Immune correlates of viral rebound during broadly-neutralizing antibody treatment in children

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Melanie Lancien[1], Aischa Niesar[1], Seohyun Hong[1], Leah Carrere[1], Ajibola Gbolahan[2], Terence Mohammed[2], Shahin Lockman[2,3], Ce Gao[1], Sikhulile Moyo[2], Bryan S. Nelson[4], Michael Hughes[4], Xu Yu[1], Daniel R. Kuritzkes[3], Roger L. Shapiro[2,5], Mathias Lichterfeld[1,3].

[1]Ragon Institute of MGB, MIT and Harvard, Cambridge, MA, USA, [2]Botswana Harvard Health Partnership, Gabarone, Botswana, [3]Infectious Disease Division, Brigham and Women's Hospital, Boston, MA, USA, [4]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA, [5]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

BACKGROUND

Determining immunologic correlates that may be associated with virologic suppression while on alternate or curative HIV therapy is a priority for children. We longitudinally investigated immune responses among participants in the Tatelo Study[1] (Trial Registration Number: NCT03707977) with and without virologic failure during 6 months of dual broadly-neutralizing antibody (bNAb) treatment (10-1074 and VRC01-LS) after ART interruption (Figure 1).

- **How does the immune system influence the outcome of bNAb-treatment in children?**

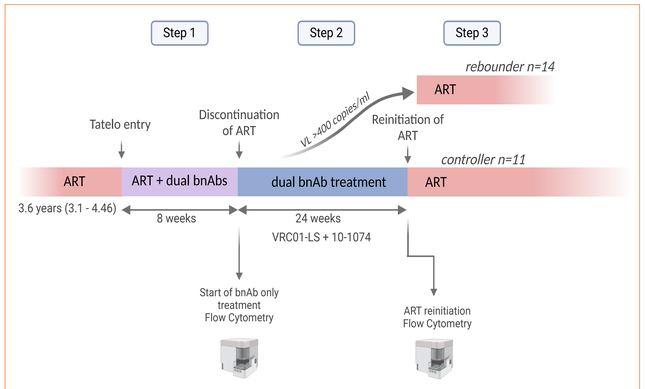


Figure 1: Schematic of Tatelo study design.

METHODS

Using multiparametric spectral flow cytometry we analyzed innate and adaptive immune cell populations at two time points:

1) the start of bNAb-only treatment
2) at ART reinitiation after six months or upon viral rebound

We correlated immunological findings with viral reservoir characteristics obtained through FLIP-seq and MIP-seq.

Bibliography: [1]Shapiro et al., Sci Transl Med. 2023

RESULTS

Of 25 participants aged 2-5 years who received the dual-bNAb treatment, 11 maintained viral suppression (controllers) and 14 rebounded (rebounders). We first focused on NK cells which play a critical role in viral infections control and quantified the different subpopulations by flow cytometry. (Figure 2).

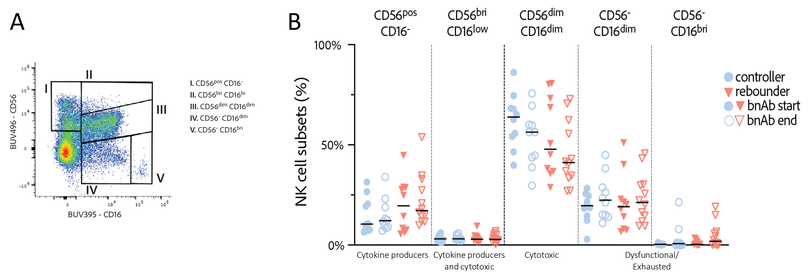


Figure 2: Representative flow cytometry pseudocolor plot highlighting subclassification of NK cell subsets stratified according to CD16 and CD56 expression. (B) Distribution of total NK cells in distinct subsets in controller and rebounder groups.

NK cell activation in mainly due to the balance of activator and inhibitory receptors expressed at the cell surface. We quantified the expression of KIR2DL1 and NKG2A by flow cytometry and correlated it to the HIV-1 intact reservoir size and the kinetic of viral rebound. We also investigated the presence of their ligands using HLA allotypes analysis (Figures 3 and 4).

