# 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 opprotunity to share our research work.

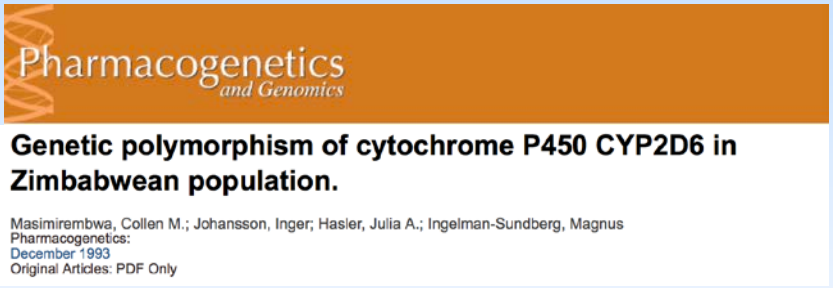
# Overview

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

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

First studies on Genetic Polymorphism in African populations

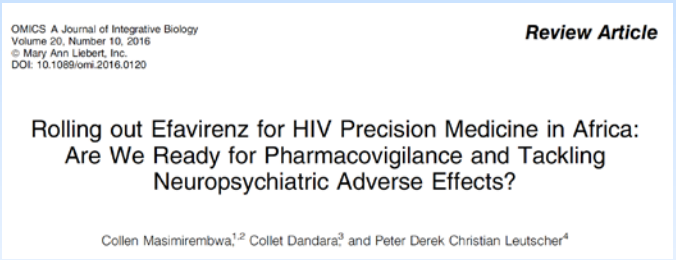
Exploring drug development & clinical applications of Pharmacogenetics in Africa



Pharmacogenetics and Genomics

**Genetic polymorphism of cytochrome P450 CYP2D6 in Zimbabwean population.**

Masimirembwa, Collen M.; Johansson, Inger; Hasler, Julia A.; Ingelman-Sundberg, Magnus
Pharmacogenetics:
December 1993
Original Articles: PDF Only

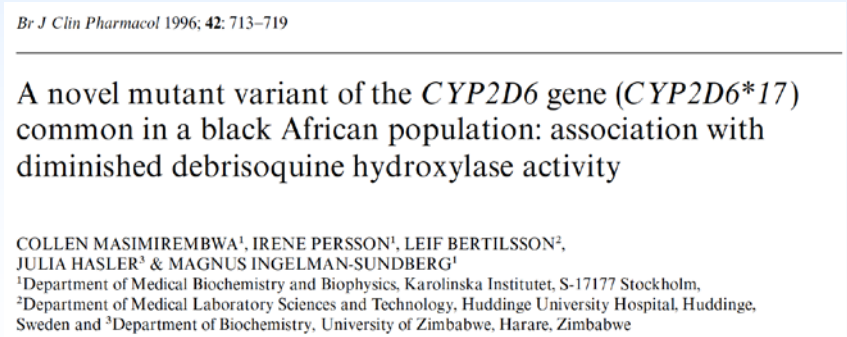


OMICS A Journal of Integrative Biology
Volume 20, Number 10, 2016
© Mary Ann Liebert, Inc.
DOI: 10.1089/omi.2016.0120

***Review Article***

Rolling out Efavirenz for HIV Precision Medicine in Africa: Are We Ready for Pharmacovigilance and Tackling Neuropsychiatric Adverse Effects?

Collen Masimirembwa,[1,2] Collet Dandara,[3] and Peter Derek Christian Leutscher[4]



*Br J Clin Pharmacol* 1996; **42**: 713–719

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

COLLEN MASIMIREMBWA[1], IRENE PERSSON[1], LEIF BERTILSSON[2], JULIA HASLER[3] & MAGNUS INGELMAN-SUNDBERG[1]
[1]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, S-17177 Stockholm, [2]Department of Medical Laboratory Sciences and Technology, Huddinge University Hospital, Huddinge, Sweden and [3]Department of Biochemistry, University of Zimbabwe, Harare, Zimbabwe

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journal homepage: www.ebiomedicine.com

Research Paper

African Genetic Diversity: Implications for Cytochrome P450-mediated Drug Metabolism and Drug Development

Iris Rajman [a,*], Laura Knapp [b], Thomas Morgan [c], Collen Masimirembwa [d]

[a] Translational Medicine, Novartis Institutes for Biomedical Research, Basel, Switzerland)
[b] PharmaGenesis London, London, UK
[c] Translational Medicine, Novartis Institutes for Biomedical Research, Cambridge, MA, USA
[d] African Institute of Biomedical Science & Technology, Harare, Zimbabwe

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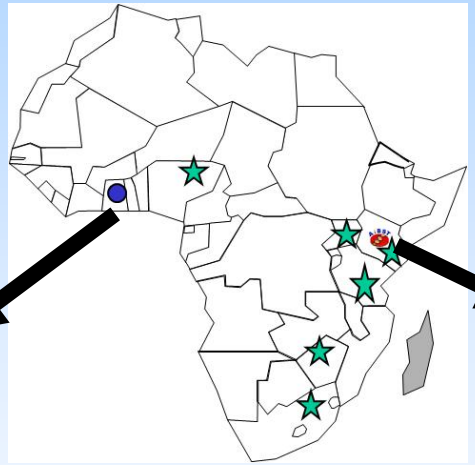
# Late but Promising Entry of Africa into Genomics Research – being part of global science

## 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



Collen Masimirembwa. DPhil, Ph.D.

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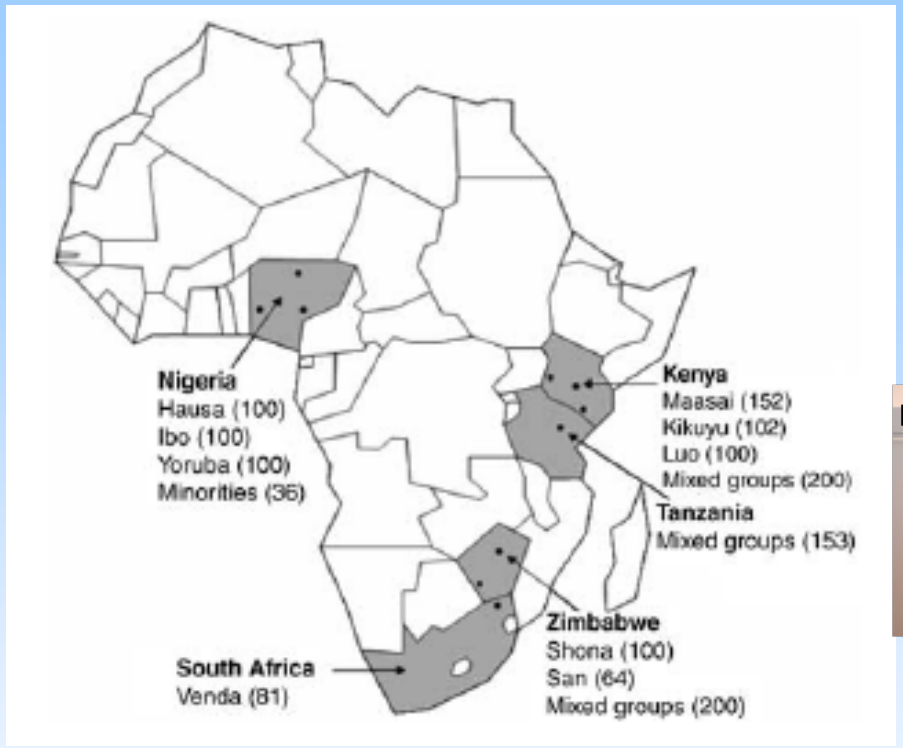
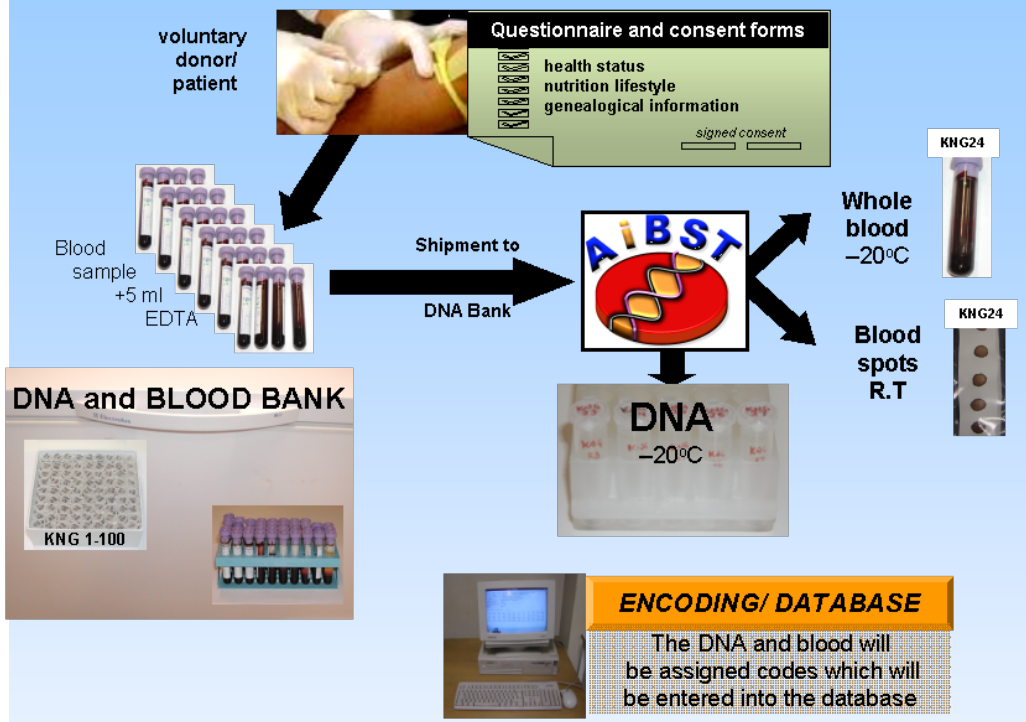
# Establishment of the AiBST Biobank for Genomics Studies




Comprehensive BioBank of African populations in terms of number of:

- **Countries (5)**,
- **Ethnic groups (9)**
- **Samples (2000)**

Matimba et al., 2008

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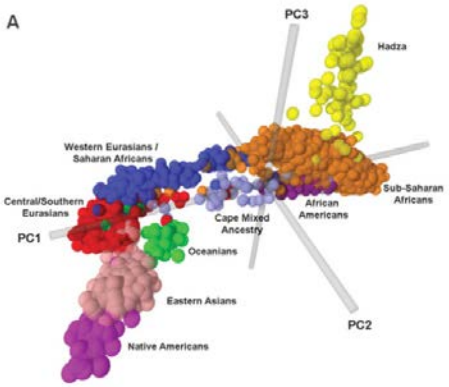
# Genomic Diversity of African Populations

## 2009

*Science*. 2009 May 22; 324(5930): 1035–1044. doi:10.1126/science.1172257.

**The Genetic Structure and History of Africans and African Americans**

Sarah A. Tishkoff[1,2,*], Floyd A. Reed[1,†,‡], Françoise R. Friedlaender[3,‡], Christopher Ehret[4], Alessia Ranciaro[1,2,5,§], Alain Froment[6,§], Jibril B. Hirbo[1,2], Agnes A. Awomoyi[1,‖], Jean-Marie Bodo[7], Ogobara Doumbo[8], Muntaser Ibrahim[9], Abdalla T. Juma[9], Maritha J. Kotze[10], Godfrey Lema[11], Jason H. Moore[12], Holly Mortensen[1,‖], Thomas B. Nyambo[11], Sabah A. Omar[13], Kweli Powell[1,#], Gideon S. Pretorius[14], Michael W. Smith[15], Mahamadou A. Thera[8], Charles Wambebe[16], James L. Weber[17], and Scott M. Williams[18]




- 185 world populations
- 1327 markers

## AiBST 2014

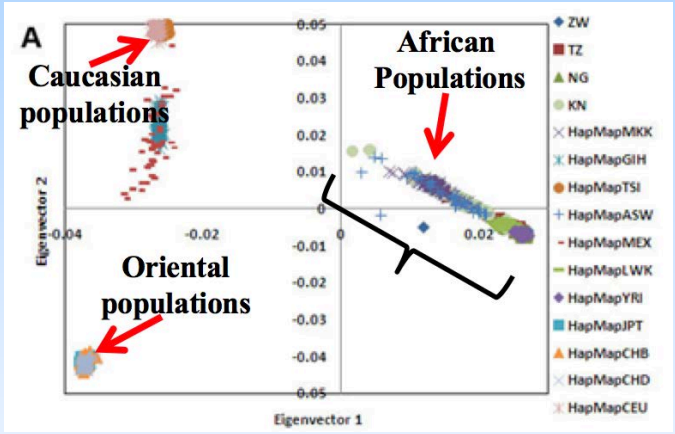
Handbook of Pharmacogenomics and Stratified Medicine

ELSEVIER

Chapter 43

**Population Diversity and Pharmacogenomics in Africa**

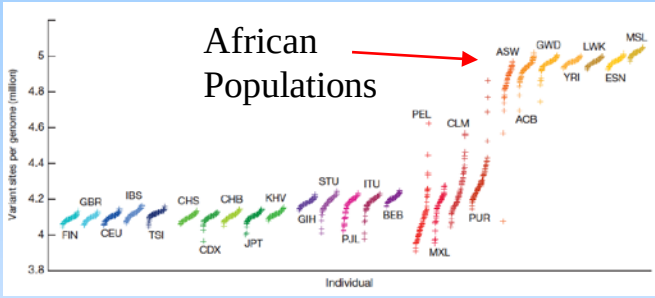
Collen Masimirembwa,* Collet Dandara,† and Julia Hasler*




- 10 African populations
- 650 000 SNPs

## 1000 Genomes 2015

Nature, 2015




- 2,504 individuals
- 26 populations

Riding the genomic wave!

