Pharmacogenetics implementation: African perspectives with a focus on HIV and Efavirenz

Collen Masimirembwa: African Institute of Biomedical Science & Technology
Eleni Aklillu: Karolinska Institute
Collet Dandara: University of Cape Town
Acknowledgements

- Joint preparation by Collen, Eleni & Collet
- Participants in our studies
- Students and staff at our institutes
- Funders to our research programs
- CPIC meeting organizers for the opportunity to share our research work.

29 March 2017
Collen Masimirembwa. DPhil, Ph.D.
Overview

- Dawn of pharmacogenetics in Africa
- Addressing Burden of ADRs to ARVs
- Pharmacogenetics of Efavirenz
- Gene-Dose Correlations
- Drug-Drug-Gene Interactions
- Is a pharmacogenetics driven precision public health solution feasible in Africa

29 March 2017
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1993-2017: how far from lab bench to patient bedside?

First studies on Genetic Polymorphism in African populations

Exploring drug development & clinical applications of Pharmacogenetics in Africa

Genetic polymorphism of cytochrome P450 CYP2D6 in Zimbabwean population.

A novel mutant variant of the CYP2D6 gene (CYP2D6*17) common in a black African population: association with diminished debrisoquine hydroxylase activity


COLLEN MASIMIREMBWA1, IRENE PERSSON1, LEIF BERTILSSON2, JULIA HASLER2 & MAGNUS INGELMAN-SUNDBERG1
1Department of Medical Biochemistry and Biophysics, Karolinska Institute, S-17178 Stockholm, 2Department of Medical Laboratory Sciences and Technology, Huddinge University Hospital, Huddinge, Sweden and 2Department of Biochemistry, University of Zimbabwe, Harare, Zimbabwe
Late but Promising Entry of Africa into Genomics Research – being part of global science

2003 1st Draft of the complete Human genome

Diasporan Africans Initiative

December, 2003 (Accra, Ghana)
The African Society for Human Genetics (AFSHG)
http://afshg.org/

AiBST Initiative

August 2003 (Nairobi, Kenya)
African Pharmacogenomics Consortium
www.aibst.com

2003 The African Pharmacogenomics Consortium (APC) formed

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Establishment of the AiBST Biobank for Genomics Studies

Comprehensive BioBank of African populations in terms of number of:
- Countries (5),
- Ethnic groups (9),
- Samples (2000)

Matimba et al., 2008
Genomic Diversity of African Populations

2009

1000 Genomes 2015

Nature, 2015

African Populations

- 2,504 individuals
- 26 populations

Riding the genomic wave!

- 10 African populations
- 650,000 SNPs

- 185 world populations
- 1327 markers

AiBST 2014

The Genetic Structure and History of Africans and African Americans

Sarah A. Tishkoff1,2,*, Floyd A. Reed1,1,*, François R. Frézal3,*, Christopher Fertig1,2,*, Alix Fronen2,*, Carl H. Glick1,*, Agnes A. Asamoye1,*, Jean-Marie Sibbald1,*, Cody gum DauB, Montasser Brahimi1,*, Abdelga Z. Juma1,*, Niththiva J. Kol2,*, Godfrey Pena1,*, Jason H. Moore1,*, Holly Mortensen1,*, Thomas B. Nyambo1,*, Saben A. Orme1,*, Keith Powell1,*, Gabriele S. Ruppert1,*, Michael W. Smith1,*, Mohamadou A. Thera1,*, Charles Wandels1,*, James L. Weber1,*, and Scott M. Williams1,8

Population Diversity and Pharmacogenomics in Africa

Genomic Diversity of African populations study

- Distinct clustering of Caucasians, Orientals and African populations
- Clustering of Orientals and Caucasians more dense than that of African populations
  - Confirms the heterogeneity of African populations shown using other markers
- African populations more genetically different compared to Caucasian or Asian populations (bottle-neck effect)
- Studying genomics of African populations should give more insight into human variation
Pharmacogenetic Diversity of African populations study

Genotyping for 15 SNPs in 5 genes of drug metabolizing enzymes important in drug metabolism & pharmacokinetics

<table>
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<th>Population</th>
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<td>22</td>
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(n = 2000 samples from the AiBST-APC Biobank)

Matimba et al., 2008

29 March 2017

Colleen Masimirembwa, DPhil, Ph.D.
Does variation in Pharmacogenes Predict likely population differences in Drug Response?

