Genetic diversity in African populations with respect to pharmacogenetically relevant genes

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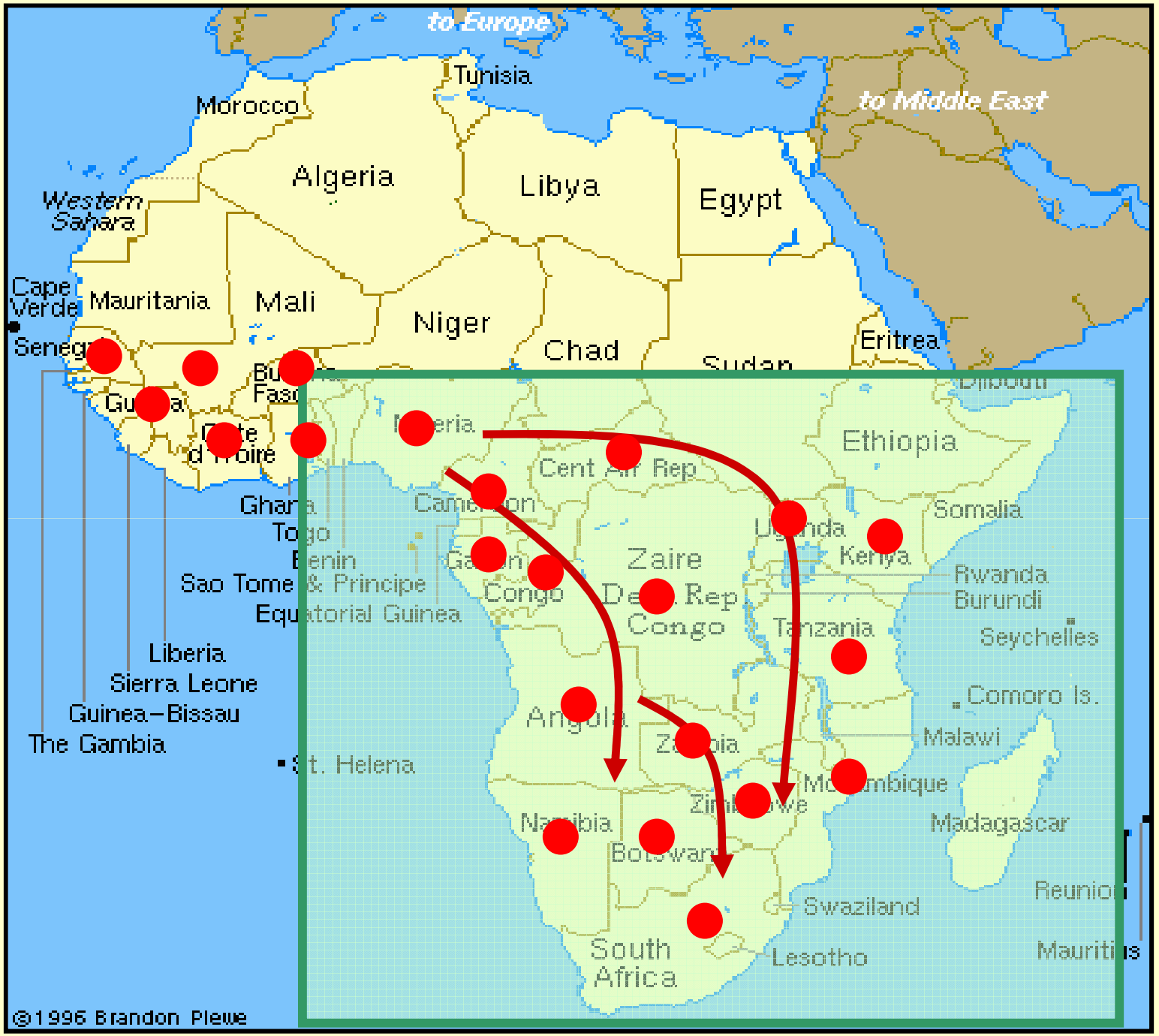
African populations

