THPE144

Predictors for the initial CD4+ decline after antiretroviral treatment interruption in the SMART study

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Background

The SMART study is an international, randomized trial comparing a CD4+-guided antiretroviral treatment (ART) interruption strategy (drug conservation or DC arm) with continuous ART in 5472 patients with CD4+ >350 cells/mm^3 at study entry. On January 11, 2006, the DC strategy was stopped due to increased risk of opportunistic disease and death compared to continuous ART, hazard ratio 2.6 (95% CI 1.9 – 3.7, p<0.0001).

We describe the CD4+ cell count decline after stopping ART in ART-experienced patients.

Methods

In the DC arm, patients were to discontinue ART at study entry, and re-initiate at CD4+ < 250 cells/mm^3, followed by episodic ART; re-initiation at higher CD4+ levels was recommended under certain conditions. CD4+ was collected at baseline, months 1, 2, and every two months in year 1, every four months thereafter. Additional CD4+ counts were collected prior to baseline. This analysis is restricted to DC patients who were on ART, discontinued ART at study entry, and stayed off ART for at least 2 weeks. We describe changes in CD4+ through the first 12 months off ART, censored at ART re-initiation.

Statistical Methods: The CD4+ trajectories in Figures 2-4 plot the observed mean decline in CD4+ from baseline to each follow-up visit as cross-sectional snapshots; averages include all patients who were still off ART at the visit. Predictors for CD4+ decline in the first month of the ART interruption were determined by multiple regression, with change in CD4+ from baseline to month 1 as response. CD4+ were censored at ART re-initiation or January 11, 2006. Tests results are considered statistically significant for p-values ≤0.05, borderline significant for p-values ≤0.10. All p-values are 2-sided.

Results

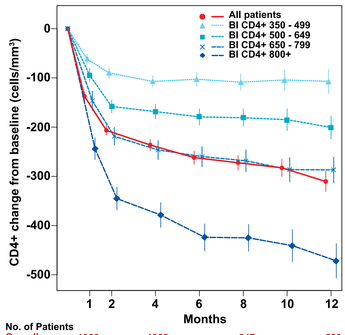
- 2025 patients were included in the analyses. Of these, 567 stayed off ART for ≥ 12 months, median time to ART re-initiation was 15 months. Baseline characteristics are shown in Table 1, the distributions of baseline and screening CD4+ counts are shown in Figure 1.
- The solid red lines in Figures 2-4 show the mean CD4+ decline during the first ART interruption, starting at study entry. At each visit, change in CD4+ from baseline was averaged over all patients who were still off ART. During the first month, CD4+ declined by a median of 126 (IQR 13 – 246) cells/mm^3, during the first 2 months by 187 (IQR 80 – 317) cells/mm^3, and by 12 (IQR 3 – 22) cells/month from month 2 to 12. The blue lines in Figures 2-4 show the mean CD4+ decline by baseline CD4+, nadir CD4+, and baseline HIV RNA.
- According to study protocol, ART was to be re-initiated when CD4+ declined to <250 cells/mm^3. By 12 months, 704 patients (35% of 2025) had re-initiated ART, about 2 out of 3 at CD4+ < 250 cells/mm^3; 750 (37%) of patients were censored on January 11, 2006 while still off ART, and 13 (0.6%) had died or were lost to follow-up, see Figure 5.

Table 1. Baseline characteristics

	Population[1] (N=2025)	
Demographics		
Age (years; mean)	44.8	
Gender (% female)	24.4	
Race		
Black (%)	26.8	
White (%)	59.7	
Other (%)	13.5	
Mode of infection (more than one possible)		
Sexual contact, same sex (%)	53.4	
Sexual contact, opposite sex (%)	42.6	
Injection drug use (%)	9.8	
Other/ unknown (%)	7.5	
Baseline CD4+ (cells/mm^3; median, IQR)	633	(490, 832)
Screening[2] CD4+ (cells/mm^3; median, IQR)	635	(487, 836)
CD4% (median, IQR)	31	(25, 38)
CD4+ nadir (cells/mm^3; median, IQR)	235	(134, 342)
HIV RNA ≤ 400 copies/mL (%)	81.9	
Highest prior recorded HIV RNA ($\log_{10}$ copies/mL; median, IQR)	4.8	(4.1, 5.3)
ART History		
PI experienced (%)	72.8	
NNRTI experienced (%)	68.8	
Time since first prescribed ART (years; median, IQR)	6	(4, 9)
Prior AIDS-related illnesses (%)	26.4	
Hepatitis B (%)	2.3	
Hepatitis C (%)	15.2	

