Safety of Nevirapine Compared to Abacavir on a Background of Zidovudine/Lamivudine as First-line Antiretroviral Therapy: a Randomised Double-Blind Trial conducted in Uganda

P Munderi on behalf of the DART Trial Team
Background

- Standard 1st line regimen in Africa is 2NRTI/NNRTI
  - Nevirapine (NVP) is the most frequently used NNRTI
- Consideration of an Abacavir-based regimen in Africa remains warranted
  - High rates of TB co-infection
  - Initiation of treatment in women
- High rates of HSR may limit use of Abacavir (ABC)
  - In Africa HSR may be difficult to distinguish from intercurrent infections, for example malaria
- No randomised trials have reported on toxicity of nevirapine and abacavir in Africa
NORA Trial Design

- A randomised, double-blind, 24 week, phase II trial at 2 centres in Uganda
- Evaluating the safety of Nevirapine OR Abacavir [NORA]
- A substudy of the DART Trial
- 600 ARV naïve adults with symptomatic HIV infection CD4<200 cells/mm3 and no contraindications to ART were randomised in a 1:1 ratio, to receive: zidovudine/lamivudine (Combivir) twice daily, plus - 300 mg ABC and nevirapine placebo twice daily - 200 mg NVP and abacavir placebo twice daily
Endpoints

- Primary: SAE as defined by ICH-GCP definitely/probably or uncertainly related to blinded nevirapine/abacavir (SAR)
  - Independently adjudicated by clinicians blind to randomised allocation
  - Secondary: AE of any grade leading to permanent discontinuation of blinded nevirapine/abacavir
  - Secondary: Grade 4 events irrespective of whether or not they resulted in nevirapine/abacavir discontinuation
Follow-up

Randomised 600

CBV+bABC+pNVP

300

9 died
2 lost to f/u

289

CBV+bNVP+pABC

299*

15 died
4 lost to f/u

280

5 Jan to 28 Oct 2004

Initiated allocated ART

Lost before 24 weeks

Completed 24 weeks, went onto open label

* 1 patient excluded due to previous ART
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ABC</th>
<th>NVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>300</td>
<td>299</td>
</tr>
<tr>
<td>Women</td>
<td>72%</td>
<td>71%</td>
</tr>
<tr>
<td>Prior ART to prevent MTCT</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Age mean</td>
<td>37.6</td>
<td>36.3</td>
</tr>
<tr>
<td>CD4 at randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm$^3$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-49</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>50-99</td>
<td>25%</td>
<td>21%</td>
</tr>
<tr>
<td>100-149</td>
<td>25%</td>
<td>28%</td>
</tr>
<tr>
<td>150-199</td>
<td>25%</td>
<td>22%</td>
</tr>
<tr>
<td>WHO stage at randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>58%</td>
<td>53%</td>
</tr>
<tr>
<td>4</td>
<td>18%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Outcome

- 34 SAEs occurred on blinded drug in 33 patients

Primary endpoint: 20 SAEs in 20 patients were definitely/possibly related to blinded abacavir/nevirapine and classified as Serious Adverse Reactions (SAR)
  - 6 (2.0%) on ABC
  - 14 (4.7%) on NVP \( p=0.06 \)

- 14 SAEs considered unlikely to be related to blinded drug were anaemia (n=7), pancytopenia, death from unknown cause, head trauma, DVT, duodenal ulcer/haematemesis, fever*, rash**

* rabies vaccination
** open label NVP following discontinuation of blinded ABC for HSR
Time to first SAR

Proportion SAR-free

RR = 0.41 (95% CI 0.06-1.08) logrank p = 0.06

ABC (2.0%)

NVP (4.7%)
• 19/20 SAR were considered consistent with diagnosis of hypersensitivity reaction (HSR)

<table>
<thead>
<tr>
<th></th>
<th>ABC (N=6)</th>
<th>NVP (N=13)</th>
<th>Total (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Hepatic involvement</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Oral/mucosal involvement</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

- 1 SAR was asymptomatic elevation of ALT/AST (NVP)
### Discontinuation of blinded trial drug

<table>
<thead>
<tr>
<th></th>
<th>ABC (N=300)</th>
<th>NVP (N=299)</th>
<th>Total (N=599)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of blinded drug percent (%) for adverse events (secondary endpoint) (%)</td>
<td>14 (5%)</td>
<td>30 (10%)</td>
<td>44 (7%)</td>
</tr>
<tr>
<td></td>
<td>6* (2%)</td>
<td>15* (5%)</td>
<td>21* (4%)</td>
</tr>
<tr>
<td>for anti-TB treatment</td>
<td>6</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>for pregnancy</td>
<td>0</td>
<td>1*</td>
<td>1*</td>
</tr>
<tr>
<td>for patient decision</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Proportion of time at risk to 24 weeks on allocated treatment</td>
<td>96.8%</td>
<td>92.2%</td>
<td>94.5%</td>
</tr>
</tbody>
</table>

* patients and clinicians were unblinded

exact p=0.05

exact p=0.05
Secondary endpoint: Grade 4 AE

- 187 (78 ABC, 109 NVP) Grade 4 AEs in 155 patients (64 ABC, 91 NVP) on blinded drug
  - 59 per 100 PY at risk in ABC
  - 88 per 100 PY at risk in NVP \( p=0.008 \)
- Majority were haematological
  - greatest difference in neutropenia: 46 ABC, 71 NVP
  - anaemia: 17 ABC, 16 NVP
    - d4T substituted for ZDV in 45 patients, (22 ABC, 23 NVP)
- 30 (19%) adverse reactions to blinded trial drugs
- 8 patients (all NVP) had Grade 4 elevations in LFTs
Conclusions

• In Ugandan patients with low CD4 counts initiating ART with CBV/NVP or CBV/ABC
  - A trend towards a lower rate of SARs with ABC
  - A lower discontinuation rate with ABC
  - A lower rate of any grade 4 AE with ABC

• Considerable overlap in clinical manifestations of NVP and ABC reactions

• Rate of ABC HSR in this population is 2%

• Ongoing assessment of
  - Genetic polymorphisms
  - Virological and immunological efficacy
Acknowledgments

• We thank all the patients and staff from all the centres participating in the DART trial.
• Academic Alliance, Mulago Hospital, Uganda: E Katabira, J Oyugi, A Ronald, A Kambungu, J Martin, R Naluminya, R Nairubi, E Bulume, M Teopista, C Twijukye, F Senata, E Byakwaga.
• The AIDS Support Organisation (TASO), Uganda: A Coutinho, B Etukoikt.
• Imperial College: C Gilks, K Boocock, C Puddephatt, D Winogron.
• Data and Safety Monitoring Committee: A McLaren (Chair), C Hill, J Matenga, A Pozniak, D Serwadda
• Endpoint Review Committee: T Peto (Chair), A Palfreeman, M Borok, E Katabira.
• GlaxoSmithKline, Gilead and Boehringer-Ingelheim donated first-line drugs for DART.
• Funding: DART is funded by the UK Medical Research Council, the UK Department for International Development (DFID), and the Rockefeller Foundation.