- CYP450s (drug metabolizing enzymes) responsible for differences exposure in individuals
- Affects 90% of drugs on the market
- Population data highlights major Population differences
- Predicts possible population difference in drug response!

Masimirembwa et al., unpublished
Burden of HIV/AIDS disease & ART Rollout

- Globally, 36.9 million people were living with HIV
- Sub-Saharan Africa most severely affected
- 70% of people with HIV
- >71 million people have died of HIV/AIDS
- 17 million patients on ART (2015)

If UNAIDS 90-90-90 target is achieved by 2020, 30 million people will be on ART!
Burden of ART associated ADRs – The clinical problem

(before introduction of efavirenz in the public ART programs)

East African Medical Journal Vol. 86. No. 12 December 2009
PREVALENCE OF ADVERSE DRUG REACTIONS IN ADULT PATIENTS ON ANTI-RETROVIRALS AT KENYATTA NATIONAL HOSPITAL-COMPREHENSIVE CARE CENTRE

L.E.M. Mwangangi, MPharm, Tutorial Fellow, Department of Pharmaceutics and Pharmacy Practice, College of Health Sciences, University of Nairobi,

Results: Systematic random sampling was used to pick 350 patients’ files. There were 219 recorded adverse drug reactions in 170 (48.6%) patients (some patients had more than one adverse drug reaction).
Peripheral neuropathy: 28.9%
lipid abnormalities: 14.3%.

In Kenya, an analysis of 1490 suspected ADRs reports received at the National Pharmacovigilance Centre in Kenya revealed that majority (79%) ADRs were related to antiretroviral medicines. The most common ARV-related adverse drug reactions observed in this study were lipoatrophy, nausea and vomiting, peripheral neuropathy, pruritis rash, anemia, erythema multiforme, and maculopapular rash.
A cross sectional, case-control, study of HIV/AIDS and/or TB-infected patients on treatment (n=430)

83% of the 430 patients on HIV/AIDS, HIV+TB and TB treatment exhibit at least one of the four (ADRs):

- Incidences of ADRs were: PN (63%) > LD (38%) > CNS (29%) > SH (21%).
Data are from VigiBase™ (June 2016). VigiBase is the World Health Organization Global Individual Case Safety Reports database, containing reports of adverse reactions received from 33 countries in Africa.

With reduced use of nevirapine since WHO Recommendations to use EFV instead since 2014, EFV has likely overtaken Nevirapine in this list of most common drugs reported in all ADRs in Africa.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total count of adverse events</th>
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<td>Nevirapine†</td>
<td>1195</td>
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<tr>
<td>Efavirenz‡</td>
<td>1099</td>
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<tr>
<td>Sulfamethoxazole and trimethoprimb,c</td>
<td>1068</td>
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<tr>
<td>Lamivudine</td>
<td>859</td>
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<tr>
<td>Stavudine</td>
<td>713</td>
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<tr>
<td>Zidovudinea</td>
<td>690</td>
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<tr>
<td>Ribavirina</td>
<td>682</td>
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<tr>
<td>Diclofenac</td>
<td>679</td>
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<tr>
<td>Lamivudine and zidovudineb</td>
<td>634</td>
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<tr>
<td>Ciprofloxacinc</td>
<td>631</td>
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<tr>
<td>Peginterferon alfa-2a</td>
<td>623</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>595</td>
</tr>
<tr>
<td>Lamivudine, nevirapine, and zidovudineb</td>
<td>565</td>
</tr>
<tr>
<td>Ethambutol, isoniazid, pyrazinamide, and rifampicinab,d</td>
<td>548</td>
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<tr>
<td>Carbamazepinaa</td>
<td>546</td>
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<tr>
<td>Isoniazida</td>
<td>523</td>
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<tr>
<td>Amoxicillinb</td>
<td>512</td>
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<tr>
<td>Insulin glargine</td>
<td>499</td>
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<tr>
<td>Paracetamolb</td>
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<tr>
<td>Amodiaquine and artesunateb</td>
<td>460</td>
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<tr>
<td>Ceftriaxoneb</td>
<td>457</td>
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<td>Acetylsalicylic acidb</td>
<td>441</td>
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<td>Valproic acidba</td>
<td>439</td>
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<tr>
<td>Docetaxelb,d</td>
<td>426</td>
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<tr>
<td>Rifampicinb,d</td>
<td>423</td>
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</tbody>
</table>
Biomarkers of ADRs associated with EFV

