

Pharmacogenomics: A primer for precision Medicine in Africa

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Greetings from Cape Town, South Africa



HEALTH IN THE SDG ERA



The goals within SDG 3 (Health): Ensure healthy lives and promote wellbeing for all at all ages

- **3.1:** Reduce the global maternal mortality ratio to less than 70 per 100 000 live births
- **3.2:** End preventable deaths of newborns and children under 5 years of age,
- **3.3:** End the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and
- **3.4:** Reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being
- **3.5-3.9:** Etc
- 3.

Early *Homo sapiens sapiens* in Africa



150,000 to 100,000 BP



<http://tools.medicine.yale.edu/kidd/www/point.html>

8/31/2017

Genomic Diversity of World populations

Handbook of Pharmacogenomics and Stratified Medicine

Editor-in-Chief:
Sandosh Padmanabhan

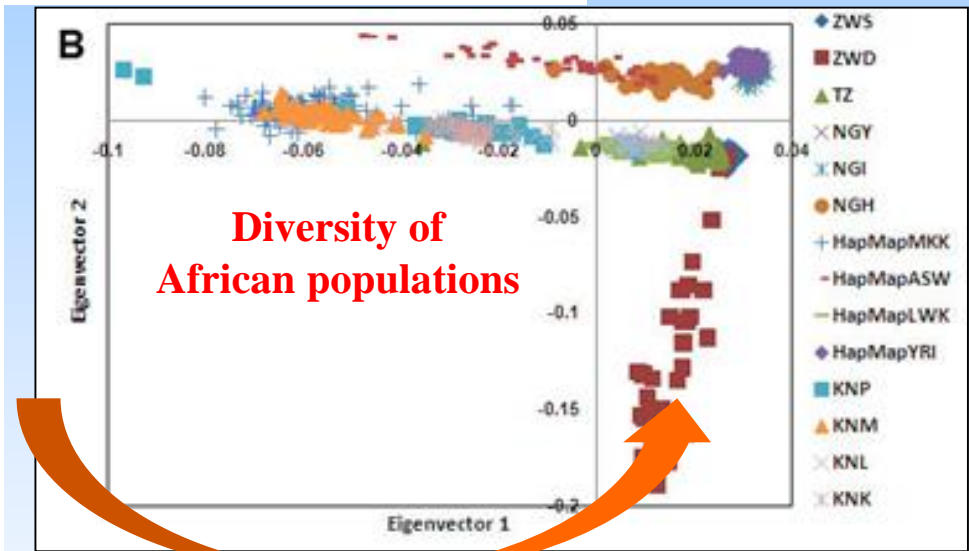
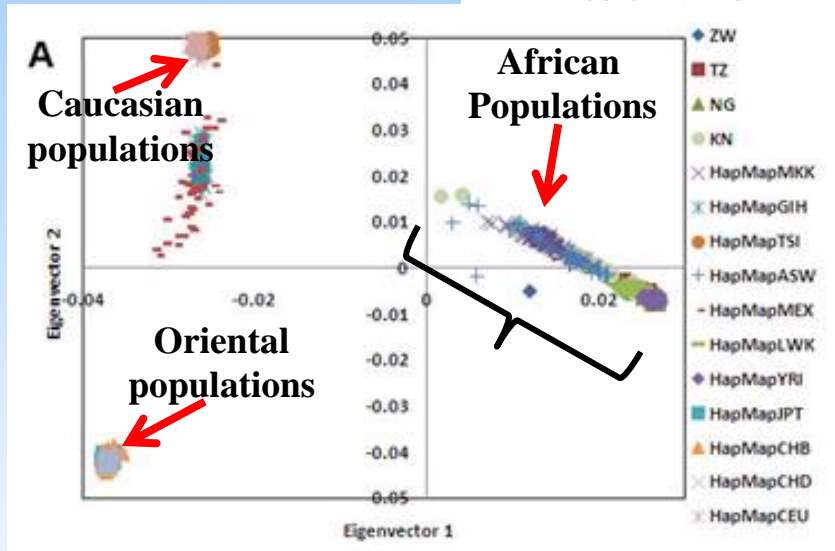
ELSEVIER