- Grouped according to language
- > 2000 languages
- Classified into 5 language groups
  - thought to represent genetic variability

Major language groups

- **Afroasiatic** - Mauritania, Morocco, Libya, parts of Egypt, Mali & Niger)
- **Nilotic** - Sudan, Chad & N.E Kenya
- **Cushitic** - N.E Africa (Ethiopia, Somalia & Eritrea)
- **Khoisan** - parts of Namibia & Botswana
- **Bantu** - East, West, Central and Southern Africa (*e.g.* Zambia, Tanzania, Mozambique, South Africa, Angola, Zimbabwe, Nigeria, Senegal, Congo


to Europe
Tunisia
Morocco
to Middle East
Algeria
Libya
Egypt
Western Sahara
Cape Verde
Mauritania
Mali
Niger
Chad
Eritrea
Liberia
Sierra Leone
Guinea-Bissau
The Gambia
Ethiopia
Somalia
Kenya
Zaire
Rwanda
Burundi
Tanzania
Seychelles
Comoro Is.
Malawi
Madagascar
Angola
Namibia
Swaziland
Lesotho
South Africa
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DME genes studied

- **Cytochrome P450 (CYP)**
  - CYP1A1
  - CYP1A2
  - CYP2B6
  - CYP2C9
  - CYP2D6
  - CYP2E1
  - CYP3A5
  - CYP3A4
- **Sulphotransferase**
  - SULT1A1
- **Microsomal epoxide hydrolase**
- **Glutathione S-transferase**
  - GSTM1
  - GSTT1
  - GSTP1
- **Alcohol metabolising enzymes**
  - ADH2
  - ADH3
  - ALDH2
- **N-acetyltransferase**
  - NAT2

Selected Results

	NAT2-G191A	*CYP2D6*17*	*CYP2D6*4*	CYP2B6-G516T
Tanzania	**11**	**20**	**1**	**-**
S. Africa	**11**	**24**	**0.5**	***32***
Zimbabwe	**14**	**34**	**2**	**49**
Asian	**0**	**0**	**1**	**14**
Caucasian	**0**	**0**	**20**	**25**

Pharmacogenetics of cytochrome P450 in African populations, In “Pharmacogenomics in Admixture Populations” by Suarez-Kurtz
Dandara et al., 2003;

Investigating effects of the African specific *CYP2D6*17* allele on drug metabolism

Wennerholm A, Dandara C, et al., 2002

Cut-off MR for EMs and PMs

	EM <	MR(log)	> PM
• Debrisoquine		12.6	(1.1)
• Dextromethorphan		0.3	(-0.5)
• Codeine		14	(1.2)
• Metoprolol		8.4	(0.9)