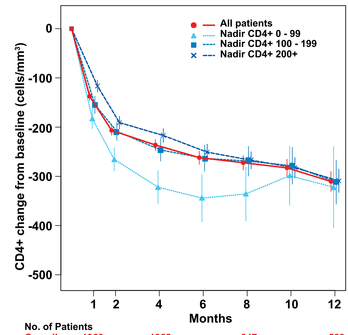
[1] On ART at baseline, randomized to DC group, stopped ART at baseline, and at least one CD4+ in year 1 before re-initiating ART.
[2] Obtained prior to study entry, median time 84 days (IQR 51 -112) prior to baseline CD4+.
Abbreviations: ART; antiretroviral therapy; DC, drug conservation; IQR, interquartile range; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor

Figure 2. Mean change in CD4+ during ART interruption, by baseline CD4+



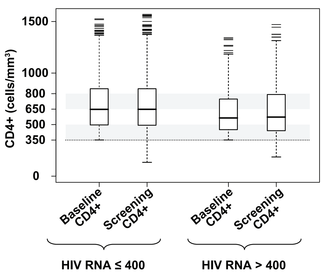
No. of Patients				
Overall:	1960	1362	847	539
350 - 499:	544	312	167	91
500 - 649:	489	340	195	116
650 - 799:	384	285	184	121
800+:	543	425	301	211

Figure 3. Mean change in CD4+ during ART interruption, by CD4+ nadir



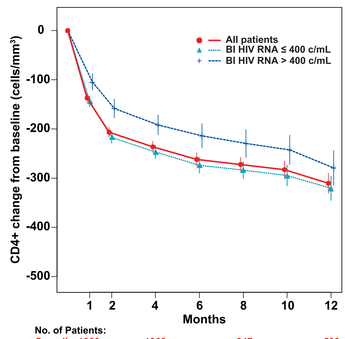
No. of Patients				
Overall:	1960	1362	847	539
0 - 99:	361	175	60	31
100 - 199:	429	273	160	88
200+:	1170	914	627	420

Figure 1. Distributions of baseline and screening CD4+, by baseline HIV RNA



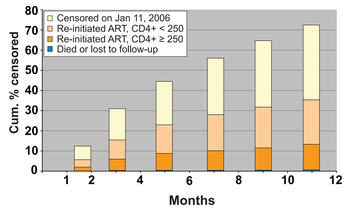
Side-by-side box plots show the distributions of CD4+ cell counts at baseline and at screening by baseline HIV RNA. Boxes extend from the 25th to the 75th percentile (IQR), the middle lines mark the medians, and whiskers show the range (up to 1.5*IQR beyond the boxes). Screening CD4+ counts were obtained median 84 days prior to baseline. Eligibility required baseline CD4+ > 350 cells/mm^3; 4.4% of patients had screening CD4+ < 350 cells/mm^3.

Figure 4. Mean change in CD4+ during ART interruption, by baseline HIV RNA



No. of Patients:				
Overall:	1960	1362	847	539
≤ 400:	1595	1095	664	406
> 400:	360	264	181	132

Figure 5. Cumulative percent of patients who re-initiated ART or were censored due to other reasons



The CD4+ averages in Figures 2-4 were taken over patients who were still off ART. By 12 months, 704 patients (35% of 2025) had re-initiated ART; follow-up for 750 patients (37%) was censored on January 11, 2006, and 13 (0.6%) had died or were lost to follow-up.

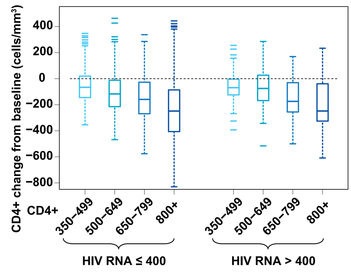
Table 2. Factors associated with CD4+ decline in the first month of the ART interruption

	Multiple Regression 1			Multiple Regression 2			Univariate Regression	
Factor	Diff. in mean CD4+ change[1]	95% CI	P-value	Diff. in mean CD4+ change[1]	95% CI	P-value	Diff. in mean CD4+ change[1]	P-value
Baseline CD4+ (per 100 cells/mm^3 higher)	-46.5	(-50.3, -42.7)	<0.001				-31.6	<0.001
Baseline CD4% (per 1 % higher)	2.8	(1.7, 3.9)	<0.001				-1.7	<0.001
Screening[2] CD4+ (per 100 cells/mm^3 higher)				-17.4	(-21.7, -13.1)	<0.001	-12.8	<0.001
Screening[2] CD4% (per 1 % higher)				0.1	(-1.1, 1.4)	0.84	-1.0	0.06
Nadir CD4+ (per 100 cells/mm^3 higher)	33.3	(27.5, 39.2)	<0.001	18.9	(12.1, 25.6)	<0.001	10.0	<0.001
Baseline HIV RNA > 400 vs. ≤ 400 copies/mL	13.3	(-7.5, 34.1)	0.21	33.2	(9.5, 56.8)	0.006	39.7	<0.001
Highest prior HIV RNA ($\log_{10}$ copies/mL)	-0.4	(-8.7, 7.9)	0.92	-7.6	(-17.2, 2.0)	0.12	-11.6	0.01
Total duration of ART at study entry 0 – 4 vs. 5+ years	-2.9	(-19.7, 13.9)	0.74	17.2	(-2.3, 36.7)	0.08	28.4	0.002
Prior AIDS Yes vs. No	-19.0	(-38.0, 0.0)	0.05	-24.2	(-46.2, -2.3)	0.03	-39.7	<0.001
Age (per 10 years higher)	7.2	(-1.3, 15.6)	0.10	7.8	(-1.9, 17.5)	0.12	4.1	0.40
Gender Male vs. Female	8.3	(-10.7, 27.4)	0.39	15.1	(-7.2, 37.3)	0.18	10.7	0.31
Race Black vs. Other	-4.2	(-22.8, 14.4)	0.66	-4.5	(-26.1, 17.0)	0.68	2.8	0.78

