IL-7 High-Affinity Receptor (CD127) Expression on Naive T cells and HIV Replication in Youths Infected in the Perinatal Period

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Background

We previously reported that naive CD4 T-cell percentages in a cohort of youths infected during the perinatal period were in the same range as those in uninfected individuals and that thymopoiesis was maintained in both viremic and aviremic patients *(Blanche et al., Clin Inf Dis, 2014, 58 : 573-587)*.

Aim

To study naive T-cell homeostasis by assaying plasma IL-7 and the cellular expression of CD127, its high-affinity receptor.

Patients

The ANRS-EP38-IMMIP study included 93 perinatally infected youths between the ages of 15 and 24; 43% were male and 39% were black. At the time of the study (February2007-February2009), 85% of the patients were under HAART and plasma HIV RNA load was <80 copies/mL in 75% of these patients. The median CD4 cell count was 581/µL (*Avettand-Fenoel, J Inf Dis, 2012, 205:1520-1528*).

Methods

Flow cytometry was performed on frozen PBMCs. Naive CD4 and CD8 T lymphocytes ($CD4_N$ and $CD8_N$) were defined as $CD45RA^+CD197^+$ cells and memory CD4 and CD8 T lymphocytes were defined as non naive T lymphocytes. CD127 expression was quantified on each subset. The gating strategy is presented in figure 1. Plasma analytes were quantified by ELISA and multiplex assays. Mann-Whitney and Spearman's rank tests were used for univariate analyses. Multivariate analyses were performed by linear regression, with $CD127^{high}CD4_N$ percentage as the dependent variable.

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Results-1

Plasma IL-7 levels were significantly higher in viremic patients than in aviremic patients (4.5 vs. 3.9 pg/ml, *P*=0.02, figure 2A). CD127 expression on memory CD4 T-cells was similar in aviremic and viremic patients (88.9 vs. 88.1, *P*=0.41, figure 2B). CD127 expression on memory CD8 T-cells was lower in aviremic than in viremic patients (41.6 vs. 59.8%, *P*=0.03, figure 2C). In sharp contrast, CD127 expression on naive T-cells was higher in viremic than in aviremic patients (CD4: 91.3 vs. 87.1%, *P*=0.007: CD8: 94.1 vs 89.9 *P*=0.07 figure 2D&E).

Figure 1: Gating strategy for CD127 expression on naive and memory CD4 and CD8 T lymphocytes

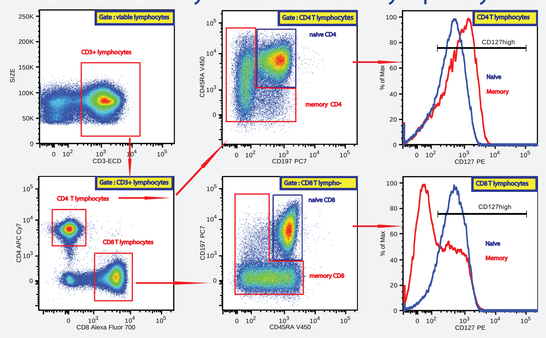
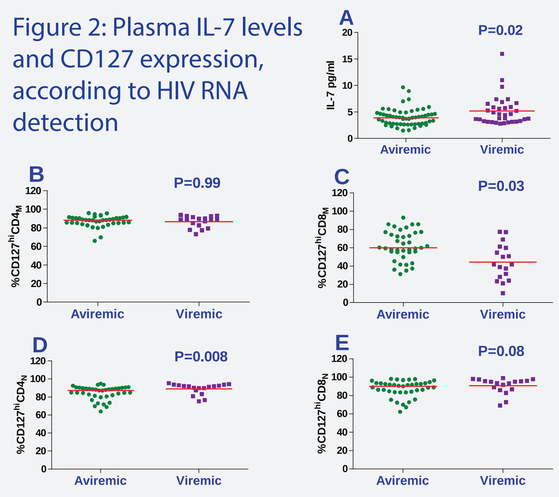


