



Can HAART Initiation at Early Acute HIV Infection Benefit the Immune-virology Outcome Despite Subsequent Treatment Cessation?

The ANRS Reservoirs' Study Group

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Abstract

Objective: To evaluate the immune-virology outcome of patients (pts) initiating HAART very early at acute HIV infection and for several years before discontinuation, and to compare it with non-treated pts after a documented HIV seroconversion diagnosed in the same multicenter observational cohort setting.

Methods: Pts were enrolled within 10 weeks after the first acute symptoms and self-decided to initiate HAART or not. Pts who received HAART (n= 20) were treated for a median period of 2.3 years (range: 1-7 years), then stopped therapy, whereas untreated pts (n=18) were those who actually refused therapy. HIV RNA levels and CD4 T cell counts were compared within the 2 groups every 12 week and at weeks 48, 96 and 144 following treatment cessation

Results: Age, sex, median CD4 T cell counts and median viral loads were similar in the two groups at the acute phase. Treated pts maintained a viral load < 400 cps/mL in 42.1%, 36% and 31% of cases at weeks 48, 96 and 144 respectively, after treatment cessation, compared to 56%, 0% and 0% at the same time points (p<0.001) for untreated pts. A viral load < 50 copies/ml was observed in 25% of pts in the treated group after treatment interruption compared to none in the untreated group at the week 144 time point (p=0.0001). After 3 years of follow up, 64% of pts in the untreated group compared with 6% in the treated group were eligible for treatment initiation or re-introduction according French guidelines (p=0.0025). In the subgroup of treated patients who maintained viral load control despite treatment cessation, CD4 T cells did not show any decrease over a median observation time of 238 weeks compared with a median loss of 8 CD4 T cells each month of follow up in patients who did not receive HAART during acute infection. In the treated group, the ratio of HAART duration over HAART delay from acute symptoms to therapy was significantly higher for pts with viral load control than for others (0.91 vs 0.56 year per week; p=0.04)

Conclusion: Early HAART initiation during primary infection and continuation for several years was associated in this cohort study with significant viral load and CD4 T cells benefits for at least 144 weeks following therapy cessation. These observational data add new evidence for considering HAART initiation at primary HIV infection

Background

To date, whether antiretroviral therapy (ART) should be initiated very early during HIV-1 infection, i.e. in patients with primary-infection (PHI), still remains controversial (1).

On one hand, among chronically infected patients HAART has proved its capacity to control viral replication durably, over years for sure, long-life may be. This is a concept which is limited to the plasmatic compartment in fact, and only if patients are still on treatment (2). Indeed, once the virus has expanded to reservoir cells, an early event during HIV infection, eradication is considered as a very unlikely goal to reach (3). During primary infection, recent studies suggest that early intervention could improve the subsequent course of the disease (4,5). Previous studies re-enforce this idea, demonstrating that not only time of HIV DNA decay is very long in these reservoirs cells, but also that its replenishment is still on-going under HAART, even if plasmatic viral control is obtained for years (4). On the other hand, authors suggest that during primary infection, the virus could disrupt the early development of the most effective immune responses against the virus and that very early antiretroviral therapy may minimized this disruption, allowing better development of these early CD4+ T cells anti-HIV responses (6). Hecht et al. (6) showed that very early initiation of HAART was associated with viral load and CD4+T cells count benefits after termination of HAART.

We present the results of a multicentric observational cohort study which compare two groups of patients diagnosed during primary infection.

Subjects and methods

All Patients from 3 french hospitals who met the criteria for Acute HIV infection between 1997 and 2005 : 1. A negative or indeterminate result of an Elisa test and an HIV RNA load of >5000 copies/mL. 2. An incomplete Western Blot test and a positive p24 antigen

Group 1: TREATED PATIENTS

- HAART initiated within 10 weeks after onset of symptomatic acute HIV infection
- HAART leading to viral load control (VL<400 copies/mL) within 3 months after HAART initiation
- HAART given AT LEAST during 12 months then interrupted

Group 2: UNTREATED PATIENTS

Analysis

The key end points of the study were defined as the HIV RNA levels and the CD4+ T cells counts determined at 48, 96, 144 weeks and last data available (up to 384 weeks):

- after treatment cessation in the TREATED GROUP
- after acute HIV infection in the UNTREATED GROUP

The Kaplan Meier method was used to construct event-free survival curves, which were compared using the log-rank test. The following 4 outcome measures were used: a HIV-RNA viral load of >50 copies/mL, >400 copies/mL, >1000 copies/mL and a CD4 T cells count of <350/mm³ leading to resume or initiate HAART.

