

Metabolic complications of efavirenz

Gary Maartens



EFV & bone density

- EFV induces the metabolism of vitamin D, resulting in lower concentrations
- EFV independently associated with lower bone mineral density in a cross-sectional study in Cape Town

EFV & dyslipidaemia

Increased triglycerides, total & LDL-chol vs comparators in RCTs:

- Nevirapine
- Rilpivirine
- Atazanavir-r
- Dolutegravir
- Raltegravir

PLoS Med 2004;1:e19
JAIDS 2012;60:33
Lancet Infect Dis 2012;12:111
Clin Infect Dis 2006;42:273
Lancet 2009; 374: 796

EFV & lipodystrophy

- Systematic review of ARV-associated lipodystrophy
- EFV associated with a higher risk of lipodystrophy than PIs
- Driven by higher risk of lipoatrophy – either due to additive mitochondrial toxicity or to protective effect of PIs, which have anti-apoptotic properties

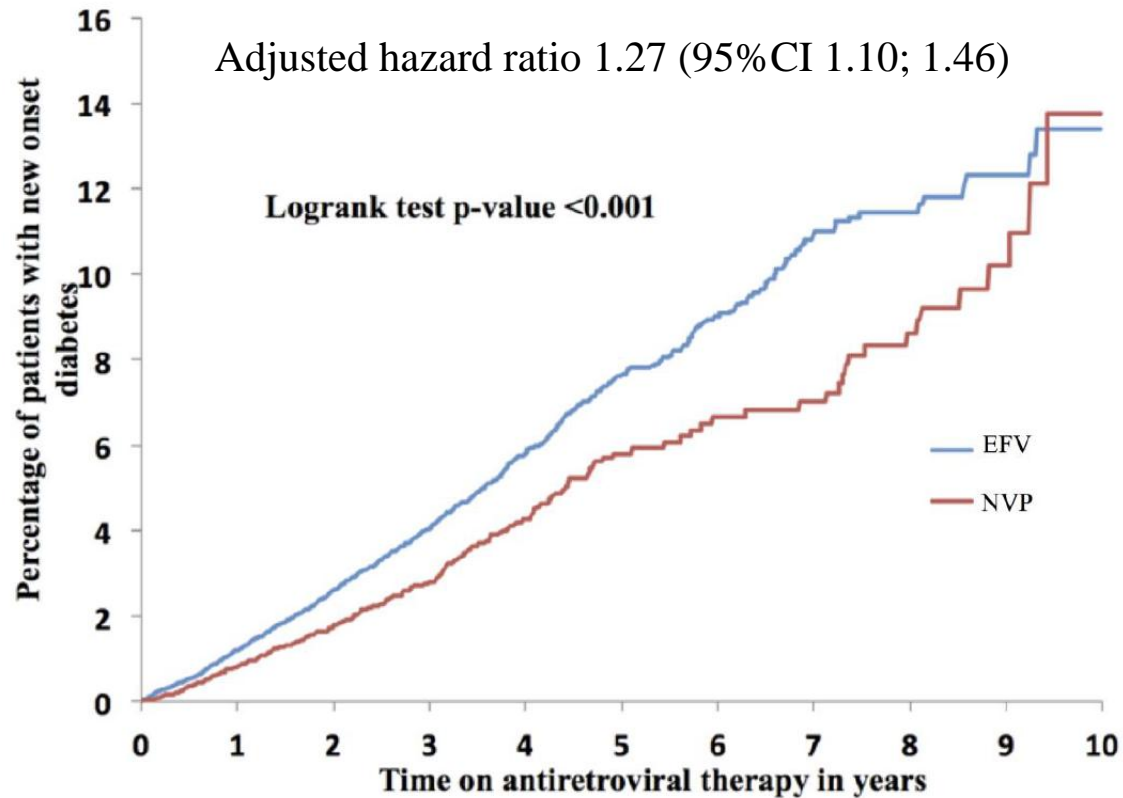
EFV & dysglycaemia

A5224s: EFV change in fasting glucose higher than ATV-r by 0.24 (95%CI 0.07-0.413) despite lower BMI in EFV arm

STARTMRK: EFV change in fasting glucose higher than RAL by 0.22 (P=0.025)

Cross sectional study Cape Town: EFV independently associated with dysglycaemia (DM or impaired glucose tolerance): adjusted OR 1.70 (95%CI 1.19-2.45)

