Rilpivirine

DR M T MATHE
MBCHB (UCT), DIP HIV MAN (SA)
PRIVATE PRACTICE
What is rilpivirine?

- 2<sup>nd</sup> generation NNRTI
- Sold as Edurant
- Dose: 25 mg po od to be taken with a meal (390 kcal/1632 kJ)
First new NNRTI for treatment-naïve patients since EFV in 1998

Approved by the FDA in 20 May 2011

Complera (TDF/FTC/RPV) approved August 2011

Odefsey (TAF/FTC/RPV) approved 2016

Pregnancy category B

1. Medscape medical News 2011
Where does it fit?

- 3rd agent in first-line regimen
- Preferred 1st line in SAHIVSoc guidelines 2017 (one of 3)
- Switch from EFV-based regimen to a RPV-based regimen
Principles of switching suppressed patients

- Do not jeopardise virological suppression

- Review possible drug-drug interactions

- Always review possible adverse events & tolerability issues

  A fully suppressive regimen is not necessarily always well tolerated

EACS Guidelines 8.1, 2016
SALIF - Distribution of subjects by country

Total = 424*

* ITT Population

P Munderi 2016, AIDS conference, Abstract THAB0104
SALIF – Study design

- **Switching At Low HIV-1 RNA Into Fixed Dose Combinations**

- A 48-week randomised, open-label study of RPV/TDF/FTC STR as an appropriate “switch” option for virologically suppressed HIV-1 infected patients in low- and middle income countries on stable NNRTI-based therapies

**Key entry criteria:**
- On first-line ART with **EFV** or **NVP** for ≥1 year*
- Plasma HIV-1 RNA <50 copies/mL
- CD4 >200 cells/mm³
- No history of virologic or immunologic failure during ART
- No known primary N[t]RTI or NNRTI mutations

**Key exclusion criteria:**
- Randomisation stratified by NNRTI at screening (EFV or NVP)
- Key exclusion criteria:
  - TB requiring rifampicin-based treatment or CrCl <50 mL/min

*P Munderi 2016, AIDS conference, Abstract THAB0104
Efficacy (HIV-1 RNA <400 copies/mL at week 48) (FDA Snapshot – ITT)

R Shah 2017, INTEREST Workshop, Abstract 112
SALIF – Virological suppression

RPV/TDF/FTC as a switch option is non-inferior to EFV/TDF/FTC regardless of suppression cut-off of <400 or <50 copies/mL

- 1 confirmed virologic failure ≥400 copies/mL in each study arm (0.5%)
- No ARV resistance observed - preserved future ARV options

P Munderi 2016, AIDS conference, Abstract THAB0104
### SALIF - Safety

<table>
<thead>
<tr>
<th>Number of Subjects with:</th>
<th>RPV/TDF/FTC (n=213)</th>
<th>EFV/TDF/FTC (n=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least possibly related</td>
<td>16 (7.5%)</td>
<td>11 (5.2%)</td>
</tr>
<tr>
<td>Fatal SAE (ML, unrelated)*</td>
<td>3 (1.4%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>AF, grade 3 or 4</td>
<td>40 (18.8%)</td>
<td>56 (26.5%)</td>
</tr>
<tr>
<td>At least possibly related</td>
<td>13 (6.1%)</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td><strong>AE of Interest (all cause)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>32 (15.0%)</td>
<td>23 (10.9%)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>60 (28.2%)</td>
<td>63 (29.9%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>38 (17.8%)</td>
<td>29 (13.7%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>/ (3.3%)</td>
<td>14 (6.6%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10 (4.7%)</td>
<td>6 (2.8%)</td>
</tr>
<tr>
<td>Nightmare/abnormal dreams</td>
<td>4 (1.9%)</td>
<td>10 (4.7%)</td>
</tr>
<tr>
<td>Potential QT prolongation</td>
<td>3 (1.4%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>AF leading to permanent stop study medication</td>
<td>8 (3.8%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

P Munderi 2016, AIDS conference, Abstract THAB0104
Low discontinuation rates with RPV compared to other ARVs

Retrospective cohort study from UK
(1949 patients on 1st line therapy)