Chapter 43

Population Diversity and Pharmacogenomics in Africa

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- 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)
- 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

Population	CYP2C19			CYP2D6						NAT2				GST		CYP2B6	
	*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)



Dandara 2003 PhD thesis & Matimba et al., 2008



A focus of PharmGX of Antiretroviral therapy (ART)

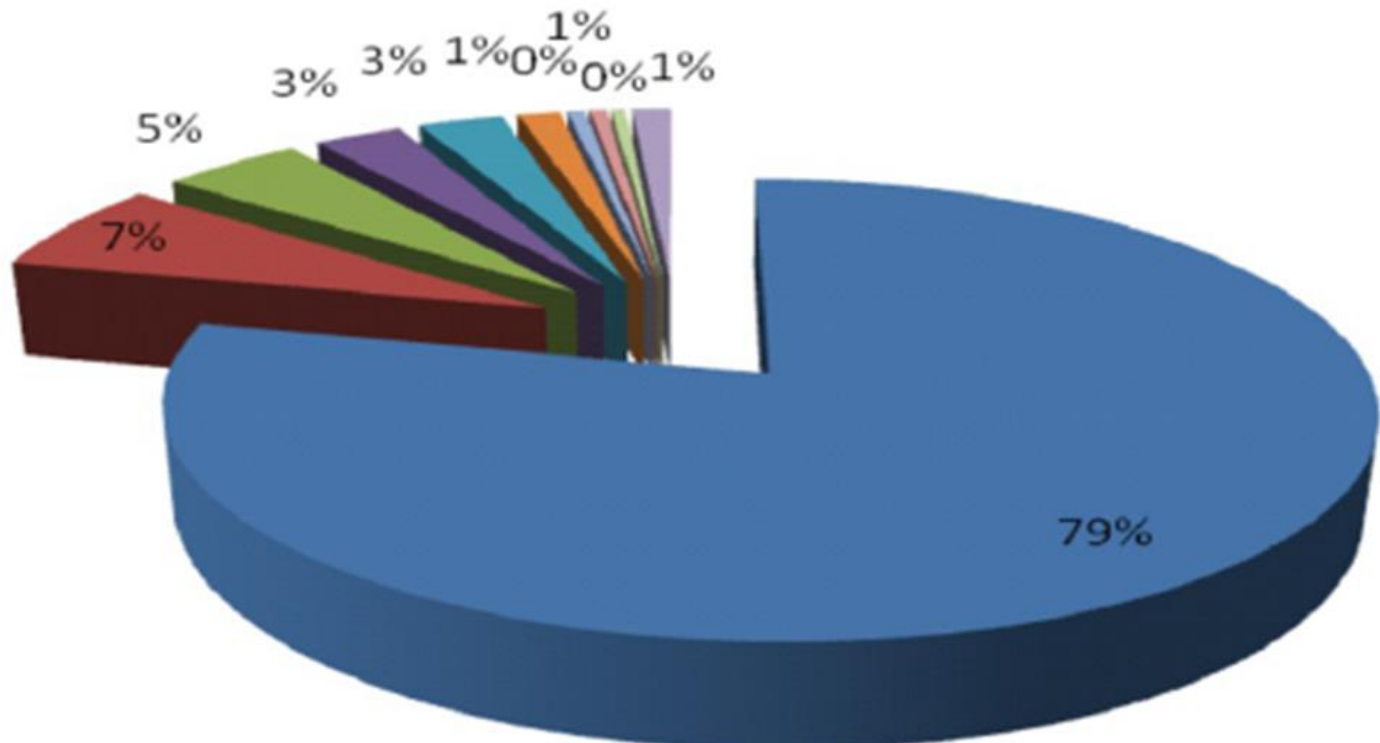
- Africa is the most severely affected by HIV/AIDS
 - With **~26 million** of the **37 million** people were living with HIV globally
- Currently, **17 million** patients are on ART (*UNAIDS, 2016*)
- UNAIDS call for 90-90-90 strategy by 2020 to combat HIV
- Patients on treatment could rise to **~33 million**



