Exploring 1st Line ART Options: Efavirenz

Sipho Dlamini

Division of Infectious Diseases & HIV Medicine
University of Cape Town
Groote Schuur Hospital

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Introduction

• Cost, availability & acceptability drive ART use
• Major disadvantage of currently available NNRTIs
  • is prevalence of NNRTI resistance mutations in ART naïve patients
• High income countries no longer recommend EFV in 1st line
• Newer regimens are more effective
<table>
<thead>
<tr>
<th>Line</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Integrase inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>TDF/FTC</td>
<td>Efavirenz</td>
<td>-</td>
<td>Dolutegravir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rilpivirine</td>
<td></td>
<td>Raltegravir</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>AZT/3TC</td>
<td>-</td>
<td>Atazanavir/r or Lopinavir/r</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>Guided by genotype</td>
<td>Possibly Etravirine</td>
<td>Darunavir/r</td>
<td>Raltegravir Dolutegravir</td>
</tr>
</tbody>
</table>

Switch from 2nd line to 3<sup>rd</sup> line only after genotype

In many instance there is compatibility between public and private sectors
### First Line Regimen: TDF/FTC/EFV

<table>
<thead>
<tr>
<th>Desirable Property</th>
<th>TDF FTC EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Resistance Barrier</td>
<td>No</td>
</tr>
<tr>
<td>Well tolerated</td>
<td>Maybe</td>
</tr>
<tr>
<td>Safe in Pregnancy</td>
<td>Yes</td>
</tr>
<tr>
<td>Low pill burden</td>
<td>Yes FDC</td>
</tr>
<tr>
<td>Use with TB -Rif</td>
<td>Yes</td>
</tr>
<tr>
<td>No lab toxicity monitoring</td>
<td>TDF creat</td>
</tr>
</tbody>
</table>
Has the time come to abandon efavirenz for first-line antiretroviral therapy?

François Raffi¹*, Anton L. Pozniak² and Mark A. Wainberg³
<table>
<thead>
<tr>
<th></th>
<th>ECHO&lt;sup&gt;9&lt;/sup&gt;</th>
<th>THRIVE&lt;sup&gt;10&lt;/sup&gt;</th>
<th>STar&lt;sup&gt;28&lt;/sup&gt;</th>
<th>STARTMRK&lt;sup&gt;30&lt;/sup&gt;</th>
<th>SINGLE&lt;sup&gt;25&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>comparator</td>
<td>16%</td>
<td>18%</td>
<td>30%</td>
<td>26%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22%</td>
</tr>
<tr>
<td>efavirenz</td>
<td>37%</td>
<td>39%</td>
<td>51%</td>
<td>59%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>comparator</td>
<td>15%</td>
<td>15%</td>
<td>16%</td>
<td>—</td>
<td>29%</td>
</tr>
<tr>
<td>efavirenz</td>
<td>25%</td>
<td>20%</td>
<td>38%</td>
<td>—</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>comparator</td>
<td>4%</td>
<td>3%</td>
<td>8%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3%</td>
</tr>
<tr>
<td>efavirenz</td>
<td>15%</td>
<td>13%</td>
<td>13%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14%</td>
</tr>
</tbody>
</table>
Efavirenz: general & pharmacological characteristics

- EFV crosses BBB, reaching concentration of 11.1-30 µg/l in CSF (0.4-1.2% plasma concentration)
- Metabolized mainly in liver (90%) via CYP450 system
- Metabolites may be implicated in EFV-related CNS adverse events
- Documented incidence of neuropsychiatric symptoms 60-90%:
  - dizziness
  - difficulty concentrating
  - sleep disturbance
  - vertigo
  - hang-over sensation
  - headache
  - euphoria
  - irritability & nervousness
- Severe neurological effects registered in few than 2% of patients:
  - severe depression
  - delirium
  - paranoia
  - depersonalization
  - anxiety
  - hallucinations
  - aggressive behaviour
  - abnormal thinking and mania
- EFV-related neuropsychiatric events lead to therapy interrupted in 2-24% of patients
- Majority of CNS symptoms diminish or disappear several weeks after initiation
  - rare cases these can persist over longer periods of time or
  - appear for the first time after several months of exposure to EFV