[1] Regression coefficients, response = CD4+ change from baseline to month 1. Negative values correspond to steeper CD4+ decline.
[2] Obtained prior to study entry, median time 84 days (IQR 51-112) prior to baseline CD4+.

Abbreviations: CI, confidence interval; IQR, interquartile range.

Figure 6. Change in CD4+ from baseline to month 1



Side-by-side box plots show the month 1 CD4+ decline for subgroups of patients by baseline CD4+ and HIV RNA. Boxes extend from the 25th to the 75th percentile (IQR), the middle lines mark the medians, and whiskers show the range (up to 1.5*IQR beyond the boxes). Patient-to-patient variability is large within subgroups.

Results (continued)

- Two multiple regression models were fitted to assess the association of baseline factors with CD4+ decline during the first month off ART. The models differ only in the way the CD4+ and CD4% levels at study entry are represented – model 1 uses baseline values, model 2 values obtained at screening (prior to study entry, median time 84 days prior to baseline). Factors and results are presented in Table 2.
- Steeper CD4+ decline during the first month was associated with higher CD4+ at study entry (-46.5 and -17.4 cells/mm^3 per 100 cells higher baseline or screening CD4+, respectively), lower CD4+ nadir, and prior AIDS.
- Steeper CD4+ decline was associated with lower CD4% at baseline, and not associated with CD4% prior to baseline.
- Patients with baseline HIV RNA ≤ 400 had a steeper initial CD4+ decline, and HIV RNA was predictive of CD4+ decline in the model adjusted for screening CD4+. However, HIV RNA was not significant as predictor after adjusting for baseline CD4+.
- Race, sex, and highest prior HIV RNA level were not significant in multiple regression.

Discussion

- It is well known that patients with higher CD4+ cell counts at ART discontinuation have steeper initial CD4+ declines. In part this is due to "regression to the mean," since CD4+ count measurements are highly variable, and an unusually high CD4+ cell count is likely to be followed by a lower measurement even on stable ART. This problem is attenuated when fitting the screening CD4+ instead. In our analyses, high screening CD4+ was independently associated with steeper CD4+ decline during the first month off ART. The lower regression coefficient of the screening CD4+ is likely a more accurate description of biological CD4+ cell count decline than that for baseline CD4+ (-17.4 versus -46.5 cells per 100 cells higher).
- Low nadir CD4+ was associated with steeper initial CD4+ decline, consistent with the results of many other studies. Interestingly, the influence of nadir CD4+ appeared stronger when adjusting for baseline CD4+ compared to the earlier screening CD4+ (33 cells steeper decline per 100 cells/mm^3 lower nadir CD4+, compared to 19 cells).
- Lower CD4% at baseline was independently associated with steeper initial CD4+ decline, after adjusting for baseline CD4+ and other factors, consistent with the results of other studies. However, in the model with screening CD4+ and CD4%, CD4% was not predictive of initial CD4+ decline. One possible explanation is again "regression to the mean" – CD4% and absolute CD4+ counts are correlated (correlation coefficient r = 0.54), and the stronger association of baseline CD4% with CD4+ decline may in part be driven by the strong association of baseline CD4+ with the CD4+ decline from baseline.
- Patients with prior AIDS had steeper initial CD4+ decline. This is consistent with other studies.
- CD4+ decline varied substantially between patients, as demonstrated by the side-by-side box plots in Figure 6. Predicting CD4+ decline for individual patients based on their baseline values would include substantial uncertainty.

Limitations

Predictors for CD4+ decline were evaluated only for the first month of ART interruption. Models for CD4+ decline through longer follow-up should take into account that (1) the CD4+ decline is non-linear (steepest during the first two months), and (2) censoring due to ART re-initiation above 250 cells/mm^3, death or loss to follow-up may be informative.

Conclusions

- The CD4+ decline was steepest during the first 2 months.
- High CD4+ at ART discontinuation, low CD4+ nadir, HIV RNA ≤ 400, and prior AIDS were independently associated with steeper initial CD4+ decline.
- If ART interruption is planned, CD4+ decline should be monitored carefully.

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