The Effect of HIV Infection at Pre-ART Initiation on the Early Innate Immune System

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BACKGROUND

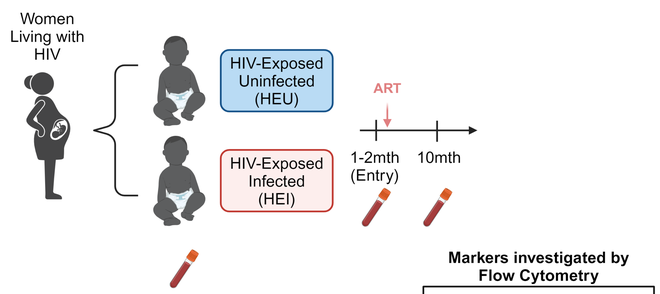
Despite the advent of antiretroviral therapy (ART), perinatal HIV infection still occurs, mostly in low-income countries. The nature of the innate immune response to HIV infection in infants is relatively unknown, as is an understanding of the effect of HIV replication on the development of the early innate immune system. The objective of the study was to evaluate the innate immune system pre-ART initiation and its development in HIV exposed infected (HEI) in comparison to HIV exposed uninfected (HEU) infants.

Methods

Study Cohort: TARA (Towards AIDS Remission Approaches) from Maputo, Mozambique.

	Entry (1-2 months)		10 months of age		
	HEU	HEI	HEU	Viremic HEI	Aviremic HEI
# of participants	35	33	30	15	11
M/F Ratio	18/17	13/20	14/16	6/9	4/7
Median CD4 Count	N/A	1,986 (1,155-5,713)	N/A	2191 (755-3006)	3024 (1011-4756)
Median Viral Load	N/A	503,691 (695-10,000,000)	N/A	123,261 (749-4,641,635)	20 (20-166)

All infants were prescribed nevirapine at birth for 6 weeks. Upon positive HIV PCR test at 1-2 months of age, infants were prescribed AZT+3TC+lopinavir/ritonavir. Cryopreserved PBMC were shipped to Miami.



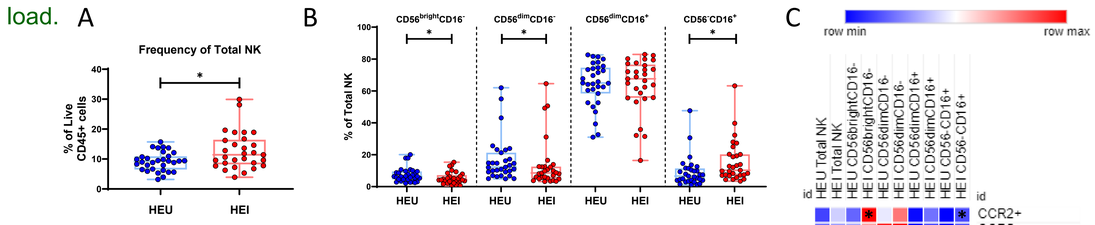
Markers investigated by Flow Cytometry

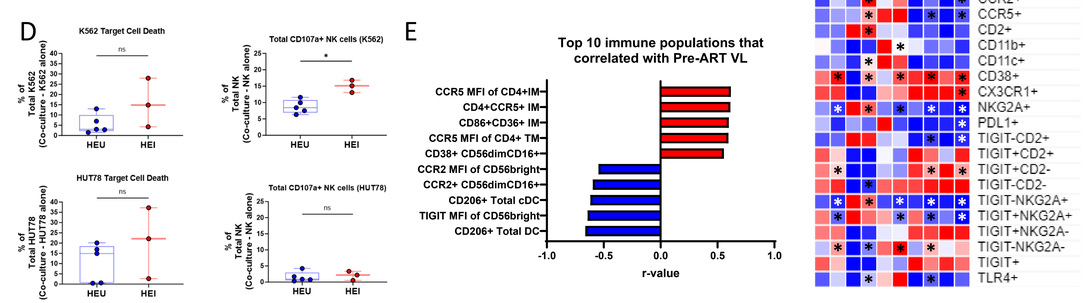
- CD38 (Activation)
- CD2 (Co-stimulation)
- CD86 (Activation)
- NKG2A (Inhibition)
- TIGIT (Inhibition)
- PD-L1 (Inhibition)
- CCR2 (Trafficking)
- CCR5 (Trafficking)
- CX3CR1 (Trafficking)
- CD11b (Integrin)
- CD11c (Integrin)
- CD36 (Scavenging)
- CD163 (Scavenging)
- CD206 (Scavenging)
- TLR4 (TLR for LPS)
- CD4 (HIV entry)

