

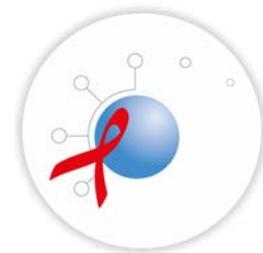


“Children age, antiretroviral treatment and CD4 count are major determinants of HIV-1B evolution in pediatric patients”

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Determining the factors that modulate the genetic diversity of HIV-1 populations

Essential to understand

- Viral responses to ART
- Disease progression
- May help to predict the appearance of resistant variants

adult

HIV-1 genetic diversity associated with:

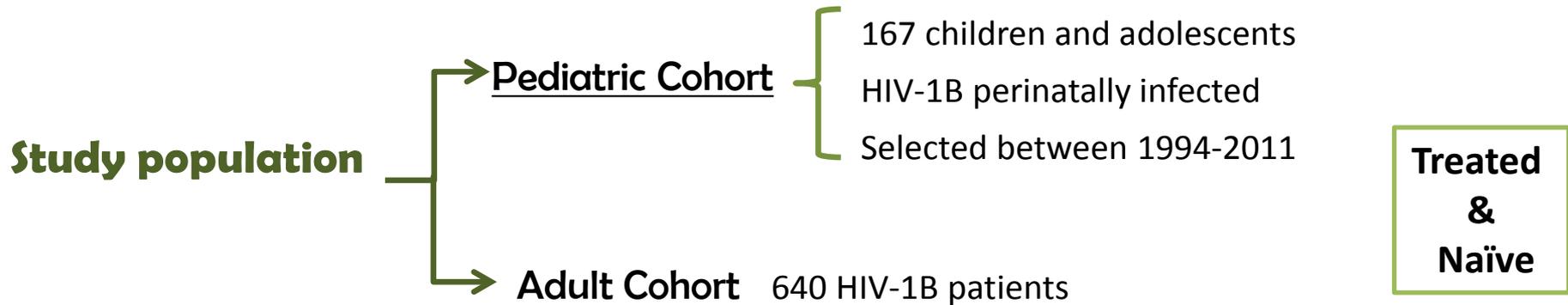
- Age
- CD4 cells (% and count)
- Viral Load
- ART experience

kid

?

This is the first study analyzing in detail the role of five clinical factors in HIV-1 evolution in a large number of infected children, and in an adult population





For children, we analyzed the relative importance of

Age
CD4+ T cells counts
VL
ART experience



For each of these 807 patients, one HIV-1B *pol* sequence was obtained and were used to

1. Estimate nucleotide substitution rates (subs/site/year)
2. Genetic diversity (π)
3. Rates of synonymous (dS) and nonsynonymous (dN) changes
4. Selection pressures (dN/dS)
5. Frequency of DRMs in the virus population

The effect of clinical factors in the inferred evolutionary variables was analyzed by principal component (CPA)



Relative contribution of clinical factors to the evolution of pediatric HIV-1B population

Principal Component	PC1	PC2	PC3	PC4	PC5
Percent association component-variable					
Age	91.2	1.9	0.3	0.1	7.5
ART experience	0.0	93.7	2.3	3.9	0.1
CD4/mm ³	1.0	2.2	94.7	2.0	0.1
VL	0.3	5.4	2.7	84.6	7.0
% CD4	11.6	0.1	0.2	8.4	79.7
Expected values under broken-stick model	20.8	20.3	20.2	19.8	18.9
Total variance explained by the component	40.7	30.0	13.6	10.5	5.2

Children age was highly associated with **PC1**

ART experience with **PC2**

CD4/mm³ with **PC3**

Age, ART experience and CD4 count were the primary predictors of evolutionary parameters and are the more important on the pediatric cohort



To analyze the effect of **children age** in the evolution of HIV-1B, we divided the pediatric cohort into four age categories following the CDC recommendations