Figure 2: Plasma IL-7 levels and CD127 expression, according to HIV RNA detection

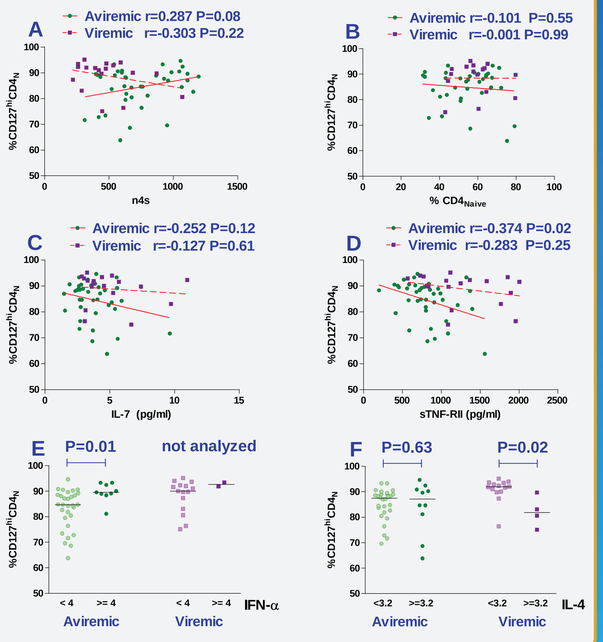


Results-2

The $CD127^{hi}CD4_N$ percentage was correlated with CD4 T-cell count only in aviremic patients (figure 3A). However, it was not associated with plasma IL-7 level or the naive CD4 T-cell percentage (figure 3B&C). Viremic patients infected with HIV B subtype viruses had a higher $CD127^{hi}CD4_N$ percentage than those infected with a non-B subtype viruses (92.3 vs 89.7%, P=0.05). The $CD127^{hi}CD4_N$ percentage was not associated with sex, ethnicity nor with HIV disease history (data not shown).

The plasma levels of several cytokines were associated with $CD127^{hi}CD4_N$ percentages: IFN-α and sTNFR2 level in aviremic patients (Figure 3D and E). In viremic patients, the $CD127^{hi}CD4_N$ percentage was significantly lower in patients with detectable IL-4 in plasma (Figure 3F).

Figure 3: Association between $CD127^{hi}CD4_N$ percentage and immune parameters



Results-3

The associations between $CD127^{hi}CD8_N$ percentage and HIV disease parameters were similar to those described for $CD127^{hi}CD4_N$ percentage (data not shown).

Multivariate analysis showed that $CD127^{hi}CD4_N$ percentage was independently associated with CD4 T-cell count, IFN-α and sTNFR2 levels in aviremic patients. In viremic patients, $CD127^{hi}CD4_N$ percentage was associated with plasma IL-4 detection but not with CD4 T-cell count (Table 1).

Table 1: Multivariate analysis of factors associated with $CD127^{hi}CD4_N$ percentage

Parameter	Estimate [95% CI]	P
Model 1 : Aviremic patients		
CD4 T-cell count (per 100 cells/µl)	1.2 [0.3;2.0]	0.007
IFN-α		
< 4 pg/ml	Reference	0.004
≥ 4 pg/ml	7.1 [2.4;11.8]	
sTNFR-2 (per ng/ml)	-9.9 [-16.7;-3.1]	0.006
Model 2: Viremic patients		
CD4 T-cell count (per 100 cells/µl)	-0.4 [-1.7;0.8]	0.50
HIV subtype		
B	Reference	0.56
Non B	-1.6 [-7.1;4,0]	
IL-4		
< 3.2 pg/ml		
≥ 3.2 pg/ml	-7.8 [-14.2 ;1.4]	0.02

Conclusions

After at least 15 years of exposure to perinatally acquired HIV infection, adolescents and young adults have high levels of CD127 expression on naive CD4 T cells in the presence of active HIV replication. This contrasts with the down-regulation of CD127 reported in viremic adults, but is consistent with the preservation of naive CD4 T-cell homeostasis in these young patients.