This house believes that efavirenz should remain as an option to treat HIV in the UK

Alejandro Arenas-Pinto
MRC-Clinical Trial Unit
University College London

23rd Annual Conference of the British HIV Association (BHIVA)
5th April 2017
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Shall we keep EFV as a treatment option in the UK?

- Potency and efficacy
- Resistance profile
- Tolerability profile
- Toxicity profile
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What would be the right place for EFV in 2017?
Potency compared to other NNRTI

**Doravirine vs EFV: 48 week results**

- HIV RNA <40 copies/mL (NC-F Approach)
- % of Patients (95% CI)
- Treatment Week:
  - 0: 6.5 (CI: 3.7 - 9.3)
  - 4: 15.7 (CI: 12.0 - 19.4)
  - 8: 27.8 (CI: 23.1 - 32.5)
  - 12: 25.9 (CI: 21.6 - 30.2)
  - 16: 47.2 (CI: 40.3 - 54.1)
  - 20: 42.1 (CI: 36.6 - 47.6)
  - 24: 57.5 (CI: 51.7 - 63.3)
  - 32: 63.0 (CI: 57.2 - 68.8)
  - 36: 72.9 (CI: 68.1 - 77.7)
  - 40: 73.1 (CI: 68.3 - 77.9)
  - 44: 81.5 (CI: 76.7 - 86.3)
  - 48: 78.7 (CI: 73.9 - 83.5)

**Rilpivirine vs EFV: 96 week results**

- Participants with HIV-1 RNA <50 copies/mL %
- Study week:
  - 4: 100 (CI: 98 - 100)
  - 8: 98 (CI: 96 - 100)
  - 12: 95 (CI: 93 - 97)
  - 16: 92 (CI: 90 - 94)
  - 20: 89 (CI: 87 - 91)
  - 24: 86 (CI: 84 - 88)
  - 30: 83 (CI: 81 - 85)
  - 36: 80 (CI: 78 - 82)
  - 40: 77 (CI: 75 - 79)
  - 44: 74 (CI: 72 - 76)
  - 48: 71 (CI: 69 - 73)
  - 52: 68 (CI: 66 - 70)
  - 56: 65 (CI: 63 - 67)
  - 60: 62 (CI: 60 - 64)
  - 64: 59 (CI: 57 - 61)
  - 68: 56 (CI: 54 - 58)
  - 72: 53 (CI: 51 - 55)
  - 76: 50 (CI: 48 - 52)
  - 80: 47 (CI: 45 - 49)
  - 84: 44 (CI: 42 - 46)
  - 88: 41 (CI: 39 - 43)
  - 92: 38 (CI: 36 - 40)
  - 96: 35 (CI: 33 - 37)

**Legend**
- DOR: 84/108 (77.8%)
- EFV: 85/108 (78.7%)
- Difference (95% CI): -1.1 (-12.2, 10.0)

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2 van Lunzen et al. AIDS 2016; 30(2): 251–9
STARTMRK: EFV vs RAL in ART-naïve patients¹

DTG + two NRTI vs. EFV + two NRTIs. Viral suppression to non-detectable (<50 copies/mL) at 96 weeks²

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DTG-based regimen</th>
<th>EFV-based regimen</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE</td>
<td>331 Events</td>
<td>414 Events</td>
<td>419 Weight</td>
</tr>
<tr>
<td>SPRING-1</td>
<td>45 Events</td>
<td>51 Events</td>
<td>50 Weight</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>465 Events</td>
<td>469 Events</td>
<td>1.12 [1.04, 1.21]</td>
</tr>
</tbody>
</table>

Total events: 376 338

Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 3.14 (P = 0.002)

STARTMRK: EFV vs RAL in ART-naïve patients

There are other options with similar or even better efficacy

DTG + two NRTI vs. EFV + two NRTIs. Viral suppression to non-detectable (<50 copies/mL) at 96 weeks