• Major ADRs associated with EFV
  – Neuropsychiatric side effects
  – Drug induced liver injury
Main metabolite

M1
UGT

M4
CYP2B6
(CYP3A4/5)

M8
CYP2B6

M2
UGT

M5
CYP2A6

M14
UGT

M6
UGT

M7

Effavirenz

M1

O-Glu

Cl
F\textsubscript{3}C
O
N
H
O

M2

Glu

Cl
F\textsubscript{3}C
O
N
H
O

M4

OH

Cl
F\textsubscript{3}C
O
N
H
O

M6

Glu-O

Cl
F\textsubscript{3}C
O
N
H
O

M8

OH

Cl
F\textsubscript{3}C
O
N
H
O

M14

O-Glu

Cl
F\textsubscript{3}C
O
N
H
O

M7

HO\textsubscript{3}SO

Cl
F\textsubscript{3}C
O
N
H
O
High prevalence of the *CYP2B6* 516G→T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe

- Gene-Dose Effect
- Females higher drug conc.
- All above 1.0 ug/L
- 50% > 4.0 ug/L
• Incidence 73.6%

• Predictors
  ✓ EFV plasma conc
  ✓ *CYP2B6* genotype

• No association with rifampicin, *CYP3A5, CYP2A6, ABCB1, NR113 rs3003596 T/C*,
High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-based HAART-induced liver injury in the treatment of naïve HIV patients from Ethiopia: a prospective cohort study

G Yimer1,2, W Amogne3,4, A Habtewold1,2, E Makonnen2, N Ueda1, A Suda1, A Worku5, WE Haefeli6, J Burhenne6, G Aderaye3, L Lindquist4, and E Aklillu1

The Pharmacogenomics Journal (2012) 12, 499–506

Incidence of DILI: 15.7%
Importance of Ethnicity, CYP2B6 and ABCB1 Genotype for Efavirenz Pharmacokinetics and Treatment Outcomes: A Parallel-Group Prospective Cohort Study in Two Sub-Saharan Africa Populations

Eliford Ngaimisi\textsuperscript{1,2,9}, Abiy Habtewold\textsuperscript{1,3,9}, Omary Minzi\textsuperscript{2}, Eyasu Makonnen\textsuperscript{3}, Sabina Mugusi\textsuperscript{5,6}, Wondwosen Amogne\textsuperscript{2,8}, Getnet Yimer\textsuperscript{3}, Klaus-Dieter Riedel\textsuperscript{4}, Mohammed Janabi\textsuperscript{9}, Getachew Aderaye\textsuperscript{8}, Ferdinand Mugusi\textsuperscript{9}, Leif Bertilsson\textsuperscript{8}, Eleni Aklilu\textsuperscript{1,5}, Juergen Burhenne\textsuperscript{4,5}

**Tanzania**  
P<0.0001 (week-4)  
P=0.002 (week-16)  
P=0.006

**Ethiopia**  
P=0.84

High predictive value of CYP2B6 SNPs for steady-state plasma efavirenz levels in South African HIV/AIDS patients
Marelize Swart\textsuperscript{a}, Michelle Skelton\textsuperscript{a}, Yuan Ren\textsuperscript{b}, Peter Smith\textsuperscript{b}, Simbabrashe Takuva\textsuperscript{c} and Collet Dandara\textsuperscript{a}

\section*{Introduction}
Efavirenz is primarily metabolized by CYP2B6, with a minor contribution from CYP1A2, CYP2A6, CYP3A4 and CYP3A5. Genetic variability in these genes contributes towards differences in plasma efavirenz concentration, which ultimately leads to either development of adverse drug events or emergence of virus resistance. However, the clinical utility or validity of introducing genotype-assisted dosing is not known. The aim of this study was therefore to evaluate the effects of 14 single-nucleotide polymorphisms (SNPs) in five drug-metabolizing enzyme genes on steady-state plasma efavirenz levels in South African HIV/AIDS patients as well as their clinical validity.

