HIV Replication History is Associated with Plasma IL-7 levels in Aviremic Youths-The ANRS-EP38-IMMIP study

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Background

Interleukin-7 (IL-7) is a key molecule regulating thymopoiesis and peripheral T-lymphocyte proliferation. We showed that thymopoiesis is maintained and that naive T cells have high levels of IL-7 high-affinity receptor in both viremic and aviremic youths infected with HIV-1 during the perinatal period *(Blanche et al., Clin Inf Dis, 2014, 58: 573-587; Scott-Algara et al., CROI2014, Abst.#915).*

Aim

To study the factors of HIV disease history associated with plasma IL-7 in youths with suppressed viral replication.

Patients

The ANRS-EP38-IMMIP study included 93 perinatally HIV-1 infected youths between the ages of 15 and 24; 43% were boys and 39% black. At the time of the study (February2007-February2009), 85% of them were under cART and plasma HIV RNA load was <80 copies/mL in 75% of those under cART. The median CD4 cell count was 581/µL *(Avettand-Fenoel, J Inf Dis, 2012, 205:1520-1528).*

Methods

T-lymphocyte subsets were quantified by flow cytometry using frozen PBMCs. Naive T cells (T_N) were defined as CD45RA+CCR7+ and central memory T cells (T_{CM}) as CD45RA-CCR7+. Plasma IL-7 was quantified by ELISA (R&D systems Europe, Lille, France). Total cell-associated HIV-1-DNA was quantified by real-time PCR using the HIV-1 DNA assay (Biocentric, Bandol, France). HIV-1 subtype and tropism were determined by sequencing *RT* and *env* genes. Univariate and multivariate linear regression analyses were performed.

Acknowledgments

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Results: Associations with current status

Median (interquartile range) plasma IL-7 concentration at the time of the study was 3.9 (2.7-4.6) pg/ml. Univariate regression analyses are presented in **Figure 1** and selected associations are shown in **Figure 2**.

Plasma IL-7 levels:

- were not associated with sex, ethnicity, previous CDC stage C events, HIV-1 subtype, HIV-1 tropism and CMV serostatus;
- *were not associated with age, CD4 T cell counts* and percentages;
- tended to *be associated with the level of blood HIV-DNA.*

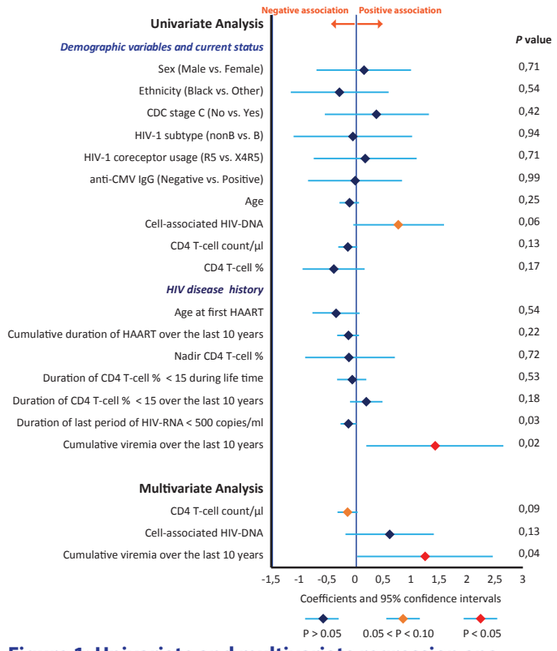


Figure 1: Univariate and multivariate regression analyses of HIV infection factors associated with IL-7 levels

Results from linear regressions are presented as forest plots. Univariate analysis is presented for the main variables related to HIV infection and multivariate analysis for the variables included in the model. Diamonds represent regression coefficients and lines 95% confidence intervals. *P* values are indicated on the right side. Results are expressed per year, per $\log_{10}$ HIV DNA/10^6 PBMCs, per 100 CD4 T cell/µl, per 10 CD4 T-cell percents, per 10 000 days x $\log_{10}$HIV RNA copies/ml of plasma.

