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The impact of switching to raltegravir based therapy on efavirenz-related CNS toxicity:
a phase IV open label pilot study

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EFV-related CNS toxicities: the main driver of poor adherence

• Central Nervous System (CNS) adverse events (AEs) common on EFV-based regimens\(^1,2\)
• Most are transient
• Some experience ongoing severe AEs
• New evidence emerging of direct CNS toxic effects of EFV\(^3\)
• Drug-related toxicity difficult to differentiate from other causes

\(^1\)Waters L et al. *AIDS* 2011;25:65-71
\(^2\)Scourfield A et al. *AIDS* 2012; 26:1399-1401
STARTMRK – comparison of toxicity profiles*

<table>
<thead>
<tr>
<th></th>
<th>RAL Group (N = 281)</th>
<th>EFV Group (N = 282)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>57</td>
<td>(20.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14</td>
<td>(5.0)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>10</td>
<td>(3.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>(8.9)</td>
</tr>
<tr>
<td>General Disorders</td>
<td>28</td>
<td>(10.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>(4.3)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>51</td>
<td>(18.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
<td>(7.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>(9.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>52</td>
<td>(18.5)</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>19</td>
<td>(6.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>21</td>
<td>(7.5)</td>
</tr>
<tr>
<td>Nightmare</td>
<td>8</td>
<td>(2.8)</td>
</tr>
<tr>
<td>Skin And Subcutaneous Tissue Disorders</td>
<td>16</td>
<td>(5.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>(1.1)</td>
</tr>
</tbody>
</table>

*Adapted from: Long-Term Safety and Efficacy of Raltegravir-Based Versus Efavirenz-Based Combination Therapy in Treatment-Naïve HIV-1 Infected Patients: Final 5-Year Double-Blind Results From STARTMRK. AIDS 2012. Poster #LBPE19
Objectives

• To assess the impact of switching from EFV-based cART to RAL-based cART on CNS toxicity

• To assess the impact of EFV-RAL switch on lipid profile

• To assess the ongoing efficacy of RAL at maintaining virologic suppression
Methods

• HIV-1 infected individuals virologically suppressed on EFV-based cART

Baseline
CNS toxicity
M-MASRI
HADS
Sleep Q

Week 4
CNS toxicity
Sleep Q

Week 12
CNS toxicity
M-MASRI
HADS
Sleep Q

4 week follow-up

• At all visits
  – FBC
  – Biochemistry
  – Lipids
  – CD4, VL

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Questionnaire scoring

- **CNS toxicity questionnaire**
  - 10 items based on EFV SPC
  - DAIDS grading system
  - Converted to % of 100
  - Low score = low CNS toxicity

- **Sleep questionnaire**
  - 19 standardised items
  - Converted to % of 100
  - Low score = better quality sleep

- **HADS**
  - 14 items: 7 anxiety, 7 depression
  - Converted to % of 100
  - Low score (≤7/21 for A or D): unlikely A or D
Endpoints

• Primary
  – Rate of neuropsychiatric & CNS toxicity after 4 wks of RAL (measured by proportion with any grade 2-4 CNS toxicity, CNS toxicity score and sleep quality questionnaire)

• Secondary
  – Rate of neuropsychiatric & CNS toxicity after 12 wks of RAL
  – Change in CD4 from B/L to wk 12
  – Proportion of patients with VL <50 copies/mL & <400 copies/mL at wks 4 & 12
  – Change in fasting lipids from B/L to wk 4 & wk 12
  – Proportion of patients with grade 2-4 laboratory AEs from B/L to wk 12
  – Proportion of patients with grade 2-4 non-CNS AEs from B/L to wk 12
  – Change in adherence (M-MASRI) from B/L to wk 12
  – Change in CNS toxicity (HADS) from B/L to wk 12
  – Change in inflammatory markers from B/L to wk 4 & wk 12 (pending)
Endpoints

