

HIV-1 RNA Viral Load Dynamics after Discontinuation of Early and Effective HAART Initiated During Primary HIV-1 Infection

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ABSTRACT

Background: The aim of the study was to estimate viral load (VL) level during the year following the first interruption of early effective HAART among HIV-1 infected patients enrolled in the prospective PRIMO cohort, and to compare it with VL reached spontaneously in natural history among seroconverters from the prospective SEROCO cohort.

Methods: The French ANRS PRIMO cohort involved 393 VIH+ patients enrolled during primary-infection (PI) since 1996 confirmed by: incomplete Western blot (WB), positive p24 antigenemia; Elisa test: -/+ ≤ 6 months. The study population consisted of 58 patients who started HAART within six months following infection and who had a sustained virological response (below 500 copies/ml until HAART interruption). A linear mixed-effects model with two slopes was used to describe the dynamics of VL after interruption among the 58 selected patients (a total of 220 VL values were available during HAART). The time threshold was estimated by the profile likelihood method. Among the 116 patients enrolled within six months since infection in the SEROCO cohort, VL in natural history was estimated by calculating the mean VL 36 months after infection by using values measured nearest this time point (± 3 months).

Results: The VL reached 3.57 and 3.94 log copies/ml at 27 days (estimated time threshold) and 12 months after interruption respectively, which leads to a second slope of +0.03 log copies/ml per month. This VL level was independently associated with VL at HAART initiation and CD4+ cell counts at HAART interruption. The precocity of HAART (0 or 1 WB band; 1st symptoms of PI < 3 weeks after enrollment; time since infection < 1.5 month) and duration of the sustained responses to HAART before interruption were not associated with VL during treatment interruption. The VL level reached after a time between infection to interruption of 24 months and an interruption of 12 months was compared to the observed mean of VL at M36 since infection: 3.86 versus 3.94 log copies/ml respectively.

Conclusion: We found that HAART, initiated early during primary HIV-1 infection, had little impact on viral load measured during HAART interruption 1 or 2 years later. Randomized trials such as early versus deferred treatment with a long-term follow-up are needed to assess long-term potential benefits after infection between VL levels during natural history and after interruption of early effective treatment.

INTRODUCTION

Background

- Side-effects of long-term HAART such as metabolic complications, liver, mitochondrial toxicity or other intercurrent conditions often lead to antiretroviral interruption
- HAART interruption rapidly leads to a sharp increase in plasma HIV-RNA in most patients
- The influence of patient and treatment characteristics on viral load dynamics after HAART interruption have rarely been investigated
- Very few studies have focused on patient treated early, during primary-infection

Objectives

- To analyze the dynamics of HIV-1 plasma viral load (VL) after the interruption of effective HAART initiated during primary HIV-1 infection in patients enrolled in the PRIMO cohort
- To assess the influence of patient and treatment characteristics on VL after HAART interruption
- To compare estimated VL after HAART interruption with spontaneous VL reached in natural history in patients from the SEROCO cohort, at the same time since infection

METHODS

Patients

- Out of the 393 previously untreated patients enrolled during primary HIV-1 infection since 1996 in the ongoing French ANRS PRIMO cohort, the study population consisted of 58 patients who started HAART within six months following infection and who had a sustained virological response (below 500 copies/ml until HAART interruption)

- Out of the 431 seroconverters enrolled since 1988 in the ongoing French ANRS SEROCO cohort who had VL repeatedly measured from frozen sera, 116 patients who met the PRIMO inclusion criteria were then selected

Statistical Analysis

- All VL values recorded between the first HAART interruption and either the end of follow-up (when the patient remained untreated) or treatment resumption were considered for the modeling
- VL kinetics were analyzed using a linear mixed-effects model with two slopes. The time threshold was chosen by the profile likelihood method
- Among the 116 patients from SEROCO, mean VL 24 and 36 months after infection was estimated by using values measured nearest these time points (± 3 months); 79 and 66 measurements were available for these estimations

Characteristics of the 58 patients receiving early effective HAART in the PRIMO Cohort (1996 – 2003)

	N = 58
Women (%)	13 (22%)
Median age (years) (Inter Quartile Range, IQR)	33 (28-42)
Symptomatic PHI (%)	44/58 (76%)
Median VL (log ₁₀ copies/ml) (IQR)	4.9 (4.2-5.6)
Median CD4+ (cells/μl) (IQR)	560 (370-760)

0 or 1 Western blot band (%)	7/58 (12%)
Median time (days) since infection (IQR)	45 (34-70)
Time since PHI symptom onset < 3 weeks (%)	16/44 (36%)