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<th>Study or Subgroup</th>
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<tr>
<td>SINGLE</td>
<td>331</td>
<td>302</td>
<td>1.11 [1.03, 1.20]</td>
</tr>
<tr>
<td>SPRING-1</td>
<td>45</td>
<td>36</td>
<td>1.23 [1.00, 1.50]</td>
</tr>
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<td>Total (95% CI)</td>
<td>465</td>
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</tr>
<tr>
<td>Total events</td>
<td>376</td>
<td>338</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0$
Test for overall effect: $Z = 3.14$ (P = 0.002)

**Resistance profile**

![Graph showing resistance profile](image)

**Figure 4.** Incidence of resistance at week 96 in pivotal clinical trials of antiretroviral therapy in naive patients (see text for explanation and references). II: integrase inhibitors; DTG: dolutegravir; RAL: raltegravir; EVG: elvitegravir; NNRTI: nonnucleoside reverse transcriptase inhibitors; EFV: efavirenz; RPV: rilpivirine; PI: protease inhibitors; DRV/r: darunavir/ritonavir; ATV/r: atazanavir/ritonavir.
Resistance profile

TDR in ART-naïve patients (UK): predicted phenotypic resistance

**Fig. 2** Predicted phenotypic resistance (Stanford scores) for antiretroviral drugs currently recommended for first-line combination therapy in the UK, 2010—2013. 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; DRV, darunavir; EFV, efavirenz; FTC, emtricitabine; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; RPV, rilpivirine; TDF, tenofovir.
### Tolerability

**discontinuation of the therapy due to adverse events**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>efavirenz</th>
<th>InSTI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Cohen 2011</td>
<td>1</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Lennox 2009/2010 STARTMRK</td>
<td>17</td>
<td>282</td>
<td>9</td>
</tr>
<tr>
<td>Markowitz 2007/2009</td>
<td>1</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Stellbrink 2013 SPRING-1</td>
<td>5</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Walmsley 2013 SINGLE</td>
<td>42</td>
<td>419</td>
<td>10</td>
</tr>
<tr>
<td>Zolopa 2013 GS-US-236-0102</td>
<td>24</td>
<td>352</td>
<td>17</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

|                     | 1164 | 1302 | 100.0% | 2.30 [1.60, 3.31] |

**Total events**

|                     | 90   | 41   |

Heterogeneity: Chi² = 6.38, df = 5 (P = 0.27); I² = 22%

Test for overall effect: Z = 4.50 (P < 0.00001)

Can we predict tolerability?

Tolerability seems to depend on the rate of EFV metabolism.

Table 2: Incidence density rates of central nervous system (CNS) events according to cytochrome P450 (CYP) 2B6 516 T variants

<table>
<thead>
<tr>
<th>CNS events</th>
<th>Number of events</th>
<th>Cumulative time (months)</th>
<th>Incidence density rate (per 100 patient-years)</th>
<th>Confidence interval (patient-years)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6 516 G/G</td>
<td>106</td>
<td>270</td>
<td>39.2</td>
<td>38.5–40.0</td>
<td>0.02</td>
</tr>
<tr>
<td>CYP2B6 516 G/T or T/T</td>
<td>143</td>
<td>260</td>
<td>55.0</td>
<td>54.1–55.9</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>249</td>
<td>530</td>
<td>47.0</td>
<td>46.4–47.5</td>
<td></td>
</tr>
</tbody>
</table>
Extensive EFV metabolism is associated with greater CNS toxicity

Vujkovic M et al CROI 2017. Seattle, WA, USA (Abs 384)
Serious toxicity: suicidality

