Long-term trends in CD4 counts in patients starting HAART: UK CHIC study

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BACKGROUND

- Despite recommendations that all HIV-infected individuals with a CD4 count <350 cells/mm^3 should start HAART, a substantial proportion do not start until their CD4 count has fallen to lower levels.
- There is debate over whether patients who start HAART with very low CD4 counts will ultimately experience CD4 increases of the same magnitude as those who start when their CD4 counts are higher; these discussions are complicated by the fact that many individuals who start HAART with low CD4 counts may have sub-optimal adherence.
- We considered trends in CD4 counts over the first five years after starting HAART in antiretroviral-naïve individuals in the UK CHIC Study who maintained viral suppression after 6 months of HAART.

METHODS

- All antiretroviral-naïve patients starting HAART after 1997 in the UK CHIC Study with at least one CD4 measurement within the baseline period (90 days before start of HAART to 6 days after starting) and another between 6 and 60 months post HAART were included. Patients were further required to have at least one HIV-1 RNA measurement between 6 and 9 months post HAART and at intervals of less than one year thereafter until the end of their follow-up. Continuous viral suppression was defined as all HIV-1 RNA measurements ≤ 400 copies/μl after 6 months of HAART.

Statistical methods

The square root of CD4 was modeled to meet model assumptions about stability of the variance with increasing CD4. The relationship between square root CD4 and time, the growth curve, was described as a fractional polynomial. Fractional polynomials offer a greater range of curve shapes than linear or quadratic polynomials. The growth curve was fitted as a random effects model to account for repeated measurements within individuals, allowing CD4 trajectories to vary between patients. The best fractional polynomial was selected by comparing the deviance of the models and the percentage of predicted values that were within 20% of the observed values. Since the fit of the best 3-degree fractional polynomial was comparable to that of the best 2-degree fractional polynomial, the simpler 2-degree model was selected.

Patients were classified by their baseline CD4 cell count (<25, 25-49, 50-99, 100-199, 200-349, 350-499, and ≥500 copies/mm^3) Those patients with more than one CD4 cell count within the baseline period were classified using the closest measurement to start of HAART. Interaction terms (constant * baseline CD4 group and fractional polynomial terms * baseline CD4 group) were included in the growth model to allow CD4 trajectories to vary among baseline CD4 groups. To aid interpretability the predicted square root-transformed CD4 cell counts were back-transformed to their original scale and mean differences were generated from these back-transformed values. CD4 trajectories adjusted for age, sex, ethnicity and risk group was investigated.

RESULTS

- Of the 17131 patients enrolled in UK CHIC, 8577 started treatment before 1998, did not start on HAART or started treatment before entering the study. A further 2669 patients did not have any CD4 measurements within the baseline period or between 6 and 60 months post HAART. Of the remaining 5885 patients, 1674 had insufficient RNA measurements after 6 months post HAART. Of the 4112 eligible patients, 2780 maintained continuous viral suppression (HIV-1 RNA ≤400 copies/μl) from 6 months post HAART.
- A total of 39680 CD4 cell counts were measured on the 2780 eligible patients, with a median of 13 (range 2 to 60) measurements per patient. There were 1111 patients with ≤2 years follow-up post HAART, 954 with 2-4 years and 715 patients with 4-7 years follow up.
- Compared to patients with baseline CD4 count ≥200 cells/mm^3, a higher percentage of patients with baseline CD4 counts <200 cells/mm^3 were female, Black African and heterosexual (table 1).

TABLE 1: CHARACTERISTICS OF THE 2780 PATIENTS THAT MAINTAINED VIRAL SUPPRESSION 6 MONTHS POST HAART ACCORDING TO BASELINE CD4 COUNT

	Baseline CD4 count (cells/mm^3)						
	<25	25-49	50-99	100-199	200-349	350-499	≥500
Number of patients	277	185	351	828	870	178	91
Sex %							
male	70	79	77	75	76	84	82
Risk group %							
Homo/bisexual	38	56	56	58	63	70	75
IDU	2	2	3	2	2	3	4
Heterosexual	56	40	38	37	32	25	18
Other/not known	4	2	3	3	3	2	3
Ethnicity %							
White	44	58	55	57	60	71	69
Black African	35	26	27	28	24	17	13
Other	17	14	15	11	12	9	14
Not known	4	2	3	4	4	3	4
Age at starting HAART %							
16-29	11	13	9	13	15	16	12
30-39	48	39	48	47	47	44	56
40-49	32	35	29	28	28	26	23
≥50	9	13	14	12	10	14	9

NOTE: Data are percentage of patients unless otherwise indicated

RESULTS (continued)

- Table 2 (below) shows the estimated mean yearly increase in CD4 cell count, according to baseline CD4 count.
- In all groups, CD4 cell count increased most rapidly during the 1st year of HAART. However even during the 5th year of HAART increases in CD4 cell count were still evident, particularly among those with baseline CD4 cell count <200 cells/mm^3.
- After adjusting for sex, age, ethnicity and risk group, the mean yearly increases 4-5 years post HAART were 29 [95% CI 21-36], 20 [11-28], 21 [15-28] and 15 [11-20] cells/mm^3 for baseline CD4 <25, 25-49, 50-99 and 100-199 respectively. For the remaining time points and other baseline CD4 groups the adjusted estimates were also marginally attenuated, compared to the unadjusted estimates.

