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 ANRS116 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

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

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.

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.

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.

3. Total Cell-associated HIV-DNA

Figure 1 HIV-DNA levels in PHI and CHI patients

- 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).

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, andKi67 in univariable analysis (figure 2). In multivariable analysis, CD38 was the only activation marker independently associated with HIV-DNA levels.

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).

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.

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).

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.

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