514-M

LONG TERM EFFICACY OF SUBCUTANEOUS IL-2 THERAPY IN HIV-INFECTION

FINAL ANALYSIS OF THE ANRS 079 RANDOMIZED TRIAL AND LONG TERM FOLLOW-UP

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ABSTRACT

Objectives : To assess the long term efficacy of SC IL-2.

Patients and design : 118 pts naive to antiretrovirals or naive to PI were randomized to start and receive over 74 weeks (w) d4T+3TC+Indinavir either alone (HAART, n=58) or combined with SC IL-2 cycles (n=58) (5 MIU, bid, 5 days) every 4w (3 cycles) and then every 8w (7 cycles). After w74, 52 (HAART) and 50 (IL-2 arm) pts consented to an extended follow-up (EFU).

Results : Median (range) follow-up was 35 (20-45) months. Pts from the IL-2 group received 446 and 10 cycles during the randomized phase and the EFU, respectively. 8 (HAART) pts received 15 cycles during the EFU. At baseline (BL) median CD4 cell counts/ml were 342 (HAART) and 353 (IL-2 arm). The median CD4 increase was +262 (HAART) and +835 (IL-2 arm) at w74 (p<0.0001), and +365 and +604 at last assessment (LA), respectively (p=0.0002). At LA, 88 pts (90%) were on triple combination (48 and 40 pts in HAART and IL-2 groups, respectively, p=ns), 6 pts were on NRTI combinations and 4 discontinued antivirals. Mean plasma HIV RNA $\log_{10}$ cp/ml, which was 4.16 (HAART) and 3.95 (IL-2 arm) at BL, decreased repectively in those 2 groups to 1.87 (SD=0.51) and 2.08 (0.83) at w74 (p=0.16) and to 2.07 (0.92) and 2.04 (0.98) at LA (p=0.65). At LA 78% (HAART) and 76% (IL-2 arm) of pts had HIV RNA below 50 cp/ml (ns). At LA, 84% and 70% of pts respectively naive to antiretrovirals or to PI at entry had HIV RNA <50 cp/ml, with no significant differences between groups.

Conclusion : IL-2 recipients experienced a faster and a higher immunological response, which was maintained over 35 months with rare IL-2 cycles after M18, compared to pts treated with HAART who progressively increased their CD4 counts over 3 years. At LA, the decrease of plasma HIV RNA and the proportion of patients with undetectable viral load was similar in both groups.

OBJECTIVE

To assess the long term immunological and virological effects of SC IL-2 combined with HAART compared to HAART alone in a randomized controlled trial (18 months) and in an extended follow-up (24 months).

METHODS

Patients and design

118 patients naive to antiretrovirals or naive to PI were randomized to start and receive over 74 weeks d4T+3TC+Indinavir either alone (HAART, n=58) or combined with SC IL-2 cycles (n=58) (5 MIU, bid, 5 days) every 4 weeks (3 cycles) and then every 8 weeks (7 cycles).
After w74, 52 (HAART) and 50 (IL-2 arm) pts consented to an extended follow-up (EFU).

ANRS 079 Study design

Without prior AIDS-events patients with CD4 counts 200-550 cells/mm³ , naive to ART or naive to PI (pretreated with dual-nucleoside therapy)

n = 118

New combination : D4T + 3TC + Indinavir for 4 weeks

n = 58 — **D4T+3TC+Indinavir**

n = 60 — **D4T+3TC+Indinavir + SC IL-2**
5 MIU bid, 5 days
q 4 weeks for 3 cycles
q 8 weeks for 7 cycles

Duration : patients are treated for 18 months (10 cycles)

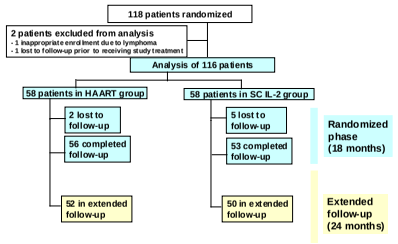
Extended follow-up : 24 months

Statistical analysis

- **Sample size** (n=60 in each group) was calculated to provide 90% power for detecting a 30% difference in the proportions of pts having a CD4 response at final evaluation (w72,w74) (at least 50% increase over baseline in the CD4 T-cell count).
- **Randomization** was **stratified** by prior antiretroviral status (naive to ART or naive to PI).
- **Intent-to-treat** approach is used.

- **Proportions** are compared by the Fisher's exact test
- **CD4 T-cell increases over baseline** are compared by the Wilcoxon-rank-sum test.
- **Viral load means** are compared by analysis of variance stratified by prior antiretroviral status.
- **HAART group vs IL-2 group** unadjusted p-values are presented.

