



BIPHASIC DECLINE OF CD4 CELL COUNT DURING SCHEDULED TREATMENT INTERRUPTIONS (STIs)



Fagard C (1), Ananworanich J (2), Bandelier CY (1), Le Braz M, Perneger T (1), Perrin L (1), Cooper D (3), Cavassini M (4), Ebnöther C (5), Genné D (6), Sukontha Saenawat (2), Sajja Wicharuk (2), Ubolyam S (2), Vernazza P(7), Bernasconi E (8), Yerly S (1), Hirschel* (1), (1) University Hospital, Geneva, Switzerland, and the Swiss HIV Cohort Study, (2) HIVNAT, Bangkok, Thailand, (3) NCECR, Sydney, Austria, (4) CHUV, Lausanne, Switzerland, (5) University Hospital, Zürich, Switzerland, (6) La Chaux de Fond, Switzerland, (7) St. Gall, Switzerland, (8) Lugano, Switzerland

Background:

Scheduled treatment interruptions (STIs) aim to diminish costs and side-effects of HAART. When treatment is stopped, HIV rebounds and CD4 cell counts tend to fall. The pattern of CD4 decline has not been well investigated. Current knowledge comes from small, often retrospective, studies enrolling highly selected subjects, and lacking uniform protocols for measuring CD4 counts, and for re-starting treatment. In order to improve our understanding of the CD4 cell count during STI, we pooled the results of three similar prospective studies and analysed in detail the kinetics of the CD4 cell count following treatment interruption.

Methods:

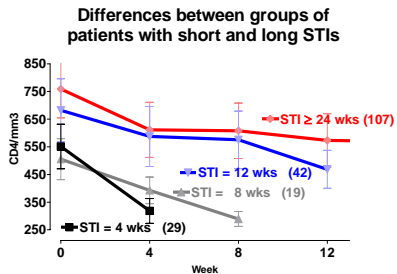
Data presented originate in three different prospective trials (2 completed and one ongoing):

- SSITT-1 (N = 78, Arch Intern Med. 2003; 163:1220)
- SSITT-2 (N = 17, AIDS 2003 ;17: 1487-92)
- Staccato (N=102, ongoing, see AIDS 2003; 17:F33-7)

These trials used uniform monitoring of CD4 counts at 0, 4, 8, 12, and 24 weeks, and relatively uniform criteria for starting therapy again (a fall in CD4 count to <350 CD4 cells, or excessive rebounds of the viral load with signs and symptoms compatible with the acute retroviral syndrome), and therefore provide a consistent database for measuring the decline in CD4 counts during STIs in 197 patients. We analyzed the rate of CD4 cell count decline in 3 groups of patients according to the duration of the treatment interruption.

Results:

1. Patients with short STIs tend to start STIs with low CD4 counts, and show steep decline in CD4 from wk 0 to 4



Differences in CD4 counts at start of STI

	STI ≥24 wks	STI=12 wks	STI = 8 wks	STI = 4 wks
STI ≥ 24 wks	X	NS p=0.1	p=0.000	p=0.000
STI =12 wks	NS p=0.1	X	p=0.002	p=0.02
STI =8 wks	P=0.000	p=0.002	X	NS p=0.4
STI =4 wks	P=0.000	p=0.02	NS p=0.4	X

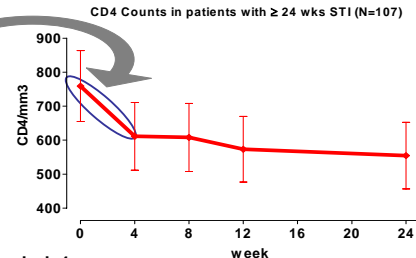
Differences in CD4 slope, week 0 to 4

	STI ≥24 wks	STI=12 wks	STI = 8 wks	STI = 4 wks
STI ≥ 24 wks	X	NS	NS	p=0.006
STI = 12 wks	NS	X	NS	p=0.002
STI = 8 wks	NS	NS	X	p=0.01
STI = 4 wks	p=0.006	p=0.002	p=0.01	X

2. In long (≥ 24 weeks) STIs, CD4 counts fall rapidly during the first four weeks, and much more slowly thereafter.

107 patients completed 24 weeks of STI. The median CD4 count before HAART was 350 (11 to 1892), with a median VL of 32608, and CD4 counts during the first 24 wks of STI are shown in the Table.

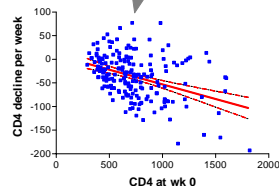
	Wk0	Wk4	Wk8	Wk12	Wk24
Median CD4 count/ μ L	731	626	586	518.5	516
Median fall/wk		-29.5	-0.25	-1	-3.65
P between decline/wk		P=0.0001	P=0.6	P=0.9	



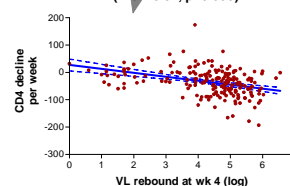
3. Multivariate analysis of correlations with CD4 decline between wk 0 and wk 4

The higher the CD4 count at week 0, and the higher the VL rebound at week 4, the steeper the decline in CD4 cells from weeks 0 to 4 ($p < 0.01$ in multivariate analysis). The correlation held true when percentage decline was substituted for absolute decline. There was no significant correlation between VL or CD4 count pre-HAART and CD4 decline during STI (not shown).

Decline in CD4 count wk 4 vs CD4 at wk 0 (Rho=0.73, p=0.000)



Decline in CD4 count wk 4 vs VL rebound wk 4 (rho = 0.34, p=0.000)



We considered the possibility that CD4 count might start to fall even before viral load rises, but did not find any evidence for this hypothesis:

27 patients had a VL<1000 at week 4. Of these 27, 10 had a VL<1000 at wk 8, and 17 had a VL > 1000 at wk 8. Does the CD4 change between week 0 and 4 differ significantly between the 10 and the 17? Answer is no.

Conclusions. In patients with long (≥24 wks) STIs,

1. The higher the CD4 count at the start of the STI, the steeper the decline during the first four weeks.
2. CD4 counts decline by 30 cells per week (median) during the first 4 weeks of STI, and by 3 cells (median) per week during the next 20 weeks. Appropriate monitoring would include a measure of CD4 cells at the start of STIs, after 4 weeks, and every 8 to 12 weeks thereafter
3. These findings raise interesting theoretical questions regarding CD4 homeostasis.