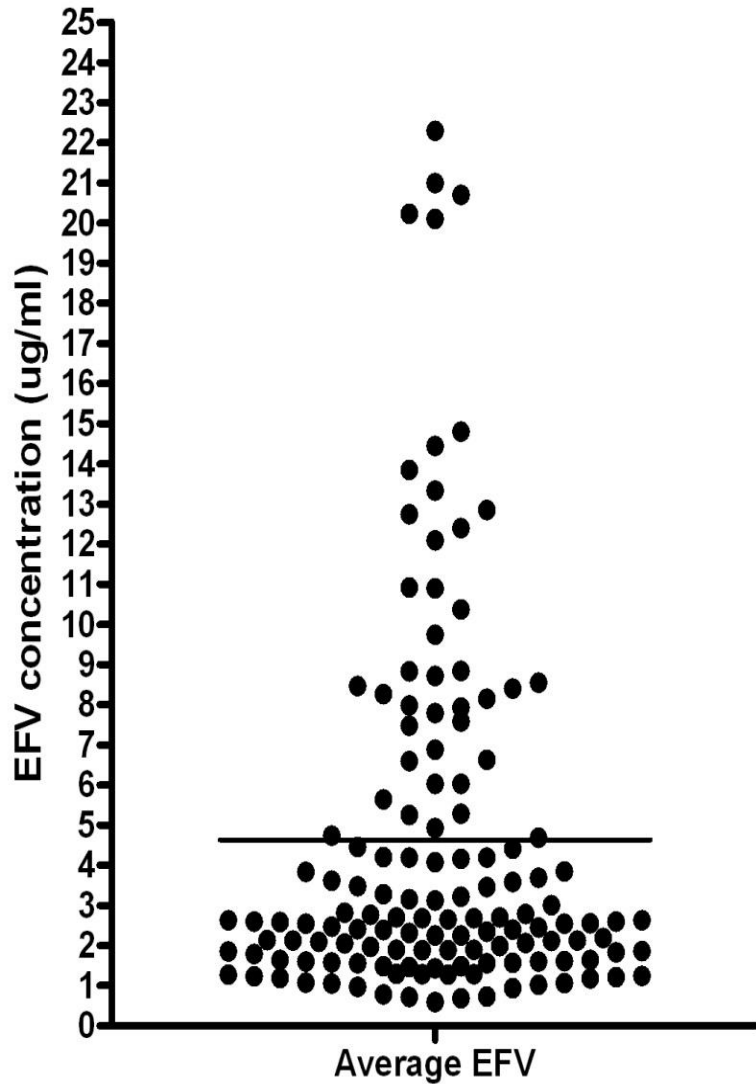
Data are from VigiBase (June 2016).

VigiBase is the WHO Global Individual Case Safety Reports database, containing reports of ADRs: data on 33 African countries

