Efavirenz as a first-line drug

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Topics to be covered

- History of EFV
- Important considerations
- Strategies for management of EFV toxicities
- Will this still work? (resistance in the community)
History of EFV

• Registered by the FDA in 1998
• Registered by the MCC in 2004
• Fixed dose combination registered in Feb 2011 with tenofovir and FTC
• A number of generic followed with either FTC or 3TC
• Currently almost 4 million South Africans take this combination
The use of EFV in pregnancy

- An accumulation of evidence indicating that EFV has superior efficacy and tolerability compared with NVP
- Substantial reductions in the price of EFV, and increased availability as part of once-daily fixed dose combinations
- Updated data suggesting a low risk of birth defects associated with EFV use during the first trimester of pregnancy
- Programmatic experience highlighting the complications associated with switching HIV-positive pregnant women and those who may become pregnant from EFV to NVP.
Important considerations (2)

• The use of EFV with Rif containing TB regimen
  – Most common infection associated with HIV
  – Rifampicin effect on EFV PK
  – PK studies in patients with TB show no significant effect
    • Spain
    • South African adults (2 studies) & children
    • India
  – Package insert says AUC reduced 26% (n=12, no P value given)
  – Retrospective TDM database found significant reduction in EFV concentrations
Use of DTG in TB

• Rifampicin reduces dolutegravir concentrations –
  Induces UGT1A1, CYP3A4 and P-glycoprotein

• In healthy volunteers, 12 hourly dosing compensated
  for this

Dooley, JAIDS 2013
Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort


Figure 2. Estimates of cumulative regimen substitutions due to toxicity by individual drug over a 3-year period

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>0.00</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
<th>0.20</th>
<th>0.25</th>
<th>Changed by 36 months, % (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>676</td>
<td>469</td>
<td>295</td>
<td>126</td>
<td></td>
<td></td>
<td></td>
<td>7.8 (5.9–10.3)</td>
</tr>
<tr>
<td>EFV</td>
<td>1,613</td>
<td>858</td>
<td>334</td>
<td>74</td>
<td></td>
<td></td>
<td></td>
<td>7.6 (5.3–10.9)</td>
</tr>
<tr>
<td>NVP</td>
<td>1,062</td>
<td>376</td>
<td>75</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td>10.0 (6.2–16.5)</td>
</tr>
<tr>
<td>d4T</td>
<td>1,996</td>
<td>782</td>
<td>137</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>20.8 (16.2–26.5)</td>
</tr>
</tbody>
</table>

Over 3 years: 2% substituted efavirenz
Use of RPV in TB

- Data on drug interactions of rifampicin and rifabutin with the NNRTI rilpivirine are limited.
- Rifampicin decreases serum rilpivirine levels substantially.
• Neuro-psychiatric side effects ranging from insomnia to over psychosis.

Dolutegravir also has CNS side effects

Walmsley, NEJM 2013
Management of side effects of EFV

- Reduce the dose of EFV to 400mg
• Large ART clinical service in Amsterdam
• Dolutegravir treatment stopped in 62/387 patients (16%)
• Reasons
  – Sleeping problems (n=19)
  – Gastro-intestinal problems (n=18)
  – Neuropsychiatric problems (n=12)
  – Fatigue (n=9)
  – Headache (n=8)
Efavirenz and suicidality

HIV TREATMENT BULLETIN

Suicide not associated with efavirenz use in the D:A:D cohort study


Simon Collins, HIV i-Base

An analysis from the D:A:D cohort study, presented as an oral abstract by Colette Smith at the 2014 HIV Drug Therapy Glasgow Congress, was notable for reporting no association between suicide in HIV positive people taking efavirenz in European cohorts. [1]

Conclusion:
In this analysis of two large real world databases, HIV patients with depression and psychiatric conditions were less likely to be prescribed EFV. Despite PS-adjustment, we did not find conclusive evidence of an increased risk of suicidality or suicide attempt among patients initiating an EFV-containing regimen.
Neuronal toxicity of efavirenz: a systematic review

Eric H Decloedt† & Gary Maartens
†Stellenbosch University, Faculty of Medicine and Health Sciences, Division of Clinical Pharmacology, Department of Medicine, Tygerberg, South Africa

“The clinical evidence that efavirenz use may worsen neurocognitive impairment or be associated with less improvement in neurocognitive impairment than other antiretrovirals is weak.”

“There is a need for large randomized controlled trials to determine if the neuronal toxicity induced by efavirenz results in clinically significant neurological impairment before any conclusions can be made about ongoing use of this widely used antiretroviral drug.”

Expert Opinion on Drug Safety, 2013
Strategies for the management of EFV toxicity

- To stay within class
- Lower dose efavirenz (400mg nocte)
  - Would need to go to split out medications
  - Three tablets and not one
  - ENCORE1 showed this strategy to be effective but not to be used in pregnancy or TB
- Change to RPV
Resistance in the community

- Resistance testing is not recommended prior to starting treatment.
- Not all patients are truly treatment naïve (sdNVP and may not admit to prior treatment).
- In one study done in KZN, 17% of patient “presenting for the first time” resistance mutations: predominantly K103N yet it did not have an impact on the outcomes.
Conclusions

• EFV has served us well for many years
• Safe in pregnancy and with rifampicin
• The alternatives are not squeaky clean either.