African Institute of Biomedical Science & Technology

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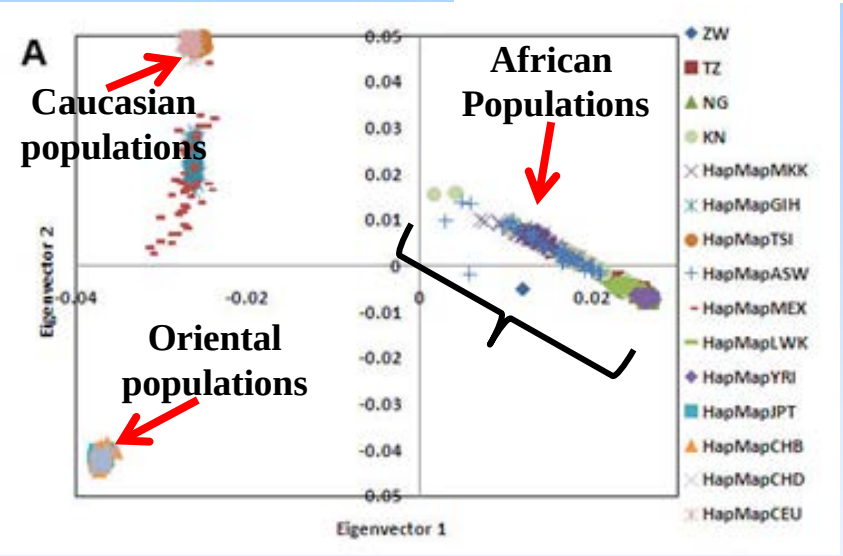
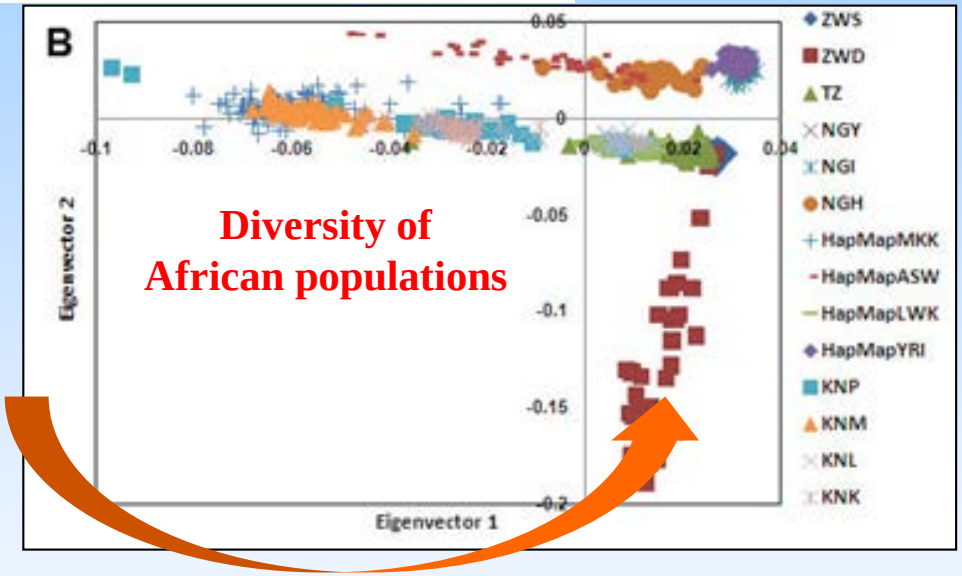
# Genomic Diversity of African populations study

Handbook of Pharmacogenomics and Stratified Medicine
Editor-in-Chief: Sandosh Padmanabhan
ELSEVIER
Chapter 43

## Population Diversity and Pharmacogenomics in Africa

Collen Masimirembwa,[a] Collet Dandara,[b] and Julia Hasler[a]
[a]African Institute of Biomedical Science and Technology, Zimbabwe, [b]Department of Clinical Laboratory Science, University of Cape Town, South Africa




- ❑ **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

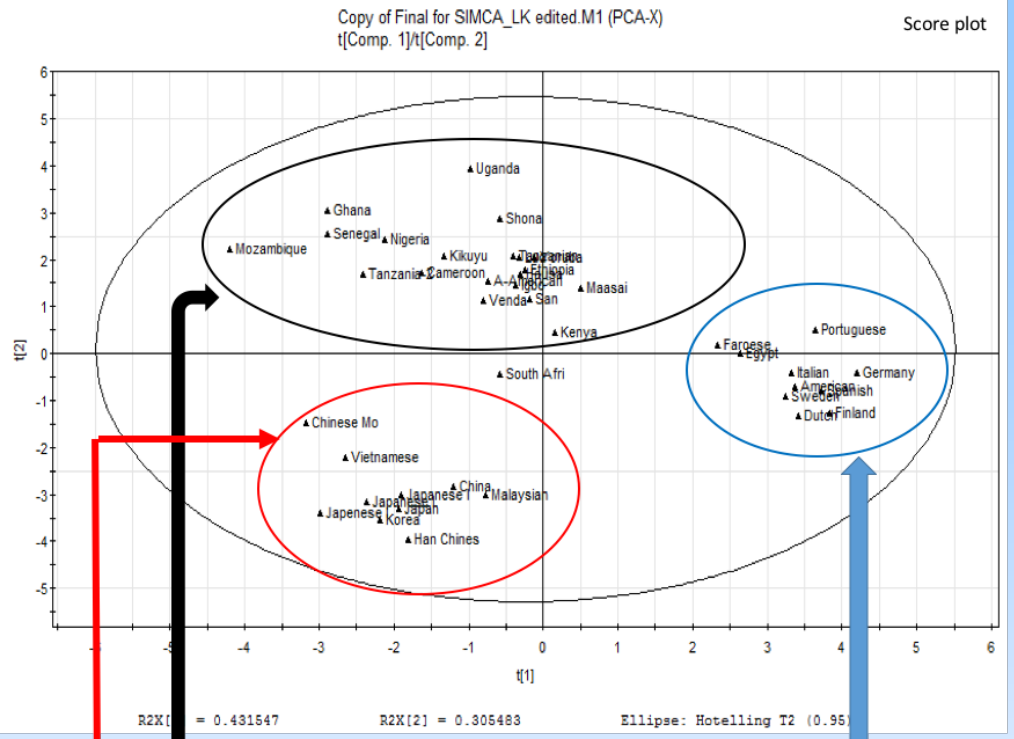
**Genotyping for 15 SNPs in 5 genes of drug metabolizing enzymes important in drug metabolism & pharmacokinetics**

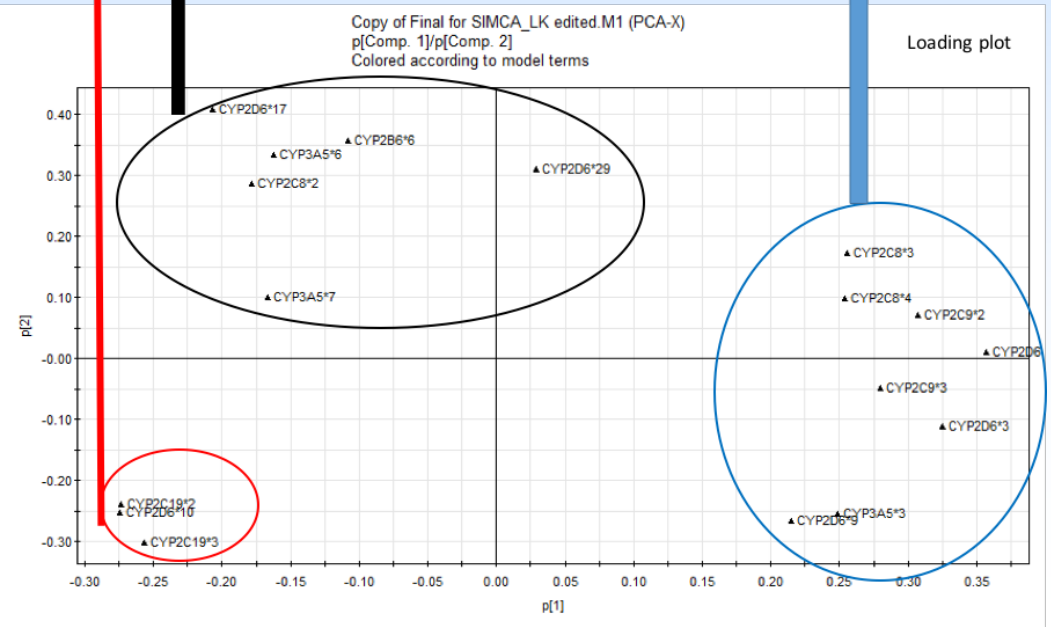
**Table 1** Allele frequencies in the African populations in this study and other ethnicities or populations

| | *CYP2C19* | | | *CYP2D6* | | | | | | | *NAT2* | | | | *GST* | | *CYP2B6* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Population* | **2* | **3* | **2/2* | **3* | **4* | **5* | **10* | **9* | **17* | **29* | **5* | **6* | **7* | **14* | *M1 del/del* | *T1 del/del* | **6* |
| Orientals | 30 | 10 | 2 | 0 | 1 | 6 | 51 | 0 | 0 | 0 | 5 | 25 | 13 | 0 | 55 | 65 | 18 |
| Chinese | 37 | 8 | 1 | 0 | 1 | 6 | 51 | 0 | 0 | 0 | 6 | 31 | 16 | 0 | 58 | 53 | 21 |
| Japanese | 35 | 11 | 1 | 0 | 1 | 3 | 43 | 0 | 0 | 0 | 2 | 19 | 10 | 0 | 44 | 44 | 16 |
| Koreans | 21 | 12 | 0 | 0 | 2 | 6 | 51 | 0 | 0 | 0 | 3 | 19 | 11 | 0 | 53 | 60 | 15 |
| Caucasian | 15 | 0 | 5 | 2 | 25 | 5 | 2 | 2 | 0 | 0 | 49 | 27 | 2 | 0 | 50 | 15 | 21 |
| Swedes | 17 | 0 | 1 | 3 | 23 | 5 | 1 | 0 | 0 | 0 | 51 | 28 | 2 | 0 | 51 | 20 | |
| Germans | 18 | 0 | 2 | 2 | 20 | 2 | 2 | 0 | 0 | 0 | 46 | 27 | 4 | 0 | 51 | 21 | |
| American | 14 | 0 | 2 | | | | | | 0 | | 45 | 28 | 2 | 0 | 54 | 15 | |
| Mixed African | 16 | 1 | 2 | <1[a] | 2 | 4 | 6 | 0 | 30 | 15 | 34 | 20 | 5 | 13 | 30 | | 40 |
| African American | 25 | 0 | 1 | <1[a] | 7 | 6 | 4 | 1 | 15 | 5 | 30 | 22 | 2 | 9 | 28 | 24 | 47 |
| Tanzanian | 18 | <1[a] | 3 | 0 | 2 | 4 | 4 | 0 | 18 | 20 | 34 | 21 | 3 | 13 | 33 | 25 | 39 |
| Shona | 13 | [b] | 2 | 0 | 2 | 4 | 6 | 0 | 34 | 17 | 31 | 21 | 6 | 14 | 24 | 26 | 38 |
| Venda | 21 | 0 | | 0 | 3 | 5 | 12 | 0 | 24 | 6 | 39 | 22 | 5 | 11 | 23 | 20 | 36 |
| Ghanaian | | | 2 | 0 | 7 | 6 | 3 | 0 | 28 | — | — | — | — | — | 39 | — | 49 |
| Ethiopians | 14 | 2 | 15 | 0 | 4 | 3 | 9 | 0 | 9 | — | — | — | — | — | — | — | — |
| Kikuyu | 16 | 0 | | 0 | 1 | | | 0 | 33 | 14 | 58 | 24 | | | 28 | 25 | 34 |
| Luo | 18 | 0 | | 0 | 4 | | 6 | 0 | 23 | 16 | 34 | 22 | 3 | 14 | 29 | 22 | 37 |
| Maasai | 11 | <1[a] | | 0 | 8 | | 5 | 0 | 18 | 8 | 42 | 27 | 4 | 9 | 16 | 40 | 35 |
| Igbo | 29 | 0 | | 0 | 8 | | 10 | 0 | 14 | 20 | 28 | 29 | 4 | 11 | 23 | 36 | 38 |
| Yoruba | 10 | 0 | | 0 | 3 | | 7 | 0 | 22 | 10 | 33 | 27 | 3 | 8 | 31 | 35 | 42 |
| Hausa | 12 | 0 | | 0 | 2 | | 13 | 0 | 18 | 10 | 27 | 33 | 3 | 3 | 37 | 42 | 42 |
| San | 12 | | | | 9 | | | 0 | 22 | 2 | 20 | 8 | | | 45 | | 40 |