\section*{Methods}
HIV/AIDS patients were recruited from Themba Lethu Hospital, Durban, South Africa, from 2005 to 2010. The diagnosis of HIV was based on the patient's report of HIV infection and confirmed by Western Blot. Efavirenz was administered at a dose of 600 mg/day for 74 weeks. The 14 SNPs tested were CYP2B6 516G $>$ T; CYP2B6 785A $>$ G; CYP2B6 983T $>$ C; and CYP2B6 1459C $>$ T. The sensitivity, specificity and positive predictive values for the CYP2B6*6/*6 genotype in predicting efavirenz levels above 4$\mu$g/ml were 46, 97 and 88\%, respectively. However, these values improved to 49, 100 and 100\%, respectively, when either the CYP1A2 - 163A (*1F) allele or the NR1I3 8784C/C genotype was present.

\section*{Conclusion}
Screening for CYP2B6 516G $>$ T SNP has a high specificity and positive predictive value for efavirenz.
• Cohort of HIV/AIDS

• At least 12 months on EFV

• Range of EFV plasma conc, $0.04$–$34.4$
  – 860-fold variability
Number of patients likely to carry CYP2B6 c.516T/T genotype among South African patients

• **CYP2B6 c.516T/T** frequency: 0.14 – 0.20

• Nearly 3.5 million (5.5 mil) HIV/AIDS are on HAART
  – at least 80% are on EFV-based regimens

• Translating into 2.8 million (4.4 mil) patients
  – patients with CYP2B6 c.516T/T genotype account would account for 400K – 600K (620K – 880K)

• **CYP2B6 c.516T/T** PPV of 78%
  – Thus, 300K- 450K (480K-690K), are likely to present with EFV > 4 ug/ml
Drug-Drug-Gene Interactions in clinical settings co-infections & co-treatment are common

• Two Diseases
• One Patient
Rifampin Effects on HIV Drugs

- **Protease inhibitors**
  - Saquinavir 80 % decrease
  - Ritonavir 35 % decrease
  - Indinavir 92 % decrease
  - Nelfinavir 82 % decrease
  - Amprenavir 81 % decrease

- **Nonnucleoside reverse transcriptase inhibitors (NNRTI)**
  - Nevirapine 37 % decrease
  - Efavirenz 26 % decrease

- **Reverse transcriptase inhibitors**
  - No effect
ART/ anti-TB/ anti-malarial drug interactions

Induction
- Treatment failure
- Resistance

Inhibition
- Drug toxicity
- No PD effects

No effects
- Treatment response
Sustiva labeling update / dosing adjustment with rifampin

FDA recently approved revisions to the Sustiva (efavirenz) package insert to include dosing with Sustiva and rifampin (an antimycobacterial agent). The Dosage and Administration and Drug Interaction sections of the package insert were updated to include the following:

If Sustiva is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of Sustiva to 800 mg once daily is recommended.

The recommendation to increase the dose of efavirenz to 800 mg in patients weighing 50 kg or more when efavirenz is co-administered with rifampin is based on empirical data from two drug-drug interaction trials (one trial in healthy volunteers and one trial in HIV-1 infected patients) and semi-mechanistic population pharmacokinetic modeling. The population pharmacokinetic model was constructed using data collected in the drug-drug interaction trials and single-and multiple dose pharmacokinetic data of efavirenz from other healthy volunteer trials.

