# Characterization of the naïve B-cell repertoire and antigen-specific B-cell precursors in a South African population to inform the development of germline-targeting HIV immunogens.


J. Magura[1], S. Rasehlo[1], P. Mamofalali[1], M. Muthui[2], P. Thami[1], C. Muriuki[3], L. Murungi[4], E. Landais[4], D. Sok[4], E. Nduati[2], D. Muema[3], T. Ndung'u[1,5]

*1. Africa Health Research Institute*

*2. KEMRI- Wellcome Trust Research Programme, Kilifi, Kenya*

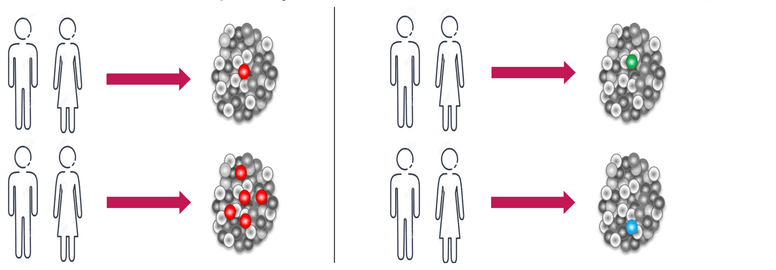
*3. KAVI Institute of Clinical Research (KAVI-ICR), College of Health Sciences, University of Nairobi, Nairobi, Kenya.*

*4. International AIDS Vaccine Initiative . 5. HIV Pathogenesis Programme, The Doris Duke Medical Research Institute, University of KwaZulu-Natal*


## 1. Introduction

- It is well established that an effective preventative HIV-1 vaccine would almost certainly need to elicit broadly neutralizing antibodies (bnAbs).
- Developing germline-targeting (GL) immunogens is one approach used to activate the rare naïve B-cell precursors with unique features favorable to their development into bnAbs.
- eOD-GT8 is one well characterized GL immunogen eliciting VRC01-like class of bnAbs.
- However, the success of GL vaccines in humans will depend on the composition of the human naïve B-cell repertoire

bNAb Precursors Frequency | Genetic diversity in antibody genes



Factors that may influence these key parameters
- Environmental exposures, Genetics, Geography

*Fig 1. Predictive factors of the naïve B-cell repertoire that could influence GL vaccine efficacy*

## 2. Methods

Study design: cross-sectional study across different countries and regions.

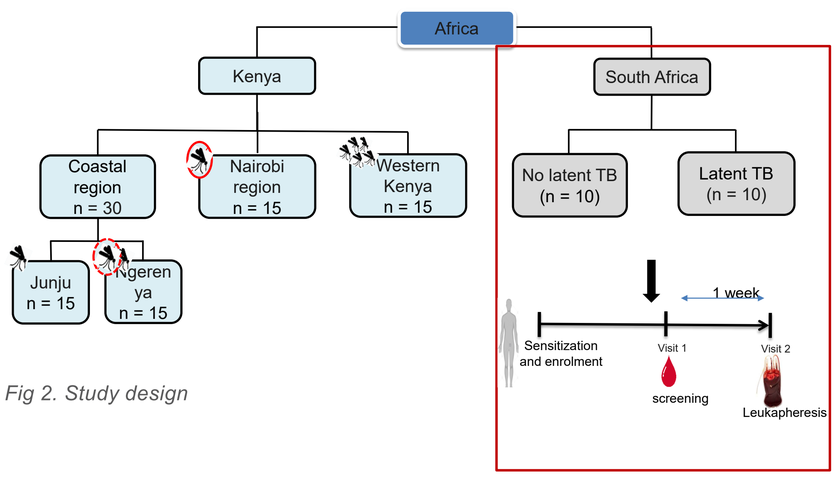



*Fig 2. Study design*

Objectives.

- Evaluate the frequencies of antigen-specific naïve B-cell precursors that bind to HIV envelope-based immunogens, such as eOD-GT8 (*FACS-sorting +10X genomics single-cell RNA-seq + bioinformatics analyses*)
- Determine the prevalence of bnAb-like features in the naïve B-cell repertoire in a South African population (Next-generation sequencing (NGS))

## 3. Results

**Evaluating the antigen-specific bnAb-like precursor frequencies.**

- Preliminary results from archived PBMCs.