**(n = 2000 samples from the AiBST-APC Biobank)**

Matimba et al., 2008




# 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

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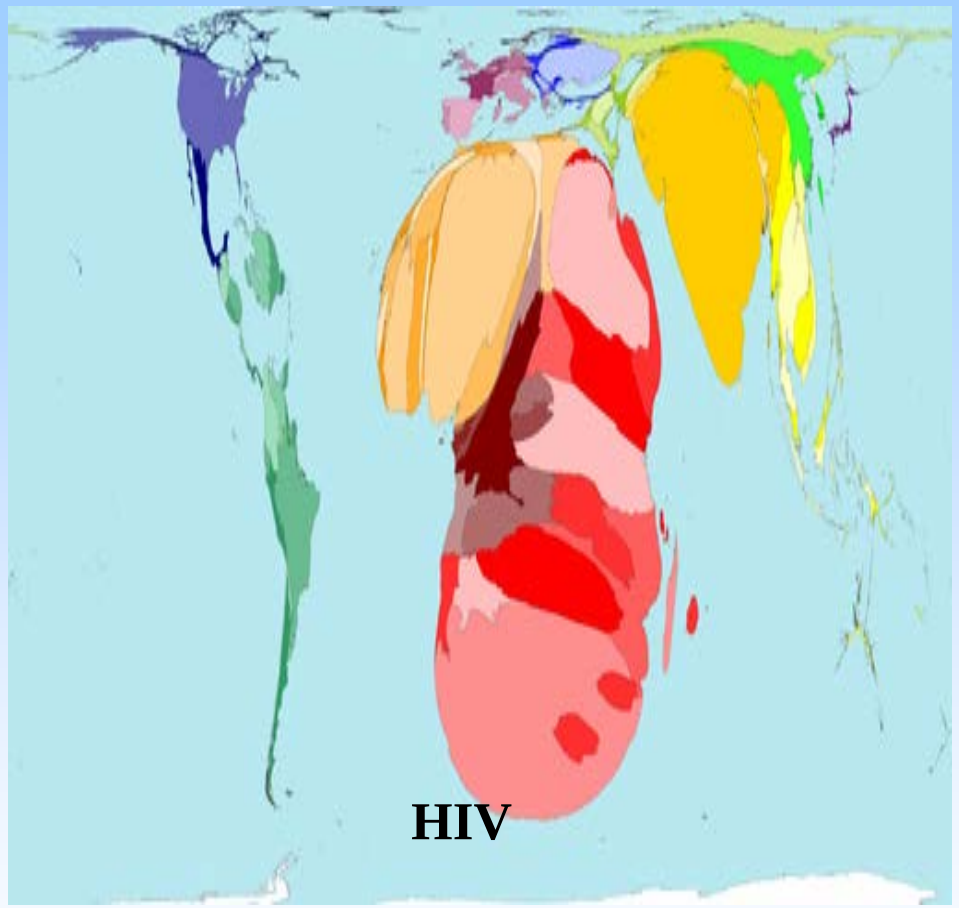
# Burden of HIV/AIDS disease & ART Rollout

- 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!**

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# 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

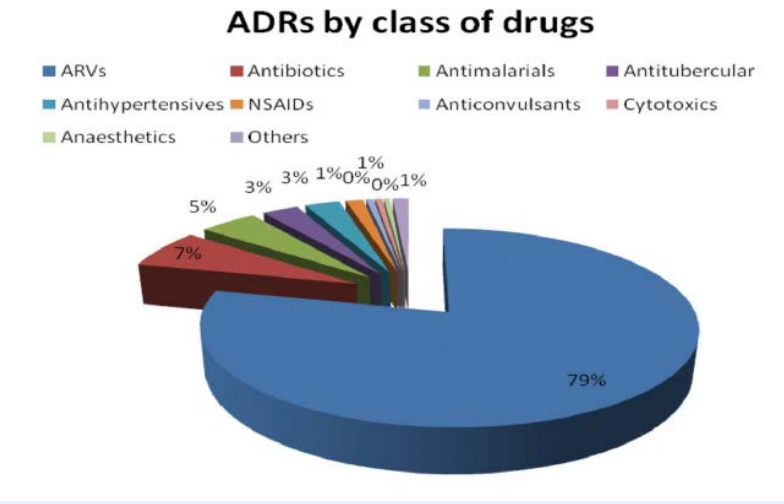
L.E.M. Mwangangi, MPharm, Tutorial Fellow, Department of Pharmaceutics and Pharmacy Practice, College of Health Sciences, University of Nairobi,

**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%.**

The Lifesaver. 2011. Kenya National Medicine Information and Pharmacovigilance Centre Newsletter. 1st Edition 1-12.




**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.

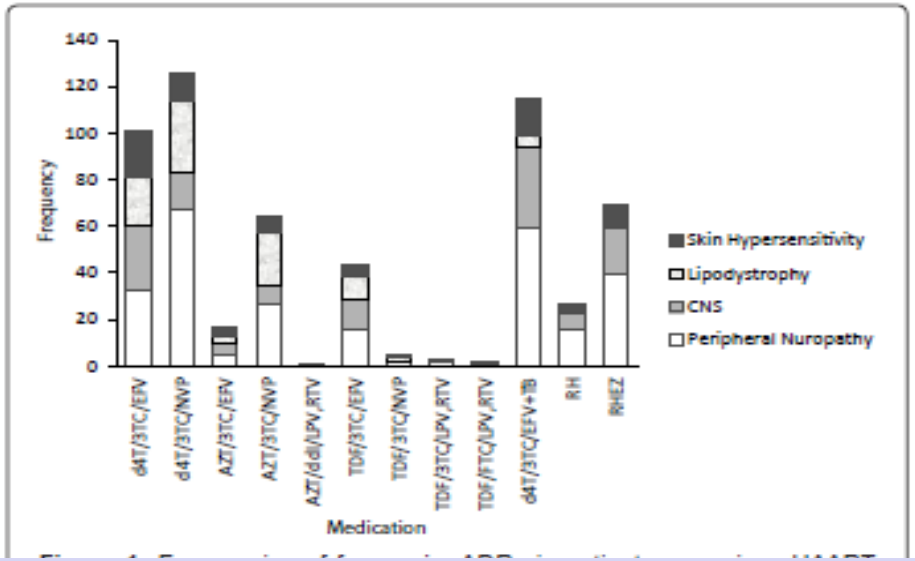
AIDS & Clinical Research

Nemaura et al., J AIDS Clin Res 2013, 4:4
http://dx.doi.org/10.4172/2155-6113.1000203

Research Article Open Access

# Evaluation of the Prevalence, Progression and Severity of Common Adverse Reactions (Lipodystrophy, CNS, Peripheral Neuropathy, and Hypersensitivity Reactions) Associated with Anti-Retroviral Therapy (ART) and Anti-Tuberculosis Treatment in Outpatients in Zimbabwe

Tafireyi Nemaura[1,2], Milcah Dhoro[1], Charles Nhachi[2], Gerard Kadzirange[3], Prosper Chonzi[3] and Collen Masimirembwa[1]*




- **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%).**

Tadesse et al. BMC Pharmacology and Toxicology 2014, 15:32
http://www.biomedcentral.com/2050-6511/15/32

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

# Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study

Wondmagegn Tamiru Tadesse[1*], Alemayehu Berhane Mekonnen[2], Wubshet Hailu Tesfaye[2] and Yidnekachew Tamiru Tadesse[3]

**Table 3 Most common self-reported adverse drug reactions of antiretroviral therapy, ART clinic, Gondar University Hospital, June 2012**

| Self-reported adverse drug reactions | n (%)*, N = 384 |
|---|---|
| Nausea | 217 (56.5) |
| Headache | 211 (54.9) |
| Fever | 157 (40.9) |
| Vomiting | 147 (38.3) |
| Lethargy/fatigue | 131(34.1) |
| Loss of appetite | 130 (34) |
| Insomnia | 102 (26.6) |
| Depression/stress | 99 (25.8) |
| Skin rash | 85 (22.1) |
| Night mare | 72 (18.8) |
| Diarrhea | 41 (10.7) |
| Oral ulceration/dry mouth | 35 (9.1) |
| Anxiety | 23 (6.3) |
| Others** | 10 (2.6) |

*number of frequency and percent proportions, total number of participants (N = 384).
**includes tingling in hands or feet, anemia.

# Data are from VigiBase¨ (June 2016). VigiBase is theWorld Health Organization Global Individual Case Safety Reports database, containing reports of adverse reactions received from 33 countries in Africa

The 25 most common drugs (international non-proprietary names) reported in all drug adverse events in Africa.

| Drug | Total count of adverse events |
|---|---|
| Nevirapine[a] | 1195 |
| Efavirenz[a] | 1099 |
| Sulfamethoxazole and trimethoprim[b,c] | 1068 |
| Lamivudine | 859 |
| Stavudine | 713 |
| Zidovudine[a] | 690 |
| Ribavirin | 682 |
| Diclofenac[a] | 679 |
| Lamivudine and zidovudine[b] | 634 |
| Ciprofloxacin[c] | 631 |
| Peginterferon alfa-2a | 623 |
| Tenofovir | 595 |
| Lamivudine, nevirapine, and zidovudine[b] | 565 |
| Ethambutol, isoniazid, pyrazinamide, and rifampicin[a,b,d] | 548 |
| Carbamazepine[a] | 546 |
| Isoniazid[a] | 523 |
| Amoxicillin[a] | 512 |
| Insulin glargine | 499 |
| Paracetamol[a] | 492 |
| Amodiaquine and artesunate[b] | 460 |
| Ceftriaxone[a] | 457 |
| Acetylsalicylic acid[a] | 441 |
| Valproic acid[a] | 439 |
| Docetaxel[a,d] | 426 |
| Rifampicin[a,d] | 423 |