Phenotypic and Genotype correlation

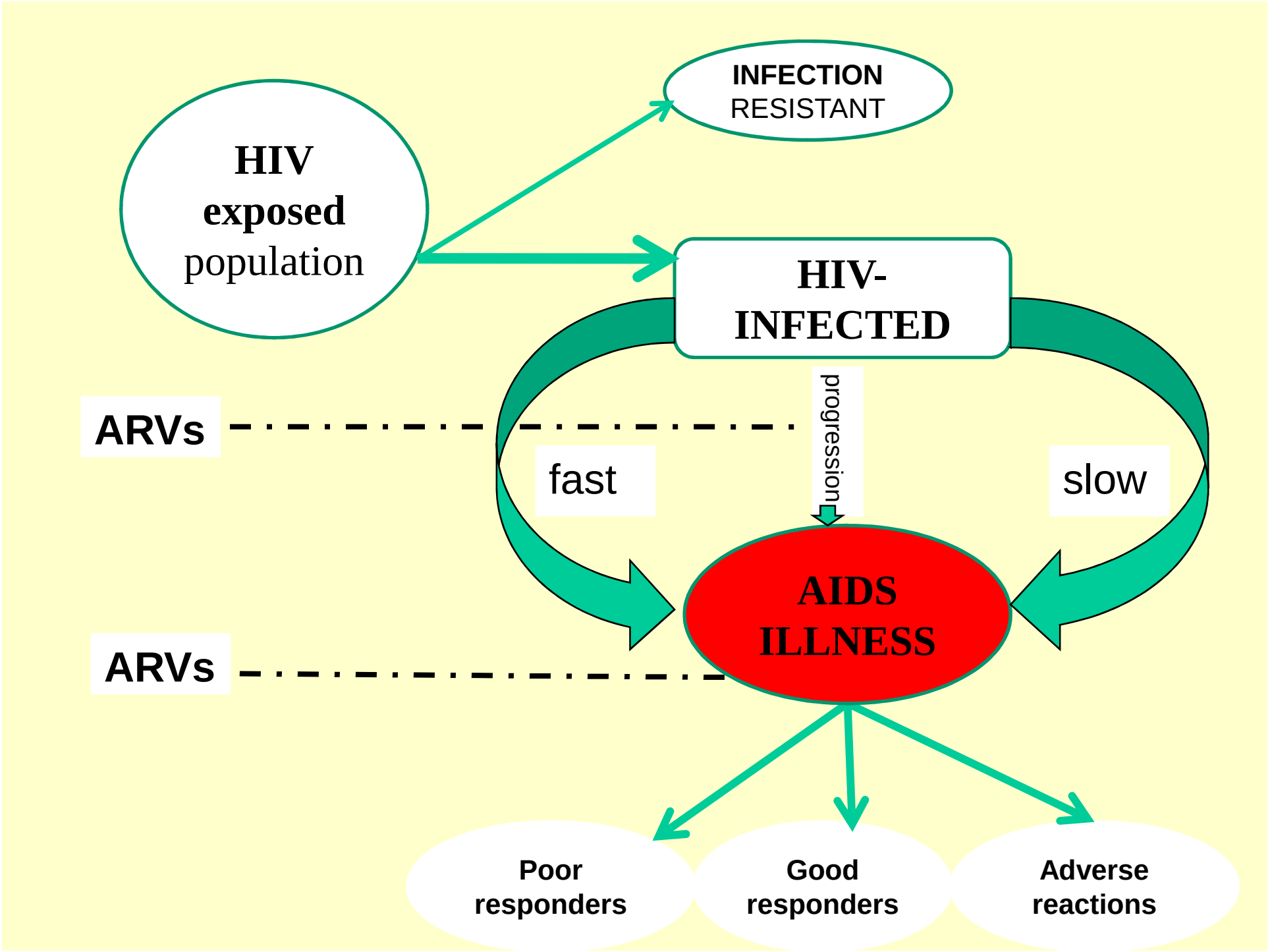
Genotype	Deb	Dex	Cod	Met
	Mean MR	Mean MR	Mean MR	Mean MR
**1/*1*	0.87	0.0089	1.35	0.37
**17/*17*	6.80	0.0996	2.20	0.76
**5/*17*	18.52	0.276	5.93	1.91
**0/*0*	267	4.31	50.9	96.1
**1/*1*	0.40	0.0065	0.96	0.25

Wennerholm A, Dandara C, et al., 2002

Classification of subjects with *CYP2D6*5/*17* genotypes

- All 4 were PMs with debrisoquine
- 1 was PM with dextromethorphan
- All 4 were EMs with both codeine and metoprolol