The goal of this study was to examine role of innate immunity in virus control in infants with perinatally acquired HIV. Immunophenotyping revealed alterations (activation, reduced NKG2A) in NK cells in 1-2 month old infants pre-ART compared to HIV exposed infants without HIV. In a limited subset, cytotoxic responses were equivalent in both groups with HEI manifesting increased degranulation and a transcriptional profile supporting NK cell cytotoxicity. Our findings favor a role for NK cells in viral control during early life in HEI.

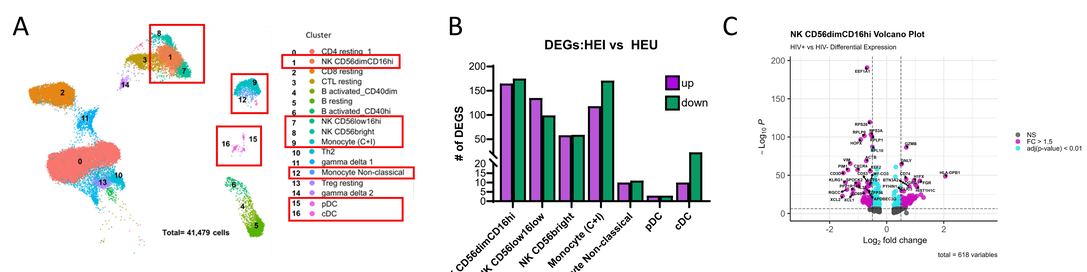
RESULTS:

I. At Pre-ART initiation, the distribution of NK subsets is altered in HEI compared to HEU (A,B), however monocyte and DC proportions are similar between the 2 groups. Cytotoxic capacity of NK is not impaired in HEI despite altered phenotype (C,D) Multiple innate immune phenotypes correlate with pre-ART virus load.



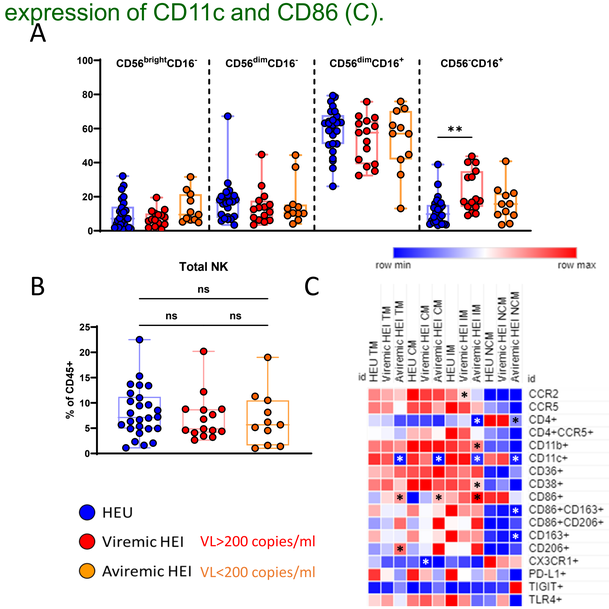


II. scRNAseq analysis reveals altered transcriptional profiles of NK cells and Monocytes in HEI (A,B). CD56dim CD16hi NK cluster in HEI have reduced *XCL1, XCL2, KLRG1* and increased *GZMB* and *GNLY* (C). See **poster 951** for additional data).



RESULTS:

III. Longitudinal effects of perinatal HIV and ART on NK cell proportion and phenotype. NK Subset frequencies normalize to HEU levels (A,B) Aviremic NK have altered expression of CD11c and CD86 (C).



CONCLUSIONS

- At Pre-ART initiation, NK cells of HEI had an altered distribution of subsets with an activated profile and a Cytotoxic capacity similar to age-matched HEU.
- Intermediate Monocytes and NK cells at Pre-ART initiation highly correlated with Pre-ART VL
- NK cells and Monocytes showed the most Differentially Expressed Genes between HEU and HEI.
- Regardless of viremic status, HEI transitioned to a similar phenotypic profile as HEU by 10 months of age.

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