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

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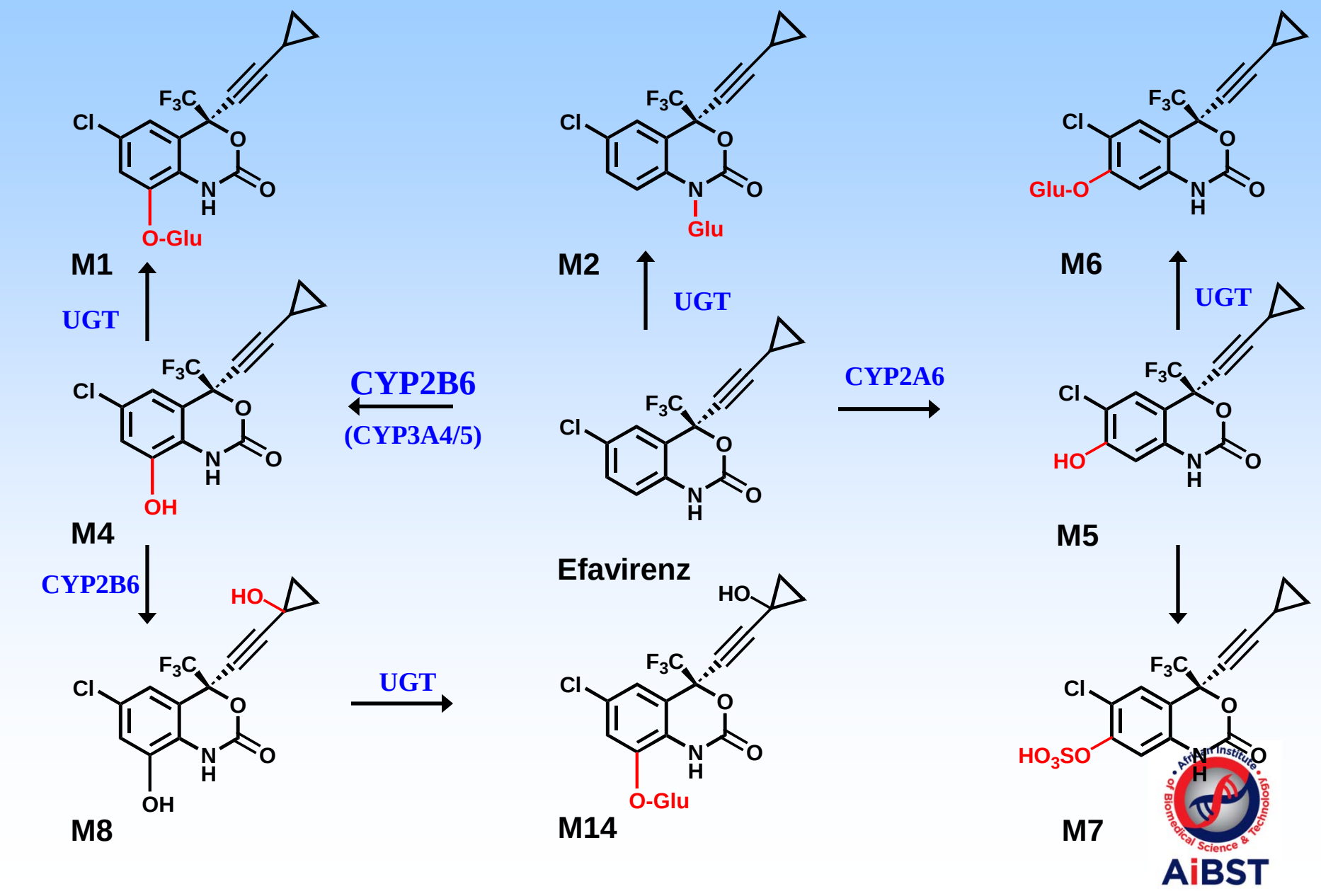
# Biomarkers of ADRs associated with EFV

- **Major ADRs associated with EFV**
  - Neuropsychiatric side effects
  - Drug induced liver injury

## Main metabolite

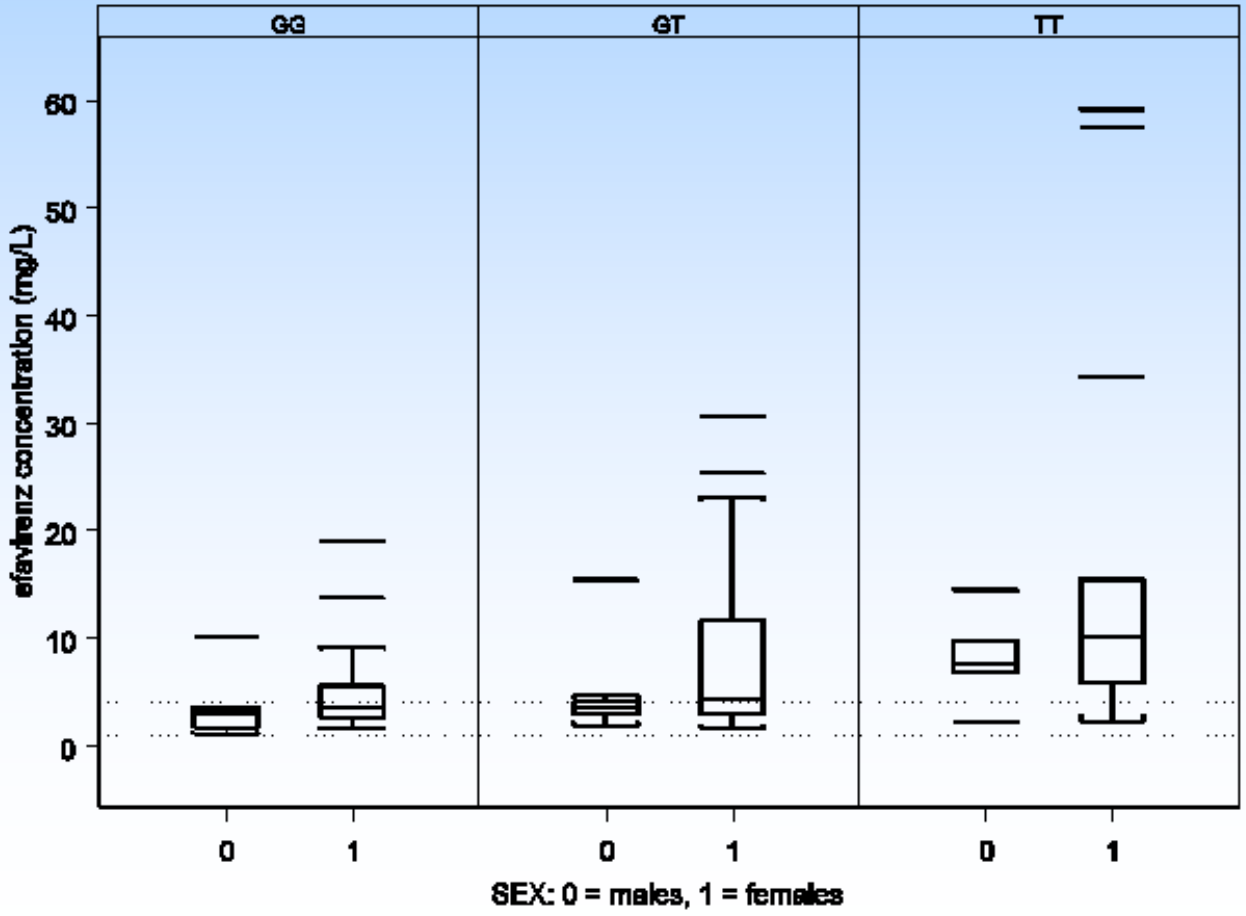


Eur J Clin Pharmacol
DOI 10.1007/s00228-007-0412-3

PHARMACOGENETICS

# High prevalence of the *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




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

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Mukonzo et al. BMC Infectious Diseases 2013, 13:261
http://www.biomedcentral.com/1471-2334/13/261

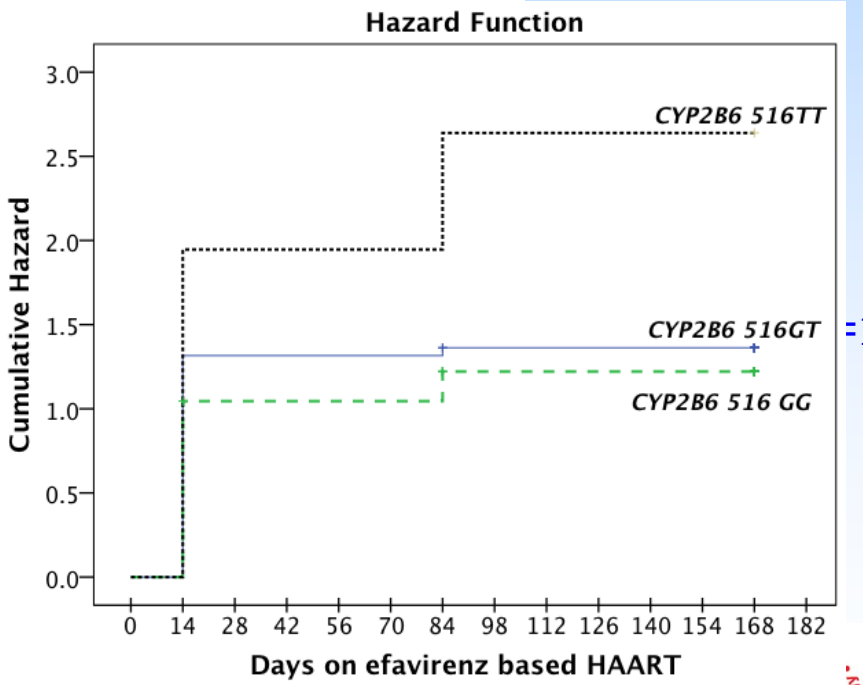
BMC Infectious Diseases

RESEARCH ARTICLE Open Access

# Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: a prospective cohort study

Jackson K Mukonzo[1,2], Alphonse Okwera[3], Neoline Nakasujja[4], Henry Luzze[3], Deogratious Sebuwufu[5], Jasper Ogwal-Okeng[2], Paul Waako[2], Lars L Gustafsson[1] and Eleni Aklillu[1*]

- Incidence 73.%
- Predictors
  - ✓ **EFV plasma conc**
  - ✓ ***CYP2B6* genotype**
- No association with rifampicin, *CYP3A5, CYP2A6, ABCB1, NR113 rs3003596 T/C,*

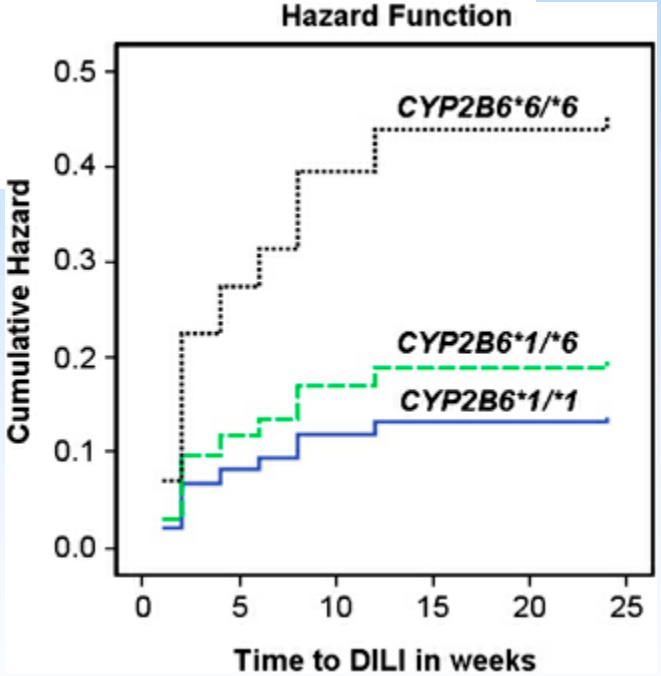



=197

# 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 Yimer[1,2], W Amogne[3,4], A Habtewold[1,2], E Makonnen[2], N Ueda[1], A Suda[1], A Worku[5], WE Haefeli[6], J Burhenne[6], G Aderaye[3], L Lindquist[4] and E Aklillu[1]

