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

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

De Waal PLoS ONE 8(5): e63623
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

Adjusted hazard ratio 1.27 (95% CI 1.10; 1.46)

Logrank test p-value < 0.001

Time on antiretroviral therapy in years

Percentage of patients with new onset diabetes

Numbers at risk

<table>
<thead>
<tr>
<th></th>
<th>EFV</th>
<th>NVP</th>
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<td>9632</td>
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<tr>
<td>10</td>
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<td>3</td>
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</tbody>
</table>

Karamchand Medicine 2016:95:e2844
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

<table>
<thead>
<tr>
<th>Metabolic measure</th>
<th>Beta coefficient (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>0.62 (0.14 to 1.10)</td>
<td>0.012</td>
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<tr>
<td>Triglycerides</td>
<td>0.58 (0.09 to 1.08)</td>
<td>0.022</td>
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<tr>
<td>Glucose (fasting)</td>
<td>0.60 (0.11 to 1.10)</td>
<td>0.017</td>
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<tr>
<td>Glucose (2 hours)</td>
<td>1.14 (0.28 to 2.00)</td>
<td>0.010</td>
</tr>
</tbody>
</table>
Pharmacogenetics of EFV metabolism

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

Sinxadi Br J Clin Pharmacol. 2015;80:146
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
HIV MAN GROWS BOOBS
Condition a side-effect of ARVs – medical experts
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 Macías¹², Ana Fernández-Palacín⁶, Jesús Gómez-Mateos² and Juan A Pineda¹²* 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)
Acknowledgements

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Funders

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*Discovery*