Abstract #0804

# Immuno-Virological Impact of Early vs Late ART Initiation in Children and Adolescents

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## BACKGROUND and AIMS

**Few data are available on the long-term benefit of early cART initiation for children and adolescents. The ANRS-EP59-CLEAC study aimed to assess the immunological and virological characteristics of HIV-1-infected children and adolescents who achieved initial virological suppression, according to the age at cART initiation: <6 months of age (« Early group ») versus ≥ 24 months of age (« Late group »)**

## METHODS

### Study population

**The CLEAC study included HIV-1 perinatally infected patients between 5 and 17 years of age followed in Paris area. Inclusions criteria were: to have initiated treatment before 6 months or after 24 months of age and to have reached initial virological success (HIV-1 RNA < 400 copies/ml achieved < 24 months after cART initiation).**

### Variables

**Blood samples were collected at the time of inclusion (2016-2018). PBMC-associated HIV-1 DNA levels were quantified using ultrasensitive qPCR (adapted from Biocentric, France) (Avettand-Fenoel J Med Virol 2009). CD4 and CD8 CD45RA+CCR7+ naive T lymphocytes were quantified in fresh blood by flow cytometry.**

### Statistical analysis

**For each dependent variable, we first assessed association with age at cART initiation in the two age groups [children (5-12 years) and adolescents (13-17 years)] and the interactions between age at cART initiation and age at inclusion. Factors associated with naive CD4 and CD8 T cells were studied separately in children and in adolescents because the interactions were significant. Wilcoxon and Spearman rank tests were used. Factors associated with HIV-1 DNA levels were studied for the whole group, as interaction was non significant. Univariate and multivariate linear regression models were built.**

## RESULTS 1- Patients

**We prospectively enrolled 27 children and 9 adolescents in the Early group , and 19 children and 21 adolescentsin the Late group.**

**Table 1. Characteristics**

| | Children | | Adolescents | | All |
|---|---|---|---|---|---|
| | Early (n=27) | Late (n=19) | Early (n=9) | Late (n=21) | n=76 |
| **Age (months) at first cART** (median [IQR]) | 2[0;3] | 54[49;80] | 2[0;2] | 92[55;136] | 25[2;78] |
| **Male sex** | 33 % | 42 % | 44 % | 67 % | 46 % |
| **Geographic origin** | | | | | |
| Europe | 11 % | 15 % | 11 % | 19 % | 14 % |
| Sub-Saharan Africa | 74 % | 74 % | 78 % | 76 % | 75 % |
| Other | 15 % | 11 % | 11 % | 5 % | 11 % |
| **Place of birth** | | | | | |
| Mainland France | 93 % | 26 % | 100 % | 29 % | 59 % |
| Sub-Saharan Africa | 0 % | 63 % | 0 % | 57 % | 32 % |
| Other | 7 % | 11 % | 0 % | 14 % | 9 % |
| **Age (years) at evaluation** (median [IQR]) | 9[6;11] | 8[7;10] | 15[14;16 ] | 15[13;15] | 11[8;14] |
| **On cART** | 100% | 100% | 100% | 100% | 100% |
| **Current HIV-RNA < 50 copies/mL** | 89 % | 89 % | 67 % | 76 % | 83 % |
| **CD4 T-cell count/µL** (median [IQR]) | 951 [725;1320] | 1009 [745;1527] | 840 [713;1078] | 740 [622;1092] | 856 [622;1092] |

## RESULTS 2- Naive CD4 and CD8 T cells

**Associations between treatment initiation and naive T cell levels differ between children and adolescents (Test for interaction CD4: *P*=0.008 , CD8: *P*=0.09). Early treated children had significantly higher naive CD8 T cell levels (*P*=0.0009); early treated adolescents had significantly lower naive CD4 T cell levels (*P*=0.05).**

**Figure 1. Naive CD4 and CD8 T cell percentages in earrly and late treated patients** **Early treated patients are presented by blue symbols and late treated patients by red symbols. Circles represent CD4 T cells and square CD8 T cells.**