0-2 years old
2-8 years old
8-13 years old
13-21 years old

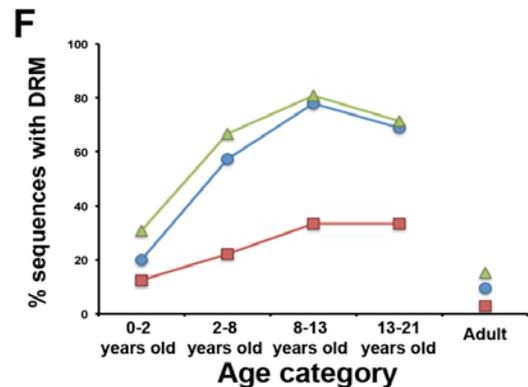
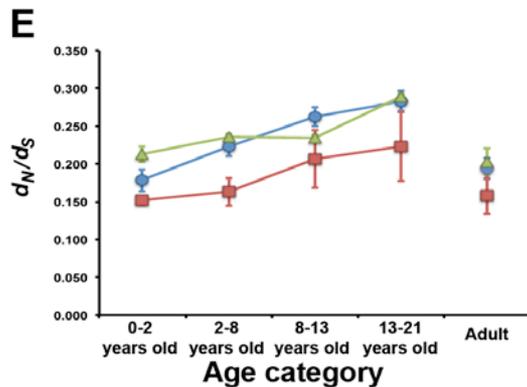
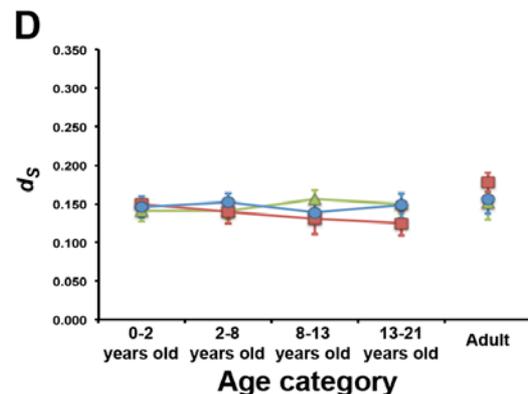
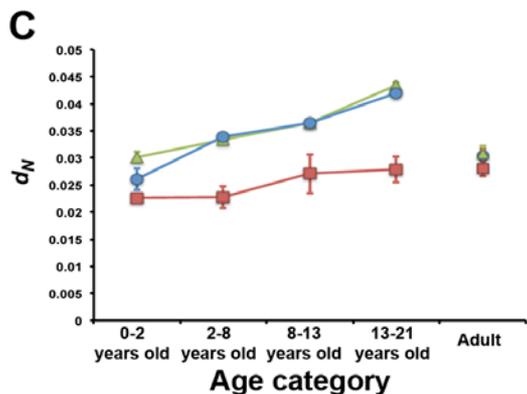
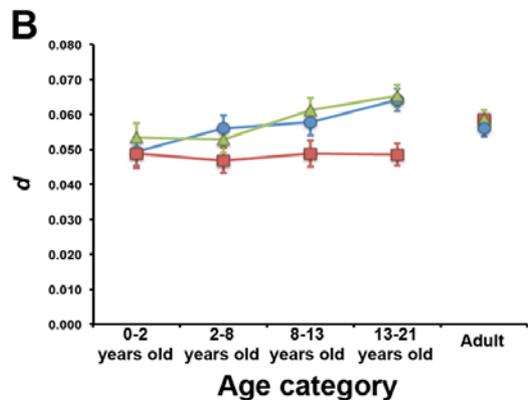
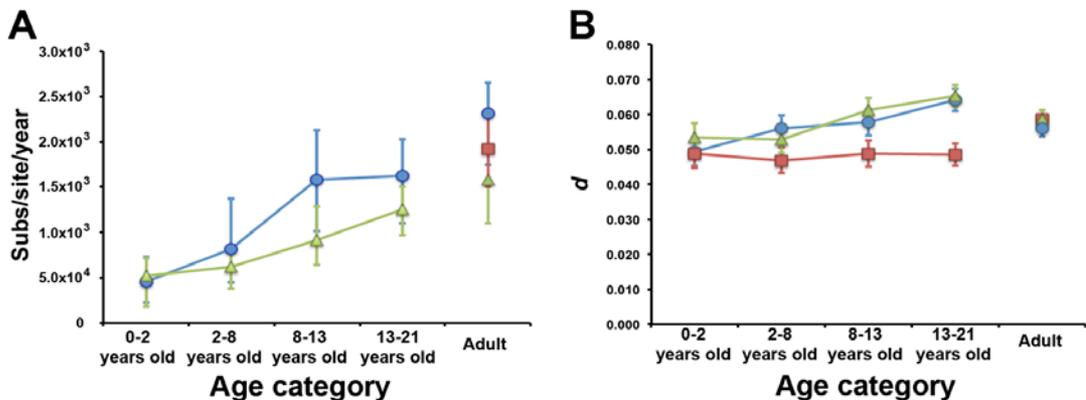
We also included the adult cohort as an additional age category



Five age categories
+
Naive & Treated



■ HIV-1B in All patients
 ■ HIV-1B in Naive patients
 ■ HIV-1B in Treated patients



