Plasma Levels of Nevirapine following Interruption of ZDV/3TC/NVP in African Adults within the DART Trial

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DART Trial

- Development of AntiRetroviral Therapy in Africa

Objectives

- To compare different ART monitoring strategies
- To assess safety of structured treatment interruptions (STI)

STI in DART

LB Session: Thursday 17th August 06
Abstract No: THLB0207
Session Room 1
NNRTIs have a longer elimination half life than NRTIs

Simultaneous interruption of all drugs exposes the patient to NNRTI monotherapy

Current recommendation: continuation of dual NRTI for 7 days

Few data on plasma clearance of NVP in patients on stable HAART in our population
Objectives

To measure rate of elimination of Nevirapine in patients undergoing structured treatment interruptions in DART

To inform the approach to STIs within DART and optimise patient safety
Methods (1)

• 21 patients undergoing STI
  - 52 weeks on NVP based HAART
  - Achieved CD4 > 300
  - No clinical events in preceding 3 months

• Plasma samples at 0, 1, 2, 3 & 4 weeks after stopping NVP

• 2 NRTIs (ZDV + 3TC or d4T + 3TC) continued for 7 days
Methods (2)

- Plasma levels of NVP analyzed by high performance liquid chromatography (HPLC)
- Lower Limit of Quantification (LLQ) = 100 ng/ml
- Lowest Limit of Detection, based on a chromatogram peak was ~20 ng/ml
- Therapeutic range: 3400-8000 ng/ml
# Results

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>21</td>
<td>16 female, 5 male</td>
</tr>
<tr>
<td>Excluded from analysis</td>
<td>2</td>
<td>1- no NVP levels at baseline, 1- barely detectable NVP levels</td>
</tr>
<tr>
<td>ART Regimen n=19</td>
<td>18</td>
<td>ZDV/3TC/NVP</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>d4T/3TC/NVP</td>
</tr>
</tbody>
</table>
## Baseline Characteristics
(at the time of STI)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>(Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35</td>
<td>(23-61)</td>
</tr>
<tr>
<td>Body Weight (Kgs)</td>
<td>61</td>
<td>(52-77)</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td>341</td>
<td>(301-692)</td>
</tr>
</tbody>
</table>

Mean plasma NVP level **6479 ng/ml** (Range 3720 - 9500 ng/ml)
Levels of NVP over time

Patient with 415 ng/ml at week 2 had no sample at week 1 or 3
## NVP levels over time

<table>
<thead>
<tr>
<th>Week</th>
<th>NVP Levels</th>
<th>%</th>
<th>Max NVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;200 ng/ml</td>
<td>28%</td>
<td>555 ng/ml</td>
</tr>
<tr>
<td>2</td>
<td>100-200 ng/ml</td>
<td>21%</td>
<td>415 ng/ml</td>
</tr>
<tr>
<td>3</td>
<td>&lt;LLQ (100 ng/ml)</td>
<td>74%</td>
<td>N1</td>
</tr>
<tr>
<td>4</td>
<td>undetectable</td>
<td>17%</td>
<td>N1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>
Estimated days to reach different plasma NVP thresholds

Days to reach various NVP thresholds

Sex  ng/ml  M  F  M  F  M  F
~20  13.2 (12.3-18.4)  9.3 (8.7-13.0)  7.6 (7.0-10.1)
100  9.3 (8.7-13.0)  7.6 (7.0-10.1)  7.6 (7.0-10.1)
200  7.6 (7.0-10.1)  7.6 (7.0-10.1)  7.6 (7.0-10.1)
Conclusions

• 7 - 10 days after stopping NVP based HAART plasma levels of NVP were < 200 ng/ml in all but 1 patient

• 200 ng/ml level previously defined by Muro et al

• These data suggested the practice of continuing the dual - NRTI cover for 1 week is acceptable

• Elimination of NVP after STI, among patients on stable HAART is faster than previously reported following single dose NVP
Limitations

- Small number of patients sampled
- Long sample collection intervals
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- **Data and Safety Monitoring Committee:** A McLaren (Chair), C Hill, J Matenga, A Pozniak, D Serwadda
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Thank you