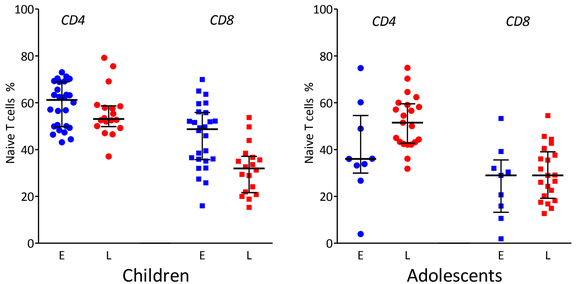


**Table 2: Univariate analysis of parameters associated with naive T cells**

| | Children | | | | Adolescents | | | |
|---|---|---|---|---|---|---|---|---|
| | Naive CD4% | | Naive CD8% | | Naive CD4% | | Naive CD8% | |
| | Median [IQR] or correlation coefficient | *P* value | Median [IQR] or correlation coefficient | *P* value | Median [IQR] or correlation coefficient | *P* value | Median [IQR] or correlation coefficient | *P* value |
| **Treatment initiation** | | | | | | | | |
| Early | 61[50;69] | | 49[36;56] | | 36[33;49] | | 29[16;32] | |
| Late | 53[50;59] | 0.33 | 31[22;37] | 0.0009 | 52[43;59] | 0.05 | 29[20;38] | 0.50 |
| **Demographics** | | | | | | | | |
| Sex | | | | | | | | |
| Male | 53[50;66] | | 44[26;52] | | 50[42;59] | | 26[18;38] | |
| Female | 58[50;63] | 0.59 | 36[29;52] | 0.75 | 44[35;59] | 0.48 | 30[19;38] | 0.60 |
| Sub-Saharan Africa Origin | | | | | | | | |
| No | 63[53;71] | | 35[27;60] | | 57[42;60] | | 32[17;36] | |
| Yes | 57[50;63] | 0.12 | 38[32;50] | 0.92 | 45[36;59] | 0.66 | 29[18;39] | 0.98 |
| Born in Metropolitan France | | | | | | | | |
| No | 54[51;59] | | 34[24;47] | | 50[42;59] | | 24[18;36] | |
| Yes | 59[50;69] | 0.39 | 39[33;52] | 0.15 | 43[34;60] | 0.40 | 32[21;39] | 0.20 |
| **Virological status** | | | | | | | | |
| Current HIV RNA < 50 copies/ml | | | | | | | | |
| Yes | 57[57;58] | | 26[24;36] | | 40[33;56] | | 19[14;29] | |
| No | 57[49;66] | 0.73 | 38[32;52] | 0.19 | 51[42;59] | 0.29 | 31[23;41] | 0.05 |
| Total exposition to HIV RNA > 400 copies/ml (months) normalized per year | -0.114 | 0.46 | -0.622 | <0.0001 | 0.250 | 0.18 | -0.044 | 0.82 |
| **Immunological status** | | | | | | | | |
| CD4/µl | 0.333 | 0.03 | 0.119 | 0.44 | 0.538 | 0.002 | 0.456 | 0.01 |
| CD8/µl | 0.117 | 0.45 | -0.354 | 0.02 | -0.094 | 0.62 | -0.564 | 0.001 |
| CD4/µl at first HAART | 0.160 | 0.39 | 0.479 | 0.006 | -0.097 | 0.64 | -0.142 | 0.50 |
| CD8/µl at first HAART | -0.373 | 0.04 | -0.290 | 0.11 | -0.335 | 0.12 | -0.337 | 0.12 |

Table 2: Median [IQR] and P values from Wilcoxon test are presented for qualitative variables. Spearman correlation coefficient and P values are presented quantitative variables.

| Negative | Positive | p value |
|---|---|---|
| | | <0.05 |
| | | <0.01 |
| | | <0.001 |

## RESULTS 3- Total HIV-1 DNA levels in PBMC

**Early cART, current HIV RNA < 50 copies/mL and shorter duration of viremia >400 copies/mL were independently associated with lower HIV-1 DNA levels (respectively *P*=0.02, *P*=0.0007 and *P*=0.001). When restricting the analysis to the 63 patients with current viral suppression (<50 copies/mL), similar associations between HIV-1 DNA and early cART or duration of viremia > 400 copies/mL were found (*P*=0.02 and *P*=0.05, respectively, ).**