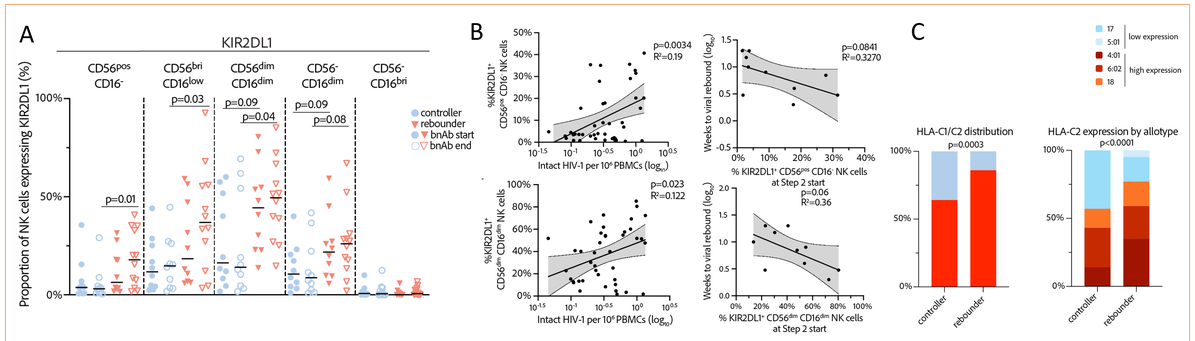


Figure 3: Relative expression of KIR2DL1 in five distinct NK cell subsets in the controller and rebounder group at Step 2 start and Step 2 end. (B) Association between indicated NK cell subsets expressing KIR2DL1 and frequency of intact proviruses (both groups, Step 2 start and Step 2 end) or weeks to viral rebound (rebounder group, Step 2 start). Linear regression coefficients are shown. (C) HLA-C allotypes in the controller and rebounder group. Chi-Square test of low-expressed vs high-expressed HLA alleles. Mann Whitney-U test was used in A.

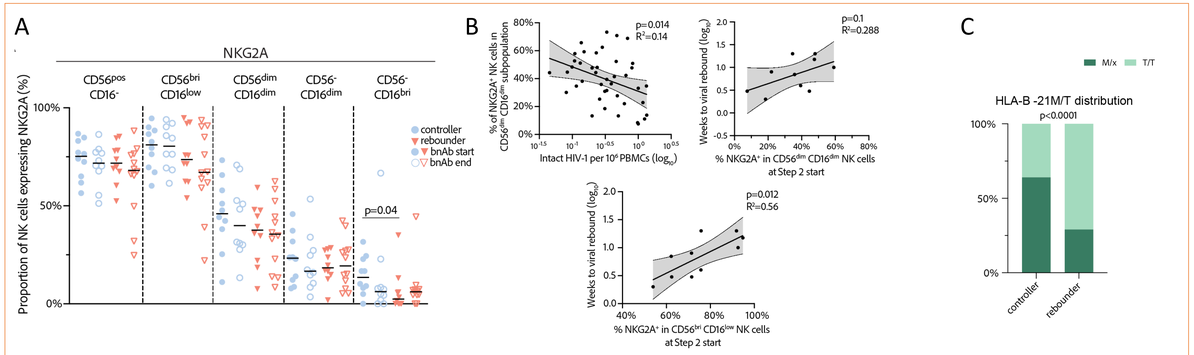


Figure 4: (A) Relative expression of NKG2A in five distinct NK cell subsets in the controller and rebounder group at Step 2 start and Step 2 end. (B) Association between indicated NK cell subsets expressing NKG2A and frequency of intact proviruses (both groups, Step 2 start and Step 2 end) or weeks to viral rebound (rebounder group, Step 2 start). Linear regression coefficients are shown. (C) HLA-B categorization based on HLA-B allotype and methionine or threonine on position 21. Chi-Square test of HLA alleles distribution. Mann-Whitney U test was used in A.

We then conducted a phenotypic and functional characterization of CD4⁺ T cells and CD8⁺ T cells after Gag *in vitro* stimulation (Figure 5).

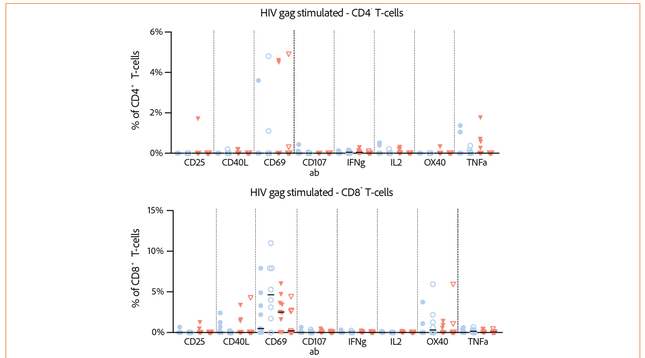
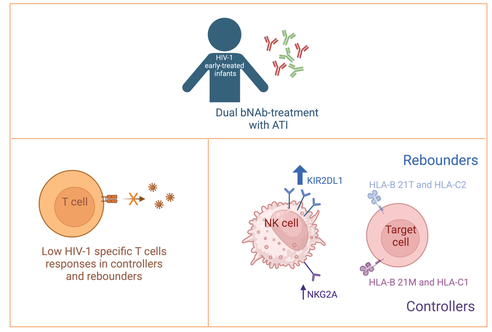


Figure 5: Frequency of CD4⁺ and CD8⁺ T-cells expressing markers and cytokines after the indicated stimulation and subtracting unstimulated marker and cytokine expression. Medians are shown.

CONCLUSIONS

We observed that KIR2DL1⁺ NK cells were expanded in rebounders and were associated with larger HIV-1 intact reservoirs and faster rebound. In contrast, NKG2A⁺ NK cells frequency was slightly elevated in controllers, which was correlated with lower HIV-1 intact reservoir levels and delayed rebound. This study highlights that innate immune mechanisms play crucial roles in determining the success or failure of bNAb treatment.



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ADDITIONAL KEY INFORMATION

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Author Contact Information:

Dr Melanie Lancien

Email: mlancien@mgh.harvard.edu