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>No. of switches</th>
<th>Total follow-up (person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>196</td>
<td>45</td>
<td>140</td>
</tr>
<tr>
<td>67</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td>105</td>
<td>34</td>
<td>134</td>
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<tr>
<td>550</td>
<td>166</td>
<td>538</td>
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<tr>
<td>61</td>
<td>8</td>
<td>43</td>
</tr>
<tr>
<td>212</td>
<td>73</td>
<td>239</td>
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<tr>
<td>88</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td>196</td>
<td>45</td>
<td>140</td>
</tr>
<tr>
<td>611</td>
<td>174</td>
<td>581</td>
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<tr>
<td>11</td>
<td>11</td>
<td>312</td>
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<tr>
<td>172</td>
<td>65</td>
<td>206</td>
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<tr>
<td>406</td>
<td>149</td>
<td>258</td>
</tr>
<tr>
<td>264</td>
<td>19</td>
<td>474</td>
</tr>
<tr>
<td>1949</td>
<td>557</td>
<td>1972</td>
</tr>
</tbody>
</table>

Lewis et al. Journal of Infection 2017
Cohort data (Real world) Sweden

- Low discontinuation rates with RPV compared to other ARVs

Swedish InfCareHIV database
(2541 patients on 1st line therapy)

Häggblom et al. PLOS One 2017
Efficacy Comparison in treatment-naïve HIV infected subjects of TMC278 and Efavirenz

- Phase 3
- 690 patients
- VL > 5000 copies/mL
- RPV + TDF/FTC vs EFV + TDF/FTC
THRIVE

- TMC278 against HIV-infected in a once-daily Regimen Versus Efavirenz
- Phase 3
- 678 participants
- VL > 5000 copies/mL
- RPV/EFV + either TDF/FTC OR 3TC/ABC OR 3TC/AZT (investigator chosen)
**ECHO—Fixed Background Regimen**

- EDURANT® + Truvada®
- Sustiva® + Truvada

**THRIVE—Investigator-selected Background Regimen**

- EDURANT® + Truvada OR Epzicom® OR Combivir®
- Sustiva + Truvada OR Epzicom OR Combivir

Pills shown not actual size.
Primary objective: to demonstrate non-inferiority of RPV vs EFV at week 48 (ITT, TLOVR)

Virological efficacy
@48 weeks: 84% (RPV) vs 82% (EFV)
@96 weeks: 78% for both RPV and EFV

Virologic failures: 14% (RPV) vs 8% (EFV)
- Most failures occurred in the first 48 weeks of treatment

Development of NNRTI-associated mutations was similar 59% (RPV) vs 55% (EFV) (Week 96)

NRTI mutations, notably M184V, occurred more in those experiencing virologic failure while taking RPV vs EFV (56% vs 26%)

The signature RPV mutation is E138K
The K103N mutation was not seen in the RPV arm

Cohen et al AIDS 2013;27:939-950
Pooled analysis at 96 weeks in patients with Baseline VL <100,000 copies/mL

<table>
<thead>
<tr>
<th></th>
<th>RILPIVIRINE</th>
<th>EFAVIRENZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological response</td>
<td>84%</td>
<td>80%</td>
</tr>
<tr>
<td>Virological failure</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Mean CD4 increase</td>
<td>224</td>
<td>206</td>
</tr>
</tbody>
</table>

**Treatment-Emergent Lipid Abnormalities (grade 2-4)**

<table>
<thead>
<tr>
<th></th>
<th>RILPIVIRINE</th>
<th>EFAVIRENZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>7%</td>
<td>23%</td>
</tr>
<tr>
<td>LDL</td>
<td>7%</td>
<td>18%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Switching Atripla to Complera vs continuing Atripla in HIV patients with complete virological suppression

Thailand – 244

Primary outcome: sustained virological response

Secondary outcome:
- Lipid adverse outcomes = different in blood lipid profiles including triglycerides, cholesterol, HDL and LDL.
- Neurological adverse outcome = such as dizziness
- Cost-saving after switching regimen

NCT03251690. clinical trials.gov
Switching from EFV to RPV is safe and effective
DISADVANTAGES

- VL >100 000 copies/mL
- Not available as FDC in SA
- Must be taken with a meal
- Drug interactions: rifampicin, PPIs, carbamazepine, phenytoin
ADVANTAGES

- Cheap (SEP R58.52) vs EFV (SEP R106.62)

- Small size pill

- Fewer side effects compared to EFV

- Better control of HIV in semen

1. [http://generic.co.za/](http://generic.co.za/)
2. Cohen et al. AIDS 2013. 27;939-950
FUTURE

- Dual regimen with DTG\textsuperscript{1}
- Dual regimen with boosted darunavir\textsuperscript{2}
- Injectables