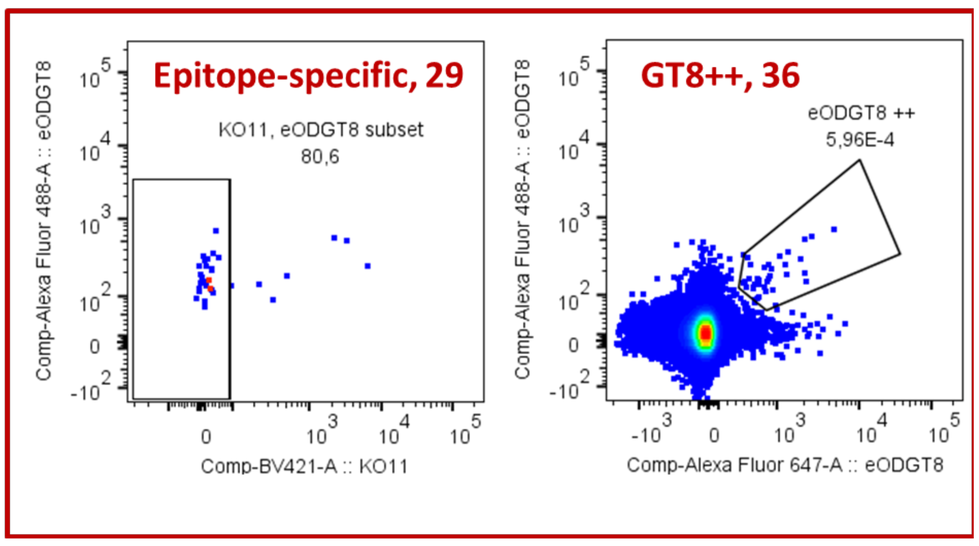



*Fig 3. FACS-sorted eOD-GT8 double positive B-cells*

Total B-cells = 10 x $10^6$ ,total antigen-specific =36

- **Ratio 1 in 278 000** (eOD-GT8 specific: total B-cells from a single donor)

**Comparison to literature**

- 1 in 280 00, 1 in 140 000 and 1 in 160 000 Lee *et al*. 2021
- 1 in 400 000; Havenar-Daughton, C. *et al*. 2018

.

**Characterization the overall naïve B-cell repertoire**

Key features to be defined

- Immunoglobulin gene usage
- Amino acid (aa), and CDRL3 length

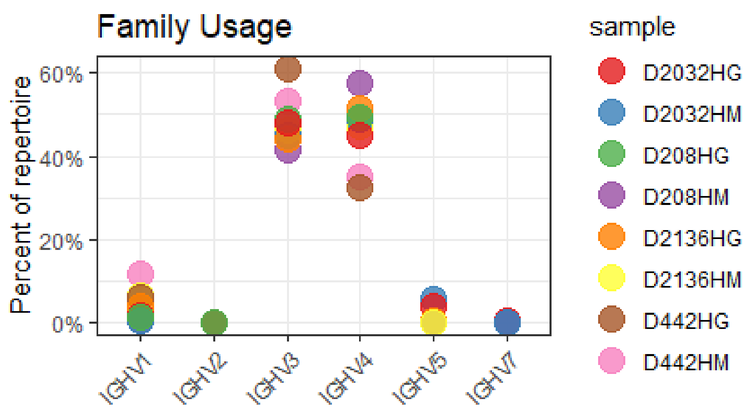



*Fig 4. IGHV family usage among HIV-negative individuals*

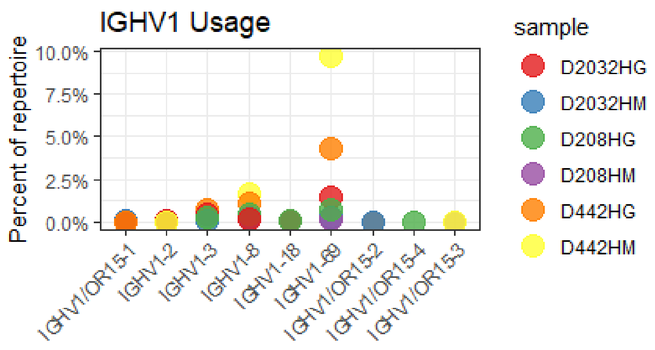



*Fig 5. IGHV1 usage among HIV-negative individuals*

- Diverse gene usage observed among individuals..

## 4. Conclusions

- Findings from this study will provide actionable information on population immune baseline characteristics that will be important to consider during vaccine design, besides the generation of promising vaccine candidates
- Inform selection of appropriate populations for vaccine trials and roll-out
- Predict responsiveness to vaccine candidates
- Update online databases with African alleles to facilitate more accurate interpretation of B-cell/antibodies data

.

## 5. References


1. Havenar-Daughton, C. et al. The human naive B cell repertoire contains distinct subclasses for a germline-targeting HIV-1 vaccine immunogen. Sci. Transl. Med vol. 10 http://stm.sciencemag.org/ (2018).

2. Lee, J. H. et al. Vaccine genetics of IGHV1-2 VRC01-class broadly neutralizing antibody precursor naïve human B cells. NPJ Vaccines 6, (2021).

3. Joyce, C., Burton, D. R. & Briney, B. Comparisons of the antibody repertoires of a humanized rodent and humans by high throughput sequencing. Sci Rep 10, (2020).