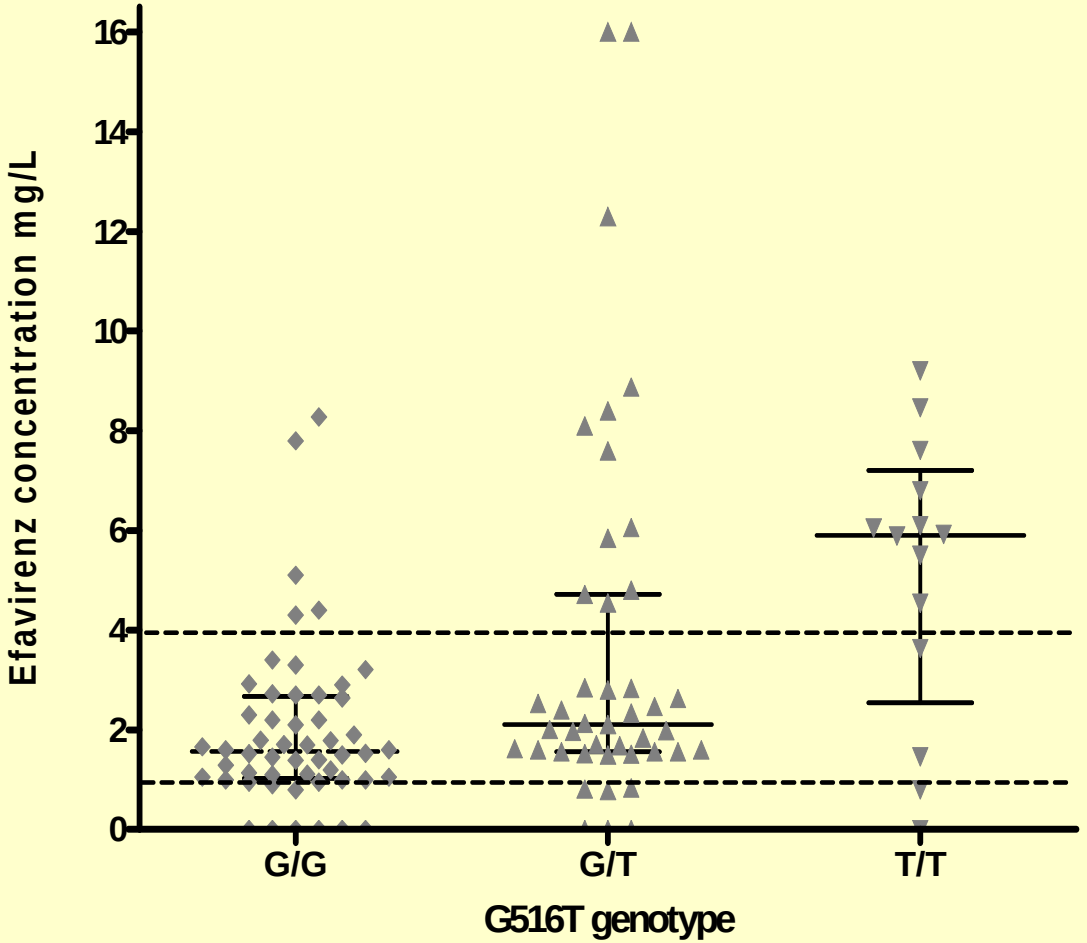
HIV/AIDS


INFECTION
RESISTANT
HIV
exposed
population
HIV-
INFECTED
ARVs
progression
fast
slow
AIDS
ILLNESS
ARVs
Poor
responders
Good
responders
Adverse
reactions

Efavirenz and CYP2B6

- Efavirenz is a potent NNRTI
- Part of first line therapy
- Principally metabolized by CYP2B6
  - Common SNP, 516G>T
  - 516TT genotype associated with reduced enzyme activity

Efavirenz conc. Vs CYP2B6 genotype among Xhosa HIV/AIDS patients



SA Pharmacogenomics Initiative

- Healthy individuals
  - Blood & saliva
- HIV/AIDS patients
  - Access to an HIV/AIDS clinic (>10,000 patients)
- Psychiatric patients
  - Planning stage

An African Pharmacogenetics Database & Biobank

- Consortium of BioBanking of Pharmacogenetics in Africa
  - Tanzania (Dr Sayi)
  - Kenya (Dr Oluka)
  - Uganda (Dr Obua)
  - Nigeria (Dr Bolaji)
  - South Africa (Dandara)

Challenges

- Unclear regulations
- Funding
- Capacity to carry out high throughput analysis of samples
- Need for establishing partnerships

Acknowledgements

- Organizers for invitation
- ESF-for sponsorship
- Co-authors