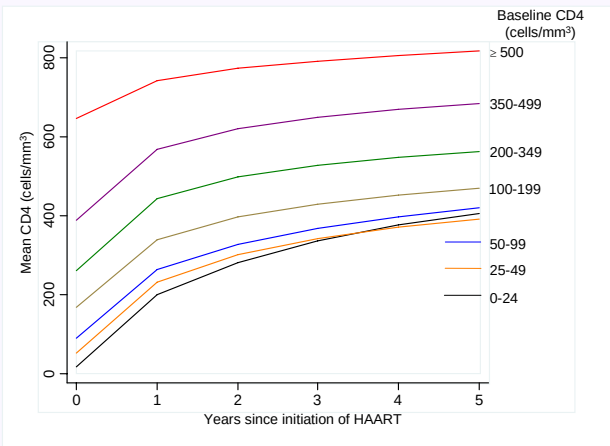
TABLE 2: UNADJUSTED ESTIMATES OF MEAN YEARLY INCREASES IN CD4 COUNT FROM START OF HAART TO 5 YEARS, ACCORDING TO BASELINE CD4 COUNT, AMONG PATIENTS WITH CONTINUOUS VIRAL SUPPRESSION

Baseline CD4 count (cells/mm^3)	Estimated mean yearly increase in CD4 count (cells/mm^3) [95% CI] Number of years since start of HAART				
	0-1 years	1-2 years	2-3 years	3-4 years	4-5 years
<25	181 [169,192]	83 [77,89]	55 [49,62]	40 [33,47]	30 [23,37]
25-49	181 [166,195]	69 [61,76]	43 [35,51]	29 [21,38]	21 [12,29]
50-99	175 [164,186]	64 [59,70]	41 [35,47]	29 [23,36]	22 [15,28]
100-199	172 [163,180]	56 [52,60]	34 [30,38]	23 [19,28]	17 [12,21]
200-349	184 [175,193]	54 [49,58]	31 [26,36]	20 [15,25]	13 [8,18]
350-499	180 [157,203]	52 [41,62]	30 [19,41]	19 [8,31]	13 [2,24]
≥500	98 [61,135]	30 [13,48]	19 [1,37]	13 [-5,31]	10 [-8,28]

NOTE: Differences between consecutive years are calculated using the back-transformed values

- Figure 1 (below) shows mean CD4 trajectories among baseline CD4 groups
- Differences in mean baseline CD4 trajectories were maintained during the first 5 years after initiation of HAART, among baseline CD4 groups 100-199, 200-349, 350-499 and ≥500.
- At 5 years post HAART mean CD4 was 169 cells/mm^3 [95% CI 129-210] lower in patients with baseline CD4 25-49 than in patients with baseline CD4 200-349 cells/mm^3. Corresponding differences were 142 [108-177] and 92 [64-121] in patients with baseline CD4 50-99 and 100-199 respectively.
- For patients with baseline CD4 350-499 and ≥500 cells/mm^3, mean CD4 counts at 5 years were respectively 121 cells/mm^3 [95% CI 69-174] and 255 [176-334] higher than in patients with baseline CD4 200-349 cells/mm^3.
- After adjusting for sex, age, ethnicity and risk group, mean CD4 was 269 cells/mm^3 [95% CI 187-352] higher in patients with baseline CD4 ≥500 cells/mm^3 than in patients with baseline CD4 200-349 cells/mm^3. For the other baseline CD4 groups the corresponding adjusted estimates were marginally attenuated, compared to the unadjusted estimates.

FIGURE 1: UNADJUSTED ESTIMATED MEAN CD4 TRAJECTORIES IN PATIENTS WITH CONTINUOUS VIRAL SUPPRESSION 6 MONTHS POST HAART



CONCLUSIONS

- In patients with continuous viral suppression 6 months post HAART, CD4 counts continued to increase up to 5 years post HAART, though a slower rate than in the 1st year post HAART.
- Despite this sustained CD4 cell recovery, baseline differences in CD4 counts were maintained up to 5 years post HAART.
- We await further follow-up information on these patients to establish if patients with baseline CD4 <350 cells/mm^3 can eventually attain CD4 levels > 500 cells/mm^3.

United Kingdom Collaborative HIV Cohort (UK CHIC)

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