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Factors associated with HIV DNA levels in children starting antiretroviral therapy (ART) early in infancy

Man Chan (PhD)[1], Alfredo Tagarro (MD, PhD)[2], Paola Zangari (MD)[3], Sarah Watters (PhD)[4], Ruth Bridget Ferns (PhD)[5], Riccardo Freguja (PhD)[6], Nicola Cotugno (MD)[3], Ali Judd (PhD)[1], Caroline Foster (MD)[7], Anita De Rossi (PhD)[6], Eleni Nastouli (MD, PhD)[4], María Angeles Muñoz-Fernández (MD, PhD)[8], Claudia Fortuny (MD, PhD)[9], María Luisa Navarro (MD, PhD)[10], María José Mellado (MD, PhD)[11], Diana Gibb (MD, PhD)[1], Paolo Rossi (MD, PhD)[3], Carlo Giaquinto (MD)[12], Abdel Babiker (PhD)[1], Paolo Palma (MD, PhD)[3], Pablo Rojo (MD, PhD)[2] on behalf of EPIICAL Consortium

[1] MRC Clinical Trials Unit at University College London, Institute of Clinical Trials & Methodology, London, UK; [2] Department of Pediatrics, Hospital 12 de Octubre, Madrid, Spain; [3] University Department of Pediatrics, Unit of Immune and Infectious Diseases, Children's Hospital Bambino Gesù, Rome, Italy; [4] UCL GOS Institute of Child Health, London UK; [5] UCL/UCLH NIHR Biomedical Research Centre; [6] Section of Oncology and Immunology-DiSCOG, University of Padova, Padova, Italy; [7] Imperial College healthcare NHS trust; [8] ImmunoMolecular Laboratory and HIV HGM BioBank, Hospital General Universitario, Madrid, Spain; [9] Hospital Sant Joan de Deu, Barcelona, Spain; [10] Pediatrics Infectious Diseases Unit, Hospital Universitario Gregorio Marañón, Madrid, Spain; [11] Pediatrics Infectious Diseases Unit, Hospital Universitario La Paz Madrid, Spain; [12] Department of Women and Child Health, University of Padova , Padova , Italy

Background

Future strategies aimed at achieving ART-free HIV-1 remission in perinatally infected children are likely to target individuals with low levels of HIV-1 proviral DNA. These individuals are likely to have initiated ART very early in life.

However, determinants of low viral reservoir in early treated HIV-1 infected children are yet to be established.

Objectives

To investigate factors associated with lower HIV-1 DNA in European HIV-1 infected children with supressed viral load on long term ART, having started ART early in life.

Methods

♦ Inclusion ♦

- Children with perinatal HIV-1 infection aged<6 months at start of standard combination ART from 5 European sites/cohorts (1 UK, 2 Spain, 2 Italy) with ≥1 HIV-1 DNA measures.

♦ Methods ♦

- HIV-1 DNA was measured from purified CD4+ T cells or total PBMCs across four laboratories based in UK, Spain and Italy.
- Measurements were carried out at a median of 6.3 years after initial viral suppression whilst on ART.
- CD4+ T cell data were converted to HIV-1 DNA copies/10^6 PBMC for analysis.
- Factors associated with $\log_{10}$ HIV-1 DNA levels were investigated using linear regression. Backward elimination was applied to reach the final multivariable model.

♦ Definitions ♦

- **Baseline viral load (VL):** closest VL measurement within 6 months before and 1 week after ART start.
- **Baseline CD4%, CD8%, lymphocyte:** closest measurement within 6 months before and 1 month after ART start.
- **Viral suppression**: ≥2 consecutive VL<50 copies/ml.
- **Blips:** single VL50-400 preceded and followed by VL<50.
- **Spikes:** single VL≥400 preceded and followed by VL<400.
- **Suboptimal viral response:** ≥2 consecutive VL 50-400 followed by VL<50. **Viral failure**: ≥2 consecutive VL≥400.

Results

- In total, 51 HIV-1 infected children were included in the analysis. Baseline characteristics (at ART start) are summarised in **Table 1**.

HIV-1 DNA — ***Median:***
- **HIV-1 DNA level:** 43.0 copies/10^6 PBMC [IQR:6.1,195.0].
- **Age at HIV-1 DNA determination:** 7.3 years [IQR:4.2,10.9].

Viral Load — ***Median:***
- **Time to viral suppression:** 8.0 months [IQR:4.6,19.3].
- **Proportion of time suppressed (%):** 85% [IQR:61,94].

- Following viral suppression, 23 (45%) of children had ≥1 blip; 11 (22%) had ≥1 spike; 13 (25%) had suboptimal viral response and/or failed.

Table 1. Baseline characteristics

	Median [IQR] or N (%)
Age at ART start (months)	2.3 [1.2,4.1]
CD4%	37 [24,45]
CD8%	28 [18,36] (36)
CD4 count† (cells/mm^3)	1495 [620,2885]
Lymphocyte count (cells/mm^3)	5600 [2800,7070]
Log_{10} VL (copies/ml)	5.4 [4.4,5.9]
Gender	
Male	23 (45%)
Female	28 (55%)
Country (Site/Cohort)	
UK (CHERUB-YC)	8 (16%)
Spain (Madrid; Catalonia)	16 (31%)
Italy (Padova; Rome)	27 (53%)
AIDS diagnosis	
No	33 (65%)
Yes	15 (29%)
Missing	3 (6%)
Initial ART Regimen	
NNRTI based*	25 (49%)
PI based#	16 (31%)
Other	10 (20%)

†**CD4 count calculation:** CD4% x Lymphocyte count/100; ***NNRTI based regimen:** Nevirapine + ≥ 2 NRTIs; **#PI based regimen:** Lopinavir/r or Nelfinavir + ≥ 2 NRTIs; data missingness in CD4%, CD8%, total lymphocyte, VL ranged from 20-42%.