ADRs by class of drugs



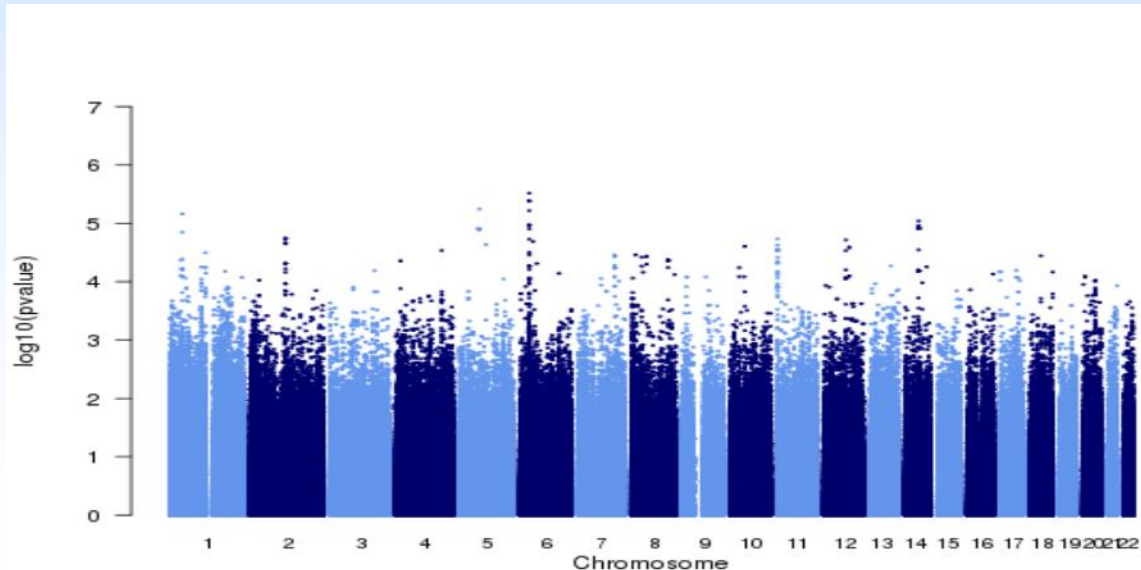
Efavirenz (EFV) plasma concentration



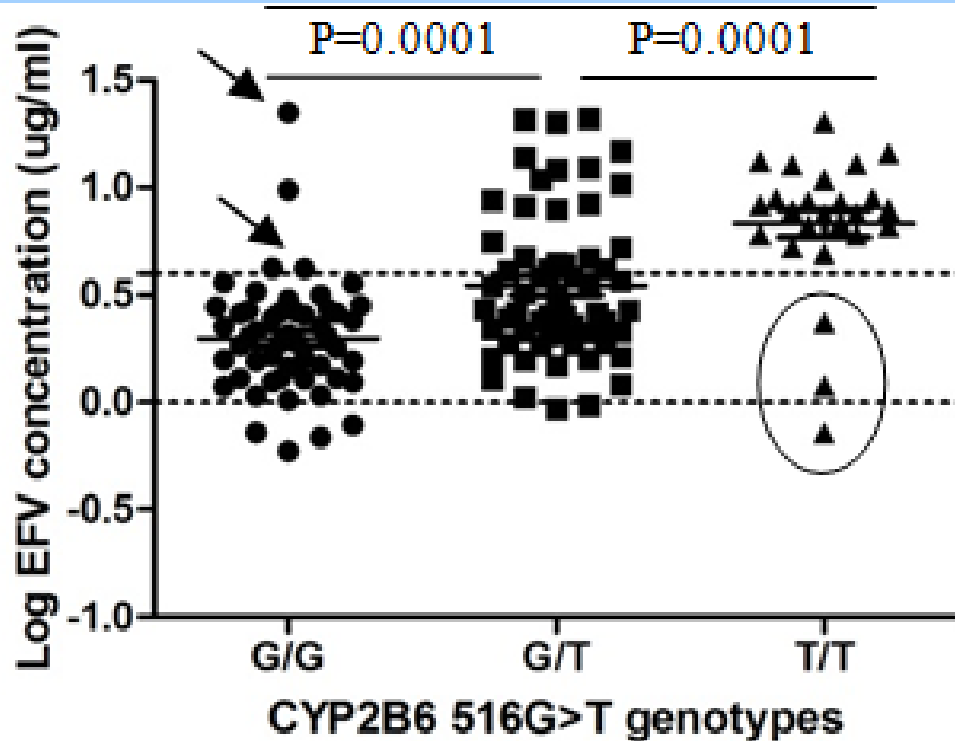
- Cross-sectional view
- Cohort of HIV/AIDS
- At least 12 months on EFV
- Range of EFV plasma conc, ***0.04-34.4***
 - 860-fold variability

Major **ADRs** associated with **Efavirenz (EFV)**

- Neuropsychiatric side effects
- Drug induced liver injury (***DILI***)
- EFV metabolized by polymorphic CYP2B6
 - **A typical mutation: CYP2B6 c.516G>T**
- SNP causes lose of enzyme activity



