



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 / mm³ 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



The DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. Lancet 2010 ; 375: 123-131

- 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

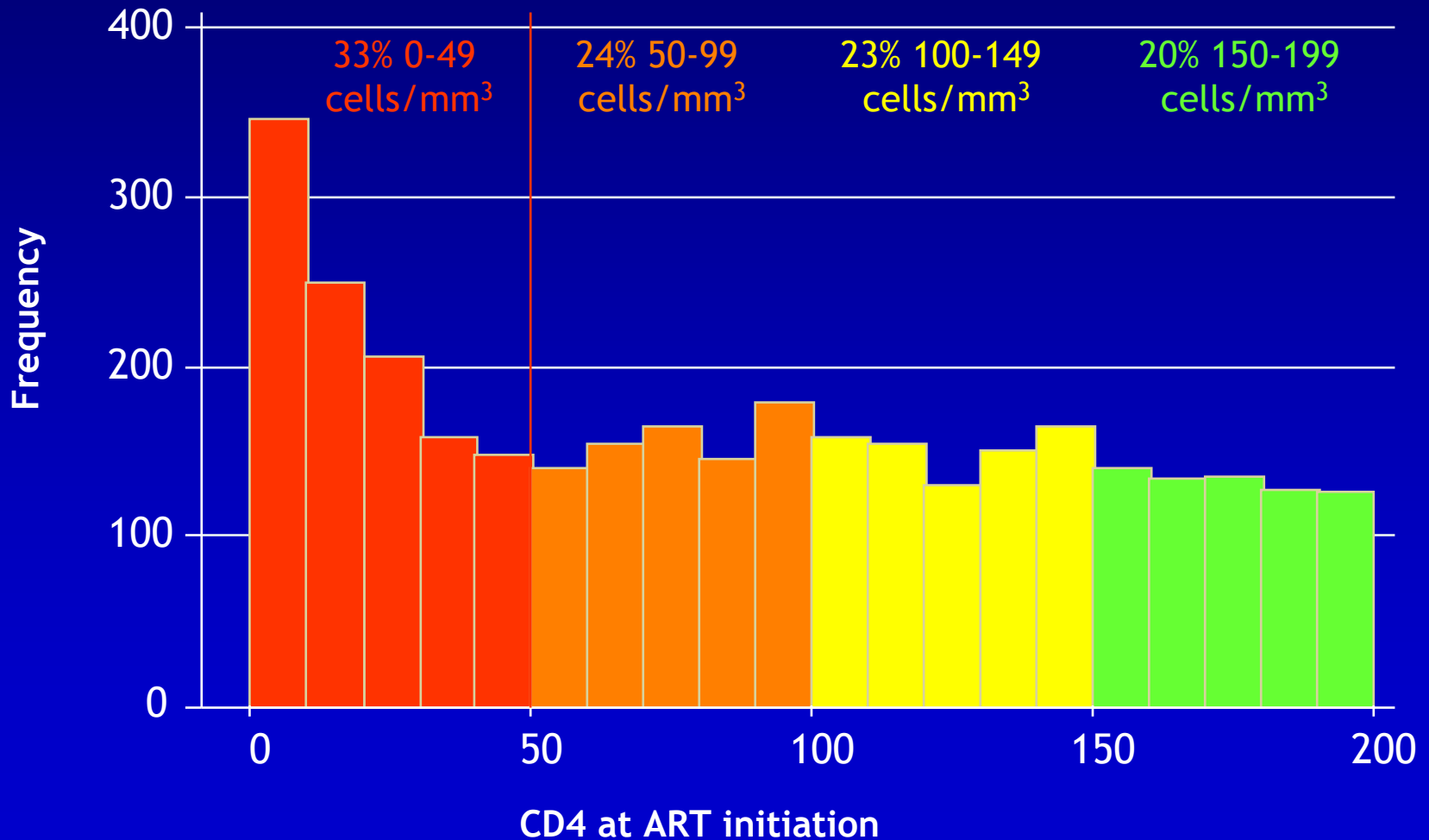


- Estimated time to confirmed CD4 thresholds among patients remaining on 1st line regimen
 - ≥ 200 cells/mm³
 - ≥ 350 cells/mm³
 - ≥ 500 cells/mm³
- *using cumulative incidence to calculate conditional probabilities, treating deaths on 1st line and switch to 2nd line as competing risks*
- ROC curves to identify CD4 levels with good sensitivity & specificity for predicting failure to achieve a threshold CD4 count after 48 weeks on 1st line



