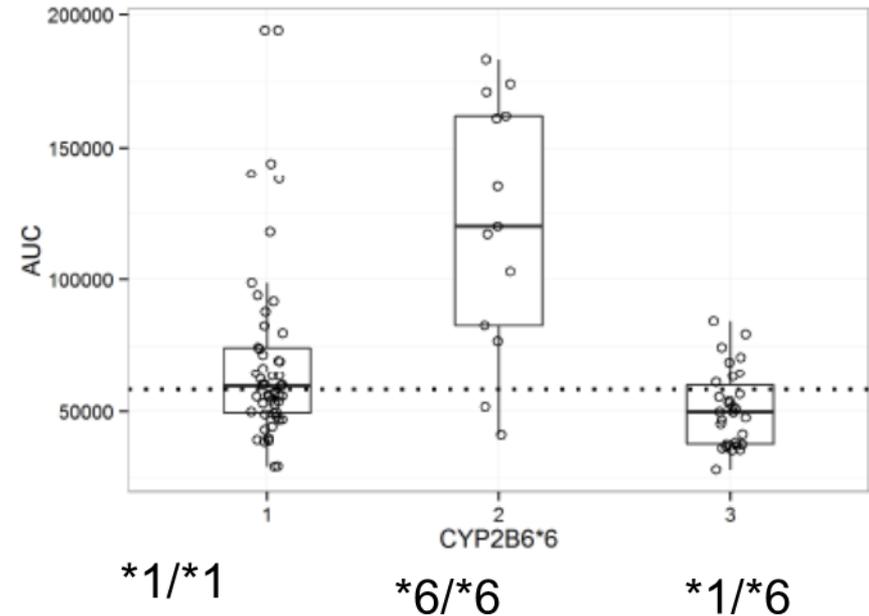


Implications

AUCs for CYP2B6 sub-populations

The following are suggested

- Efavirenz dose reductions for African Populations
- No need for dose increment during TB co-treatment



- **450mg** daily dose for the Ugandan population
- **300mg** daily dose for CYP2B6*6/*6

Challenges during student-research

- Administrative (Joint/ Double degrees)
- Fulfilling requirements for two universities/ RECs
- Booking/ securing time at different labs
- Sample movement for analysis requiring different labs

Stage 2 in Efavirenz studies

PhD project: 1 KI Student (2014 - Date)

Studying pharmacokinetics and genetics of efavirenz in Ugandan children aged 3-12 years, including TB-cotreated

Study 1A

100 ART-naive children

3-7 years

8-12 years

One samples taken at 2, 6, 12 & 24 wks

Study 1B

20 TB co-treated
EFV naive/ experienced

3-12 years

To Study Variability in Rifampicin PK
among HIV-TB Co-treated Children

NESTED RIF PK PROTOCOL

Sampling for RIF plasma levels
2 additional samples,
interspaced by 1hr

Study Update

- Started recruiting Feb 2015
- Study closure Aug 2016 (Duration 18 months)

- Recruited all arm A patients
- Only 9 for arm B

Challenges

- **Recruitments challenges**
 - Changes in guidelines (ART to all children, INH prophylaxis)
 - **Resulted:** Recruitment slower than forecast
- **General: Difficult with timely protocol approvals**
 - Resulted: delayed recruitment and changed timelines
 - Missed initial Rifampicin samples for first ARM 1A patients
- **Administrative complexity**
 - Different insitutions and management requirements
 - Changes in study staff
 - Planning for different lab needs: in blood draws, transfers, etc--

Challenges

- **Unforeseen implications from study design**
 - **ARM 1A children who develop TB cross to ARM 1B**
 - Resulted: Amendment to prolong follow-up while under ARM 1B
 - **Strict amounts of drawn blood**
 - Resulted: May prioritise some tests

Strengths and successes

- Utilisation of different expertise
 - Example: different tasks by institutions with expertise/ abilities
 - Easier planning and problem resolution
Example: (discussion that led to protocol amendment)
- Flexibility and changing of plan
 - Recruitment boosted by referral from nearby clinics
- Good communication
 - Skype, mail, telephone
 - Results: quick problem solving, frequent training

Direct Benefits

Exposure

- Learnt from each other- expertise, culture
- We are utilising resources, strength/expertise of @institution (Africa has HIV burden, Europe better in other resources)
- Higher expectations improving quality of young institutions

Expanding our collaboration with respect to:

- **Partnership**- Addition of institutions (Mbarara for-instance)
- **Areas of research**
 - Long term F/up of pediatric pharmacogenetic participants
 - Study of HIV and Antiepileptic co-Medication (HAART-AED)
 - Filter paper and other field adaptive methods

Expanding Research - Direct Benefit

- 1) Long term follow-up of the pediatric PG study
 - **Conception stage:** Will include studying HIV-resistance and long-term virological/ immunological outcomes

- 2) Study of HAART-AED bi-directional interactions (Protocol stage)
 - I. To study effect of AED on PK and clinical outcomes of HAART
 - Cross-sectional, case control study of children and adolescents at Baylor Cases are HAART-AED co-treated; controls are HAART only
 - Only efavirenz and lopinavir/r PK will be studied

 - II. To study effect of HAART on PK and clinical outcomes of AEDS
 - Cohort, case control of AED-naive patients
Cases are HAART-AED co-treated, controls are AED only
 - Only carbamazepine and valproic acid will be studied

Expanding Research- Indirect Benefit

Supervising masters projects in same area

1. Effect of Efavirenz on contraception
2. Development of an HPLC-UV Multiplex Assay for several ARVs
(Efavirenz, Nevirapine, Etravirine, Atazanavir, Lopinavir, Darunavir, Raltegravir)

About the Collaboration

Major Lesson, main strength

Foundation:

The collaboration started with a detailed background
Knowledge of each other encompassing expertise & freindship



The end

Thanks to Muria sponsorship

Special appreciation to collaborating researchers

Higher appreciation to the founders and funders

Thank you all