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.

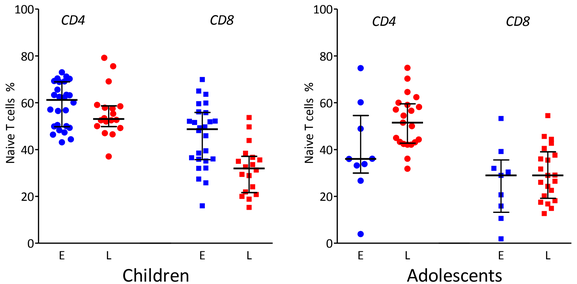


Table 2: Univariate analysis of parameters associated with naive T cells

	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.

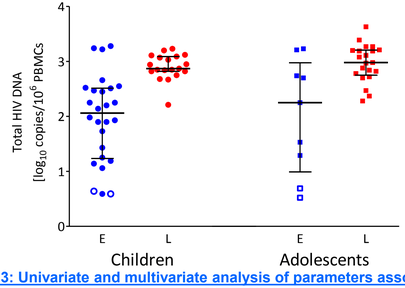


Table 3: Univariate and multivariate analysis of parameters associated with total HIV-1 DNA level in PBMCs (log_{10}copies/10^6 PBMCs)

		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.

Acknowledgments

We thank all the patients, their families, the clinical investigators (MF. Courcoux, MD. Tabone (Trousseau Hospital, Paris), C. Fourcade (Bicêtre Hospital, Le Kremlin Bicêtre), I. Hau (Centre Hospitalier Intercommunal, Créteil), C. Gakobwa (Delafontaine Hospital, Saint Denis), N. Mahlaoui, F. Veber (Necker – Enfants malades Hospital, Paris), A. Chacé (Centre Hospitalier Intercommunal, Villeneuve Saint Georges)) and the members of the ANRS CLEAC study group (D. Scott-Algara, A. Saez-Cirion (Pasteur Institute, Paris), B. Autran and A. Samri (Pitié Salpêtrière Hospital, Paris), S. Caillat-Zucman (Saint Louis Hospital, Paris), O. Dialla, L. Ait Si Selmi, I. Leymarie, T. Wack and L. Boufassa (INSERM, Le Kremlin Bicêtre), C. Floch-Tudal (Louis Mourier Hospital, Colombes), E. Lachassine (Jean Verdier Hospital, Bondy), A. Diallo, L. Marchand, C. Paul and V. Petrov-Sanchez (ANRS), H. Pollard (TRT-5)).
We thank the logistic platform from Institut Pasteur in Paris, S. Novault and P.H. Commere from Utechs Cytometry and Biomarkers from Institut Pasteur Paris.
We thank the nurses and staff from clinical sites, S. Leveillé, MC. Mourey, G. Vaudre and M. Vassal.