

A-152 Marginal zone memory B-cell populations are irreversibly depleted in paediatric HIV infection

University College London
Institute of Child Health
30 Guilford Street
London
WC1N 1EH
m.jacobsen@ich.ucl.ac.uk
Phone: +442079052307
FAX: +442078138494

Marianne C. Jacobsen, Rodolphe Thiebaut, Christopher Fisher, Delali Sefe, Margaret Clapson, Nigel J. Klein and Helen E. Baxendale

Infectious Diseases and Microbiology Unit, Institute of Child Health, University College London



Background/Introduction

HIV infection is associated with increased susceptibility to invasive pneumococcal disease. Recent data in adults suggests a persistent depletion of IgD positive memory B-cells occurs soon after HIV infection, and this depletion is not reversed by HAART. This loss correlates with reduced humoral immunity to pneumococcal polysaccharides which may contribute to the persistent susceptibility to pneumococcal disease in HIV infected patients. As B-cell lineage development continues through childhood, we proposed to evaluate whether irreversible B cell lineage specific depletion occurs in the paediatric HIV infected population.

Methods

Naïve/transitional (CD27⁻), IgD positive memory (CD27⁺IgD⁺) and switched memory (CD27⁺IgD⁻) B cell numbers were measured in whole blood from untreated HIV infected children (n=24), HAART treated children (n=77) and age matched healthy controls (n=42). These data were then correlated with CD38 expression as a surrogate of B cell activation, HIV viral load (VL), duration of disease (age) and CD4 count. Data was expressed as median and interquartile range. Comparisons between groups were performed using Wilcoxon tests. Multivariable analyses of factors associated with IgD⁺ memory B cell levels were performed using multiple linear regression.

Summary/Conclusions

Paediatric HIV infection is associated with irreversible depletion of IgD⁺ memory B-cell numbers despite control of viral load with HAART. The positive association between viral load, B-cell activation status and IgD⁺ memory B cell numbers suggests that the IgD⁺ memory B-cell population may be selectively targeted by HIV early in the course of infection ultimately resulting in a permanent depletion of this lineage.

Results

	Children Control	HIV untreated	HIV HAART VL+	HIV HAART VL-
N	42	24	39	38
Age*	9 (4-13)	9 (5-11)	11 (9-14)	9 (7-13)
Sex (F/M)	12/30	11/13	23/16	16/22
CD4 count*	N/A	563 (328-750)	394.5 (252-663)	838 (528-980)
CD4 %	N/A	22 (18-29)	19 (14.-28.)	30 (25-38)
Log10 Viral Load**	N/A	4.3 (4.0-4.9)	3.8 (2.8-4.4)	1.7 (1.7-1.7)
CD19 count cells/μl	364 (260-627)	504 (159-1049)	309 (154-470)	358 (245-592)
CD19 %	16.8 (9.8-23.4)	17.7 (11.5-27.0)	14.2 (8.4-20.4)	16.6 (11.6-21.3)

*cells/ml; **RNA copies/ml

Table 1: Demographic and immune parameters of controls and patient groups

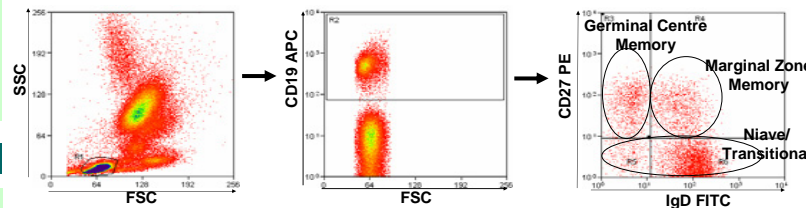


Figure 1: B-cell phenotype FACS plots of a healthy child. Gates were set around lymphocytes and CD19⁺ B-cells, and B-cell subsets were defined as IgD⁺ memory (IgD⁺CD27⁺), switched memory (IgD⁻CD27⁺) and naïve/transitional cells (CD27⁻).