*The Pharmacogenomics Journal (2012) 12, 499–506*




Incidence of DILI: 15.7%

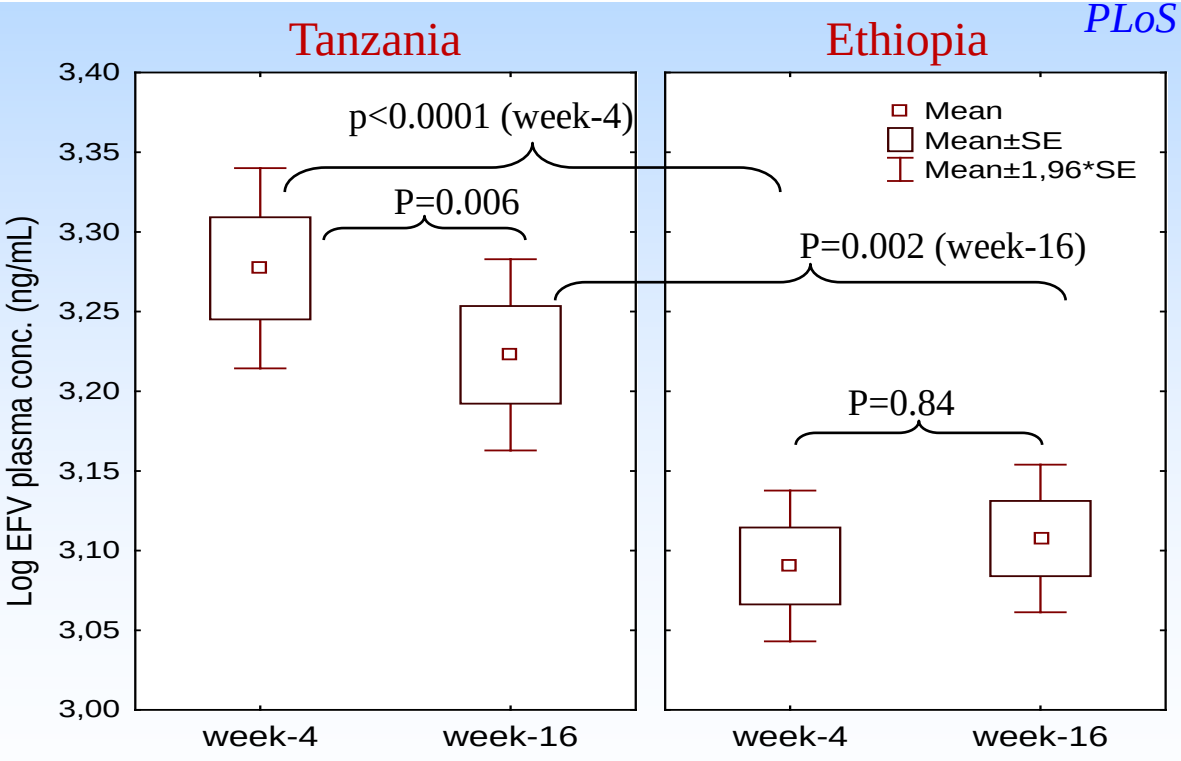
OPEN ACCESS Freely available online

PLOS | ONE

# 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[1,2☯], Abiy Habtewold[1,3☯], Omary Minzi[2], Eyasu Makonnen[3], Sabina Mugusi[5,6], Wondwossen Amogne[7,8], Getnet Yimer[3], Klaus-Dieter Riedel[4], Mohammed Janabi[9], Getachew Aderaye[8], Ferdinand Mugusi[9], Leif Bertilsson[1], Eleni Aklillu[1*¶], Juergen Burhenne[4¶]

*PLoS One. 2013 Jul 5;8(7):e67946.*




Weeks after initiation of EFV based ART

African Institute of Biomedical Science & Technology
AiBST

# High predictive value of *CYP2B6* SNPs for steady-state plasma efavirenz levels in South African HIV/AIDS patients

Marelize Swart[a], Michelle Skelton[a], Yuan Ren[b], Peter Smith[b], Simbabrashe Takuva[c] and Collet Dandara[a]

***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.

***Methods*** HIV/AIDS patients were recruited from Themba

***516G>T***; ***CYP2B6 785A>G***; ***CYP2B6 983T>C***; and ***CYP2B6 1459C>T***) were associated with higher levels of efavirenz, whereas ***G-G-A-T-C*** and ***A-G-A-T-C*** haplotypes showed significantly lower levels of efavirenz. The ***CYP2B6*1/*6*** genotype was significantly associated with an increased risk of loss to follow-up. The sensitivity, specificity and positive predictive values for the ***CYP2B6*6/*6*** genotype in predicting efavirenz levels above 4 μg/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.

***Conclusion*** Screening for ***CYP2B6 516G>T*** SNP has a high specificity and positive predictive value for efavirenz



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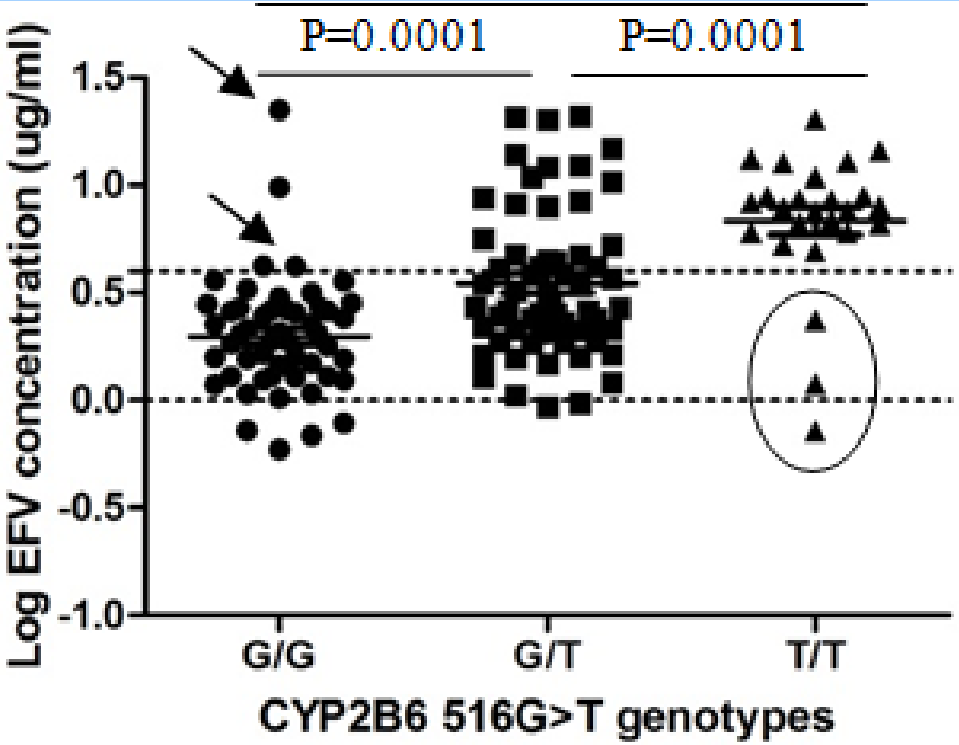


- Cohort of HIV/AIDS
- At least 12 months on EFV
- Range of EFV plasma conc, ***0.04-34.4***
  - 860-fold variability

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# 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

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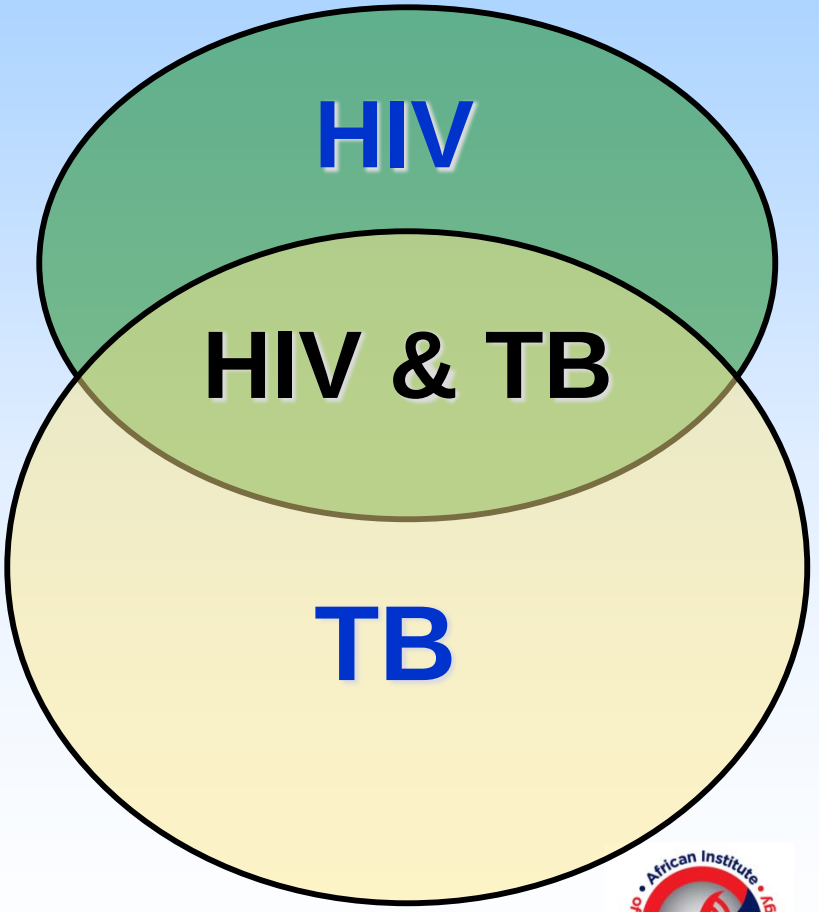
# Drug-Drug-Gene Interactions in clinical settings co-infections & co-treatment are common

- Two Diseases
- One Patient






Collen Masimirembwa. DPhil, Ph.D.

AiBST

# 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

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# 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.

British HIV Association
BHIVA

## 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<br><br>If side effects occur, efavirenz therapeutic drug monitoring (TDM) may be useful |

OPEN ACCESS Freely available online

PLoS one

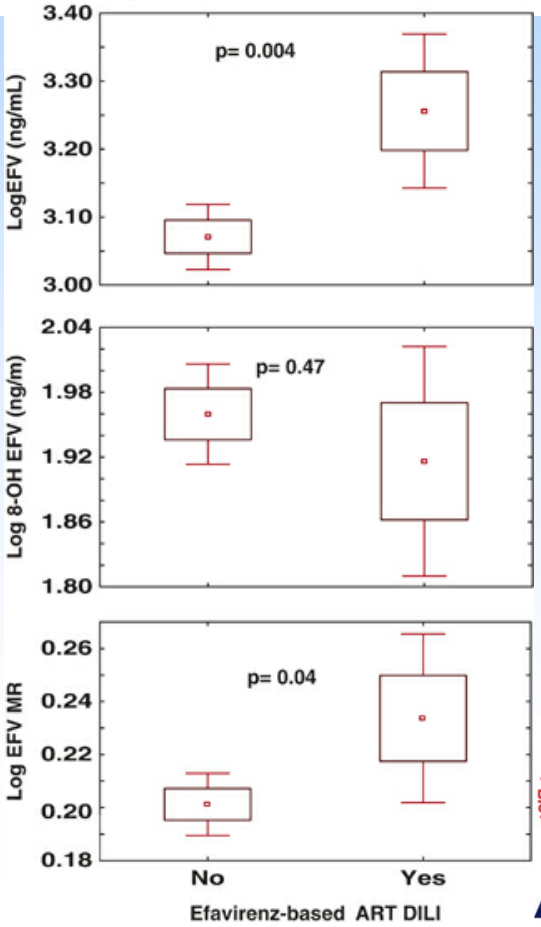
# Pharmacogenetic & Pharmacokinetic Biomarker for Efavirenz Based ARV and Rifampicin Based Anti-TB Drug Induced Liver Injury in TB-HIV Infected Patients

Getnet Yimer[1,2], Nobuhisa Ueda[1], Abiy Habtewold[1,2], Wondwossen Amogne[3,4], Akira Suda[1], Klaus-Dieter Riedel[5], Jürgen Burhenne[5], Getachew Aderaye[3], Lars Lindquist[4], Eyasu Makonnen[2], Eleni Aklillu[1]*

*PLoS ONE 2011: 6(12): e27810.*

DILI: 30.0%,
Severe DILI: 18.4%

- DILI predictors
  - ✓ EFV plasma conc
  - ✓ *CYP2B6*6* genotype,
  - ✓ NAT2 slow metabolizers



OPEN ACCESS Freely available online

PLoS one

# Liver Enzyme Abnormalities and Associated Risk Factors in HIV Patients on Efavirenz-Based HAART with or without Tuberculosis Co-Infection in Tanzania

Sabina Mugusi[1,2], Eliford Ngaimisi[3,4], Mohamed Janabi[5], Omary Minzi[4], Muhammad Bakari[5], Klaus-Dieter Riedel[6], Juergen Burhenne[6], Lars Lindquist[7], Ferdinand Mugusi[5], Eric Sandstrom[1], Eleni Aklillu[3]*