Risk of DM – SA private sector



Numbers at risk

EFV	46666	29898	17158	9647	5159	2160	1447	915	544	239	1
NVP	9632	7088	4613	2883	1688	768	594	457	318	121	3

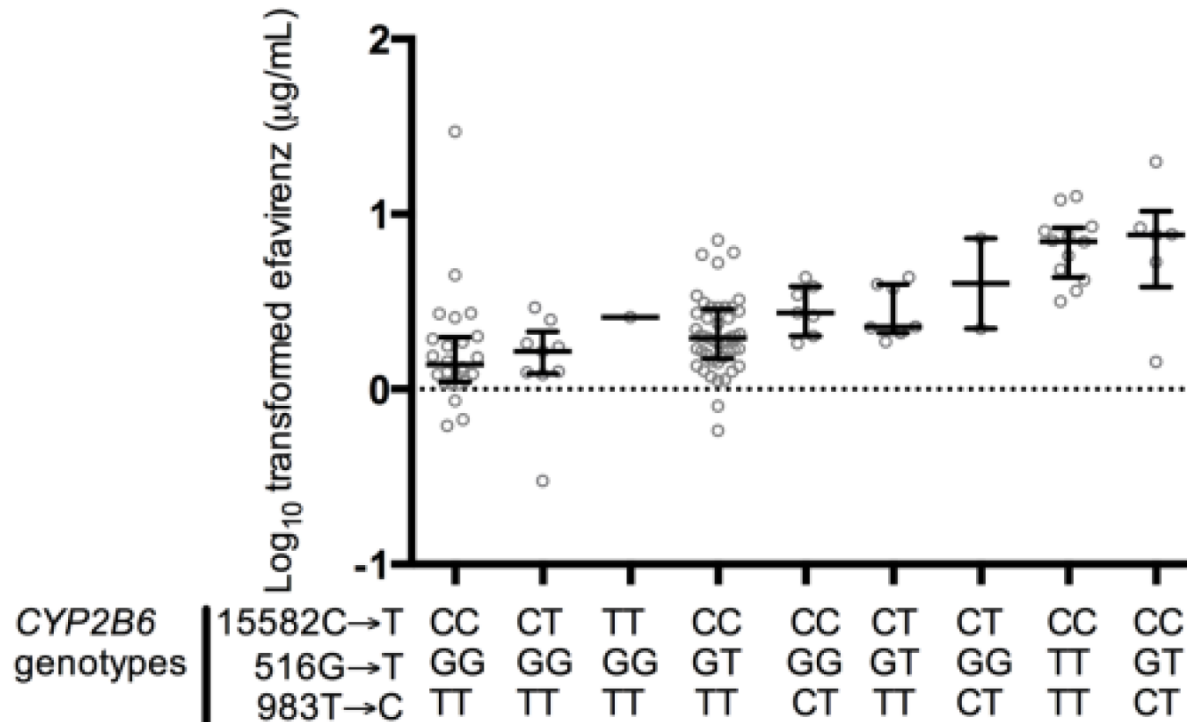
Risk of DM – Botswana

- Retrospective case-control study
- 48 HIV-infected cases with DM
- Efavirenz independently associated with increased risk of DM (OR 4.58; 95% CI 1.44 - 14.57)

EFV concentrations & metabolic effects

Metabolic measure	Beta coefficient (95% CI)	P
LDL cholesterol	0.62 (0.14 to 1.10)	0.012
Triglycerides	0.58 (0.09 to 1.08)	0.022
Glucose (fasting)	0.60 (0.11 to 1.10)	0.017
Glucose (2 hours)	1.14 (0.28 to 2.00)	0.010

Pharmacogenetics of EFV metabolism



17% in SA genetic slow metabolisers (vs 3% Caucasians)

EFV mitochondrial toxicity

Inhibits Complex I of the electron transport chain, resulting in reduced mitochondrial transmembrane potential, thus compromising oxidative phosphorylation and ATP generation

Reduces complex IV mRNA (a marker gene of mitochondrial function), and impairs mitochondrial function in adipocytes.

Efavirenz-associated mitochondrial dysregulation in adipose tissue causes impaired adipogenesis, increased lipolysis, apoptosis of adipocytes and release of free fatty acids and inflammatory cytokines – contributes to insulin resistance

Br J Pharmacol 2010;160:2069

J Acquir Immune Defic Syndr 2008;48:381

Antimicrob Agents Chemother. 2002;46:2687

Curr HIV Res. 2010;8:545

Wednesday October 31 2007 Late Final

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**BAFANA
NAME
CHANGE
POLL
RESULTS**

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**BARALWA FUMES
OVER SICK JOKE**

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HIV MAN GROWS BOOBS

**Condition a side-effect of
ARVs – medical experts**

EXCLUSIVE



Sabete Muzira, not his real name

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Gynaecomastia in HIV-infected men on highly active antiretroviral therapy: association with efavirenz and didanosine treatment

José A Mira¹, Fernando Lozano², Jesús Santos³, Emilia Ramayo⁴, Alberto Terrón⁵, Rosario Palacios³, Eva M León², Manuel Márquez³, Juan Macías^{1,2}, Ana Fernández-Palacín⁶, Jesús Gómez-Mateos² and Juan A Pineda^{1,2} for the Grupo Andaluz para el Estudio de las Enfermedades Infecciosas (GAEI)*

EFV and ddI associated with the emergence of gynaecomastia.

EFV activates oestrogen receptor in vitro

Conclusion

- EFV associated with multiple metabolic toxicities
- Mitochondrial toxicity responsible for most metabolic toxicities
- Generally effects are modest, but likely to be worse in patients with CYP2B6 slow metaboliser genotypes (17% in SA)

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