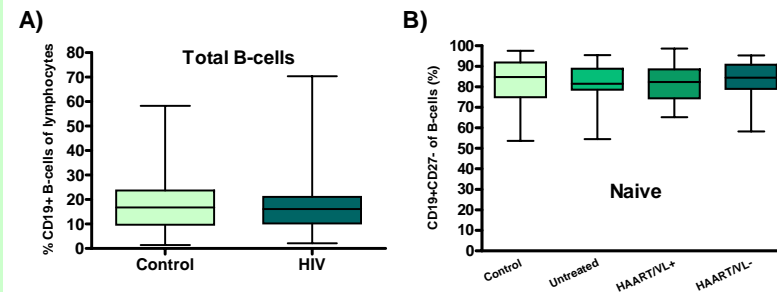


Figure 2: Total (A), naïve (B) and switched memory (C) B-cell percentages in HIV infected children and controls. There was no significant difference in total, naïve or switched memory B percentages between control and HIV infected children despite control of viral load with HAART.

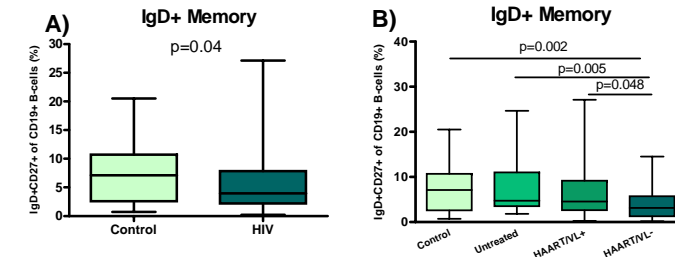
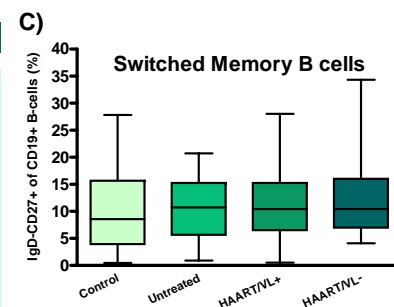


Figure 3: IgD⁺ memory B-cell percentages in HIV infected children and uninfected controls. A) IgD⁺ memory B-cells percentage in HIV⁺ children and controls. B) IgD⁺ memory B-cell levels in controls and HIV children subdivided into untreated, HAART treated with detectable VL, and HAART treated with undetectable VL. Wilcoxon t test. IgD⁺ memory B-cells were significantly reduced in HIV infected children with controlled VL (HAART/VL⁻).

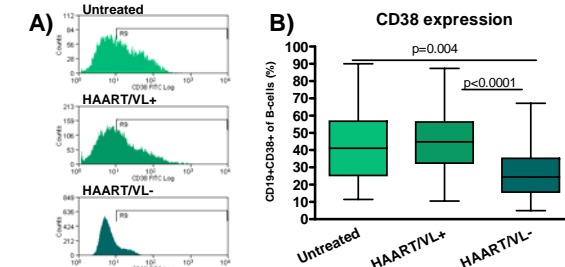


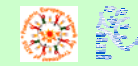
Figure 4: CD38 expression on B cells in HIV infected children subdivided into untreated, HAART treated with detectable VL, and HAART treated with undetectable VL. A) Representative FACS histograms of CD38 expression on B cells of each treatment group. B) CD38 expression on B cells of HIV children: untreated, HAART VL⁺, and HAART VL⁻. Median (+/-IQR), Wilcoxon t test. HIV infected children with controlled VL had significantly lower levels of CD38 expression on their B-cells.

	VL	CD4%	CD4 count	Duration of disease (age)	CD38 expression
IgD ⁺ memory	0.22015	-0.04945	0.05970	-0.17909	0.13989
	0.03	0.63	0.56	0.07	0.16

Table 2: Correlation of IgD⁺ memory B-cell percentage with CD4 %, CD4 count, duration of disease (age) and CD38 expression. There was no correlation between IgD⁺ memory B-cells and CD4% and count, duration of disease (age) or expression of CD38 on B-cells, however, IgD memory correlated with VL.

Acknowledgements:

*Participating children and their families from GOSH
*Collaborative HIV Paediatric Study (CHIPS)
*Clinical Immunology Laboratory at GOSH
*GOSH HIV clinical team
*HEB: work supported by the Special Trustees of GOSH
*RT: supported by a grant from the French national agency for research on AIDS and viral hepatitis ANRS.
*MCJ: supported by PENTA



Agence nationale de recherche sur le sida et les hépatites virales
French National Agency for research on AIDS and viral hepatitis