T-cell activation positively correlates with cell-associated HIV-DNA level in PBMCs in viremic patients with acute or chronic HIV-1 infection

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Introduction

Low level viremia supported by latently infected cells might contribute to chronic T-cell activation, while immune activation may in turn be involved in HIV reservoir seeding. The aim of this study was to evaluate the relationship between levels of T-cell activation and total cell-associated HIV-DNA in PBMCs in viremic patients with primary HIV infection (PHI) or with chronic HIV infection (CHI) before and after antiretroviral treatment (ART) interruption (TI).

1. Patients/Methods

Patients with **chronic HIV infection (CHI)** selected for this study were included in a substudy of the ANRS 116 SALTO trial, a multicenter study of treatment interruption that enrolled patients who started ART with CD4 count >350 /mL and VL <50,000 copies/mL and undergoing **treatment interruption** with baseline CD4 counts >450/mL and VL <400 copies/mL. Patients were monitored at baseline and month 12 (M12) of treatment interruption.
Patients diagnosed with **primary HIV infection (PHI)** were also investigated, before receiving any treatment.

CD4 and CD8 T cell activation were analyzed in relation with total HIV-DNA level in PBMCs using Spearman tests. Total HIV-DNA was quantified by real time PCR (Biocentric, Bandol France). Variables with p-values below 0.05 were then entered in multivariable linear regression models.

2. Patients' characteristics

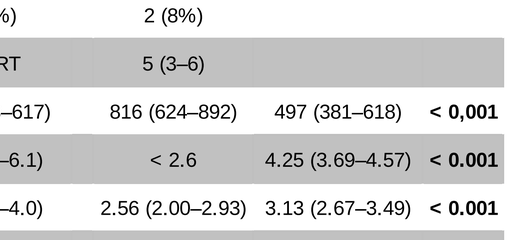
		Acute infection	Chronic infection		
			BL (before TI)	M12 after TI	p-value*
Number of patients		22	25		
Gender (male), n (%)		18 (82%)	18 (72%)		
Age		39 (30–46)	41 (37–47)		
Transmission group, n(%)	heterosexuals	4 (18%)	8 (32%)		
	homo/bisexuals	18 (82%)	14 (56%)		
	IV drug users	0 (0%)	2 (8%)		
Duration of ART (years), median (IQR)		no ART	5 (3–6)		
CD4 cell counts (/mm^3), median (IQR)		516 (373–617)	816 (624–892)	497 (381–618)	**< 0,001**
Plasma HIV-RNA (log$_{10}$ copies/mL), median (IQR)		5.7 (4.8–6.1)	< 2.6	4.25 (3.69–4.57)	**< 0.001**
HIV-DNA (log$_{10}$ copies/10^6 PBMCs), median (IQR)		3.7 (3.0–4.0)	2.56 (2.00–2.93)	3.13 (2.67–3.49)	**< 0.001**
% HLA-DR$^+$CD38$^+$ among CD8 T cells, median (IQR)		35 (21-50)	0.4 (0.2–0.6)	0.5 (0.2–1.7)	**0.011**
% CD38$^+$ among CD8 T cells, median (IQR)		57 (47-80)	8.8 (5.8–11.1)	11.9 (7.7–17.3)	**0.001**
% HLA-DR$^+$ among CD8 T cells, median (IQR)		38 (26-51)	3.2 (1.7–5.0)	3.6 (1.5–5.4)	0.904
% Ki-67$^+$ among CD8 T cells, median (IQR)		51 (21-64)	ND	ND	-
% HLA-DR$^+$ among CD4 T cells, median (IQR)		4.6 (3.7-6.8)	3.4 (2.0–4.4)	2.6 (1.8–4.6)	0.767
% Ki-67$^+$ among CD4 T cells, median (IQR)		9.2 (5.0-15.3)	ND	ND	-

* Wilcoxon paired test (BL vs. M12)

3. Total Cell-associated HIV-DNA

In untreated PHI patients, median (IQR) level of HIV-DNA was 3.7 log copies/10^6 PBMCs (3.0; 4.0). In ART-suppressed CHI patients, at baseline, HIV-DNA level was 2.56 (2.00; 2.93), while at M12 of treatment interruption, HIV-DNA level significantly increased to a median (IQR) of 3.13 (2.67; 3.49) (p<0.0001) *(figure 1)*.

