

Implications of post HAART virological failure in CD4 counts : UK CHIC study



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BACKGROUND

- Virological failure after starting HAART may result from imperfect adherence or the development of resistance.
- Patients with virological failure will have lower subsequent CD4 counts than those maintaining virological suppression. However, the duration of any effect of transient virological failure on subsequent CD4 trends is unclear.
- Our objective was to use models of long term trends in CD4 count following initiation of HAART to quantify the implications of virological failure for subsequent trends in CD4 count.

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 post HAART were included. Patients were further required to have a HIV-1 RNA measurement recorded within 179 days prior to all CD4 counts.

Statistical methods

The square root of CD4 was modeled to meet 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; these offer a greater range of curve shapes than linear or quadratic polynomials. Fractional polynomials of one, two and three degrees with powers {-2, -1, -0.5, 0, 0.5, 1, 2, 3} were considered, including models with repeated powers. The growth curve was fitted as a random effects model, with the intercept and fractional polynomial terms random at the patient level, 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 (powers 1,1,2) was comparable to that of the best 2-degree fractional polynomial (powers 0.5, 0.5), 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/mm³). 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. Mean square-root CD4 trajectories were generated separately for those patients who did and did not maintain viral loads ≤1000 copies/ml six months post HAART.

Four time-dependent variables were generated denoting the maximum HIV-1 RNA measurement recorded in the previous 44, 45-104, 105-194 and 195-374 days, with HIV-1 RNA categorised as ≤1000, >1000 to ≤10000 and >10000 copies/ml. To isolate the effects of post HAART viral loads, two sets of the time-dependent variables were added to the model. One set covers the period from baseline to 374 days post HAART and the second set, our main interest, covers the period from 375 days post HAART until end of follow-up. Adjustment for age, sex, ethnicity and risk group was investigated.

To aid interpretability the Delta method was used to back-transform the results to their original scale. The Delta method is a technique for approximating the mean of a non-linear function of a random variable X. For mean E[X] and variance V[X], $E[X^2] \cong (E[X])^2 + V[X]$. For each comparison group we calculated the mean and variance of the predicted square-root CD4 cell counts. The Delta method was then used to approximate the means on the original CD4 scale. We then calculated the differences between these back-transformed means.

RESULTS

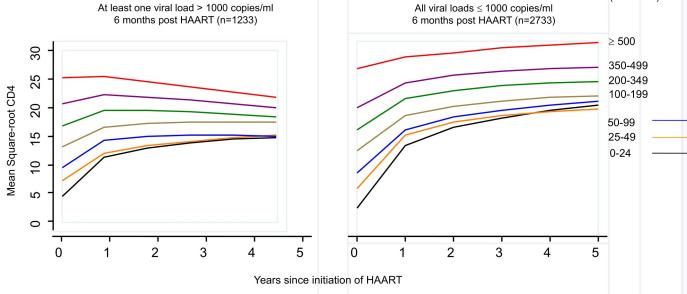
- Of the 17131 patients enrolled in UK CHIC, 8577 started treatment before 1998, did not start on HAART or started treatment before entering the study. A further 2669 patients did not have any CD4 measurements within the baseline period or between 6 and 60 months post HAART. Of the remaining 5885 patients, 1896 had insufficient HIV-1 RNA measurements, leaving a dataset of 3989 patients.
- A total of 57398 CD4 cell counts and 58001 HIV-1 RNA measurements were observed on the patients included in analyses. There were 1403 patients with ≤2 years follow-up post HAART, 1340 with 2-4 years and 1246 patients with 4-7 years follow up.
- Most patients were men and approximately half of the patients were homosexual or bisexual, white and aged 30-39 (table 1).

