The Development of AntiRetroviral Therapy in Africa (DART) trial

Immune restoration over 5 years on ART among patients initiating treatment with advanced immune-deficiency in the DART trial

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Background

- CD4 count decline is a marker of immune deficiency and predictor of mortality in untreated HIV infection.
- Restoring CD4 count to at least 500 cells / mm$^3$ has been suggested as a goal for effective antiretroviral therapy.
- Few patients in resource limited settings achieve this treatment goal.
- Recent treatment guideline revisions urge earlier diagnosis and treatment.
Setting – the DART trial


- 3316 ART-naive adults with advanced immune deficiency

- First-line regimens were
  - ZDV + 3TC + TDF in 2469 (74%)
  - ZDV + 3TC + NVP in 547 (16%)
  - ZDV + 3TC + ABC in 300 (9%)

- CD4 counts performed every 12 weeks in all participants

- Median follow-up on 1st line regimen 4.8 years (IQR 4.1 - 5.2)
Methods

- Estimated time to confirmed CD4 thresholds among patients remaining on 1st line regimen
  - ≥200 cells/mm³
  - ≥350 cells/mm³
  - ≥500 cells/mm³

- using cumulative incidence to calculate conditional probabilities, treating deaths on 1st line and switch to 2nd line as competing risks

- ROC curves to identify CD4 levels with good sensitivity & specificity for predicting failure to achieve a threshold CD4 count after 48 weeks on 1st line
Results - Baseline CD4

median pre-ART CD4 = 86 cells/mm³ (IQR: 31-139)  33% < 50 cells/mm³
CD4 after ART initiation

Proportion of randomised patients

Years from randomisation

Proportion of randomised patients

Died
LTFU
2nd line
350+
250-349
100-249
50-99
0-49
CD4 $\geq 350$ cells/mm$^3$ by baseline CD4

Weeks from ART initiation

Pre-ART CD4

- 0-24
- 25-49
- 50-74
- 75-99
- 100-124
- 125-149
- 150-174
- 175-199

Proportion
3158/3316 (95%) participants had 2 or more post-enrolment CD4 counts and are included in subsequent analyses.

Of those on 1st line:
- 69% ever achieved CD4 ≥ 250 cells/mm³ (confirmed)
- 46% ever achieved CD4 ≥ 350 cells/mm³ (confirmed)
- 19% ever achieved CD4 ≥ 500 cells/mm³ (confirmed)

*median 4.8 years follow-up on first-line*
Time to achieving CD4 thresholds on 1st line regimen

- >=250: 1.8 (0.7-3.3) years
- >=350: 3.9 (2.1 to >6) years
- >=500: >6 years (25th percentile 4.8 years)
CD4 counts at 1 and 5 years after ART initiation

- 3056 participants had CD4 counts 48 weeks after ART initiation
- 1808 participants had CD4 counts at 252 weeks (4.8 years)
Predicting failure to attain $\geq 250$ cells/mm$^3$ on first-line

• The majority of participants remaining on first-line attained CD4 $\geq 250$ cells/mm$^3$

• Question: is there a level of CD4 at week 48 which is associated with very low chance of subsequently reaching this threshold?

<table>
<thead>
<tr>
<th>CD4 at week 48</th>
<th>N</th>
<th>n (%) subsequently attaining CD4 $\geq 250$ cells/mm$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-49</td>
<td>87</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>50-99</td>
<td>226</td>
<td>55 (24%)</td>
</tr>
<tr>
<td>100-199</td>
<td>1160</td>
<td>634 (55%)</td>
</tr>
<tr>
<td>200-249</td>
<td>527</td>
<td>413 (78%)</td>
</tr>
</tbody>
</table>
Predicting failure to attain $\geq 250$ cells/mm$^3$ on 1$^{st}$ line

- ROC analysis identified week 48 CD4 $< 125$ cells/mm$^3$ as the best cut-off for identifying failure to subsequently attain CD4 $\geq 250$ cells/mm$^3$

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>93%</td>
<td>42%</td>
<td>74%</td>
<td>78%</td>
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-ROC area-under-the-curve 0.83

- rate of change in CD4 between weeks 24-48 could not identify patients with week 48 CD4 $\geq 125$ cells/mm$^3$ who nevertheless failed to subsequently attain CD4 $\geq 250$ cells/mm$^3$

- ROC area-under-the-curve 0.60
Conclusions

• The proportion of patients with advanced immune deficiency who achieve >500 cells/mm$^3$ within 5 years of ART initiation is ~ 25%

• CD4 responses continue to improve over time

• The rate of WHO stage 4 clinical events >250 cells/mm$^3$ was under 2.5/100 PY and the rate of death under 1/100 PY

  - S Walker on behalf of the DART trial team, Wednesday 17$^{th}$ Abstract 56

• CD4 <125 at week 48 is the best predictor for not reaching 250 cells/mm$^3$ on the 1$^{st}$ line regimen - ? consider switch to 2$^{nd}$ line

• These data highlight the importance of expanded earlier diagnosis and initiation of treatment at higher CD4 counts
We thank all the patients and staff from all the centres participating in the DART trial.