Effect of c.516G>T on EFV plasma concentration



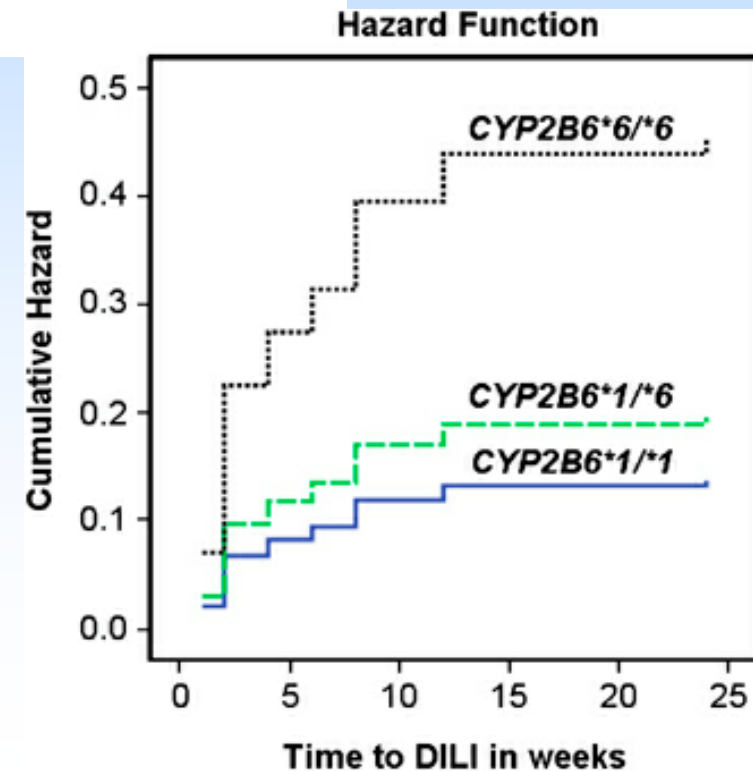
- Patients on EFV for at least 12 months
- 860-fold variability in EFV plasma conc.
- Role of minor variants for outliers
 - CYP2B6 c.983T>C in G/G
 - NR1I3 rs3003596T>C (in constitutive androstane receptor gene)

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 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%



Genomic-led Solution: Precision Efavirenz Dosing

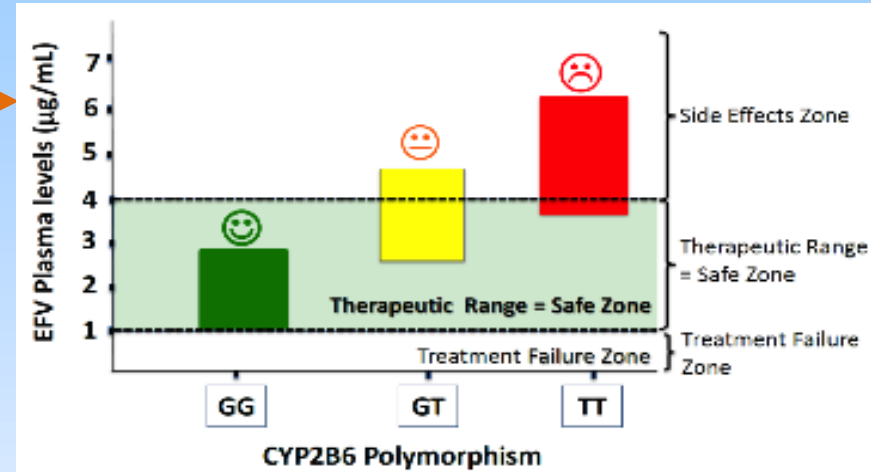
Current Practice



600 mg EFV/day



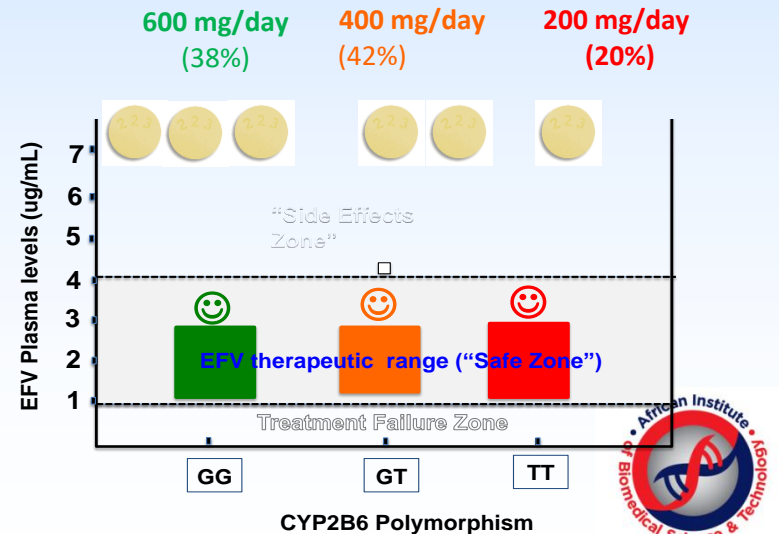
Patients with same
Diagnosis – ‘one
Treatment fits ALL’