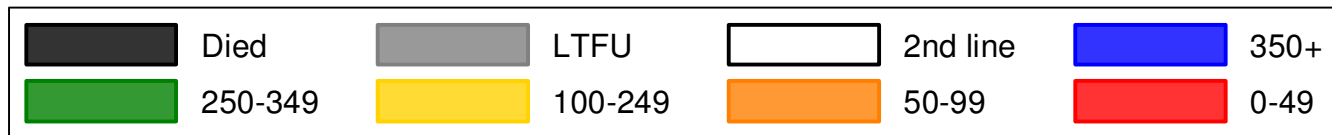
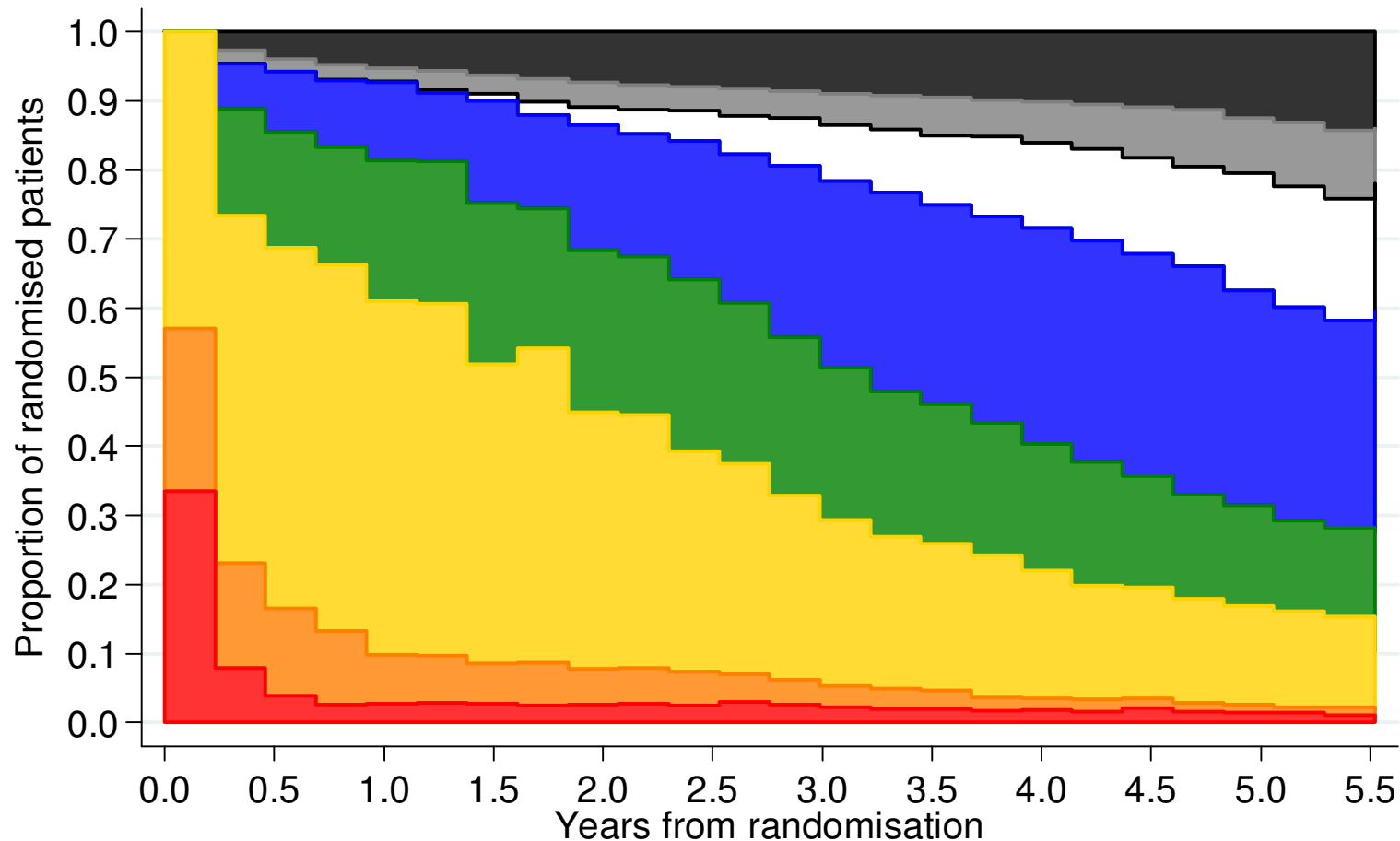
Results - Baseline CD4