*PLoS One. 2012;7(7):e40180.*

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*

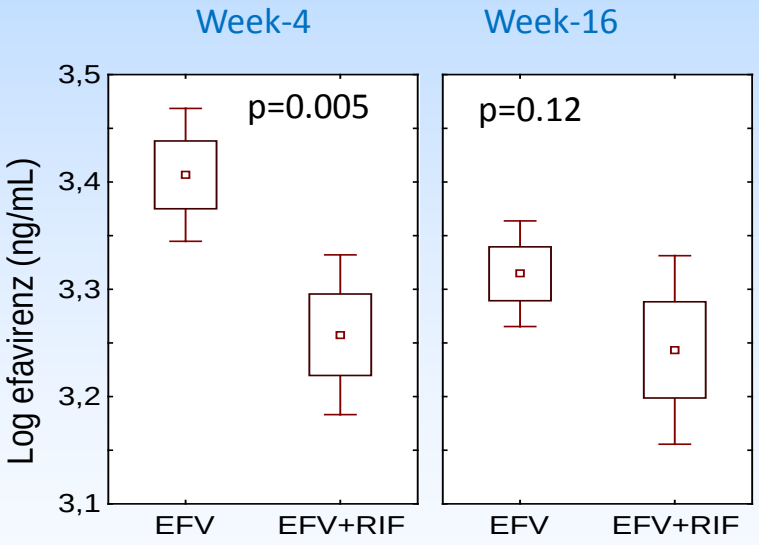


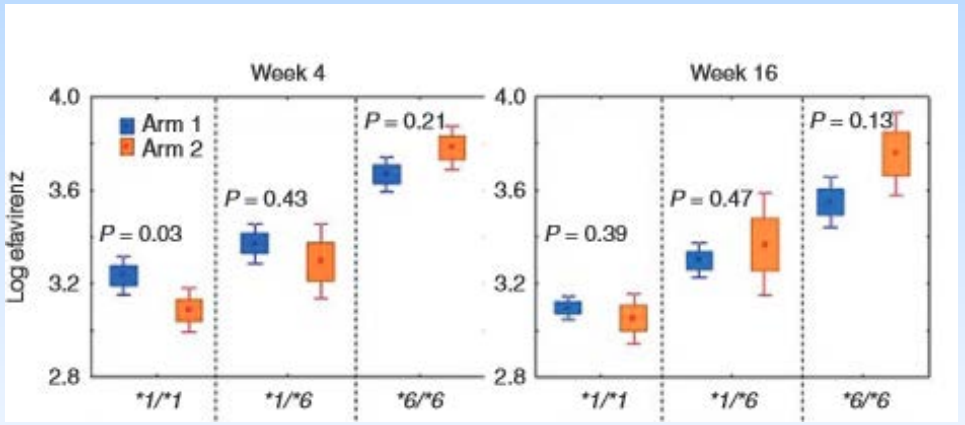
AiBST

ARTICLES nature publishing group

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**



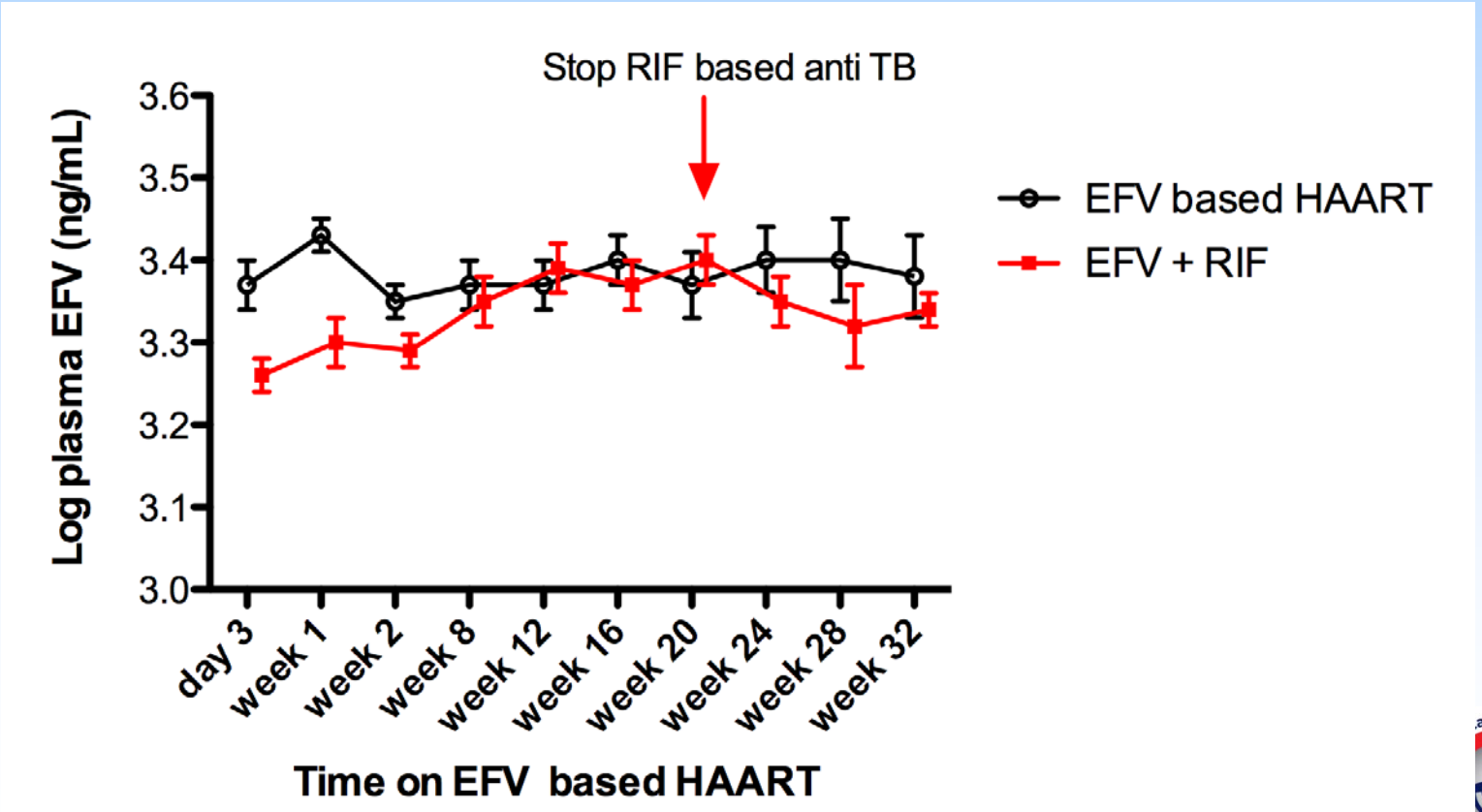

***CYP2B6* genotype**

- *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

Jackson KM, Nanzigu S,· Waako P, Ogwal –Okeng J, Gustafson LL,· Aklillu E.

*Pharmacogenomics 2014;15:1423-35*



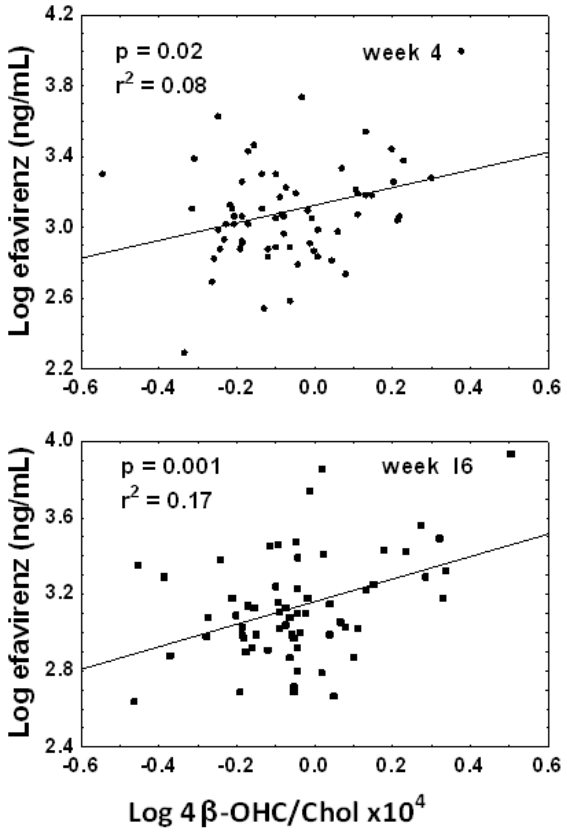
The Pharmacogenomics Journal (2013) 13, 484–489

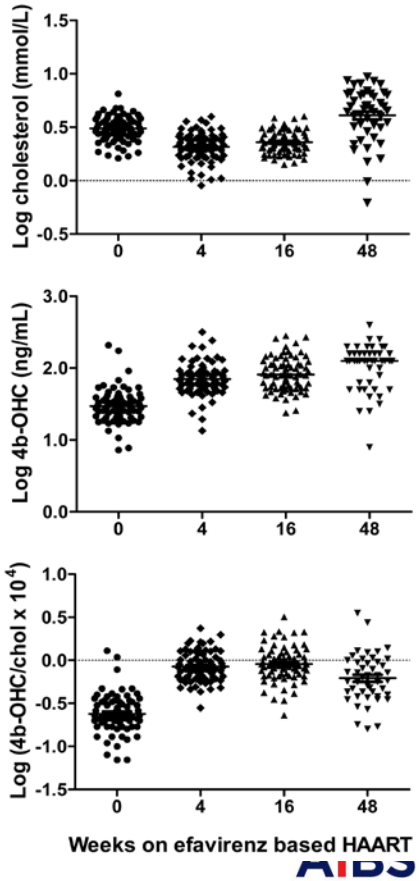
www.nature.com/tpj

**CONSENSUS ARTICLE**

# Pharmacogenetic and pharmacokinetic aspects of CYP3A induction by efavirenz in HIV patients

A Habtewold[1,2], W Amogne[3,4], E Makonnen[2], G Yimer[1,2], H Nylén[5], K-D Riedel[6], G Aderaye[3], L Bertilsson[1], J Burhenne[6], U Diczfalusy[5] and E Aklillu[1]

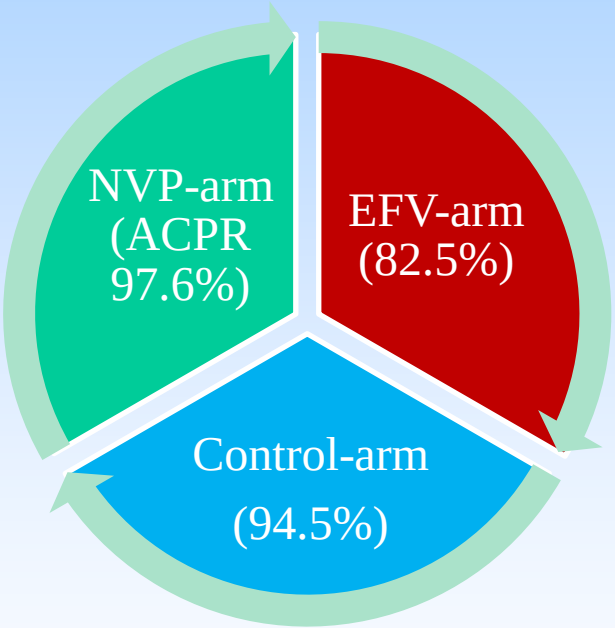


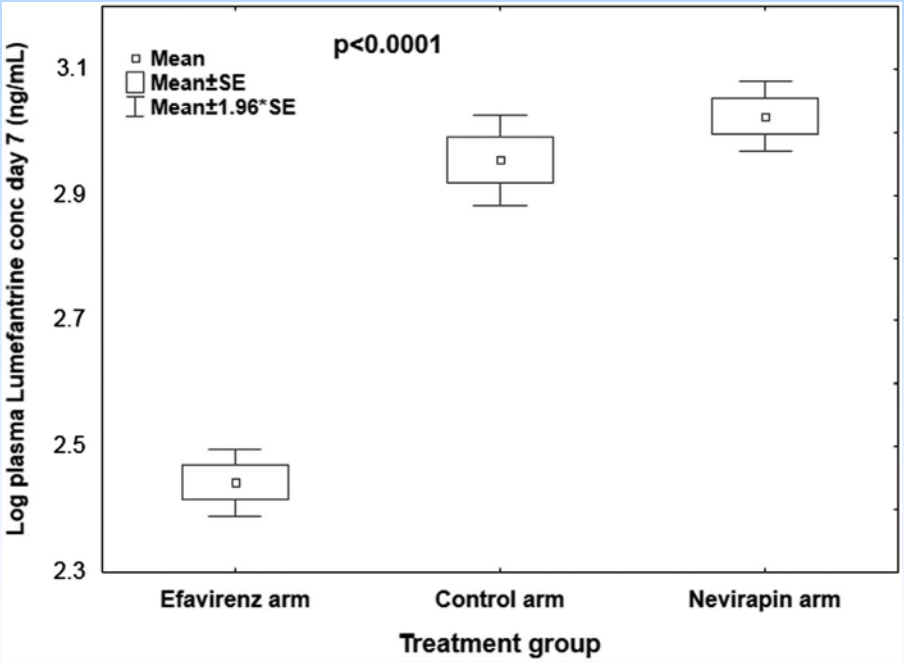



ORIGINAL ARTICLE

# *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

BA Maganda[1], OMS Minzi[2], E Ngaimisi[2], AAR Kamuhabwa[2] and E Aklillu[3]




*Pharmacogenomics J, 2016: Feb;16(1):88-95.*

African Institute of Biomedical Science & Technology
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# Can CYP2B6 genotype be used to guide the dose of efavirenz?

