

CD4 Response to ART in Previously Untreated Adults with HIV Infection in Africa: the DART Trial

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ABSTRACT (updated)

Background: Although access to ART is increasing in developing countries, there are few data on the predictors of immunological response in previously untreated adults in such settings.

Methods: DART (Development of Anti-Retroviral Therapy in Africa) is an open label randomised trial comparing two therapeutic approaches relevant to resource poor settings: clinical monitoring only versus laboratory plus clinical nonitoring, and structured treatment interruptions versus continuous therapy in patients who achieve CD4 cell counts >200 cells/mm³ after 24 or 48 weeks of continuous ART. 3000 symptomatic ART-naive adults from 3 sites (2 Uganda, 1 Zimbabwe) with CD4 <200 cells/mm³ will receive 3-drug ART and are to be followed for up t 5 years. We used logistic regression models to investigate the association between CD4 responses (increase 100 cells/mm³, or to \geq 200 cells/mm³) 24 weeks after ART initiation and sex, age, disease stage, weight, and CD4 count at ART initiation. This was a global analysis, not broken down by randomised group.

Results: To 7 January 2004, 1919 adults have been randomised (64% women: median age 37 years (IOR 32-42): 27% WHO Stage 4, median CD4 82 (35% <50 cells/mm³)). All received ZDV/3TC/TDF as first line ART. Only 46 (3%) patients have thus far switched their treatment (all switching ZDV to d4T for toxicity). As expected, baseline CD4 was significantly lower in patients with later stage disease, and in men compared to women (both p<0.001), 474 patients have reached 24 weeks, of whom 154, 121, 110 and 89 initiated ART with CD4 0-49. 50-99, 100-149, and 150-199 cells/mm³, respectively. 210 (44%) adults have increased CD4 by at least 100 cells/mm³ at 24 weeks (median increase 84, IOR 42-142) and 192 (42%) have achieved a CD4 of >200 cells/mm3. Among the 154 patients initiating ART with CD4 <50 cells/mm3, 63 (41%) had CD4 increases >100 cells/mm³ and 19 (12%) had CD4 >200 by week 24: among those with CD4 50-199 at ART initiation (n=320) CD4 increased by \geq 100 cells in 147 (46%) and 173 (54%) had CD4 \geq 200 by week 24. We found no evidence to suggest that the chance of CD4 increases >100 cells/mm³ at 24 weeks were significantly influenced by pre-ART CD4 (OR=1.12, p=0.16), or the other factors described above.

Conclusion: Achieving CD4 increases of >100 cells/mm3 after 24 weeks on ART in Africa appears to occur regardless of pre-ART factors including low baseline CD4. The CD4 increases observed are comparable with those obtained in patients with low CD4 counts in industrialised countries.

OVERVIEW of PATIENTS ENROLLED in DART

1919 patients have been randomised to 7 January 2004

- ★ 64% are women
- ★ median age is 37 years 14% under 30 years and 15% over 45 years
- * 27% have been enrolled from the MRC Progamme on AIDS/Uganda Virus Research Institute (Uganda); 31% from the Joint Clinical Research Centre (Uganda); 12% from the Academic Alliance (Uganda); and 30% from the University of Zimbabwe (Zimbabwe)
- ★ 98% acquired HIV through sex between men and women
- ★ 45% were first diagnosed HIV positive when screened for entry to DART
 - > those with a positive HIV test before DART screening had been diagnosed for a median of 1.1 years (IQR 0.4 to 3.9 years)
- ★ 27% were WHO stage 4, 55% WHO stage 3 and 18% WHO stage 2
- ★ 43 women (2% of total, 3% of women) had previously received ART for prevention of mother-to-child transmission
 - single dose nevirapine in 86% of cases
- ★ median haemoglobin was 11.5 mg/dl (IQR 10.3 to 12.7: range 5.8 to 18.5) ★ median ALT was 26 IU/I (IQR 18 to 37: range 3 to 193)
- all patients started ART with ZDV/3TC/TDF
 - > 46 patients (3%) have substituted ZDV for D4T for toxicity

