Influence of early combined antiretroviral therapy on maintenance of long term serological and cellular immune responses to varicella vaccination of perinatally HIV infected children and adolescents

German A. Contreras[1,2] , James R. Murphy[1], Gloria. P. Heresi[1]

1.Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Texas UTHealth, Houston, Texas. 2..Molecular Genetics and Antimicrobial Resistance Unit, Universidad El Bosque, Bogotá, Colombia.

INTRODUCTION

It is not clear if cART started prior to the initiation of the standard American Academy of Pediatrics recommended vaccinations results in improved levels of immunity among perinatally HIV infected individuals. In this study, we seek to gain insight on the timing of cART initiation with respect to vaccination on the capacity of perinatal HIV infected children and adolescents to maintain humoral and cellular immunity to varicella (VAR).

METHODS

Varicella specific antibody titers (Abs) and memory antibody secreting cells (mASC) are measured by ELISA or ELISPOT. We compare a HIV+ population with an adult HIV- population as a rigorous test of persistence of memory. HIV+ are parsed into 4 groups based on the time of cART initiation (before or after immunization) and plasma HIV RNA viral load (VL) level (< 50 or ≥ 50 copies/ml). Group 1: before, VL < 50; group 2: before, VL ≥ 50; group 3: after, VL <50 and group 4: after, VL ≥ 50. We use Wilcoxon rank-sum to compare groups and linear regression to determine predictors of immune response.

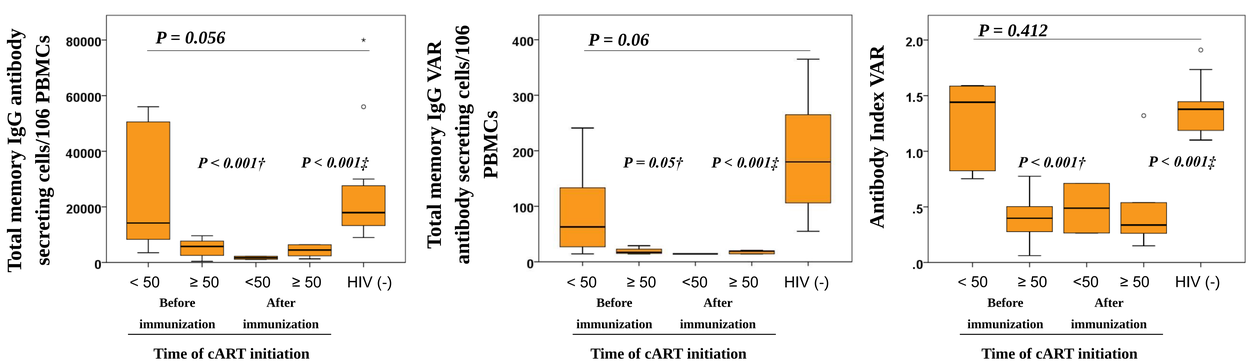
RESULTS

Table 1. Demographics

	cART started prior Immunization		cART started after Immunization	
Variables	HIV RNA ≤ 50 (n=9)	HIV RNA > 50 (n=7)	HIV RNA ≤50 (n=2)	HIV RNA > 50 (n=6)
Age (years) †	12.5 (8.2-15.1)	13.1 (9.9-18.1)	10.4 (10.2-10.5)	12.8 (9.8-20)
Ethnicity				
Black	5 (56)	6 (86)	2 (100)	5 (83)
Hispanic	3 (33)	1 (14)		1 (17)
White	1 (11)			
Sex				
Female	6 (67)	3 (43)	2 (100)	4 (67)
Historical Data				
CD4 % nadir †	21 (18-27)	18 (17-23)	13.8 (10-17.5)	16.5 (10-28.5)
Peak HIV RNA copies/ml log_{10} †	5 (3-5.3)	4.6 (4.3-5.8)	4.7 (4.6-4.8)	5.1 (4.8-5.9)
Age at cART initiation (years) †	1.3 (0.7-1.6)	0.8 (0.2-5.3)	6.1 (5.1-7.1)	11.4 (7.5-12)
cART				
PI-based regimen	6 (66.7)	5 (71.4)	2 (100)	6 (100)
NNRTI-based regimen	3 (33.3)	2 (28.6)		
Time since the last VZV immunization (years) †	4.8 (4-7.6)	3.1 (1.8-7.4)	6.4 (5.5-7.2)	5.6 (4.2-9.9)
At the time of serology and B cell evaluation				
CD4 % †	39.4 (30.8-45)	34 (26.2-37)	25.8 (23.6-28)	24.5 (10.9-41)
CD8 % †	28 (26-39.7)	49 (41-54)	53.8 (48.7-59)	42.7 (32-57.2)
CD38% †	8 (8-10)	22 (18-30)	22 (22-22)	20.5 (16-23)
HLA-DR % †	4 (3-9)	24 (15-31)	25.5 (23-28)	24 (9-34)
CD4/CD8 < 1	3 (33)	5 (71)	2 (100)	3 (50)
Cumulative years of HIV RNA suppression †	6.7 (2.8-9.2)	2.2 (1.1-4.3)	4.2 (2.2-6.1)	1.5 (0.0-1.8)

† Data are median and IQR; cARV: combine antiretroviral therapy.