• Primary
  – Rate of neuropsychiatric & CNS toxicity after 4 wks of RAL (measured by proportion with any grade 2-4 CNS toxicity, CNS toxicity score and sleep quality questionnaire)

• Secondary
  – Rate of neuropsychiatric & CNS toxicity after 12 wks of RAL
  – Change in CD4 from B/L to wk 12
  – Proportion of patients with VL <50 copies/mL & <400 copies/mL at wks 4 & 12
  – Change in fasting lipids from B/L to wk 4 & wk 12
  – Proportion of patients with grade 2-4 laboratory AEs from B/L to wk 12
  – Proportion of patients with grade 2-4 non-CNS AEs from B/L to wk 12
  – Change in adherence (M-MASRI) from B/L to wk 12
  – Change in CNS toxicity (HADS) from B/L to wk 12
  – Change in inflammatory markers from B/L to wk 4 & wk 12 (pending)
Results

- 40 patients enrolled
- 38 male
- 2 female
- Mean age 43 (range 29-62) years
Baseline regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>TDF/FTC + EFV</td>
<td>40 (100%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
</tbody>
</table>
Results – median time on EFV

Median time on EFV 27.5 months (4-145)
Results – proportion with any grade 2-4 CNS toxicity

Proportion with any grade 2-4 CNS toxicity

<table>
<thead>
<tr>
<th>Time point</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100</td>
</tr>
<tr>
<td>Week 4</td>
<td>50</td>
</tr>
</tbody>
</table>

p<0.001
Results – proportion with any grade 2-4 CNS toxicity

Proportion with any grade 2-4 CNS toxicity

Time point

Baseline
Week 4
Week 12

Proportion (%)

Baseline: p<0.001

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Results – CNS toxicity scores

Median CNS toxicity score

- Baseline: Median score of 50%
- Week 4: Median score of 10%

*p < 0.001*
Results – CNS toxicity scores

Median CNS toxicity score

- Baseline: Score (%)
- Week 4: Score (%)
- Week 12: Score (%)

p<0.001
Results – sleep scores (SQ)

Median sleep scores

<table>
<thead>
<tr>
<th>Time point</th>
<th>Sleep score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30</td>
</tr>
<tr>
<td>Week 4</td>
<td>20</td>
</tr>
</tbody>
</table>

p<0.001
Results – sleep scores (SQ)

Median sleep scores

- Baseline
- Week 4
- Week 12

Sleep score (%)

Time point

$\text{p}<0.001$
Results – CNS toxicity scores

Individual proportions of Grade 2-4 CNS AEs

$p<0.05$ for all CNS AEs except headache ($p=0.386$ and $0.125$ at wks 4 & 12)
Comparison with EFV-ETR switch study

CNS grade 2-4 toxicity change from baseline on 12 weeks of ETR

*Adapted from: Waters L et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. AIDS 2011;25:65-71
Results – HADS scores

HADS scores (median)

- Overall score
- Anxiety
- Depression

Time point: Baseline, Week 12

$P \leq 0.001$
Results - change in CD4 and viral load suppression

All subjects maintained virologic suppression to wk 12

Change in CD4 (median)

Baseline
Wk 4
Wk 12

Absolute CD4 cells/mm^3

0
100
200
300
400
500
600
700
800

Time point

p=0.188 to wk 12
Results – change in lipids

Trends in serum lipids

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Total chol**</th>
<th>LDL**</th>
<th>HDL</th>
<th>TAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 12</td>
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** achieved statistical significance
Conclusions

• Switching EFV to RAL results in significant improvement of CNS AEs

• Virologic suppression is maintained

• Important to identify individuals with EFV toxicity as switching to alternative agents may result in better tolerability of cART, adherence* and quality of life
Acknowledgements

• MSD: financial support for this study
• Subject volunteers for participating
• SSAT
British HIV Association
BHIVA

19th Annual Conference of the British HIV Association (BHIVA)

16–19 April 2013

Manchester Central Convention Complex