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Normalisation of CD4 counts in HIV-infected patients with maximal virological suppression (<50 copies/ml) taking combination antiretroviral therapy

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INTRODUCTION

The goal of combination antiretroviral therapy (cART) is to reduce HIV viral replication to below the limit of detection. As viral replication falls, the CD_4 count increases. The initial increase is rapid and usually lasts 3-6 months, followed by a phase of slower CD_4 count increases, lasting 3-5 years. It is currently unclear whether CD_4 counts will continue to increase to the levels seen in HIV-negative populations.

OBJECTIVES

Describe the relationship with CD_4 count increases of
- duration of treatment
- CD_4 count at starting cART
- current CD_4 count

in antiretroviral naïve patients starting cART who currently have viral load [VL] < 50 copies/ml.

METHODS

Patients

1517 antiretroviral naïve patients from EuroSIDA, a pan-European observational study who satisfied the following inclusion criteria

Inclusion criteria

- 2 consecutive VL < 50 copies/ml
- on cART at both VL measurements
- no change in antiretrovirals (start or stop) between the VL
- CD_4 count measured in the 6 months prior to starting cART
- distinct CD_4 measured within at most 4 weeks of each VL measure

Statistical methods

Change in CD_4 occurring between each pair of consecutive VL<50 copies/ml was calculated and standardized for the time between viral load measurements to give the rate of change in CD_4 (units of cells/mm³ per year). Each patient could contribute data from > 1 pair.

Generalised linear models, using a normal distribution and an identity link function, adjusted for repeated measures, were used to describe rate of CD_4 change stratified by time since starting cART, CD_4 at starting cART and current CD_4.

Baseline (for descriptive purposes) was arbitrarily defined as the 1st VL< 50copies/ml after starting cART.

Table 1

Characteristics of 1517 ARV-naive patients starting cART with ≥2 consecutive VL < 50 copies/ml

Variable	Median (interquartile range)
Baseline CD_4	410/mm³ (254 – 580/mm³)
CD_4 increase from cART to baseline	179/mm³ (72 – 306/mm³)
Nadir CD_4 before cART	171/mm³ (72 – 288/mm³)
Peak VL before cART	4.96 (4.40 – 5.45 $\log_{10}$copies/ml)
Date of starting cART	January 1999 (7/97 – 3/01)
CD_4 at starting cART	210/mm³ (91 – 340/mm³)
Months between VL pairs	3 (2 – 4)
Number VL pairs per patient	6 (3 – 11)
Age	38.8 (33.2 – 46.0)

Table 2

Demographics of included patients (N, %)

Gender Male:Female	1202 (79.2) : 315 (20.8)
Risk group Hom:IDU:Het	737 (48.3) : 252 (16.6) : 417 (27.5)
Prior AIDS	341 (22.5)
HCV negative:positive*	862 (56.8) : 244 (16.1)
HBV negative:positive*	1136 (74.9) : 85 (5.6)

12137 pairs of VL < 50 copies/ml included in analyses
- 5614 in patients taking a PI-based regimen (46.3%)
- 4923 in patients taking a NNRTI-based regimen (40.6%)
- 1600 (13.1%) in patients taking a triple-nucleoside regimen containing abacavir.

*remainder of patients had unknown HBV/HCV serostatus

Table 3

Crude rate of CD_4 increases (per year) with VL < 50 copies/ml:Relationship with current CD_4

Current CD_4 (/mm³)	N+ (%)	Change in CD_4* Mean (95% CI)	Current CD_4 Median (IQR)
?200	1169 (9.6)	67.7 (48.9 to 86.5)	154 (110 – 180)
201 – 300	1669 (13.8)	73.3 (54.1 to 92.5)	253 (230 – 280)
301 – 400	1852 (15.3)	56.2 (35.4 to 77.0)	355 (330 – 380)
401 – 500	1924 (15.9)	45.3 (23.0 to 67.6)	450 (426 – 475)
501 – 600	1661 (13.7)	49.3 (23.2 to 75.4)	550 (525 – 573)
601 – 700	1356 (11.2)	43.2 (11.1 to 75.3)	648 (622 – 675)
>700	*2506 (20.6)*	*19.3 (-7.2 to 45.8)*	*855 (766 – 979)*

+ Number of VL pairs included in analysis
* unadjusted per year spent with VL < 50 copies/ml

RESULTS

Baseline characteristics of the patients at baseline are described in **Table 1** and **2**.

Table 3 shows the mean, crude rate of change in CD_4 per year stratified by current CD_4, i.e., the CD_4 immediately prior to the CD_4 used with the viral load pair. The correlation between the pair of CD_4 used in analyses was 0.876, with 12.4% estimated regression to the mean.

The only group without statistically significant increases in CD_4 was those with a current CD_4 of >700/mm³, where the mean rate of increase in CD_4 was 19.3/mm³ per year (95% confidence interval [CI] -7.2 to 45.8/mm³). The current median CD_4 in these patients was 855/mm³ (IQR 766-979/mm³).

A multivariate model adjusted for nucleoside pair, cART regimen, age, change in CD_4 and time since starting cART, showed no evidence of any group of patients in which CD_4 was not increasing (**Figure 1**). After adjustment, there was a slightly lower, but still significantly increasing, rate of change in CD_4 among patients with a current CD_4 count of >700/mm³ (mean 28.3/mm³; 95% CI 2.7 – 53.9/mm³, p=0.030). This increase is likely underestimated due to regression to the mean.

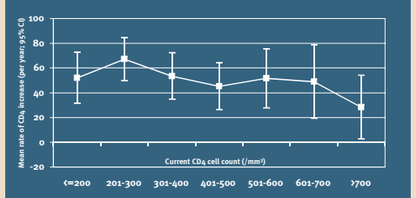
This analysis was then stratified by current CD_4 and time since starting cART, (**Figure 2**). The greatest rates of increase in CD_4 were seen in the first year after starting cART, approximately 100/mm³, regardless of the absolute CD_4 at cART initiation. Lower increases in CD_4 (approximately 50/mm³ per year) continued to be observed up to 5 years after starting cART in patients whose current CD_4 was below 500/mm³. The only group without significant increases in annual CD_4 was in patients who had taken cART for more than 5 years with a current CD_4 >500/mm³. The current median CD_4 in this patient group was 701/mm³ (IQR 601-863/mm³).

CONCLUSIONS

- Due to the inclusion criteria, all patients had VL < 50 copies/ml and were taking cART with no interruptions between VL < 50 copies/ml.
- Little evidence of plateau effect in CD_4 rise except at near-normal CD_4 levels, particularly if VL is maintained at <50 copies/ml for a sufficiently long period of time
- The majority of patients continued to experience significant rises in CD_4 count, even after 5 years of cART
- Normalization of CD_4 counts in HIV-infected patients for all infected individuals may be achievable if viral suppression with cART can be maintained for a sufficiently long period of time

Figure 1

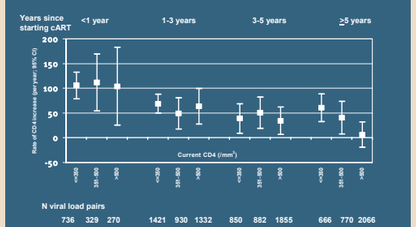
Adjusted rate of CD_4 increases (per year) with VL <50 copies/ml



Adjusted for nucleoside pair, cART regimen, age, change in CD_4 count from baseline and time since starting cART

Figure 2

Rate of CD_4 count increase (per year) while VL < 50 copies/ml



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