METHODS

- Randomised allocation to clinical monitoring only versus laboratory plus clinical monitoring was not considered in any analysis.
- Factors associated with CD4 at randomisation in DART were assessed on the total population randomised to 7 January 2004 (n=1919) using normal regression and adjusting for DART clinical site. The effects of demographics (age and sex), WHO disease stage, weight, and haematology (haemoglobin, white cell count, neutrophils, total lymphocytes, platelets) and biochemistry (urea, creatinine, bilirubin, ALT) at baseline were investigated, but only those with p<0.01 on multivariable analyses are reported, in view of the large number of observations.
- CD4 counts from scheduled tests at 12 and 24 weeks after initiating therapy were considered in patients with available results. Multilevel models with random intercept, and slope before and after 12 weeks were used to assess the relationship between CD4 at randomisation and subsequent changes
- We then focussed on 24 week response, which has usually been considered in studies in industrialised countries, considering the proportion of patients achieving increases in absolute CD4 count of 0, 50, 100, 150 and 200 cells/mm³ or more; and achieving absolute CD4 counts above thresholds of 200, 250, 300, 350 and 400 cells/mm³. Factors associated with a CD4 increase of 100 cells/mm³ or more at 24 weeks were then identified using logistic regression. All treatment changes were ignored.



100-149

CD4 at randomisation

CD4 at randomisation was **lower** in patients

- who were **male** (by, on average, 18 cells/mm³ [95% CI 12-24] p<0.001)
- who had WHO stage 3 or 4 disease (by, on average, 18 and 34 cells/mm³ [95% CI 25-42 and 10-25] respectively compared to WHO stage 2, p<0.001)
- who were **younger** (by, on average, 5 cells/mm³ for every 10 years younger [95% CI 1-9] p=0.009)

> this probably represents a complex relationship between duration of infection and survival to DART enrolment

Whilst some haematology and biochemistry counts did provide additional predictive information, effects were small in magnitude. In particular, CD4 at randomisation was **lower** in patients

- who had lower total lymphocytes (by, on average, 38 cells/mm³ for every 1x10⁹/l lower [95% CI 34-41] p<0.001)
- who had higher ALT (by, on average, 2 cells/mm³ for every 10 IU/l higher [95% CI 1-4] p<0.001)

OVERALL CD4 INCREASES IN DART

- ★ Median CD4 increase at 12 and 24 weeks was 70 cells/mm³ (IQR 29 to 123) and 84 cells/mm³ (IQR 42 to 142) respectively (Figure 1)
 - mean increase was 6.7 cells/mm³ per week to week 12, then 1.1 cells/mm³ per week from week 12 to week 24
 - CD4 increases in these 2 periods differed significantly (p<0.0001)
- ★ 402/1157 (35%) had achieved a CD4 count of 200 cells/mm³ or higher at 12 weeks; and 192/474 (41%) at 24 weeks (Figure 2)

Figure 1: CD4 counts through 24 weeks in DART (boxplot)



CD4 RESPONSE at 24 WEEKS

- CD4 at randomisation was not significantly associated with short-term CD4 response, defined as an increase of 100 cells/mm³ or more at 24 weeks
 - >OR=1.12 per 50 cells/mm³ higher baseline CD4 [95% CI 0.96-1.31, p=0.16] (Figure 4)
 - >therefore, by week 24 most patients appear to be able to achieve similar CD4 increases regardless of baseline
- CD4 at randomisation was strongly associated with achieving threshold levels at 24 weeks, because smaller CD4 increases are needed to achieve these thresholds for patient with 150-199 cells/mm³ at randomisation, compared with patients with 0-49 cells/mm³ at randomisation

Figure 2: Proportion of patients reaching CD4 cell count levels at 24 weeks



Figure 3: Proportion of patients with absolute CD4 increases from randomisation to 24 weeks



OTHER PREDICTORS of CD4 RESPONSE at 24 WEEKS

- ★ in univariate analysis, only baseline haemoglobin was associated with the chance of achieving a CD4 increase of 100 cells/mm³ or more at 24 weeks (Figure 4)
- >OR=0.87 per 1mg/dl higher baseline CD4 [95% CI 0.79-0.97, p=0.01]
- \star there was no additional effect of CD4 (p=0.2), or any other factor, after adjusting for baseline haemoglobin

CD4 at RANDOMISATION in DART





SUMMARY

- ♦ We have not been able to identify important predictors of achieving CD4 increases of 100 cells or more after 24 weeks on triple-drug ART in Africa
- ✤ In particular, CD4 increases at 24 weeks appear to occur regardless of low baseline CD4: however, preliminary data suggest early increases (to 12 weeks) may be greater in those with higher pre-ART CD4 (data not shown)
- S The CD4 increases observed are in line with those obtained 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, leaving them at risk of new WHO events
- ♦ We will continue to monitor short-term response, as the remaining 1000 patients are enrolled and followed
- ✤ Follow-up in DART is planned to continue until the end of 2007

Figure 4: Predictors of 24 week CD4 response (increase of 100 cells/mm³ or greater)



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