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



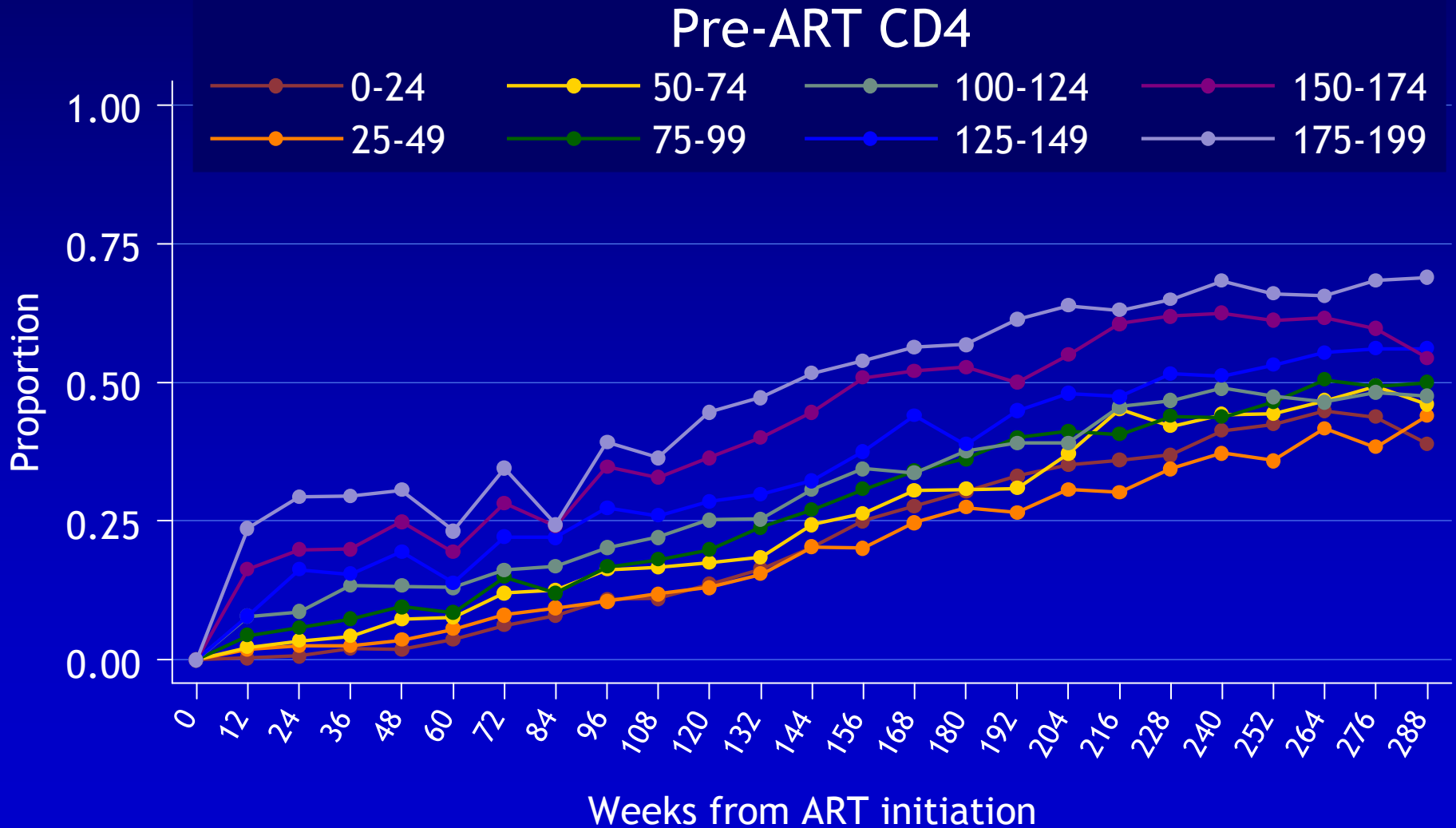


CD4 after ART initiation





CD4 \geq 350 cells/mm³ by baseline CD4





Cumulative Incidence

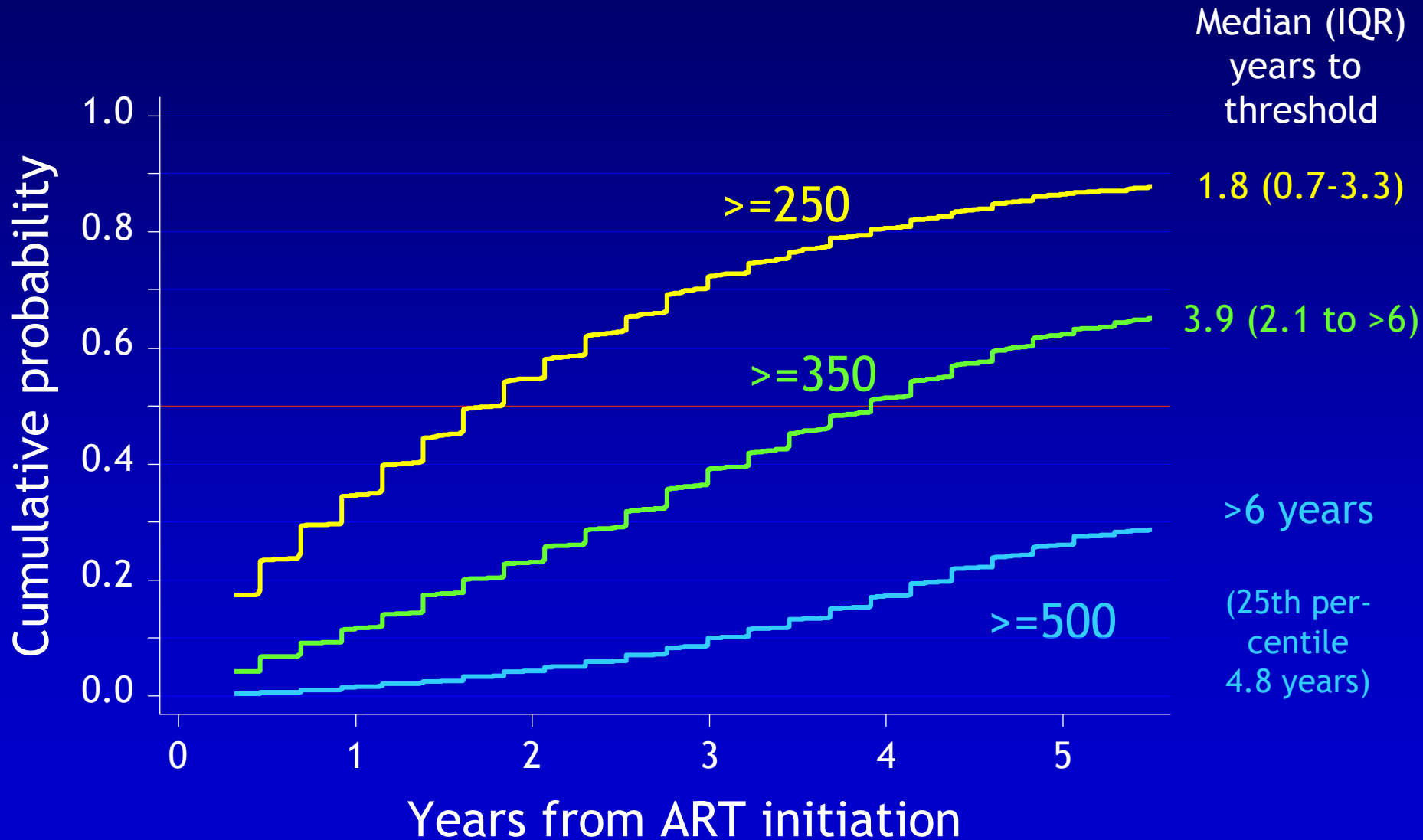


- 3158/3316 (95%) participants had 2 or more post-enrolment CD4 counts and are included in subsequent analyses
- Of those on 1st line :
 - 69% ever achieved CD4 \geq 250 cells/mm³ (confirmed)
 - 46% ever achieved CD4 \geq 350 cells/mm³ (confirmed)
 - 19% ever achieved CD4 \geq 500 cells/mm³ (confirmed)