**Figure 2. Total HIV-1 DNA levels ($log_{10}$copies/$10^6$ PBMCs) and treatment initiation.** **Early treated patients are presented by blue symbols and late treated patients by red symbols. Circles represent children and square adolescents.**

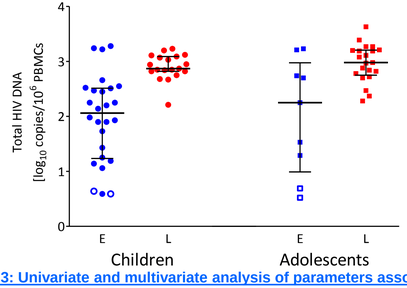


**Table 3: Univariate and multivariate analysis of parameters associated with total HIV-1 DNA level in PBMCs ($log_{10}$copies/$10^6$ PBMCs)**

| | | Univariate linear regression | | | Multivariate linear regression | |
|---|---|---|---|---|---|---|
| | N | Median [IQR] or Pearson correlation coefficient | Regression coefficient | *P* value | Adjusted regression coefficient [95%CI] | *P* value |
| **Treatment initiation** | | | | | | |
| Early | 36 | 2.17[1.27;2.61] | -0.90 | <0.0001 | -0.45[-0.81;-0.08] | 0.02 |
| Late | 40 | 2.95[2.80;3.15] | Reference | | Reference | |
| **Demographics** | | | | | | |
| Sex | | | | | | |
| Male | 35 | 2.84[2.37;3.20] | 0.23 | 0.16 | | |
| Female | 41 | 2.66[1.93;3.04] | Reference | | | |
| Age | | | | | | |
| 13-17 years | 30 | 2.86[1.93;2.94] | 0.32 | 0.07 | 0.026[-0.23;0.28] | 0.84 |
| 5-12 years | 46 | 2.61[1.98;2.94] | Reference | | Reference | |
| Sub-Saharan African Origin | | | | | | |
| No | 19 | 2.68[2.20;2.82] | 0.05 | 0.80 | | |
| Yes | 57 | 2.84[2.21;3.11] | Reference | | | |
| **Virological status** | | | | | | |
| Current HIV RNA ≥ 50 copies/mL | | | | | | |
| Yes | 13 | 3.19[2.84;3.23] | 0.62 | 0.0005 | 0.57[0.25;0.89] | 0.0007 |
| No | 63 | 2.67[1.93;2.95] | Reference | | Reference | |
| % of time exposed to HIV RNA > 400 copies/mL since birth to period previous to inclusion | 76 | 0.64 | 1.58 | <0.0001 | 0.99[0.40;1.57] | 0.001 |
| **CD4 nadir while on treatment** | 76 | -0.06 | -0.00013 | 0.56 | | |

## DISCUSSION and INTERPRETATION

**Naive CD4 T cells are associated with current CD4 T cell counts. Early and late-treated children had similar naive CD4 T cell levels. The robust thymic activity of late-treated children may have supported an efficient immune restoration of their CD4 T cells.**
**In adolescents, the paradoxally higher level of naive CD4 T cell % in late-treated patients may reflect new T cell production by the thymus to compensate their destruction by virus replication. An indication bias in early-treated group is possible.**

**Naive CD8 T cells are associated with both immune status and HIV replication. In children and adolescents, higher naive CD8 T cell levels are associated with higher CD4 T cell count and with lower exposition to HIV replication, a major driver of their differentiation into memory T cells.**

**Total HIV-DNA levels were associated with the virologic history and cumulative viremia. Interestingly the level from aviremic adolescents (median 1.42 [IQR: 1.08-2.25] $log_{10}$ copies/$10^6$ PBMCs) were comparable to those observed in adults with spontaneous or post-treatment HIV control** (Avettand-Fènoël V, *et al*. Clin Microbiol Rev 2016).

## CONCLUSIONS

**Early cART initiation during infancy is associated with lower short- and long-term total HIV-DNA levels, as targeted in HIV-1 remission strategies.**

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