♦ Lower HIV-1 DNA was associated with ♦

- ▶ Younger age at ART start **(Table 2; Fig 1)**.
- ▶ Higher proportion of time spent virally suppressed **(Fig 2).**
- ▶ Absence of VL failure/suboptimal response **(Fig 3).**

- Effect of site/cohort was present with HIV-1 DNA levels highest in UK and ROME sites.
- There was suggestive evidence for an association with baseline immunological parameters (CD4, CD4/CD8 ratio and total lymphocyte) and AIDS diagnosis. However, these associations failed to reach significance after adjustment.

Fig 1. Age at ART start (months)

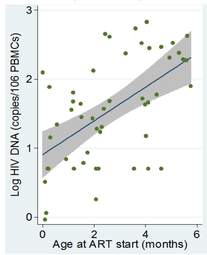

Fig 2. Proportion of time suppressed (%)

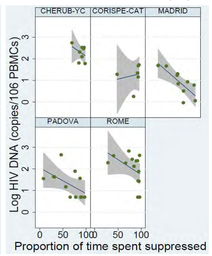

Fig 3. Fail/Suboptimal response

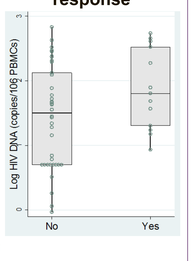

Table 2. Multivariable factors associated with HIV-1 DNA

	Univariable Models			Multivariable Model[a]		
	% Diff	β (95% CI)	P-value	% Diff	β (95% CI)	P-value
Age at ART start (per month older)	27.7	0.24 (0.14 , 0.35)	**2.15E-05**	12.7	0.12 (0.03 , 0.21)	**0.0091**
Age at HIV DNA measure (per year older)	5.3	0.05 (0.00 , 0.10)	**0.0395**	---	---	---
Duration of ART (per year longer)	5.0	0.05 (-0.00 , 0.10)	0.0528	---	---	---
Proportion of time suppressed (per 10% higher)#	-3.5	-0.04 (-0.13 , 0.06)	0.4454	-9.9	-0.10 (-0.17 , -0.04)	**0.0022**
Time to viral suppression (per month longer)#	0.2	0.00 (-0.01 , 0.01)	0.6976	---	---	---
Previous AIDS Diagnosis						
Yes [Ref: No]	93.2	0.66 (0.20 , 1.11)	**0.0054**	---	---	---
Composite: Fail/Suboptimal Response						
Yes [Ref: No]	55.0	0.44 (-0.05 , 0.92)	0.0758	40.1	0.34 (0.00 , 0.67)	**0.0483**
Baseline immunological data						
CD4 count (per 500 cells higher)	-8.7	-0.09 (-0.18 , 0.00)	0.0541	---	---	---
CD4% (per 10% higher)	-13.2	-0.14 (-0.29 , 0.01)	0.0625	---	---	---
CD4/CD8 ratio (per unit higher)	-19.0	-0.21 (-0.42 , -0.00)	**0.0479**	---	---	---
Total lymphocyte (per 500 cells higher)	-4.3	-0.04 (-0.09 , 0.00)	0.0678	---	---	---
Site/Cohort [Ref: Italy: Rome**]**						
UK: CHERUB-YC/CHIPS	43.1	0.36 (-0.19 , 0.90)	0.1934	29.5	0.26 (-0.17 , 0.69)	0.2326
Spain: CORISPE-CAT	-49.5	-0.68 (-1.29 , -0.08)	**0.0270**	-38.6	-0.49 (-0.97 , -0.01)	**0.0468**
Spain: MADRID	-64.1	-1.02 (-1.53 , -0.52)	**0.0002**	-68.3	-1.15 (-1.59 , -0.71)	**4.696E-06**
Italy: PADOVA	-46.2	-0.62 (-1.10 , -0.14)	**0.0130**	-59.6	-0.91 (-1.30 , -0.51)	**3.118E-05**

[a]Criteria for inclusion into the multivariable model: univariable model p-value<0.10 or defined "a priory"#; **β,** regression coefficient estimates; **95% CI,** confidence interval; **% Diff, %** difference in HIV-1 DNA: a unit change in factors investigated is associated with a Y% change in HIV-1 DNA. For example, a month increase in age at ART start is associated with a 12.7% increase in HIV-1 DNA (multivariable model).

Conclusions

- Our study shows that even among HIV-1 infected children initiating ART<6 months of age, starting ART at a younger age, and spending a higher proportion of time on effective ART treatment was linked with lower HIV-1 DNA.
- Our findings support early ART start and adherence support in children as a strategy to minimise the size of viral reservoir.
- Future larger studies will be required to confirm results.

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