The data from the drug-drug interaction trials showed that rifampin decreased the exposure of efavirenz 600 mg once daily. Further, the systemic exposure of efavirenz, when efavirenz 800 mg was coadministered with rifampin, was similar to the systemic exposure of efavirenz when efavirenz 600 mg once daily was given alone. The results from the population pharmacokinetic analysis were consistent with the empirical data.
Treatment of TB/HIV coinfection (2011)

Rifampicin + efavirenz

Use efavirenz 800 mg/day in patients weighing > 60 kg and standard dose 600 mg/day in patients weighing < 60 kg

If side effects occur, efavirenz therapeutic drug monitoring (TDM) may be useful
DILI: 30.0%,
Severe DILI: 18.4%

- DILI predictors
  - EFV plasma conc
  - CYP2B6*6 genotype,
  - NAT2 slow metabolizers
Liver Enzyme Abnormalities and Associated Risk Factors in HIV Patients on Efavirenz-Based HAART with or without Tuberculosis Co-Infection in Tanzania

Sabina Mugusi¹,², Eliford Ngaimisi³,⁴, Mohamed Janabi⁵, Omary Minzi⁴, Muhammad Bakari⁵, Klaus-Dieter Riedel⁶, Juergen Burhenne⁶, Lars Lindquist⁷, Ferdinand Mugusi⁵, Eric Sandstrom¹, Eleni Aklillu³


**Tanzania**
DILI among patients receiving ART only = 5.9%
DILI among patients receiving anti-TB and ART = 10.0% p>0.05

**Ethiopia**
DILI among patients receiving ART only = 15.7%
DILI among patients receiving anti-TB and ART = 30.0%, p<0.005
Effect of rifampicin and CYP2B6 genotype on long-term efavirenz autoinduction and plasma exposure in HIV patients with and without tuberculosis

Clin Pharmacol Ther 2011:90;406-13

- the first report of the CYP2B6 genotype-dependent effect of RIF on long-term EFV autoinduction.
CYP2B6 genotype but not rifampicin-based antituberculosis co-treatment explains variability in long term efavirenz plasma exposure


*Pharmacogenomics 2014;15:1423-35*
Pharmacogenetic and pharmacokinetic aspects of CYP3A induction by efavirenz in HIV patients

A Habtewold1,2, W Amogne3,4, E Makonnen2, G Yimer1,2, H Nylen5, K-D Riedel6, G Aderaye3, L Bertilsson1, J Burhenne6, U Diczfalussy5 and E Aklillu1
CYP2B6*6 genotype and high efavirenz plasma concentration but not nevirapine are associated with low lumefantrine plasma exposure and poor treatment response in HIV-malaria-coinfected patients

Can CYP2B6 genotype be used to guide the dose of efavirenz?

- Case studies of dose reduction or treatment discontinuation based on CYP2B6 genotype

- PK Modeling and Simulation based dose adjustment prediction

29 March 2017
Collen Masimirembwa. DPhil, Ph.D.
Case report: Severe central nervous system manifestations associated with aberrant efavirenz metabolism in children: the role of CYP2B6 genetic variation

Francoise Pinillos¹, Collet Dandara², Mareline Swart², Renate Strehlau¹, Louise Kuhn³, Faeezah Patel¹, Ashraf Coovadia¹ and Elaine Abrams⁴*

Abstract

Background: Efavirenz, widely used as part of antiretroviral drug regimens in the treatment of paediatric human immunodeficiency virus infection, has central nervous system side effects. We describe four children presenting with serious, persistent central nervous system adverse events who were found to have elevated plasma efavirenz concentrations as a result of carrying CYP2B6 single nucleotide polymorphisms, known to play a role in the metabolism of EFV. None of the children had a CYP2B6 wildtype haplotype. We believe this is the first case of cerebellar dysfunction associated with efavirenz use to be described in children.
PHARMACOGENETICS

High prevalence of the \textit{CYP2B6} 516G→T\(^{*6}\) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe

Christopher Nyakutira · Daniel Röshammar · Emmanuel Chigutsa · Prosper Chonzi · Michael Ashton · Charles Nhachi · Collen Masimirembwa

Table 2 Simulated treatment outcomes\(^{a}\) after adjusted dosing strategies in poor, intermediate and extensive efavirenz metabolizers

