We should switch to dolutegravir in 1st line

Gary Maartens
EFV resistance

- Low genetic barrier to resistance
- Several single mutations confer high level resistance
- Variable cross-NNRTI resistance
Prevalence of transmitted HIV drug resistance to NNRTI increased between 2004 and 2010. This estimated increase was particularly apparent in the areas surveyed in the African region.
Figure 2 Relationship between transmitted resistance to NNRTI drugs and antiretroviral therapy coverage

Prevalence of NNRTI resistance mutations: % of genotypes

Antiretroviral therapy coverage: % of people living with HIV receiving ART

P-value adjusted for region = 0.039; Odds-ratio per 10% increase in ART coverage = 1.49 (95% C.I: 1.07 - 2.08)
Early EFV neuropsychiatric toxicity
EFV CNS symptoms over time

- ACTG study of EFV in ART naives
- Neurocognitive test improved
- “small increases from baseline in EFV-associated symptoms, bad dreams, and anxiety were detected.”
ART & neurocognitive function

- ART improves HIV-associated neurocognitive dysfunction
- ACTG observational study of people stopping ART for median 4.5 years
- Neurocognitive tests IMPROVED after stopping ART, significantly more in those on EFV
- Many ARVs, especially EFV (mostly its 8-OH metabolite) are toxic to neuronal cells in vitro
EFV & suicidality
4 ACTG RCTs EFV n=3241; comparator n=2091
EFV metabolic effects

• Increased triglycerides, total & LDL-chol vs nevirapine, rilpivirine, atazanavir-r, dolutegravir, & raltegravir
• EFV fasting glucose higher than ATV
• Cross sectional study Cape Town dysglycaemia risk higher on EFV aOR 1.70 (95%CI 1.19-2.45)
• Higher risk of DM than NVP cohort study

JAIDS 2012;60:33
Lancet Infect Dis 2012;12:111
Clin Infect Dis 2006;42:273
Lancet 2009; 374: 796
AIDS 2014;28(10):145
JAIDS 2011;57:2841
Karamchand Medicine 2016
## Meta-analysis: EFV discontinuations for toxicity

<table>
<thead>
<tr>
<th>Arms</th>
<th>Studies</th>
<th>Relative risk (95% CI)</th>
<th>I-squared</th>
<th>Risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>9</td>
<td>0.72 (0.53, 0.98)</td>
<td>34.10%</td>
<td>−3.6 (−6.6 − −0.6)</td>
</tr>
<tr>
<td>Efaviren stepped dose</td>
<td>1</td>
<td>1.62 (0.55, 4.80)</td>
<td>N/A</td>
<td>5.4 (−6.6 − 17.4)</td>
</tr>
<tr>
<td>Efaviren low dose</td>
<td>1</td>
<td>3.12 (1.25, 7.75)</td>
<td>N/A</td>
<td>4.0 (1.0 − 3.6)</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>4</td>
<td>1.97 (1.02, 3.82)</td>
<td>71.80%</td>
<td>4.1 (1.3 − 6.8)</td>
</tr>
<tr>
<td>Etravirine</td>
<td>1</td>
<td>2.02 (0.64, 6.45)</td>
<td>N/A</td>
<td>5.2 (−3.1 − 13.5)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1</td>
<td>3.64 (1.38, 9.59)</td>
<td>N/A</td>
<td>7.7 (2.4 − 13.0)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>1</td>
<td>1.96 (0.75, 5.09)</td>
<td>N/A</td>
<td>4.6 (−1.2 − 10.5)</td>
</tr>
<tr>
<td>Atazanavir/ritonavir</td>
<td>5</td>
<td>1.41 (1.10, 1.79)</td>
<td>0.00%</td>
<td>2.6 (0.6 − 4.6)</td>
</tr>
<tr>
<td><strong>Lopinavir/ritonavir</strong></td>
<td>5</td>
<td>1.14 (0.76, 1.72)</td>
<td>19.00%</td>
<td>0.6 (−4.4 − 5.5)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>3</td>
<td>2.70 (1.10, 6.90)</td>
<td>0.00%</td>
<td>1.7 (−0.7 − 4.2)</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>2</td>
<td>4.29 (2.22, 8.32)</td>
<td>0.00%</td>
<td>5.0 (−0.8 − 10.9)</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>1</td>
<td>3.26 (0.64, 6.45)</td>
<td>N/A</td>
<td>9.4 (5.3 − 13.5)</td>
</tr>
</tbody>
</table>

Ford JAIDS 2015
EFV toxicity in SA

• High prevalence of slow metabolizer genotypes in SA (17% vs 3% Caucasians)

• Increased risk of dose-related toxicity:
  – Neuropsychiatric
  – Hepatitis
  – Lipids
  – Glucose

Sinxadi BJCP 2015
Sinxadi Medicine 2016
Haas AIDS 2004
Mollan IAS 2015
Dolutegravir vs EFV in ART naive

A Proportion of Participants with HIV-1 RNA Level <50 Copies/ml

- DTG ABC 3TC
- EFV TDF FTC

Difference in response at wk 48, 7 percentage points (95% CI, 2–12)  
P=0.003

DTG vs EFV: Safety

A Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>DTG-ABC-3TC</th>
<th>EFV-TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>▲</td>
<td>□</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>△</td>
<td>□</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>▲</td>
<td>□</td>
</tr>
<tr>
<td>Nausea</td>
<td>△</td>
<td>□</td>
</tr>
<tr>
<td>Headache</td>
<td>▲</td>
<td>□</td>
</tr>
<tr>
<td>Insomnia</td>
<td>△</td>
<td>□</td>
</tr>
<tr>
<td>Fatigue</td>
<td>▲</td>
<td>□</td>
</tr>
</tbody>
</table>

Stopped for toxicity: DTG ABC 3TC 2%  EFV TDF 3TC 10%

Incidence of Event (%) vs Relative Risk (95% CI)
Dolutegravir resistance

- Single mutation results in moderate resistance, which impedes replicative capacity
- With other integrase inhibitors (raltegravir & elvitegravir), initial resistance mutation is rapidly followed by compensatory mutations that restore replicative capacity, which doesn’t appear to occur with DTG
- Selection of resistance hasn’t been seen when used in initial therapy
- R263K mutation only confers low level resistance
Dolutegravir & rifampicin

AUC$_{0-24}$ DTG 50 mg/d  32.1
DTG 50 mg 12 hourly + rif  42.6
Conclusions

- EFV low barrier to resistance major drawback
- EFV toxicity has been under-estimated – no longer recommended 1\textsuperscript{st} line in high-income countries
- The high prevalence of EFV slow metabolizer genotypes in SA increases risk of dose-related toxicity
- DTG is more effective, less toxic, much more robust – will virtually abolish need for 2\textsuperscript{nd} line
- DTG will be cheaper to manufacture
- We should follow Botswana’s lead & switch to the better drug