- ACTG meta-analysis: 4 ART-naïve RCTs

A. ITT DSMB

<table>
<thead>
<tr>
<th>Variable</th>
<th>Events/PYs (IR per 1000 PYs)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EFV</td>
<td>EFV-Free</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>47/5817 (8.08)</td>
<td>15/4099 (3.66)</td>
<td>2.28 (1.27–4.10)</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5095</td>
<td>6/739 (8.12)</td>
<td>1/364 (2.75)</td>
<td>3.00 (0.36–24.88)</td>
</tr>
<tr>
<td>A5142</td>
<td>8/1001 (7.99)</td>
<td>2/510 (3.92)</td>
<td>2.04 (0.43–9.62)</td>
</tr>
<tr>
<td>A5175</td>
<td>13/1763 (7.38)</td>
<td>2/889 (2.25)</td>
<td>3.28 (0.74–14.52)</td>
</tr>
<tr>
<td>A5202</td>
<td>20/2315 (8.64)</td>
<td>10/2336 (4.28)</td>
<td>2.02 (0.94–4.31)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>39/4346 (8.97)</td>
<td>13/3354 (3.88)</td>
<td>2.32 (1.23–4.38)</td>
</tr>
<tr>
<td>Multinational</td>
<td>8/1471 (5.44)</td>
<td>2/745 (2.68)</td>
<td>2.02 (0.43–9.53)</td>
</tr>
</tbody>
</table>
Suicidal behaviour by Pre-specified ART and Prior Psychiatric Diagnosis in START

- **Efavirenz** (n=3516):
  - Prior Diagnosis: 3.1% (No. of Events: 7, Rate: 2.0 per 100 PY)
  - No Prior Diagnosis: 96.9% (No. of Events: 22, Rate: 0.2 per 100 PY)

- **Other ART** (n=1169):
  - Prior Diagnosis: 13.9% (No. of Events: 8, Rate: 1.7 per 100 PY)
  - No Prior Diagnosis: 86.1% (No. of Events: 14, Rate: 0.5 per 100 PY)
Suicidal behaviour by Pre-specified ART and Prior Psychiatric Diagnosis in START

Overall Rate: 0.28 per 100 PY

Overall Rate: 0.63 per 100 PY

Efavirenz (n=3516)

Other ART (n=1169)

Pre-specified ART
Suicidal/self harming events by randomisation arm in START

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Immediate ART</th>
<th>Deferred ART</th>
<th>HR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
<th>P</th>
<th>Int. P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Events</td>
<td>Rate</td>
<td>Events</td>
<td>Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT analysis, year 1 only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV pre-specified</td>
<td>3516</td>
<td>9</td>
<td>0.52</td>
<td>2</td>
<td>0.11</td>
<td>3.75 (0.8, 17.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Other ART pre-specified</td>
<td>1169</td>
<td>7</td>
<td>1.25</td>
<td>7</td>
<td>1.19</td>
<td>1.02 (0.4, 2.9)</td>
<td>0.96</td>
</tr>
<tr>
<td>Censoring deferred arm participants at ART initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV pre-specified&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3516</td>
<td>17</td>
<td>0.35</td>
<td>3</td>
<td>0.08</td>
<td>4.16 (1.2, 14.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Other ART pre-specified&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1137</td>
<td>9</td>
<td>0.59</td>
<td>8</td>
<td>0.69</td>
<td>1.04 (0.4, 2.7)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimated in Cox proportional hazards models, stratified by psychiatric diagnosis.

<sup>b</sup> Interaction between indicators for treatment group and pre-specified regimen.

<sup>c</sup> Of these events, 6 and 0, in the immediate vs deferred arms, respectively, occurred among 108 participants with prior psychiatric diagnoses.

<sup>d</sup> Of these events, 5 and 2, in the immediate vs deferred arms respectively, occurred among 162 participants with prior psychiatric diagnoses.

Of the 1169 participants without EFV in the pre-specified regimen, 32 were excluded (in the immediate group, 7 never started ART, and for 25, the first ART regimen contained EFV). Follow-up in the immediate group was censored at EFV start.

Arenas-Pinto et al. AIDS 2016 Conference. Durban, SA (Abstract THAB0202)
Conclusion

- EFV is a very good drug that deserves a prominent place,
Conclusion

- EFV is a very good drug that deserves a prominent place,

Not here
• EFV is a very good drug that deserves a prominent place,

Not here

But, there

British HIV Association
BHIVA
CLINICAL GUIDELINES

British Society for the History of Medicine
Many thanks to

- Prof David Dunn, MRC-CTU at UCL
- START trial team
- Insight network
- You all for your attention