Severe Anaemia and Associated Risk Factors following Initiation of ZDV-containing Regimens in Adults with HIV Infection in Africa within the DART Trial

F Ssali, P Munderi, A Reid, AS Walker, W Stöhr, and C Gilks, on behalf of the DART Trial Team
Background

• Anaemia is common in advanced HIV disease
  - associated with poor survival in untreated patients, independent of CD4 and viral load

• 1% incidence of grade 4 anaemia during ZDV-based therapy in industrialised countries
  - peak 4-12 weeks after initiating ART
  - baseline CD4 an important risk factor

• Few data in resource-limited settings
DART trial: Uganda & Zimbabwe

3315 previously untreated HIV-infected patients
stage WHO 2, 3 or 4 and CD4<200 cells/mm³

randomise to
initiate triple
drug ART with

Clinical and
Laboratory Monitoring
(including FBC
at weeks 4 & 12,
and then every 12 weeks)

Clinical Monitoring
Only
(FBC results available
if requested for clinical
reason, or Grade 4 toxicity)

• First line regimens: Combivir (ZDV/3TC) plus
  - tenofovir DF (TDF)  2468  (74%)
  - nevirapine (NVP)  247  (7%)
  - blinded NVP or abacavir  600  (18%)  [substudy]
Objectives

- To estimate the prevalence and incidence of anaemia over time in DART:
  - grade 1: 8.0 to <9.5 g/dl
  - grade 2: 7.0 to <8.0 g/dl
  - grade 3: 6.5 to <7.0 g/dl
  - grade 4: <6.5 g/dl

- To describe episodes of grade 4 anaemia, including concurrent clinical events
  - “episode” defined as the period between the first grade 4 measurement and first return to baseline grade or better

- To investigate predictors of developing grade 4 anaemia using multivariable logistic regression
  - age, sex, WHO stage, CD4, weight and BMI at baseline
  - haematological parameters at baseline and week 4
Baseline characteristics

3315 participants (accrual completed Oct 2004)

- **Sex**: 65% women
- **Median age**: 37 years (IQR: 32-42)
- **Median CD4**: 86 cells/mm³ (IQR: 31-140)
- **WHO stage**: 23% WHO 4, 56% WHO 3
- **Median Hb**: 11.4 g/dl (IQR: 10.3-12.7)
- **Anaemia**: 12% <9.5g/dl (grade 1)
- **Median BMI**: 21.2 (IQR: 19.2-23.6)
- **Median follow-up**: 48 weeks (IQR: 25-60, max: 96)

Data to 15 January 2005 (trial ongoing)
Haemoglobin at scheduled assessments after initiation of ART

- Haemoglobin (g/dl)
- Median
- IQR

Weeks from ART initiation:
- Number
  - 0: 3302
  - 4: 3149
  - 12: 2830
  - 24: 2407
  - 36: 1932
  - 48: 1439
  - 60: 767
  - 72: 196

Grade 1
Prevalence of anaemia at scheduled assessments

![Graph showing prevalence of anaemia over weeks from ART initiation.

- **Prevalence of anaemia at 0 weeks:**
  - Grade 1: 14%
  - Grade 2: 12%
  - Grade 3: 0%
  - Grade 4: 2%

- **Prevalence of anaemia at 4 weeks:**
  - Grade 1: 12%
  - Grade 2: 8%
  - Grade 3: 0%
  - Grade 4: 4%

- **Prevalence of anaemia at 12 weeks:**
  - Grade 1: 10%
  - Grade 2: 6%
  - Grade 3: 0%
  - Grade 4: 2%

- **Prevalence of anaemia at 24 weeks:**
  - Grade 1: 8%
  - Grade 2: 4%
  - Grade 3: 0%
  - Grade 4: 2%

- **Prevalence of anaemia at 36 weeks:**
  - Grade 1: 6%
  - Grade 2: 2%
  - Grade 3: 0%
  - Grade 4: 2%

- **Prevalence of anaemia at 48 weeks:**
  - Grade 1: 4%
  - Grade 2: 2%
  - Grade 3: 0%
  - Grade 4: 2%

- **Prevalence of anaemia at 60 weeks:**
  - Grade 1: 2%
  - Grade 2: 2%
  - Grade 3: 0%
  - Grade 4: 2%

- **Prevalence of anaemia at 72 weeks:**
  - Grade 1: 0%
  - Grade 2: 0%
  - Grade 3: 0%
  - Grade 4: 2%

- **Prevalence of anaemia at 84 weeks:**
  - Grade 1: 0%
  - Grade 2: 0%
  - Grade 3: 0%
  - Grade 4: 2%

**Legend:**
- **Green:** Grade 1 (8.0 to <9.5)
- **Yellow:** Grade 2 (7.0 to <8.0)
- **Orange:** Grade 3 (6.5 to <7.0)
- **Red:** Grade 4 (<6.5 g/dl)
### Incidence of anaemia

- **Most severe new episode:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>%</th>
<th>cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 (&lt;6.5 g/dl)</td>
<td>220</td>
<td>6.6 %</td>
<td>6.6 %</td>
</tr>
<tr>
<td>Grade 3</td>
<td>38</td>
<td>1.2 %</td>
<td>7.8 %</td>
</tr>
<tr>
<td>Grade 2</td>
<td>136</td>
<td>4.1 %</td>
<td>11.9 %</td>
</tr>
<tr>
<td>Grade 1</td>
<td>407</td>
<td>12.3 %</td>
<td>24.2 %</td>
</tr>
</tbody>
</table>