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

- PK Modeling and Simulation based dose adjustment prediction

Pinillos et al. BMC Infectious Diseases (2016) 16:56
DOI 10.1186/s12879-016-1381-x

BMC Infectious Diseases

CASE REPORT Open Access

# Case report: Severe central nervous system manifestations associated with aberrant efavirenz metabolism in children: the role of *CYP2B6* genetic variation

Francoise Pinillos[1], Collet Dandara[2], Marelize Swart[2], Renate Strehlau[1], Louise Kuhn[3], Faeezah Patel[1], Ashraf Coovadia[1] and Elaine Abrams[4*]

**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.

Eur J Clin Pharmacol
DOI 10.1007/s00228-007-0412-3

PHARMACOGENETICS

# High prevalence of the *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

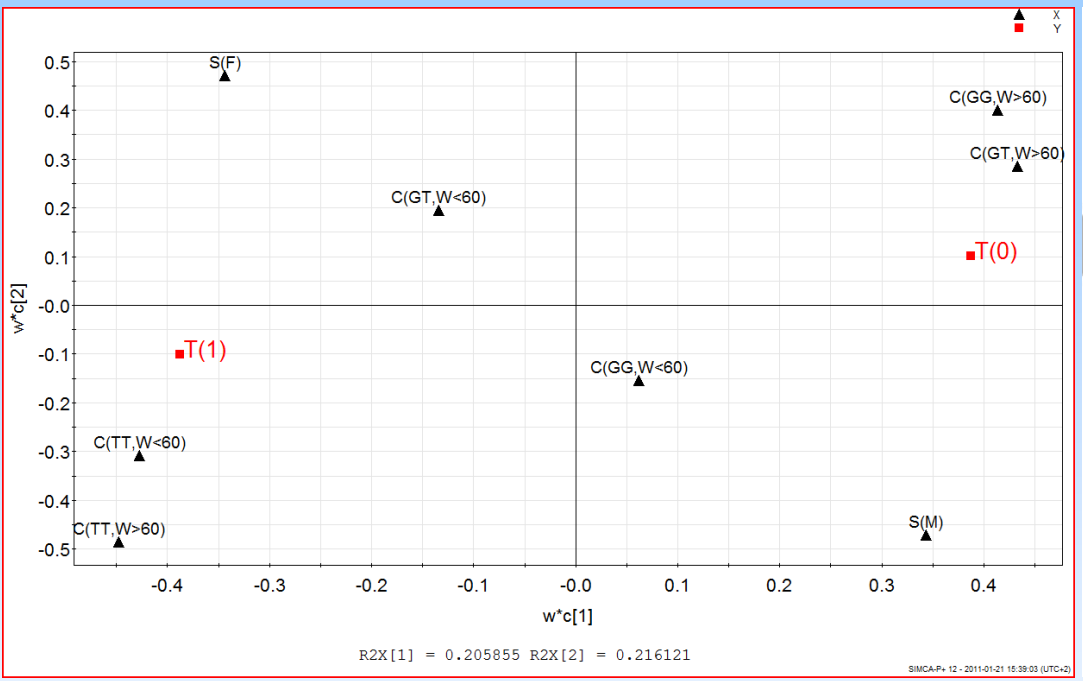
| Genotype | Dose (mg) | All patients | | Males | | Females | |
|---|---|---|---|---|---|---|---|
| | | % Patients Css > 4 mg/L | % Patients Css < 1 mg/L | % Patients Css > 4 mg/L | % Patients Css < 1 mg/L | % Patients Css > 4 mg/L | % Patients Css < 1 mg/L |
| Poor metabolizers | 600 | 77 | 0.8 | 72 | 1 | 85 | 0.5 |
| | 500 | 69 | 1.2 | 62 | 1.8 | 79 | 0.9 |
| | 400 | 59 | 2.2 | 51 | 3.6 | 68 | 1.3 |
| | 300 | 45 | 5.5 | 37 | 7.1 | 54 | 2.8 |
| | 200 | | | | | 34 | 8.2 |
| Intermediate metabolizers | 600 | 50 | 4.4 | 42 | 5.3 | 60 | 2.4 |
| | 500 | 42 | 6.5 | 32 | 8.7 | 51 | 3.6 |
| | 400 | 31 | 10.3 | | | 39 | 6.1 |
| Extensive metabolizers | 600 | 37 | 7.6 | 27 | 10.6 | 46 | 4.3 |
| | 500 | 29 | 11.3 | 21 | 15.4 | 38 | 7.0 |

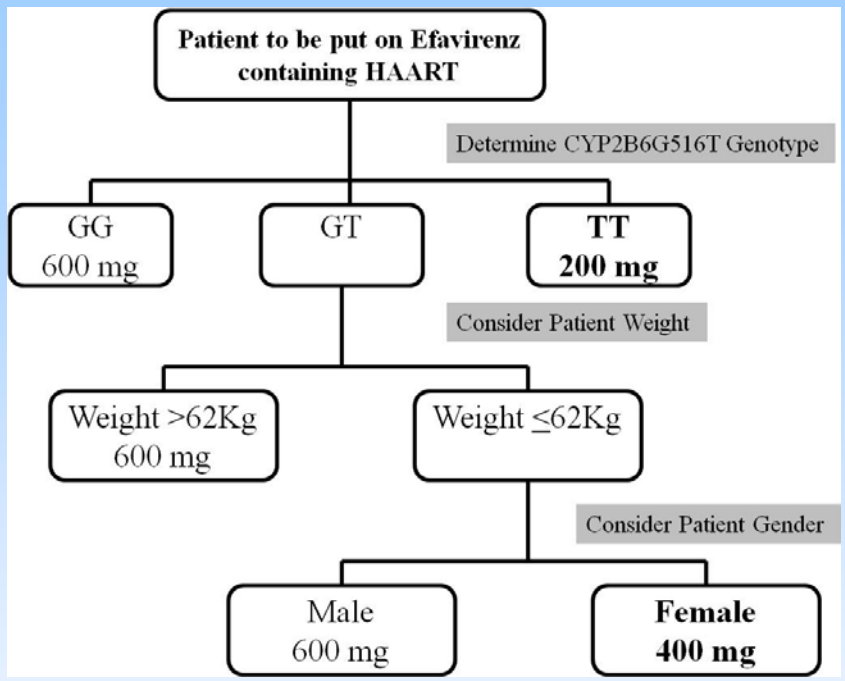
*Css* Efavirenz steady-state plasma concentration at the mid-dose interval
[a] Percentage of 2,000 virtual patients (50% males)

# Impact of gender, weight and CYP2B6 genotype on efavirenz exposure in patients on HIV/AIDS and TB treatment: Implications for individualising therapy

Tafireyi Nemaura[1,2], Charles Nhachi[1] and Collen Masimirembwa[2]*

African Journal of Pharmacy and Pharmacology
Vol. 6(29), pp. 2188-2193, 8 August, 2012




**Multivariate Partial least Squares (PLS) modelling**

- **20% of Zimbabwean patients are TT and would require only 200 mg instead of the given 600mg efavirenz**
- **Results in less CNS ADRs, greater compliance, & cheaper treatment**

Nemaura et al., 2012, Dhoro et al., 2014

AiBST

**_CYP2B6_ genotype based efavirenz dose recommendations during rifampicin based anti-tuberculosis co-treatment for a Sub-Saharan Africa population**

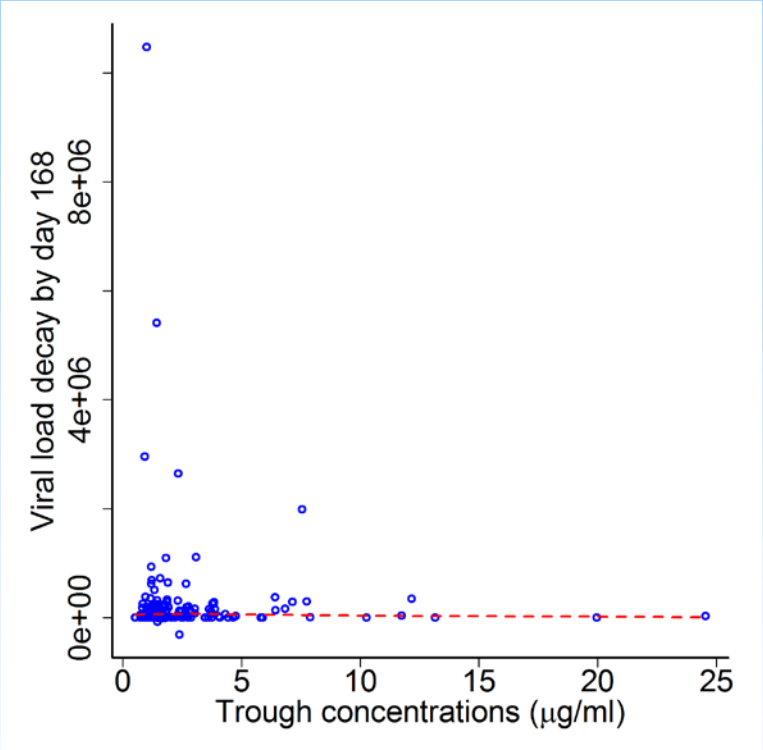
Mukonzo JK, Bisaso RK, Ogwal-Okeng J, Gustafsson LL, Owen S, Aklillu E.

*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 $C_{trough}$

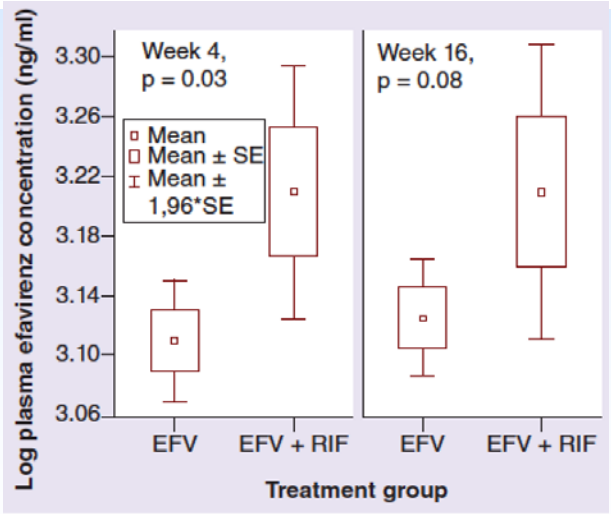
Research Article

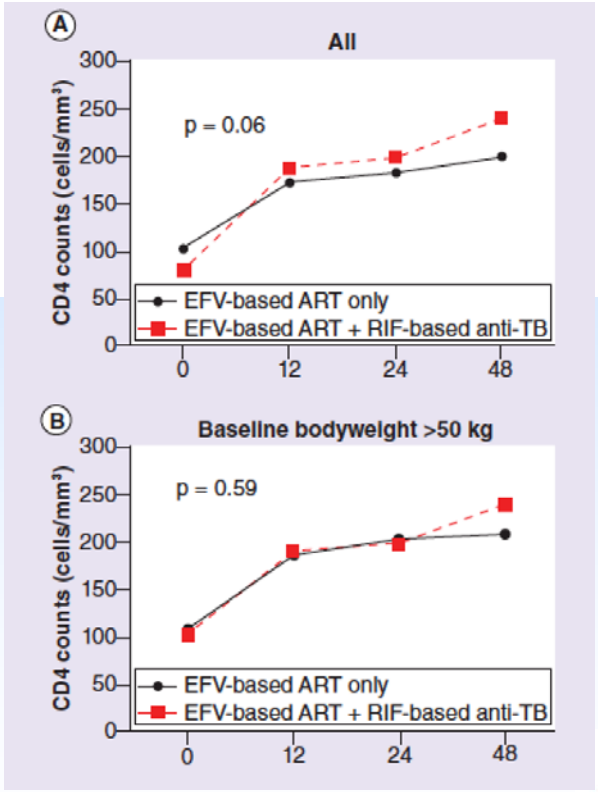
Pharmacogenomics

# 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[1,2], Eyasu Makonnen[2], Wondwossen Amogne[3,4], Getnet Yimer[1,2], Getachew Aderaye[3], Leif Bertilsson[1], Jürgen Burhenne[5] & Eleni Aklillu*[,1]

Pharmacogenomics. 2015;16:1047-64.