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<th>Genotype</th>
<th>Dose (mg)</th>
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<th>Males</th>
<th>% Patients</th>
<th>Females</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>% Patients</td>
<td>% Patients</td>
<td>% Patients</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>C(_{ss}) &gt; 4 mg/L</td>
<td>C(_{ss}) &lt; 1 mg/L</td>
<td>C(_{ss}) &gt; 4 mg/L</td>
<td>C(_{ss}) &lt; 1 mg/L</td>
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<td>Intermediate metabolizers</td>
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<td>50</td>
<td>4.4</td>
<td>42</td>
<td>5.3</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>42</td>
<td>6.5</td>
<td>32</td>
<td>8.7</td>
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<tr>
<td></td>
<td>400</td>
<td>31</td>
<td>10.3</td>
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<td>39</td>
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<tr>
<td>Extensive metabolizers</td>
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<td>37</td>
<td>7.6</td>
<td>27</td>
<td>10.6</td>
<td>46</td>
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<tr>
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<td>500</td>
<td>29</td>
<td>11.3</td>
<td>21</td>
<td>15.4</td>
<td>38</td>
</tr>
</tbody>
</table>

\(C_{ss}\) Efavirenz steady-state plasma concentration at the mid-dose interval

\(^{a}\)Percentage of 2,000 virtual patients (50% males)
- 20% of Zimbabwean patients are TT and would require only 200 mg instead of the given 600 mg efavirenz.

- Results in less CNS ADRs, greater compliance, & cheaper treatment.

Nemaura et al., 2012, Dhoro et al., 2014
CYP2B6 genotype based efavirenz dose recommendations during rifampicin based anti-tuberculosis co-treatment for a Sub-Saharan Africa population
Mukonzo JK, Bisaso RK, Ogwal-Okeng J, Gustafsson LL, Owen S, Aklillu E.

Pharmacogenomics 2016: Apr 5. [Epub ahead of print]

Recommended daily EFV dose

→ 450 mg for CYP2B6 extensive metabolizers

➢ 250 mg for homozygous for CYP2B6*6

Lack of correlation between vrological decay and trough concentrations indicating that trough EFV concentrations achieved in the study population might be far greater than the threshold required C\text{trough}.
Research Article

Is there a need to increase the dose of efavirenz during concomitant rifampicin-based antituberculosis therapy in sub-Saharan Africa? The HIV-TB pharmagene study

Abiy Habtewold\textsuperscript{1,2}, Eyasu Makonnen\textsuperscript{2}, Wondwossen Amogne\textsuperscript{3,4}, Getnet Yimer\textsuperscript{1,2}, Getachew Aderaye\textsuperscript{3}, Leif Bertilsson\textsuperscript{1}, Jürgen Burhenne\textsuperscript{5} & Eleni Aklillu*\textsuperscript{1}

Pharmacogenomics. 2015;16:1047-64.

2017-03-29 Eleni Aklillu, PhD
Recommended daily EFV dose

→ 450 mg for CYP2B6 extensive metabolizers

➢ 300 mg for homozygous for CYP2B6*6
Initial study from 2008 on PGX based Dose Optimization in Zimbabwe reproduced in:

- Uganda
- Tanzania
- South Africa

Its time to do a Non-inferiority study with Respect to efficacy and a Superiority study With respect to Adverse drug reactions!!
Our Solution: Personalized Efavirenz Dosing

**Current Practice**

- **GeneDose® - EFV**
- Genotype guided dosing of EFV

Patients with same Diagnosis – ‘one Treatment fits ALL’

- 600 mg EFV/day

**Current Practice**

- 600 mg EFV/day (38%)
- 400 mg EFV/day (42%)
- 200 mg EFV/day (20%)

**GeneDose® - EFV**

- Genotype guided dosing of EFV
Innovation wins 1st Prize GAP Award

29 March 2017
Colleen Masimirembwa, DPhil, Ph.D.
Pharmacogenetics in Africa, an Opportunity for Appropriate Drug Dosage Regimens: on the Road to Personalized Healthcare

C Masimirembwa and JA Hasler

Its possible & we are close.....
THANK!