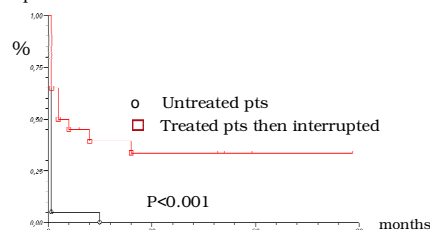
Results

There were 20 patients in the treated group (median follow-up after treatment cessation: 236 weeks, IQR: 148-284) and 18 patients in the untreated group. There were no significant differences between these groups at the time of acute HIV infection diagnosis (table 1)

	Untreated n=18	Treated n=20	p
- Age	33	32	NS
- Sex (M)	78%	75%	NS
- Sexually contaminated	89%	90%	NS
- Race (caucasian)	95%	80%	NS
- CD4+ T cells/mm ³	687	525	0.26
- CD4/CD8 ratio	0.56	0.72	NS
- Viral load (cp/mL)	76,000	123,000	NS
- Time between symptoms and HAART initiation (days)	NA	33 (8-66)	
- Duration of HAART prior interruption (years)	NA	2.3(1-7.1)	

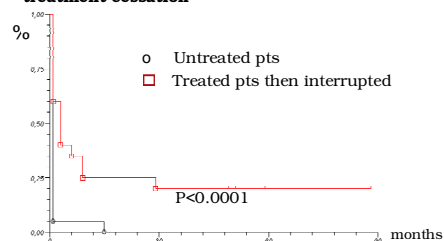
Table 1: Characteristics of patients with acute HIV infection: group 1 (untreated), Group 2 (early treatment then interrupted)

Treated subjects maintained a viral load < 400 copies/mL in 42.1%, 36% and 31% of cases at weeks 48, 96 and 144 respectively, after treatment cessation, compared to 56%, 0% and 0% at the same time points (p<0.001) for untreated pts.



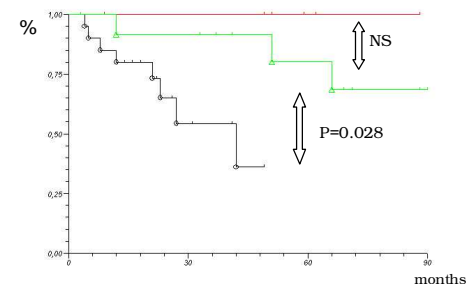
Graph 1: Survival curves comparing untreated and treated patients with HIV RNA viral load < 400 copies/mL at follow-up time points. (baseline: date of HIV diagnosis for untreated pts, date of HAART interruption for treated pts)

A viral load < 50 copies/ml was observed in 25% of pts in the treated group after treatment interruption compared to none in the untreated group at the week 144 time point (p=0.0001). **To date, these subjects continue to maintain a viral control (<20 copies/mL) 4 to 7 years (384 weeks) after treatment cessation**



Graph 2: Survival curves comparing untreated and treated patients with HIV RNA viral load < 50 copies/mL at follow-up time points.

After 3 years of follow up, 64% of pts in the untreated group compared with 6% in the treated group were eligible for treatment initiation or re-introduction according French National guidelines (p=0.0025).



Graph 3: Proportion of subjects free of HAART in three groups during the follow-up period:
 □ treated subjects who maintained a viral control
 △ treated subjects who did not maintain a viral control
 ○ untreated subjects

CD4 T cells count changes after baseline

	Median change of CD4 T cells/ month of follow-up after baseline (cells/mm ³)	p
Treated vs untreated	- 6 cells vs - 8 cells	NS
Treated who maintained a viral control vs untreated	+ 0 cells vs - 8 cells	0.015

Table 2: Subjects who did not receive treatment lost a median number of 11.1 CD4/mm³ each month during the first 3 years. The subjects who received HAART during a median period of 2.3 years and maintained a viral load < 400 copies at M144 **did not lost** any CD4 T cells and maintained their CD4 T cells baseline number after treatment cessation

Among treated patients, the subjects who maintained a viral control after treatment cessation:

- Were slightly more likely to have been under HAART for a longer period of time compared to subjects who relapsed (4.5 years vs 2.1 years; p=0.13)

- The ratio of HAART duration over HAART delay from acute symptoms to therapy was significantly higher for pts with viral load control than for others (0.91 vs 0.56 year per week; p=0.04)

- Were neither HLA B27 nor HLA B57

- Had a median HIV-DNA of 2 log copies/10⁶ PBMCs ranging from < 1.8 to 2.17 log copies/ 10⁶ PBMCs after treatment cessation, remaining stable during the subsequent follow-up period which is considered as a very low level

CONCLUSION

- Early HAART initiation during primary infection and continuation for several years was associated in this cohort study with significant viral load and CD4 T cells benefits for at least 144 weeks following therapy cessation (up to seven years).

- There could be a relationship between the precocity of the treatment after initial symptoms and the duration needed to confer a viral control after HAART interruption: (i.e. the earlier is the treatment, the shorter will be its duration)

- These observational data add new evidence for considering HAART initiation at primary HIV infection

References:

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