Nucleotide substitution rates
 (Subs/site/year)
Genetic diversity (d)
Non-synonymous mutations (d_N)

↓

Increased with :
Children age
&
ART experience

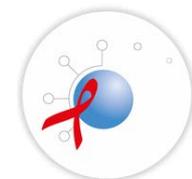


Association of children CD4 count with the evolution of the pediatric HIV-1B population

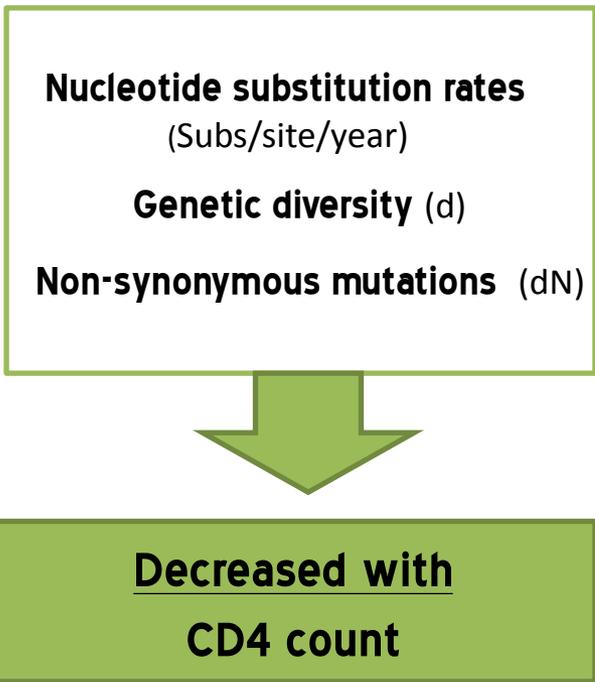
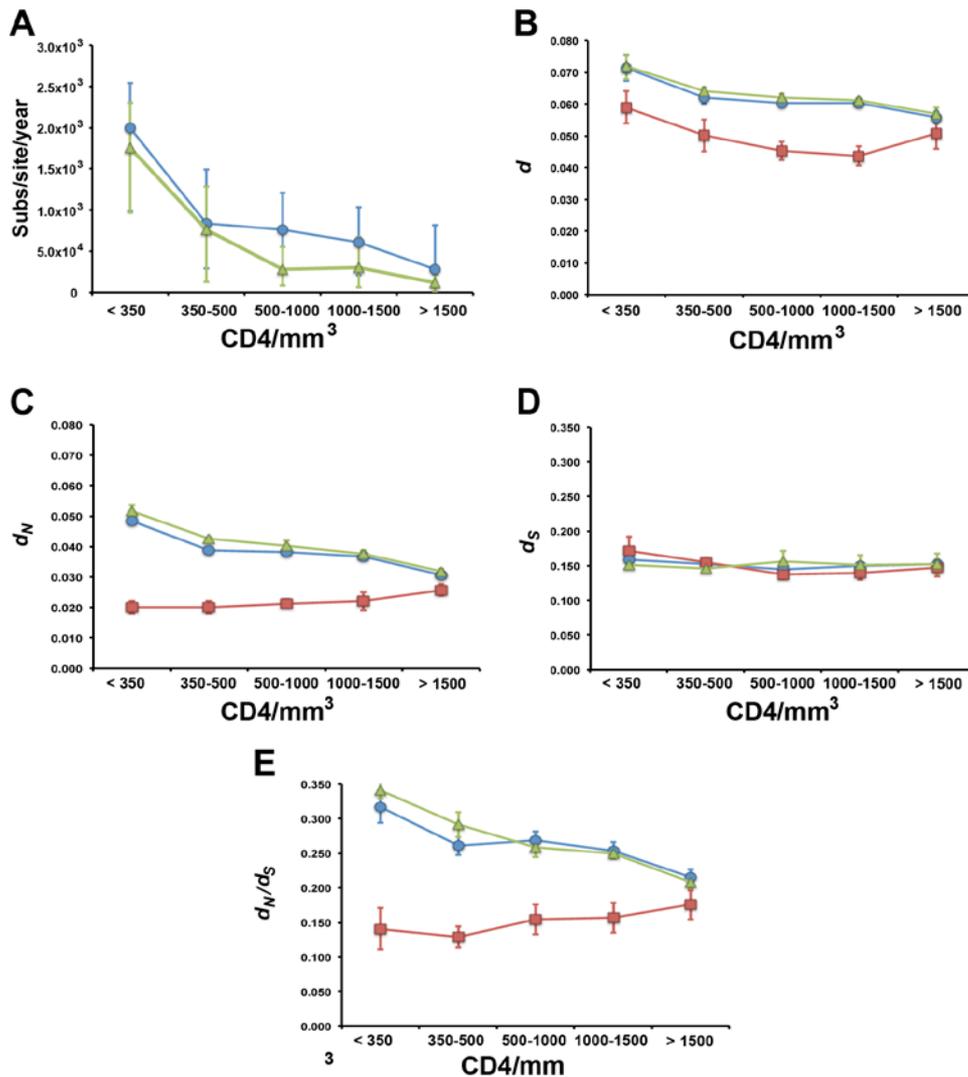
PCA indicated that **the third major factor influencing HIV-1B evolution** in pediatric patients was **CD4 cells**