Results: Associations with HIV replication history

Plasma IL-7 levels:

- *were associated with higher cumulative viremia over the last 10 years* and longer duration of continuous HIV RNA < 400 copies/ml;
- were not associated with nadir CD4 T cell percentage and duration of CD4 < 15%.

Multivariate regression analyses showed that plasma IL-7 levels were significantly associated with cumulative viremia, after adjustment for CD4 T cell count and total cell associated HIV DNA levels (**Figure 1, bottom**).

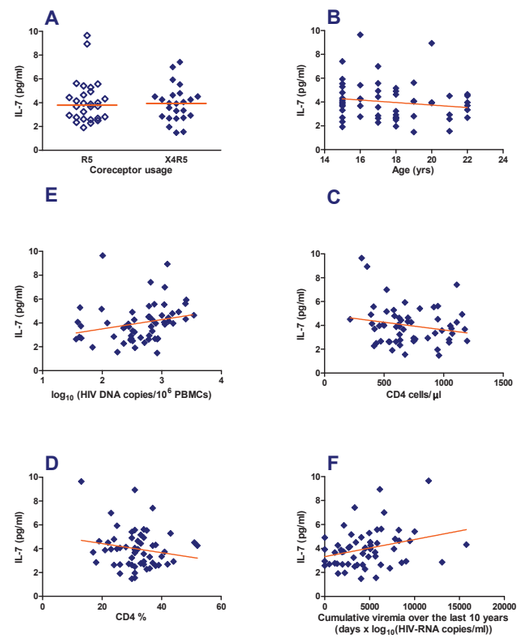


Figure 2: Associations between selected HIV infection factors and IL-7 levels

Plasma IL-7 levels are presented as a function of (A) HIV coreceptor usage, (B) age, (C) total cell-associated HIV DNA level, (D) CD4 T-cell count, (E) CD4 T-cell percentage and (F) cumulative viremia over the last 10 years. Regression lines are shown. Coefficients, 95% confidence intervals and P values from univariate regression are presented on figure 1.

Results: Association with T cell subsets

Plasma IL-7 levels:

- were not associated with naive CD4 T cell percentages and CD127 expression (**Figure 3A-C**).
- *were negatively associated with central memory CD4 T cell percentages* and with CD127 expression on these cells. (**Figure 3B-D**).

The associations were significant after adjustment for CD4 T-cell count and cumulative viremia (data not shown).

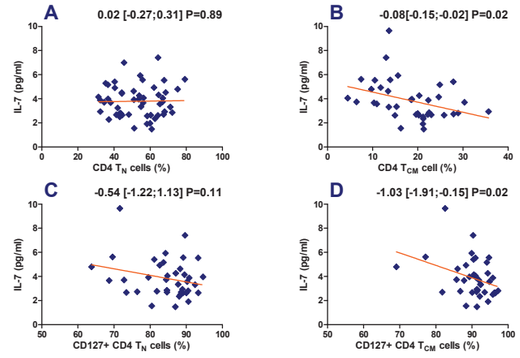


Figure 3: Associations between IL-7 and T cell subsets

Plasma IL-7 levels are presented as a function of (A) naive CD4 T lymphocyte percentages, (B) central-memory CD4 T lymphocyte percentages, (C) CD127+ cell percentages among naive CD4 T lymphocytes, and (D) CD127+ cell percentages among central memory CD4 T lymphocytes. Regression lines are shown. Coefficients, 95% confidence intervals and *P* values from univariate regression are presented above each graph.

Conclusions

In HIV-1 infected youths with viral control, plasma IL-7 levels were associated with exposure to viral replication over the previous 10 years and HIV blood reservoir level. We previously reported similar associations with the naive CD4 T cell subset, consistent with past HIV replication having a major impact for current naive CD4 T-cell homeostasis in patients with perinatally acquired HIV infection.