RESULTS



Follow-up : number of patients

		HAART	SC IL-2	Total
Entry	W0	58	58	116
End of randomized phase	W74	56	53	109
Extended follow-up		52	50	102
1st year	W122	38	35	73
2nd year	W170	17	16	33
Last assessment*	W147	52	46	98

*Median follow-up at last assessment : 146 weeks [82, 178]

Baseline characteristics of patients

	HAART group	IL-2 group
Number of patients	58	58
Age (years)	36.3 (7.8)	35.7 (7.3)
Male sex	42 (72.4)	40 (69.0)
Naive to antivirals	34 (58.6)	32 (55.2)
Dual-nucleoside pretreated	24 (41.4)	26 (44.8)
Median (range) duration of antiviral therapy (months)	22.5 (5 – 103)	17.7 (3 – 91)
CD4+ T cells /µL	342.0 (78.1)	353.3 (92.3)
CD8+ T cells /µL	818.8 (346.2)	929.4 (387.5)
CD4/CD8 ≥ 1	2 / 58 (3)	3 / 57 (5)
Plasma HIV-1 RNA, $\log_{10}$copies/mL	4.16 (0.82)	3.95 (0.97)
Naive to antivirals	4.48 (0.50)	4.46 (0.74)
Dual nucleoside pretreated	3.69 (0.97)	3.31 (0.85)
HIV-1 RNA ≤ 50 copies/mL	1 (1.7)	3 (5.2)

Data are n (%) or mean (SD) unless otherwise indicated

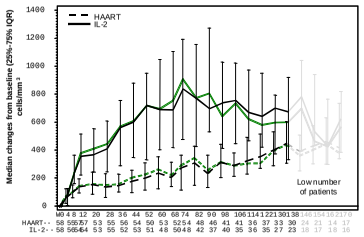
CD4-T-CELL RESPONSE

CD4-T-cell counts
Median changes from baseline
[min, max] cells/mm³

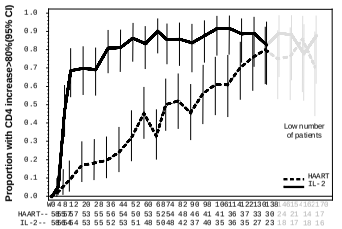
	HAART	IL-2	p
W0	334 [204,492]	343 [200, 549]	
W74	+262 [-237,658]	+835 [-62,3031]	<0.0001
W122	+354 [-101,1758]	+641 [-48,1828]	
LA*	+365 [-123,1419]	+604 [-121, 1828]	0.0002

* Last Assessment

MEDIAN CD4 COUNTS CHANGES FROM BASELINE
All patients
Patients not receiving IL-2 in extended follow-up



PROPORTION OF PATIENTS WITH CD4 INCREASE > 80%



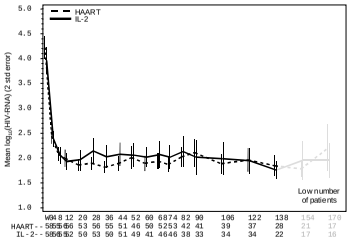
VIRAL LOAD

Mean plasma HIV-RNA (standard error)
$\log_{10}$ copies/ml

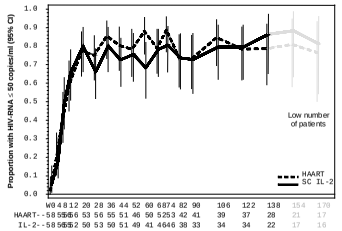
	HAART	IL-2	P*
W0	4.16 (0.82)	3.95 (0.97)	
W74	1.87 (0.51)	2.08 (0.83)	0.16
W122	1.96 (0.73)	1.95 (0.75)	
LA	2.07 (0.92)	2.04 (0.98)	0.65

* Analysis stratified by prior antiretroviral status

MEAN PLASMA HIV-RNA (log10) OVER TIME

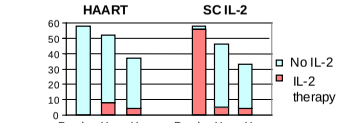


PROPORTION OF PATIENTS WITH PLASMA HIV-RNA BELOW 50 COPIES/ML



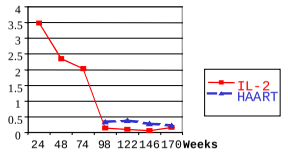
SC IL-2 THERAPY

Number of patients with SC IL-2 therapy



	HAART Random. Phase	HAART Year 1	HAART Year 2	SC IL-2 Random. Phase	SC IL-2 Year 1	SC IL-2 Year 2
Nb of cycles	0	31	19	446	10	5
Nb of recipients	0	8	4	56	5	4

Ratio of IL-2 cycles per patient 24-weeks periods
Nb of cycles / nb of patients



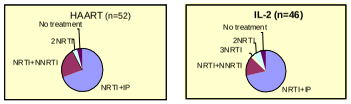
Virological response according to prior antiretroviral status

Number of patients with HIV-RNA below 50 copies/ml (percentage)

	Naive to ART HAART	Naive to ART IL-2	Naive to PI HAART	Naive to PI IL-2
W0	0/34	0/32	1/24	3/25
W74	30/32 (94%)	20/22 (91%)	17/21 (81%)	17/24 (71%)
W122	18/22	12/16	11/15	15/18
LA	24/29 (83%)	19/22 (86%)	16/22 (73%)	16/24 (67%)

All comparisons between HAART and IL-2 are not significant.

Antiretroviral therapy at last assessment



Nb of patients	HAART (n=52)	IL-2 (n=46)
NRTI+IP	36	33
NRTI+NNRTI	12	7
3NRTI	0	1
2NRTI	2	3
No treatment	2	2

CONCLUSION

- IL-2 recipients experienced a faster and a higher immunological response, compared to patients treated with HAART.

- This higher response was maintained over 35 months with rare IL-2 cycles after M18, although patients treated with HAART progressively increased their CD4 counts over 3 years.

- At last assessment (35 months), the decrease of plasma HIV RNA and the proportion of patients with undetectable viral load was similar in both groups.

ANRS 079 STUDY GROUP

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