Figure Box plot analyses



Box plot analyses of total IgG class ASC, varicella IgG ASC and plasma varicella antibodies. The top and bottom of the box correspond to the 75th and 25th percentile, respectively. The median is represented by the horizontal line inside the box. † Represent the median p value for the comparison between the HIV+ Group1 (before, VL < 50) and the other HIV+ groups (group 2: before, VL ≥ 50; group 3: after, VL <50 and group 4: after, VL ≥ 50). ‡ Represent the maximun p value for the comparison between the HIV- individuals (before, VL < 50) and the HIV+ groups 2-4 (group 2: before, VL ≥ 50; group 3: after, VL <50 and group 4: after, VL ≥.

RESULTS

Table 2 Liner regression analysis of predictors of VZV cellular and serological memory in perinatal HIV infected children and adolescents

VZV IgG memory B cells

Variables	β	95% CI	p value
Cumulative suppression years ‡ (per year of increase of plasma HIV RNA < 50 copies/ml)	**0.168**	**0.03, 0.31**	**0.02**
Age at cART initiation (per year of increase on age)	-0.02	0.12;0.08	0.693
Nadir CD4 % (per 1 % of increase in nadir CD4 %)	-0.013	-0.21; 0.19	0.895
Peak HIV RNA copies/ml log_{10} (per log_{10} increase in peak HIV RNA)	0.175	-0.87; 1.22	0.729
$CD8^+$ $CD38^+$ % (per 1 % of increase in $CD8^+$ $CD38+$ %)	-0.037	-0.10; 0.02	0.210
$CD8^+$ $HLA\text{-}DR^+$ % (per 1 % of increase in $CD8^+$ $HLA\text{-}DR^+$ %)	-0.006	-0.06; 0.04	0.798
Nadir CD4 x Peak HIV RNA ¶	-0.003	-0.04; 0.04	0.890

Plasma VZV antibodies

Variables	β	95% CI	p value
Cumulative suppression years ‡ (per year of increase of plasma HIV RNA < 50 copies/ml)	**0.088**	**0.03; 0.15**	**0.006**
Age at cART initiation (per year of increase on age)	0.026	-0.014; 0.066	0.183
Nadir CD4 % (per 1 % of increase in nadir CD4 %)	0.077	-0.04; 0.16	0.06
Peak HIV RNA copies/ml log_{10} (per log_{10} increase in peak HIV RNA)	0.398	-0.02;0.81	0.063
$CD8^+$ $CD38^+$ % (per 1 % of increase in $CD8^+$ $CD38+$ %)	-0.013	-0.04; 0.01	0.259
$CD8^+$ $HLA\text{-}DR^+$ % (per 1 % of increase in $CD8^+$ $HLA\text{-}DR^+$ %)	-0.015	-0.04; 0.01	0.146
Nadir CD4 x Peak HIV RNA ¶	-0.016	-0.01; 0.07	0.183

‡ Defined as the total of number of years with a continuous plasma HIV RNA < 50 copies/ml after the initiation of cART ¶ Interaction term.

The estimated increase of IgG varicella ASC memory B cells:

* 0.168 * 1 year = 0.168,
* This is equal to having an increase of 1.18 x10^6 memory B cells secreting IgG against varicella per year
* If the individual maintains a plasma HIV RNA < 50 for 4 years the predictive increase would be of 1.95 x10^6 memory B cells secreting IgG.

The estimated increase of varicella plasma antibodies concentration

*0.088 * 1 year = 0.088,
*This is equal to having an increase of 1.1 units of varicella antibodies per year;
*If the individual maintain a plasma HIV RNA < 50 for 4 years the predictive of increase would be of 1.42 units of varicella plasma antibodies.

CONCLUSIONS

Our study shows that an appropriate and lasting cellular and serological B cell response to varicella vaccination in perinatallly HIV infected individuals significantly improved if cART is started before immunization and viral suppression is consistent sustained < 50 copies/ml. The initiation of therapy before the beginning of the regular immunization schedule opens the possibility of having an improved and lasting immune response to vaccination in children perinatally infected with HIV