GeneDose® -EFV

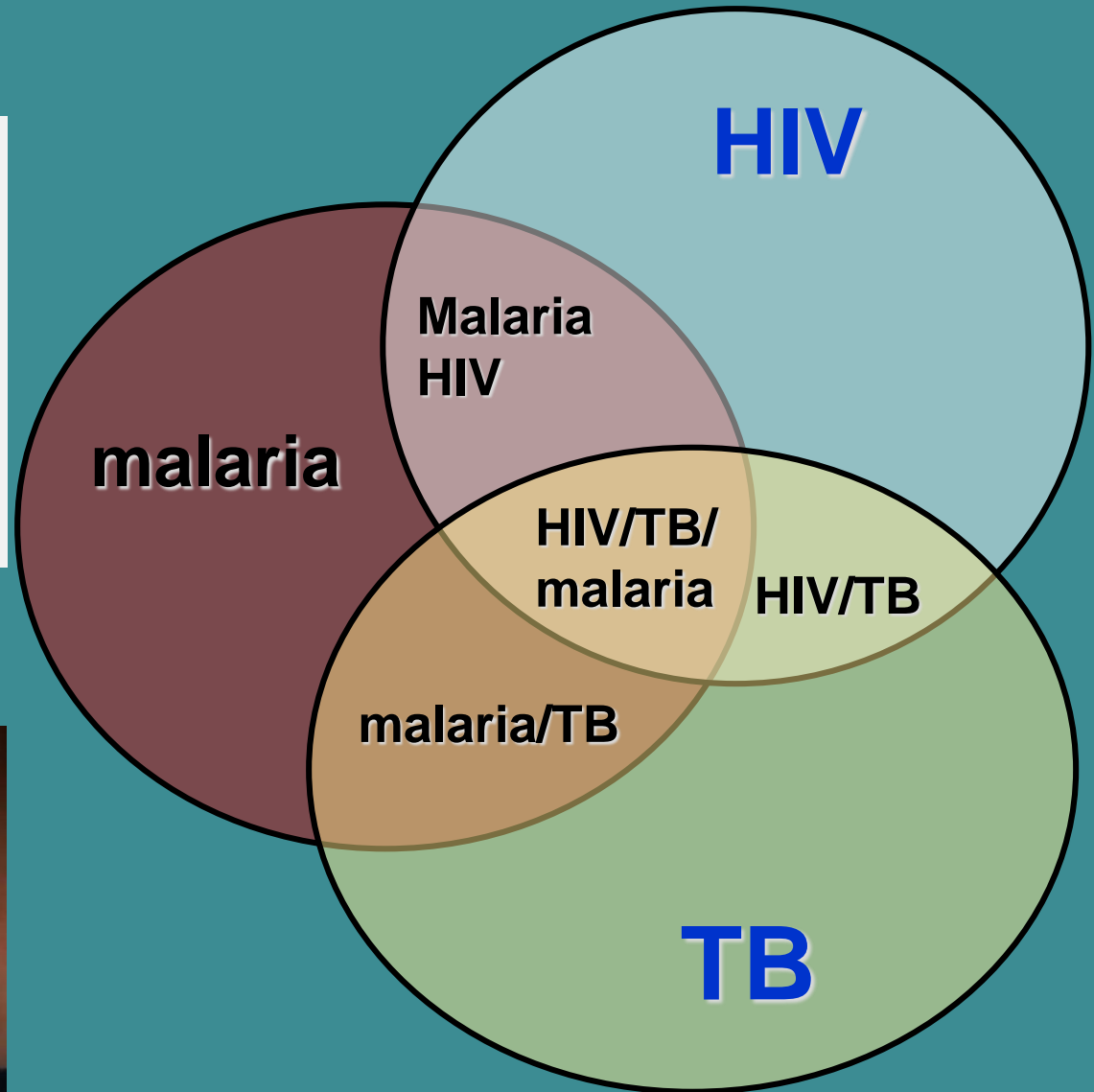


Genotype guided dosing of EFV

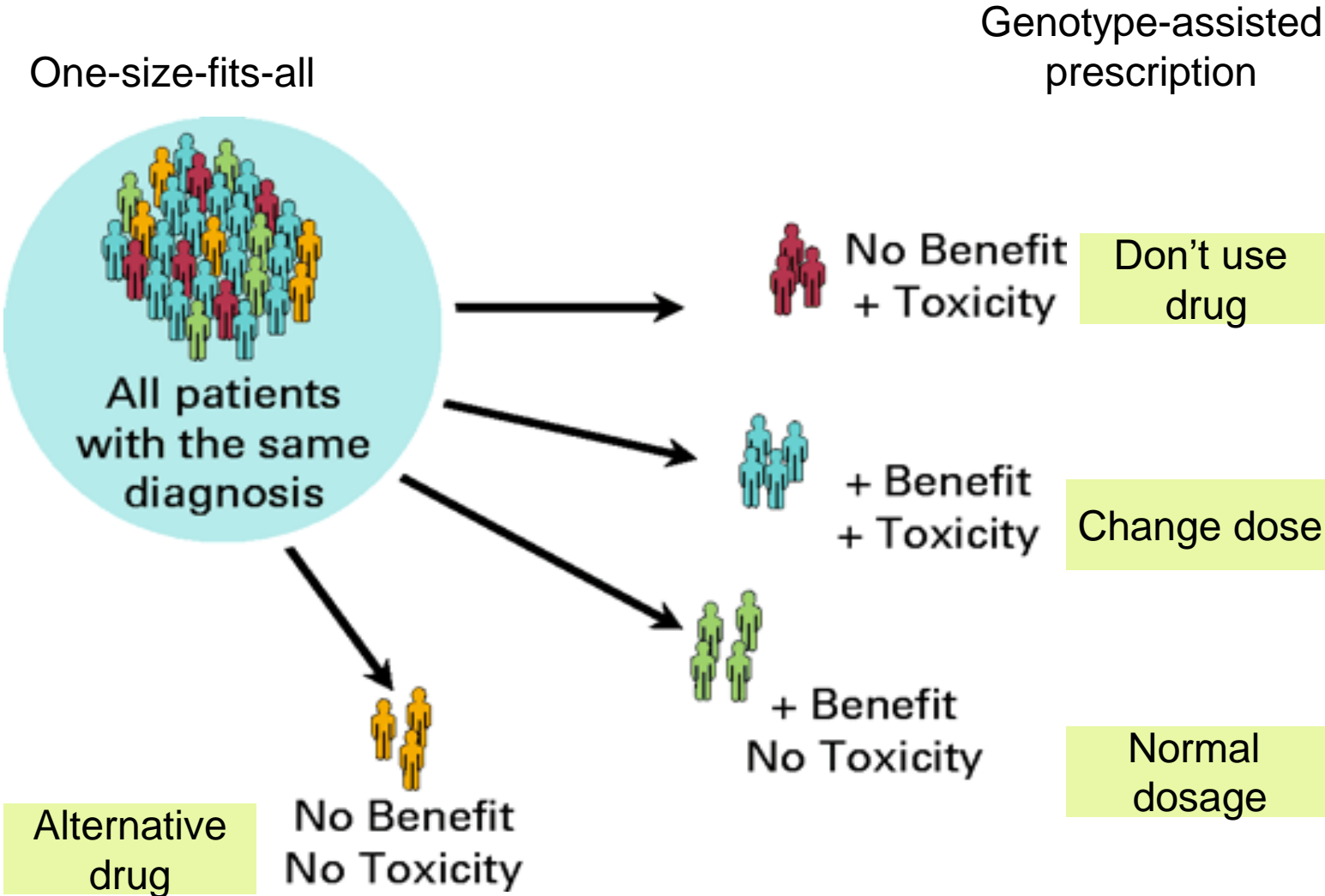


HIV does not exist alone

- **Three** Diseases
- **One** Patient



Envisaged Future of Precision Medicine



Seeding A Passion for Knowledge: High School learners



Acknowledgements

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