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PLOS ONE

# Pharmacogenetic-Based Efavirenz Dose Modification: Suggestions for an African Population and the Different CYP2B6 Genotypes

Jackson K. Mukonzo[1,2*], Joel S. Owen[3], Jasper Ogwal-Okeng[1], Ronald B. Kuteesa[1], Sarah Nanzigu[1], Nelson Sewankambo[1], Lehana Thabane[4,7], Lars L. Gustafsson[5], Colin Ross[6], Eleni Aklillu[5]

*PLoS One. 2014;9(1):e86919*

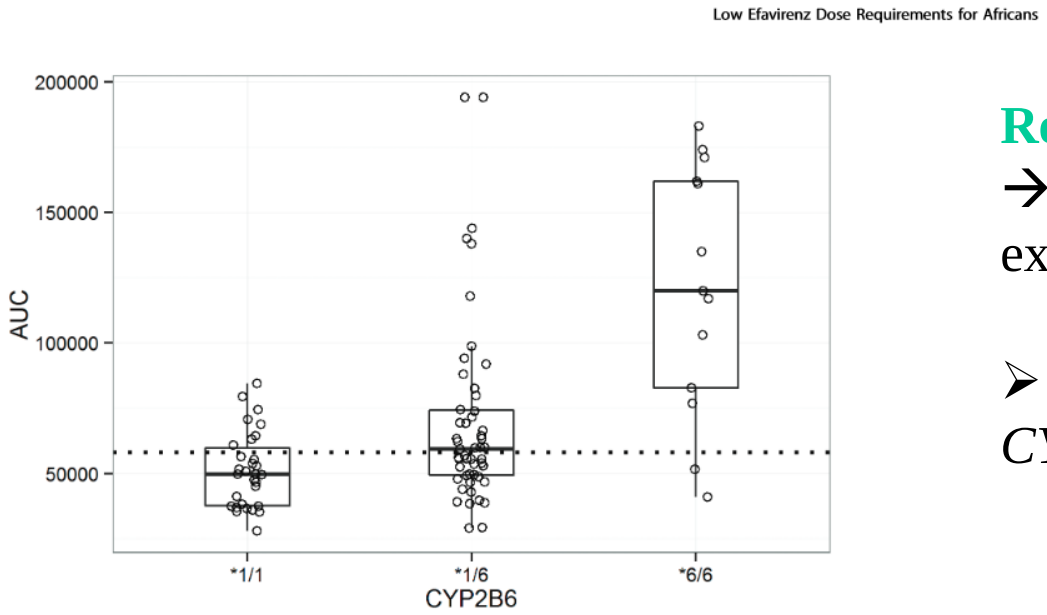


**Figure 3. Distribution of estimated patient AUC values by CYP2B6 genotype.** CYP2B6*1/*1, CYP2B6 *1/*6, and CYP2B6 *6/*6. Dotted line = the mean AUC value in the product label.
doi:10.1371/journal.pone.0086919.g003

**Recommended daily EFV dose**

→ 450 mg for *CYP2B6* extensive metabolizers

➢ 300 mg for homozygous for *CYP2B6*6*

Dhoro et al. BMC Pharmacology and Toxicology (2015) 16:4
DOI 10.1186/s40360-015-0004-2

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

# *CYP2B6*6, CYP2B6*18*, Body weight and sex are predictors of efavirenz pharmacokinetics and treatment response: population pharmacokinetic modeling in an HIV/AIDS and TB cohort in Zimbabwe

Milcah Dhoro[1,2*], Simbarashe Zvada[3], Bernard Ngara[1], Charles Nhachi[2], Gerald Kadzirange[4], Prosper Chonzi[5] and Collen Masimirembwa[1]

**Table 5 Proposed optimal doses given *CYP2B6* genotypes, weight and gender**

| Variable | | Females | | Males | |
|---|---|---|---|---|---|
| | | <58 kg | >58 kg | <58 kg | >58 kg |
| CYP2B6*18 | CYP2B6*6 | 1 -4 μg/ml | 1 -4 μg/ml | 1 -4 μg/ml | 1 -4 μg/ml |
| TT | GG | 400 | 400 | 400 | 400 |
| TT | GT | 200 | 200 | 200 | 200 |
| TT | TT | 200 | 200 | 200 | 200 |
| TC | GG | 400 | 400 | 400 | 400 |
| TC | GT | 400 | 200 | 200 | 200 |
| TC | TT | 200 | 200 | 200 | 200 |
| CC | GG | 400 | 600 | 600 | 600 |
| CC | GT | 200 | 300 | 300 | 300 |
| CC | TT | 200 | 200 | 200 | 200 |

**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!!**

African Institute of Biomedical Science & Technology
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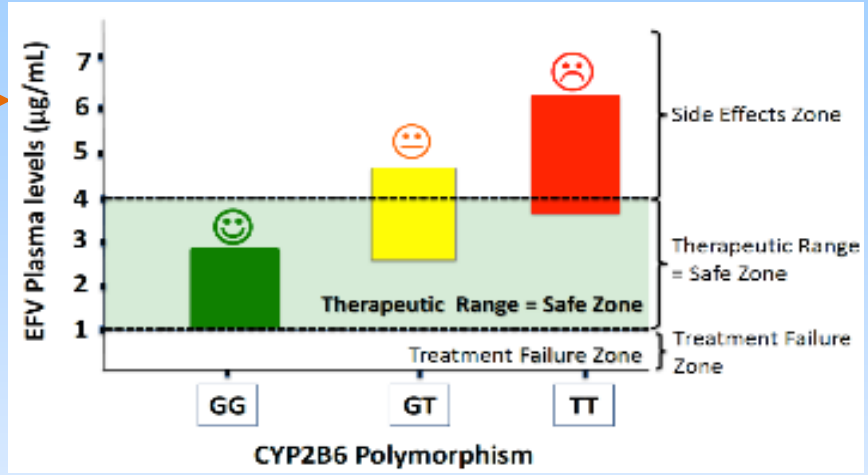
# Our Solution: Personalized Efavirenz Dosing

## Current Practice

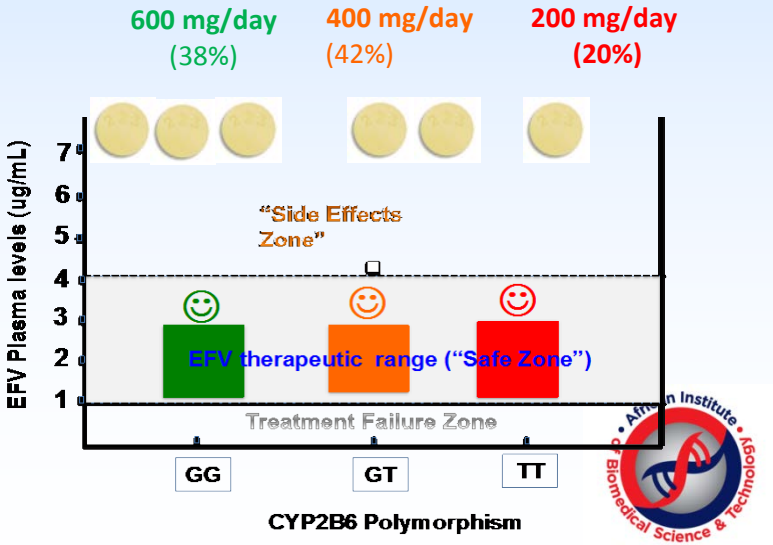
**600 mg EFV/day**

Patients with same Diagnosis – 'one Treatment fits ALL'

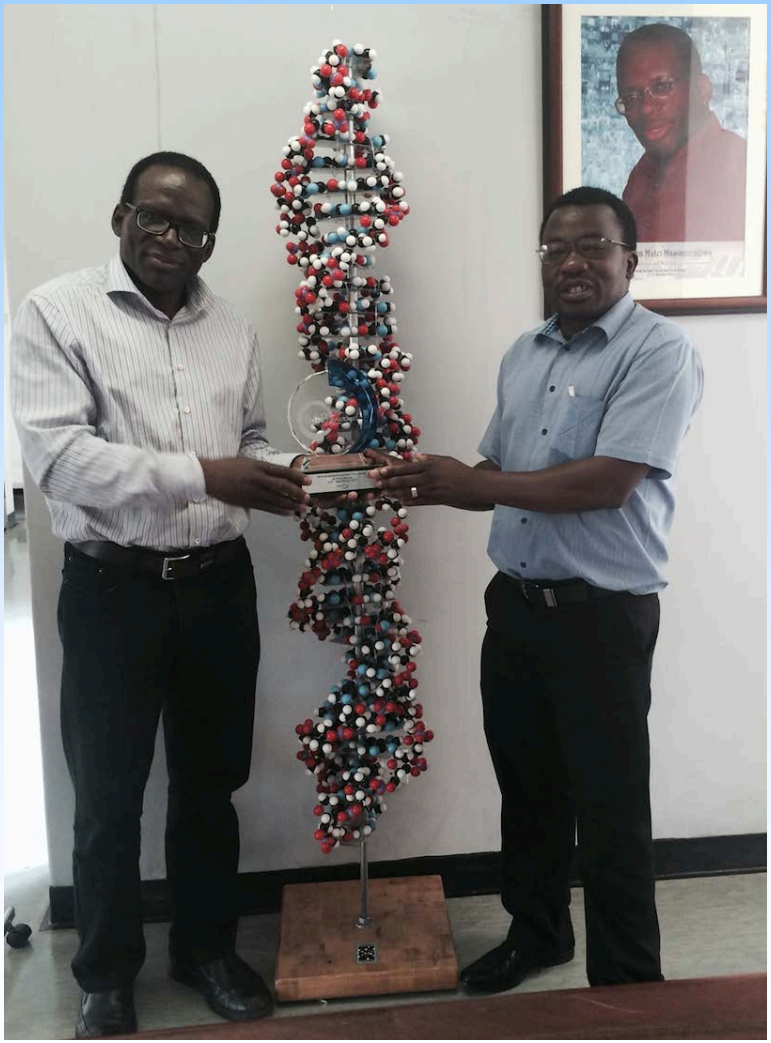



## GeneDose® -EFV


**Genotype guided dosing of EFV**



# Innovation wins 1st Prize GAP Award






**Collen Masimirembwa. DPhil, Ph.D.**

African Institute of Biomedical Science & Technology
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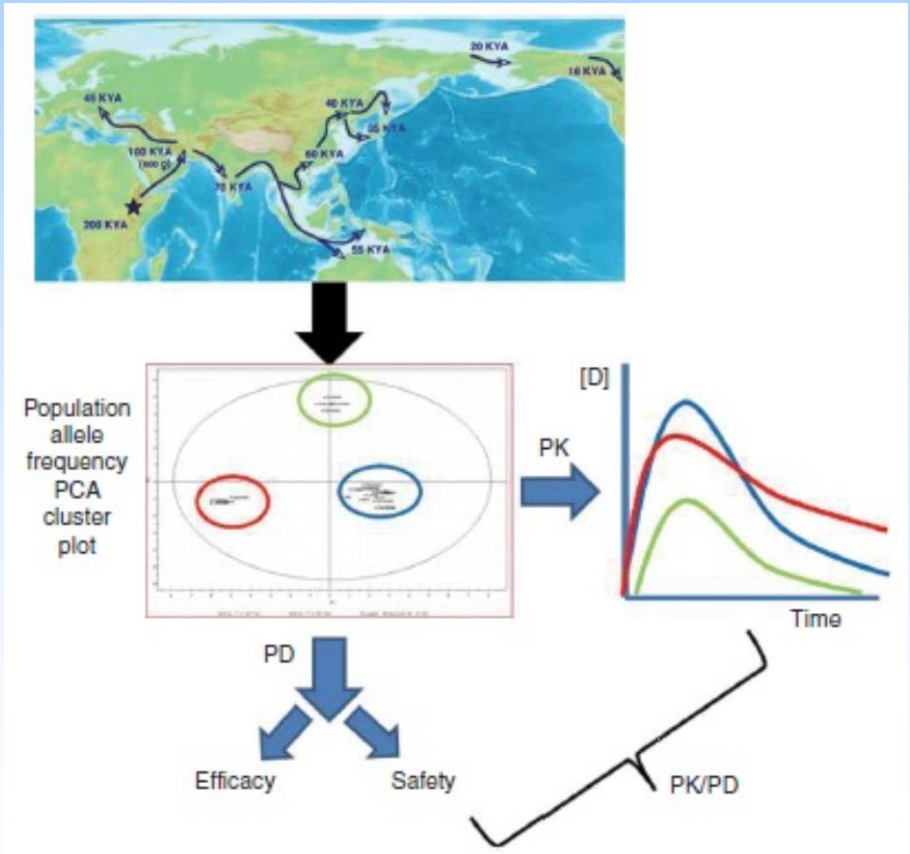
PERSPECTIVE

# Pharmacogenetics in Africa, an Opportunity for Appropriate Drug Dosage Regimens: on the Road to Personalized Healthcare

C Masimirembwa[1] and JA Hasler[1]




Its possible & we are close…..

# THANK !



**Collen Masimirembwa. DPhil, Ph.D.**