• Long-term EFV-associated symptoms (months or years)
  • Less understood
  • More difficult to foresee and control
• Long-term EFV-produced effects include sustained neuropsychological symptoms (albeit mild)
  • Elevated risk of suicide
  • Depression
  • Neurocognitive decline
- phenomena that are currently the subject of controversy
Efavirenz in Pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Relative risk (95% CI)</th>
<th>Events, Treatment</th>
<th>Events, Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral pregnancy registry</td>
<td>2013</td>
<td>0.70 (0.49, 1.28)</td>
<td>18/766</td>
<td>183/6160</td>
</tr>
<tr>
<td>Floridia et al.</td>
<td>2013</td>
<td>0.74 (0.18, 3.10)</td>
<td>2/80</td>
<td>21/622</td>
</tr>
<tr>
<td>Bera et al.</td>
<td>2010</td>
<td>0.90 (0.11, 7.43)</td>
<td>5/184</td>
<td>1/33</td>
</tr>
<tr>
<td>Townsend et al.</td>
<td>2010</td>
<td>0.75 (0.30, 1.87)</td>
<td>5/204</td>
<td>48/1478</td>
</tr>
<tr>
<td>Machado et al.</td>
<td>2010</td>
<td>6.22 (0.41, 95.10)</td>
<td>1/18</td>
<td>1/112</td>
</tr>
<tr>
<td>Gonzales-Torres et al.</td>
<td>2010</td>
<td>0.65 (0.33, 1.26)</td>
<td>7/31</td>
<td>93/266</td>
</tr>
<tr>
<td>Bussmann et al.</td>
<td>2010</td>
<td>0.75 (0.07, 7.78)</td>
<td>1/22</td>
<td>2/33</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>2010</td>
<td>1.33 (0.08, 21.51)</td>
<td>0/19</td>
<td>14/770</td>
</tr>
<tr>
<td>Cresssey et al.</td>
<td>2012</td>
<td>(Excluded)</td>
<td>0/4</td>
<td>0/21</td>
</tr>
<tr>
<td>Ekouevi et al.</td>
<td>2011</td>
<td>(Excluded)</td>
<td>0/147</td>
<td>0/102</td>
</tr>
<tr>
<td>Phanupak et al.</td>
<td>2011</td>
<td>(Excluded)</td>
<td>0/6</td>
<td>0/180</td>
</tr>
<tr>
<td>Schwartz et al.</td>
<td>2012</td>
<td>(Excluded)</td>
<td>0/9</td>
<td>0/58</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.78 (0.56, 1.08)</td>
<td>39/1490</td>
<td>563/5835</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
Plasma Efavirenz Concentrations Are Associated With Lipid and Glucose Concentrations

Phumla Zuleika Sinxadi, MBChB, MMed Clin Pharm, Helen Margaret McIlherson, MBChB, PhD,
Joel Alex Dave, MBChB, FCP(SA), PhD, Peter John Smith, PhD,
Naomi Sharlene Levitt, MBChB, MD, FCP(SA), David William Haas, MD, and
Gary Maartens, MBChB, FCP (SA)

• EFV based ART associated with dysglycemia & dyslipidemia
  • increased
    • total cholesterol : HDL cholesterol ratio
    • LDL cholesterol
    • Triglycerides

• Pathogenesis of these metabolic effects unclear
  • ? Mitochondrial toxicity by EFV
EFV induces the metabolism of vitamin D  
  • resulting in low Vit D  

Cross-sectional study in Cape Town showed  
  • EFV independently associated with lower bone mineral density
## Neuro-Psychiatry

<table>
<thead>
<tr>
<th>Psychiatric Illness</th>
<th>Consider avoiding EFV and RPV-based regimens</th>
<th>EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-associated dementia (HAD)</td>
<td>Avoid EFV-based regimens if possible</td>
<td>EFV-related neuropsychiatric effects may confound assessment of ART’s beneficial effects on HAD-related symptoms. Theoretical CNS penetration advantage</td>
</tr>
<tr>
<td></td>
<td>Favor DRV-based or DTG-based regimens</td>
<td></td>
</tr>
</tbody>
</table>
Antiretrovirals & the Blood-Brain Barrier