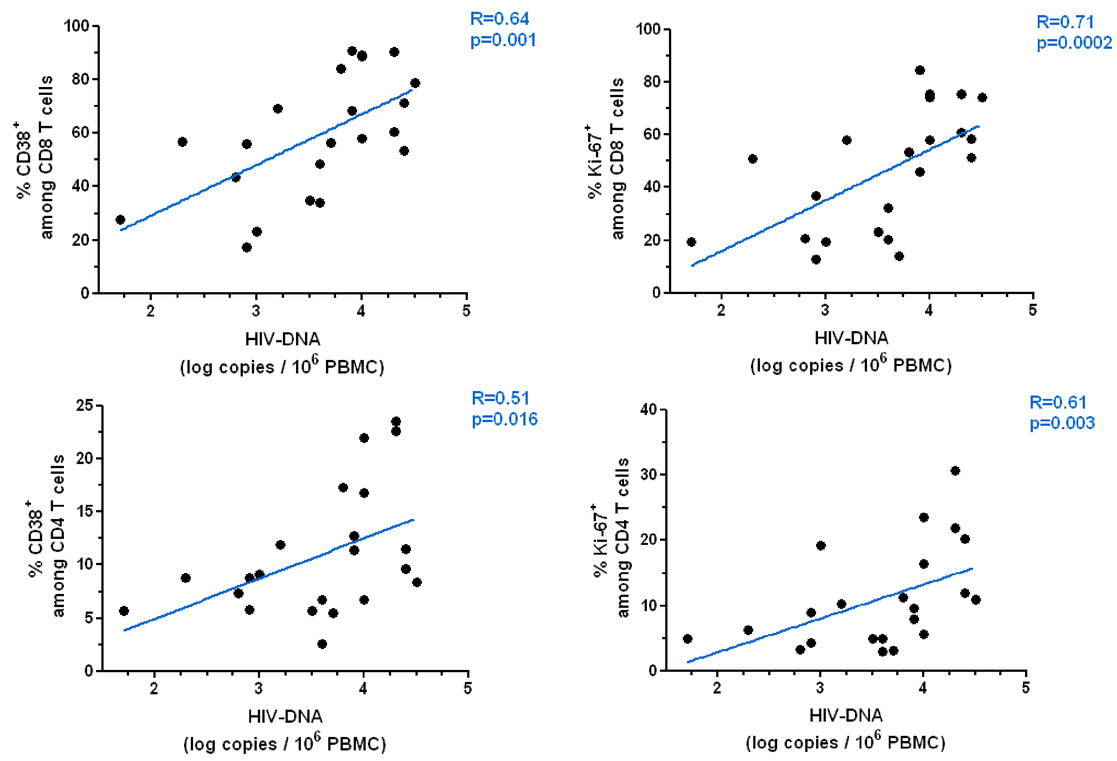
Figure 1 HIV-DNA levels in PHI and CHI patients



4. HIV-DNA and T-cell activation in patients with primary HIV infection

In PHI patients, HIV-DNA levels correlated with the proportion of CD8 T cells expressing CD38, Ki-67, and co-expressing HLA-DR and CD38. Moreover, HIV-DNA levels also correlated with the proportion of CD4 T cells expressing CD38, and Ki67 in univariable analysis (*figure 2*). In multivariable analysis, CD38 was the only activation marker independently associated with HIV-DNA levels.

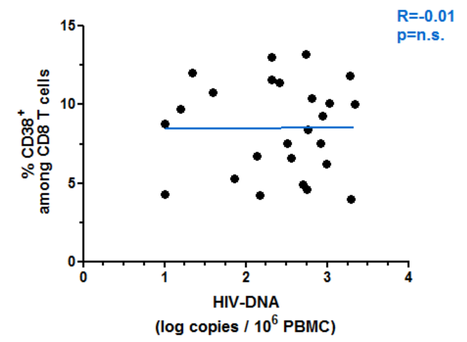
Figure 2 HIV-DNA in PBMCs is associated with CD8 and CD4 T-cell activation in PHI patients



5. HIV-DNA and T-cell activation in patients with chronic HIV infection before and after treatment interruption

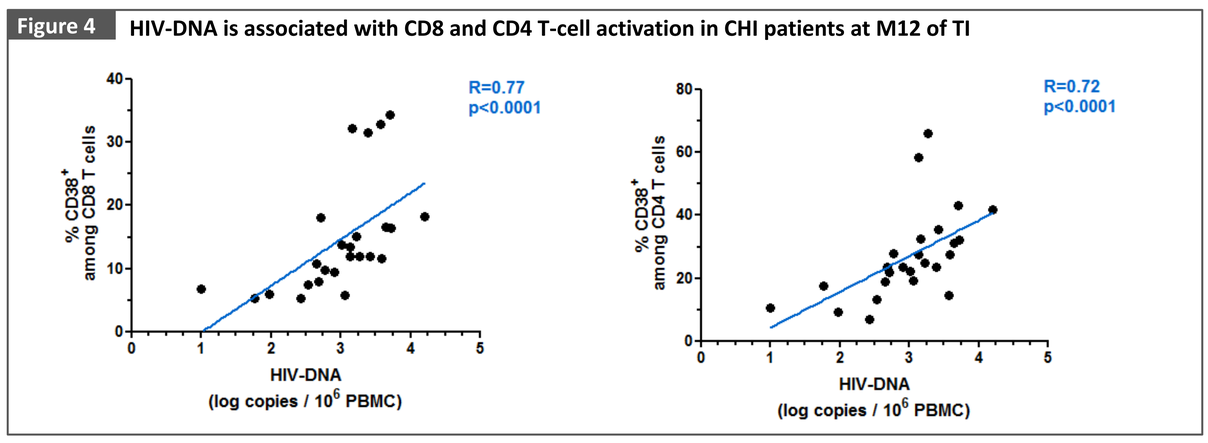
In patients with treated chronic HIV infection and undetectable viral load (baseline), there was no relationship between HIV-DNA levels and T-cell activation, whether assessed by the expression of CD38 (*figure 3*) and/or HLA-DR on CD4 and CD8 T cells.

Figure 3 CHI patients at baseline (before TI)



In contrast, at M12 of treatment interruption, HIV-DNA levels strongly correlated with the proportion of CD8 and CD4 T cells expressing CD38 (*figure 4*).

Figure 4 HIV-DNA is associated with CD8 and CD4 T-cell activation in CHI patients at M12 of TI



Conclusion

Levels of T-cell activation positively correlate with HIV-DNA levels in viremic patients with acute or chronic infection. The lack of association between HIV-DNA levels and T-cell activation in ART-treated patients suggests that residual immune activation is not directly dependent on the size of the latent HIV reservoir, at least in early ART-treated patients. Whether HIV-DNA level in a particular cell subset could be associated with immune activation may request further investigations.

Acknowledgments : We thank all patients involved in the study, and physicians from the hospitals involved in the study
Funding : This work was supported by the ANRS and Assistance Publique – Hôpitaux de Paris
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