Between HAART initiation and HAART Interruption

Median time (months) to HAART response (IQR)	2.6 (1.0-3.0)
Median time (months) between HAART response and HAART interruption (IQR)	17.3 (6.3-24.8)
Median CD4+ at HAART interruption (cells/μl) (IQR)	789 (630-983)
Median duration of HAART interruption (months) (IQR)	10.2 (2.3-23.3)
VL measurements per patient during HAART interruption (IQR)	3 (1-5)

Estimated viral load (VL) in a linear mixed-effects model after HAART interruption among the 58 PRIMO patients

	VL at 12 months after interruption (p-value)	Adjusted* VL at 12 months after interruption (p-value)
Men	4.14 (0.01)	4.15 (0.06)
Women	3.28	3.51
Age at enrollment = 25 years	3.85	4.06 (0.91)
= 35 years	3.96 (0.55)	4.04
Symptomatic PHI = yes	4.07 (0.13)	4.08 (0.48)
= no	3.56	3.83
VL at HAART initiation = 4 log ₁₀ copies/ml	3.60	--
= 5 log ₁₀ copies/ml	4.02 (< 0.01)	--
CD4+ at HAART initiation > 560 cells/μl	3.55 (0.01)	3.73 (0.06)
≤ 560 cells/μl	4.32	4.29
WB bands at HAART initiation ≥ 2	3.90 (0.52)	4.07 (0.49)
0 or 1	4.20	3.71
Time between infection and HAART > 1.5 month	3.63 (0.03)	3.83 (0.25)
≤ 1.5 month	4.24	4.18
Time between PHI symptom onset and HAART > 3 weeks*	3.90 (0.19)	4.01 (0.51)
≤ 3 weeks*	4.40	4.26
Time to HAART response > 3 months	4.32 (0.18)	4.26 (0.40)
≤ 3 months	3.83	3.96
Duration of sustained response to HAART = 1 year	3.90 (0.56)	4.07 (0.46)
= 2 years	3.98	3.98
CD4+ at HAART interruption > 870 cells/μl	3.37 (< 0.01)	3.43 (< 0.01)
≤ 870 cells/μl	4.24	4.34

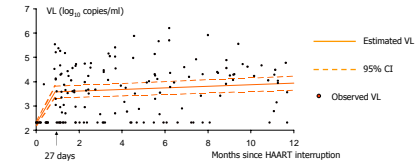
VL, HIV-1 plasma viral load (in log₁₀ copies/ml); HAART, highly active antiretroviral therapy; PHI, primary HIV-1 infection. *Among the 44 patients who presented symptomatic PHI. *Adjustment for VL at HAART initiation fixed at arbitrary 5 log₁₀ copies/ml

Estimated viral load at 24 and 36 months since infection, in HIV-1 natural history among the 116 patients from the SEROCO group and 12 months after HAART interruption among the 58 patients from the PRIMO group

	Months since infection	
	24	36
Mean observed VL (95% CI) during HIV-1 natural history (SEROCO) ^a	4.10 (3.92 - 4.28)	3.94 (3.74 - 4.14)
Estimated VL (95% CI) at 12 months after HAART interruption (PRIMO) ^b	3.91 (3.56 - 4.26)	3.86 (3.55 - 4.17)

VL expressed in log₁₀ copies/ml. *Calculated from VL measured within a window of +/- 3 months in the SEROCO cohort. ^aEstimated by linear mixed-effects model in the PRIMO cohort, by fixing proportion of women, age and time between infection and HAART interruption, at 28.5%, 29.8 years and 12 or 24 months, respectively.

Modeling of viral load after HAART interruption among the 58 patients from the PRIMO Cohort



MAIN RESULTS

Modeling of viral load (VL) after HAART interruption in PRIMO

- 12 months after HAART interruption, estimated VL was 3.94 log₁₀ copies/ml (95% CI, 3.65 - 4.23 log₁₀ copies/ml)
- Independent association with VL at HAART initiation and CD4+ at interruption
- No effect of both the precocity of treatment and the lasting of the sustained responses to HAART before interruption
- **Comparison between VL after interruption and VL in natural history from SEROCO**
- In HIV-1 natural history, VL spontaneously reached 4.10 and 3.94 log₁₀ copies/ml at M24 and M36 respectively since infection
- After HAART interruption, VL reached 3.91 and 3.86 log₁₀ copies/ml at M24 and M36 respectively since infection, comprising a 12 month period off therapy (adjusted for the same age and gender distribution than in SEROCO)

CONCLUSION

- HIV-1 plasma viral load (VL) after HAART interruption is strongly associated with VL at HAART initiation, and not with the precocity of HAART initiation
- The lack of strong difference between VL during HIV-1 natural history and after HAART interruption must be confirmed in a randomized trial involving an untreated control group and long-term post-trial follow-up

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