We divided the pediatric cohort into five groups following the CDC classification of clinical categories

>1500 CD4/mm³
1500-1000 CD4/mm³
1000-500 CD4/mm³
500-350 CD4/mm³
<350 CD4/mm³



■ HIV-1B in All patients
 ■ HIV-1B in Naive patients
 ■ HIV-1B in Treated patients



Selection pressures in aa residues associated with DRM in pediatric and adult patients according to their ART experience

HIV-1 Protein	Resistance mutation	aa Site	Resistance mutation	Pediatric				Adult					
				Naïve (n=31)		Treated (n=136)		Naïve (n=136)		Treated (n=394)			
				Selection	TDR	Selection	DRM	Selection	TDR	Selection	DRM		
PROTEASE	Major PI	24	L24I		0		-		1		-		
		30	D30N		1		12		0		6		
		32	V32I		0		4		0		3		
		46	M46I/L		0		18		3		27		
		47	I47V/A		0		4		0		2		
		48	G48V		0		0		0		0		
		50	I50L/V		0		0		0		2		
		53	F53L		0		-		3		-		
		54	I54M/L		0		15		2		14		
		58	Q58E		0		0		0		0		
		73	G73T		0		-		1		-		
		74	T74P		0		0		0		0		
		76	L76V		0		1		0		0		
		82	V82A/T/F/S/L		0		16		2		22		
		83	N83D		0		0		0		0		
		84	I84V		0		7		1		4		
88	N88S/D		1		2		1		8				
90	L90M		0		25		3		26				
RETROTRANSCRIPTASE	NRTI	41	M41L		2		45		8		54		
		62	A62V		1		3		0		0		
		65	K65R		0		2		2		5		
		67	D67N		0		49		5		41		
		69	T69		1		22		3		11		
		70	K70R/E		1		30		2		6		
		74	L74V		0		16		1		14		
		75	V75I		0		6		1		2		
		77	F77L		0		1		0		0		
		115	Y115F		0		2		1		0		
		116	F116Y		0		1		0		3		
		151	Q151M		0		2		0		2		
		184	M184V/I		0		31		6		70		
		210	L210W		1		33		7		32		
		215	T215Y/F		1		54		9		65		
		219	K219Q/E		0		26		2		31		
		RETROTRANSCRIPTASE	NNRTI	90	V90I		0		8		0		0
				98	A98G		0		3		0		0
				100	L100I		0		5		0		9
101	K101E/H/P				0		6		2		13		
103	K103N/S				1		34		8		47		
106	V106M/A/I				2		2		0		7		
108	V108I				0		3		0		0		
138	E138A/G/K/Q/R				1		9		0		0		
179	V179D/F/T/L				0		1		1		0		
181	Y181C/I/V				1		12		2		28		
188	Y188C/L/H				0		3		1		5		
190	G190S/A				0		12		2		19		
221	H221Y				0		3		1		0		
225	P225H				1		3		0		3		
227	F227C		0		0		0		0				
230	M230L/I		0		0		0		2				

- $d_N/d_S \approx 1 \rightarrow$ neutral selection
- $d_N/d_S > 1 \rightarrow$ positive selection
- $d_N/d_S < 1 \rightarrow$ negative selection

Relaxed selection pressures in the pediatric virus population



were associated with higher frequency of DRMs





Nucleotide substitution rate
Genetic diversity (d)
 dN



Increased with ART experience and children age

CD4 & ART affect the evolution of HIV-1B in children

Negative selection pressures stronger in the adult than children

DRM are more frequent in pediatric population



1

Exposure to the virus (age), ART experience and reduced number of CD4 cells promote faster HIV-1B adaptive evolution in infected children

2

These factors do not affect the evolution of HIV-1B population in adults that generally evolves at higher rates, and is more genetically diverse, than the pediatric population

3

These findings contribute to understand the factors that modulate HIV-1B evolution, and the appearance of DRMs



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