- 14 patients had >1 grade 4 episode
220 of 3315 patients had a new grade 4 anaemia episode

- first episode occurred median 12 weeks after ART initiation (IQR: 8-20, range: 2-88)
- median episode duration 26 days (IQR 6-45)
- 101 (46%) presented at a scheduled DART doctor visit (4 and 12 weeks, then every 12 weeks)
- 119 (54%) presented at 4-weekly nurse visit or other time (additional FBC performed)
- 171 (78%) had baseline haemoglobin $\geq 9.5$ g/dl
- 38% microcytic, 26% normocytic, 27% macrocytic, 9% unknown
ART following grade 4 anaemia

After start of first new grade 4 anaemia episode

<table>
<thead>
<tr>
<th>Action</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substituted d4T for ZDV</td>
<td>88</td>
<td>40</td>
</tr>
<tr>
<td>Stopped ART (median 9 days)</td>
<td>79</td>
<td>36</td>
</tr>
<tr>
<td>- subsequently substituted d4T for ZDV</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td>- subsequently restarted ZDV</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Died before stopping/substituting</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>No substitution or interruption recorded (trial ongoing)</td>
<td>44</td>
<td>20</td>
</tr>
</tbody>
</table>

- case note review to identify transfusions and other specific anaemia-related therapy ongoing
# Concomitant events during first new Grade 4 anaemia episode

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical events</td>
<td>n=51</td>
<td>(23%)</td>
</tr>
<tr>
<td>- bacterial infection</td>
<td>n=13</td>
<td>(6%)</td>
</tr>
<tr>
<td>- WHO 4 event</td>
<td>n=24</td>
<td>(11%)</td>
</tr>
<tr>
<td>• mainly cryptococcosis, extrapulmonary TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- malaria</td>
<td>n=22</td>
<td>(10%)</td>
</tr>
<tr>
<td>Laboratory events</td>
<td>n=93</td>
<td>(42%)</td>
</tr>
<tr>
<td>- Neutropenia (grade 3/4)</td>
<td>n=89</td>
<td>(40%)</td>
</tr>
<tr>
<td>- Thrombocytopenia (grade 3/4)</td>
<td>n=20</td>
<td>(9%)</td>
</tr>
<tr>
<td>• neutropenia &amp; thrombocytopenia</td>
<td>n=16</td>
<td>(7%)</td>
</tr>
<tr>
<td>None of the above</td>
<td>n=101</td>
<td>(46%)</td>
</tr>
</tbody>
</table>
Mortality

42 (19%) of 220 patients with new grade 4 anaemia have subsequently died

- 14 patients died before resolution of grade 4 anaemia
  - 11 probable sepsis/pneumonia (6 with pancytopenia)
  - 3 other (transverse myelitis, TB, cryptococcal meningitis)
  - 1 death considered directly attributable to ZDV-related anaemia in DART by Endpoint Review Committee

- 28 died after resolution of grade 4 anaemia
  - 15 deaths were considered primarily HIV-related
  - 2 lactic acidosis after substituting d4T for ZDV
Risk factors for developing grade 4 anaemia

- A higher risk of developing grade 4 anaemia was independently associated with being female; low BMI, haemoglobin or CD4 at baseline; and low neutrophils at week 4.

<table>
<thead>
<tr>
<th>Independent* factors</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>female</td>
<td>1.59</td>
<td>0.010</td>
</tr>
<tr>
<td>baseline BMI (per unit)</td>
<td>0.92</td>
<td>0.001</td>
</tr>
<tr>
<td>baseline haemoglobin (per g/dl)</td>
<td>0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>baseline CD4 (per 100 cells/mm³)</td>
<td>0.63</td>
<td>0.001</td>
</tr>
<tr>
<td>week 4 neutrophils (per 10⁹/l)</td>
<td>0.81</td>
<td>0.043</td>
</tr>
</tbody>
</table>

- Baseline neutrophils, WHO stage, cotrimoxazole and age did not predict development of grade 4 anaemia.

*C multivariable logistic regression*
Summary

- The vast majority of patients have substantial increases in haemoglobin by 24 weeks after ART initiation.
- However, the incidence of grade 4 anaemia in DART is higher than in studies in industrialised countries.
  - Patients who died all had other (mainly HIV-related) conditions.
  - 1 death considered directly attributable to anaemia in DART.
- DART population has a higher level of baseline risk.
  - Advanced disease (low CD4, haemoglobin and BMI).
  - High proportion of women (65%).
- Other possible explanations for higher incidence.
  - Poor/inadequate nutritional status.
  - More concomitant clinical events.
  - Malaria, helminthiasis.
Conclusions

• Clinicians initiating patients on ZDV-containing regimens in resource-limited settings need to be alert to clinical signs of anaemia in the minority of patients who will develop it
  - education/counselling of patients about symptoms
  - clinical vigilance of Health Care Workers

• Haemoglobin between 4-12 weeks

• Anaemia is a clinically detectable and reversible toxicity of an otherwise successful initial therapy
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- DART Data and Safety Monitoring Committee
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