 ![Graph](image-url)

Top in Antivir Med. 2011;19:4:137-142
### Table 1. Central Nervous System Penetration-Effectiveness Ranking

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>CPE Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors</strong></td>
<td>Zidovudine</td>
</tr>
<tr>
<td><strong>Nonnucleoside Reverse Transcriptase Inhibitors</strong></td>
<td>Nevirapine</td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td>Indinavir/r</td>
</tr>
<tr>
<td><strong>Entry/Fusion Inhibitors</strong></td>
<td>Maraviroc</td>
</tr>
<tr>
<td><strong>Integrase Strand Transfer Inhibitors</strong></td>
<td>Dolutegravir</td>
</tr>
</tbody>
</table>
Late Efavirenz-Induced Ataxia and Encephalopathy: A Case Series

Ebrahim Variava, MD, FCP(SA),*†‡ Farai R. Sigauke, MD, MSc,* Jennifer Norman, BPharm,§ Modiehi Rakgokong, PN,‡ Petudzai Muchichwa, MD,* Andre Mochan, MD, FCPNeuro(SA),†|| Gary Maartens, MD, FCP(SA),§ and Neil A. Martinson, MD, MPH‡¶

- 20 women
- On EFV based therapy for a median 2 years
- Median weight 34kg
- Median CD4⁺ count 299 cells/mm³
- 17 of 20 were virally suppressed
- Elevated EFV levels

This case series most likely describes women who are genetic slow metabolizers of EFV With SNPs in CYP2B6
3 distinct histological patterns of injury identified
- Submassive necrosis is the most severe of the histological spectrum & presents with jaundice + coagulopathy
- Clinical predictors of risk for severe EFV DILI
  - Younger age
  - CD4+ > 200
  - Female gender
Porphyria

• Porphyria is group of metabolic disorders
  • relatively uncommon and underdiagnosed

• Acute porphyria precipitated by ART
  • Number of case reports world wide
  • ART drugs implicated include
    • Neverapine
    • Efavirenz
    • Boosted protease inhibitors i.e. Azatanavir/ritonavir

• Antiretrovirals least likely to be porphyrinogenic
  • Tenofovir
  • Lamivudine
  • Abacavir
  • Raltegravir
  • Unboosted protease inhibitors

AIDS. 2010; 24(16): 2597-2599
Compatibility of next-generation first-line antiretrovirals with rifampicin-based antituberculosis therapy in resource limited settings

Gary Maartens\textsuperscript{a}, Marta Boffito\textsuperscript{b}, and Charles W. Flexner\textsuperscript{c}

\textbf{Summary}

Further research on drug–drug interactions between rifampicin and the next generation of first-line antiretrovirals will be needed before they can be recommended in patients with HIV-associated tuberculosis.

Dolutegravir (DTG)
Tenofovir alafenamide (TAF)
Efavirenz reduced dose 400mg

- Reduced dose EFV-
  - Non-inferior efficacy & less toxicity than standard dose (600mg)
- Primarily metabolized by cytochrome P450 enzyme CYP2B6
- 3 loss-of-function SNPs in CYP2B6 gene
  - associated with impaired metabolism resulting higher plasma EFV levels
- Rif induces CYP2B6 but EFV also auto-induces CYP2B6
  - EFV auto-induction counteracts the induction of its metabolism by Rif
- Reduced dose EFV may result in sub-therapeutic EFV levels (wild-type CYP2B6)
- Pharmacokinetic study is underway to evaluate reduced dose EFV with Rif

Curr Opin HIV AIDS. 2017; 12:355-358
Advantages/ points in favour of EFV

• Greater efficacy
• Moderate toxicity
• Broad clinical experience accumulated over several decades of use
• Existence of generic forms of EFV
• EFV remains ARV of choice in treatment of TB co-infection
Conclusion

• Future place of EFV
  ➢ maybe minimal role as 1st line ART
  ➢ ART of choice in patients in TB co-infection

• EFV low barrier to resistance major drawback

• EFV toxicity has been under-estimated
  ➢ Increased risk of dose-related toxicity
    ➢ Neuropsychiatric
    ➢ Glucose
    ➢ Lipids
    ➢ Hepatitis