A randomised trial of monitoring practice and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa: the DART Trial

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ABSTRACT

Background: DART (Development of Anti-Retroviral Therapy in Africa) is an open label randomised trial assessing feasible prospective approaches for resource poor settings: clinical monitoring only versus CD4 plus laboratory plus clinical monitoring and structured treatment interruptions (STI) versus continuous therapy.

Methods: 230 symptomatic ART naive adults from 2 urban African centres (Zimbabwe and Uganda) with CD4 ≥200 cells/mm³ will receive 3-drug ART (first and second-line) and be followed for up to 5 years. The primary outcome is WHO stage 4 disease or death. A second randomisation will assess the potential benefits and risks of STI in patients with good CD4 responses, following a 100 patient pilot (82% on 12 weeks ART in these settings CD4 ≥200 cells/mm³ at 24 weeks of continuous ART).

Results (updated): Recruitment started in January 2003. So far, 5249 and 2710 adults have been screened and randomised respectively. 54% of those eligible (88% of those scanned) received prior ART to prevent mother-to-child HIV transmission. The median age is 37 years, with 16% over 45. Most have advanced HIV disease (25%, 55% and 21% WHO stages 3 and 4 and 2, respectively; median CD4 85 cells/mm³ [34-350 cells/mm³]; median weight 57kg [IQR 51-64]). Thus 2336 patients entered ZDV/3TC/CD4 and for the first line ART, 139 ZDV/3TC/NNRTI and 237 ZDV/3TC/plus NNRTI or ABC. 5% have shown ≥4 weeks for DXD to be toxic. 43% of 1552 patients at 24 weeks have increased CD4 by at least 100 cells/mm³ (median increase 86, IQR 41-141 and 89% have achieved a CD4 ≥200 cells/mm³. 95% adherence questionnaires to 24 weeks reported no missed pills in the last 4 days; 64% patients never missing a dose through this period.

Discussion: Obstacles to widespread ART introduction in developing countries include drug costs, and the need for routine laboratory monitoring of ART for toxicity (haematology, biochemistry) and efficacy (T cell count). 7 (0.3%) patients reported being lost to follow-up.

OVERVIEW OF PATIENTS ENROLLED IN DART

64% are women
52% of patients (39 of 57 women) had previously received ART for prevention of mother-to-child transmission.
This was single dose antiretrovirals in 89% of cases
median age is 37 years - 15% under 30 years and 16% over 45 years (see Figure below)
30% have been enrolled from the MRC Programme on AIDS/Uganda Virus Research Institute (Uganda); 31% from the Joint Clinical Research Centre (Uganda); 11% from the Academic Alliance (Uganda) and 33% from the University of Zimbabwe (Zimbabwe)
98% acquired HIV through sex between men and women
25% had WHO stage 4, 55% WHO stage 3 and 21% WHO stage 2 disease
median CD4 was 85 cells/mm³ (IQR 31 to 14: range 1 to 199) (see Figure below)
- all patients started ART with combivir (ZDV/3TC) plus tenofovir (TDF) plus lamivudine (3TC) plus nevirapine (NVP) plus efavirenz (EFV) plus abacavir (ABC) [randomised NORA subset]
- 134 patients (5%) have switched ZDV/3TC to toxicity (anaemia and/or neutropaenia in the majority)

SUMMARY
Enrolment into the DART trial is complete and will continue until the end of 2004. The DART trial has been successful as it has reached its target of 5000 patients by the end of 2003. The CD4 increases observed daily are similar to those in patients with low CD4 counts in industrialised countries. Given the low CD4 counts at ART initiation, a substantial proportion of patients still have CD4 counts below 200 cells/mm³ at 24 weeks. A substudy assessing virological suppression with ZDV/3TC/TDF is underway.

DART will assess whether routine laboratory monitoring is necessary for effective ART use, and whether toxicity can be reduced by STI without compromising efficacy.

PATIENTS are prescribed 28 days ART (until their next 4-weekly clinic visit)
Patients complete an adherence questionnaire at each clinic visit
Over the first 24 weeks in DART, 9538 questionnaires have been completed
98% questionnaires reported attending clinic visit on time or early
95% questionnaires reported missing no pills in the last 4 days
the percentage reporting never having missed a pill dropped over time as expected
– from 98% at 4 weeks to 76%, 73%, 65% and 65% at 8, 12, 16, 20 and 24 weeks
– 64% reported they had never missed a pill
– 9% reported they last missed a pill more than 3 months ago
– 15% reported they last missed a pill 1-3 months ago
– 5% reported they last missed a pill 2-4 weeks ago
– 3% reported they last missed a pill 1-2 weeks ago
– 4% reported they lost a pill in the last week
– most frequent reasons for missing doses were being away from home, running out of pills, simply forgetting, feeling sick, being busy and wanting to avoid side effects

OVERALL CD4 INCREASES IN DART

<table>
<thead>
<tr>
<th>Week 12</th>
<th>Median CD4 increase (IQR)</th>
<th>CD4 increase &gt;100 cells/mm³</th>
<th>Absolute CD4 increase &gt;200 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1552</td>
<td>+47 cells/mm³ (IQR 14-120)</td>
<td>737 (36%)</td>
<td>720 (36%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 24</th>
<th>Median CD4 increase (IQR)</th>
<th>CD4 increase &gt;100 cells/mm³</th>
<th>Absolute CD4 increase &gt;200 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1552</td>
<td>+68 cells/mm³ (IQR -41 to 141)</td>
<td>674 (43%)</td>
<td>596 (38%)</td>
</tr>
</tbody>
</table>

Note: at randomisation, median CD4 was 85 cells/mm³ (IQR 31 to 14: range 1 to 199)

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