median 4.8 years follow-up on first-line



Time to achieving CD4 thresholds on 1st line regimen



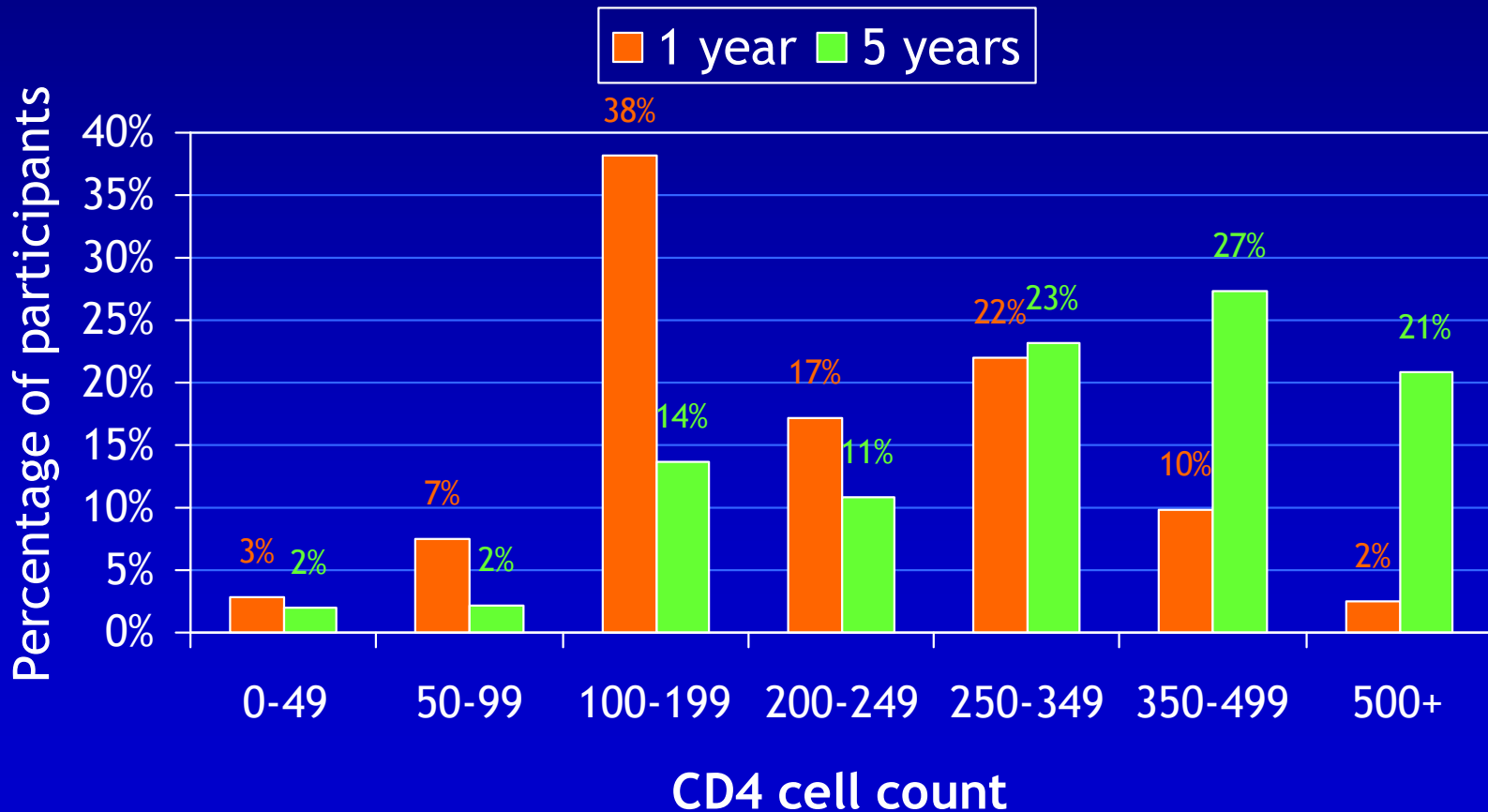


CD4 counts



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 ≥ 250 cells/mm³ on first-line



- The majority of participants remaining on first-line attained CD4 ≥ 250 cells/mm³
- Question: is there a level of CD4 at week 48 which is associated with very low chance of subsequently reaching this threshold?

CD4 at week 48	N	n (%) subsequently attaining CD4 ≥ 250 cells/mm ³
0-49	87	8 (9%)
50-99	226	55 (24%)
100-199	1160	634 (55%)
200-249	527	413 (78%)



Predicting failure to attain ≥ 250 cells/mm³ on 1st line



- ROC analysis identified **week 48 CD4 < 125 cells/mm³** as the best cut-off for identifying failure to subsequently attain CD4 ≥ 250 cells/mm³

Specificity	Sensitivity	PPV	NPV
93%	42%	74%	78%

- ROC area-under-the-curve 0.83
- rate of change in CD4 between weeks 24-48 could not identify patients with week 48 CD4 ≥ 125 cells/mm³ who nevertheless failed to subsequently attain CD4 ≥ 250 cells/mm³
 - ROC area-under-the-curve 0.60



Conclusions



- The proportion of patients with advanced immune deficiency who achieve >500 cells/mm³ 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/mm³ 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 17th Abstract 56*
- CD4 <125 at week 48 is the best predictor for not reaching 250 cells/mm³ on the 1st line regimen - ? consider switch to 2nd line
- These data highlight the importance of expanded earlier diagnosis and initiation of treatment at higher CD4 counts



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