TABLE 1: CHARACTERISTICS OF THE 3989 PATIENTS

	n (%)	
Total number of patients	3989	
Sex	Male	2985 (75)
Risk group	Homo/bisexual	2212 (55)
	IDU	152 (4)
	Heterosexual	1494 (38)
	Other/not known	131 (3)
Ethnicity	White	2240 (56)
	Black African	1103 (28)
	Other	497 (12)
	Not known	149 (4)
Age at starting HAART	16-29	632 (16)
	30-39	1964 (49)
	40-49	1003 (25)
	≥ 50	390 (10)

RESULTS (continued)

FIGURE 1: UNADJUSTED ESTIMATED MEAN SQUARE-ROOT CD4 TRAJECTORIES AMONG BASELINE CD4 GROUPS



- Among all baseline CD4 groups, CD4 continues to increase in patients who maintain viral loads ≤ 1000 copies/ml six months post HAART (figure 1). Among patients with at least one viral load > 1000 copies/ml six months post HAART, CD4 tended to decrease after 1 year, in patients with baseline CD4 counts ≥ 200 cells/mm³.
- Virological failure was associated with lower subsequent CD4 counts, with the poorest response occurring immediately after a viral load of >10000 copies/ml (table 2). For all time periods the greatest decrement occurred where viral loads exceeded 10000 copies/ml. Decrements in square-root CD4 decrease as time since virological failure increases. The corresponding adjusted estimates were marginally attenuated compared to the unadjusted estimates.

TABLE 2: UNADJUSTED ESTIMATES OF MEAN DIFFERENCES IN SQUARE ROOT CD4 AMONG PATIENTS WITH A POST HAART VIRAL LOAD > 1000 COPIES/ML COMPARED TO THOSE WITH VIRAL LOADS ≤ 1000 COPIES/ML, ACCORDING TO TIME SINCE LAST VIRAL FAILURE

Number of days since last viral failure	Estimated mean difference in square-root CD4 from those with viral loads ≤1000 copies/ml [95% CI]	
	Maximum HIV-1 RNA measurement within a period	>1000 to ≤10000 copies/ml
0 to 44	-0.84 [-0.69, -0.99]	-2.80 [-2.69, -2.92]
45 to 104	-0.38 [-0.22, -0.55]	-1.20 [-1.08, -1.32]
105 to 194	-0.39 [-0.24, -0.54]	-0.84 [-0.72, -0.95]
195 to 374	-0.24 [-0.11, -0.38]	-0.76 [-0.64, -0.87]

Note: Effects of viral load 375 days post HAART

Results from table 2 back-transformed using the Delta method

Number of days since last viral failure	Mean difference in CD4 count from those with viral loads ≤ 1000 copies/ml				
	Baseline CD4 group	>1000 & ≤ 10000	> 10000		
	2 yrs	3 yrs	2 yrs	3 yrs	
0-44	0-24	-26	-28	-81	-89
	200-349	-36	-37	-116	-118
45-104	0-24	-12	-13	-37	-40
	200-349	-17	-17	-51	-52
105-194	0-24	-12	-13	-26	-28
	200-349	-17	-17	-36	-37
195-374	0-24	-8	-8	-24	-25
	200-349	-10	-11	-33	-33

- Since the mean and variance of the predicted values vary depending upon the other variables in the model, mean differences that are fixed on the square-root scale vary with time and baseline CD4 group when back-transformed using the Delta method.

CONCLUSIONS

- In patients taking HAART there is a clear reduction in CD4 count during the period immediately after a viral load of >10000 copies/ml. CD4 counts are moderately lower after a viral load of >1000 to ≤10000 copies/ml. The negative impact on CD4 counts of a viral load > 1000 copies/ml is still evident up to 374 days later.
- Detectable viremia may have other negative impacts, which are associated with a poorer prognosis. Future work will incorporate the effects of other factors such as drug class and age.
- For a model fitted on the log scale the exponentiated parameters have a meaningful interpretation as geometric means. However this option may produce a model fit that is inferior to a model fitted on the square-root scale.
- To overcome the problem of variance that increases with CD4 count, multilevel models can be extended to model the level 1 (within-person) variation as a function of the fixed predicted CD4. However, relationships that are additive on the square-root scale will be non-linear on the CD4 scale, so that absence of interaction in one model implies interaction in the other.