# Profiling the HIV Env-Specific Antibody Response in Mother-Infant Transmission

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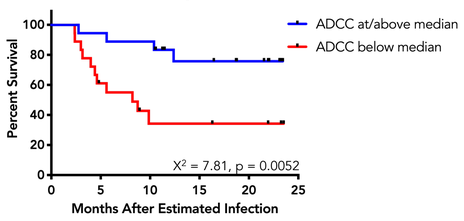
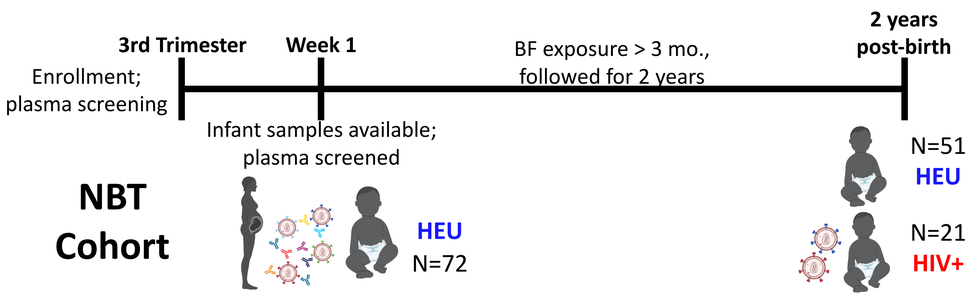
## Introduction

- In an anti-retroviral naïve setting, approximately 65% of infants born to HIV+ mothers remain uninfected from gestation through breastfeeding
- During the 3rd trimester, infants passively receive HIV-specific antibodies (**Abs**) from their mothers via passive-antibody transfer
- Mother to child transmission (**MTCT**) therefore represents one of few means to determine whether HIV-specific antibodies present during HIV exposure influence HIV acquisition or disease progression
- Plasma ADCC mediated by passively-transferred Abs is associated with improved survival in infants that acquire HIV



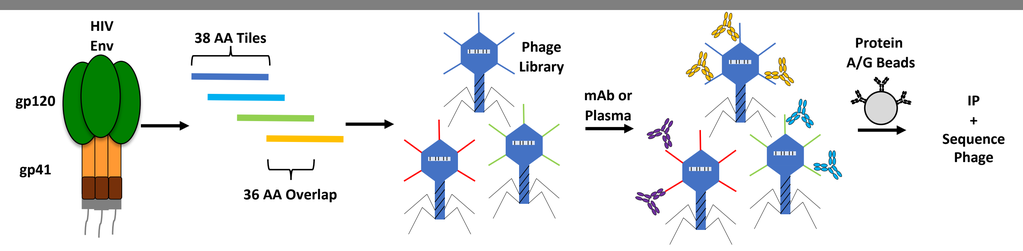

- **Hypothesis**: Abs targeting specific HIV Envelope (**Env**) epitopes are associated with either reduced MTCT risk and/or improved clinical outcome

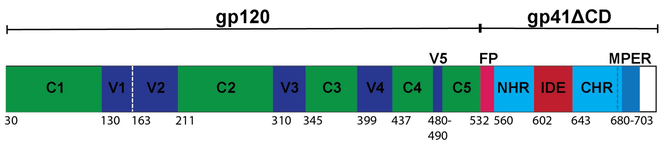
## Overview of the Nairobi Breastfeeding Trial (NBT Cohort)




Samples from a Kenyan cohort of breastfeeding (**BF**) infants were included in this study: the Nairobi Breastfeeding Trial (**NBT**; 1992-1998). Mothers were enrolled during late pregnancy and tested HIV+ at enrollment. Included infants tested HIV-negative at delivery (filter paper PCR or plasma RNA), acquired HIV during the follow-up period (HIV+), and were breastfed until at least the time of HIV transmission. Infant samples from the first week of life and maternal plasma from late pregnancy were tested in PhiP-seq. HEU: HIV exposed, uninfected.

## PhIP-seq Overview and Library Design



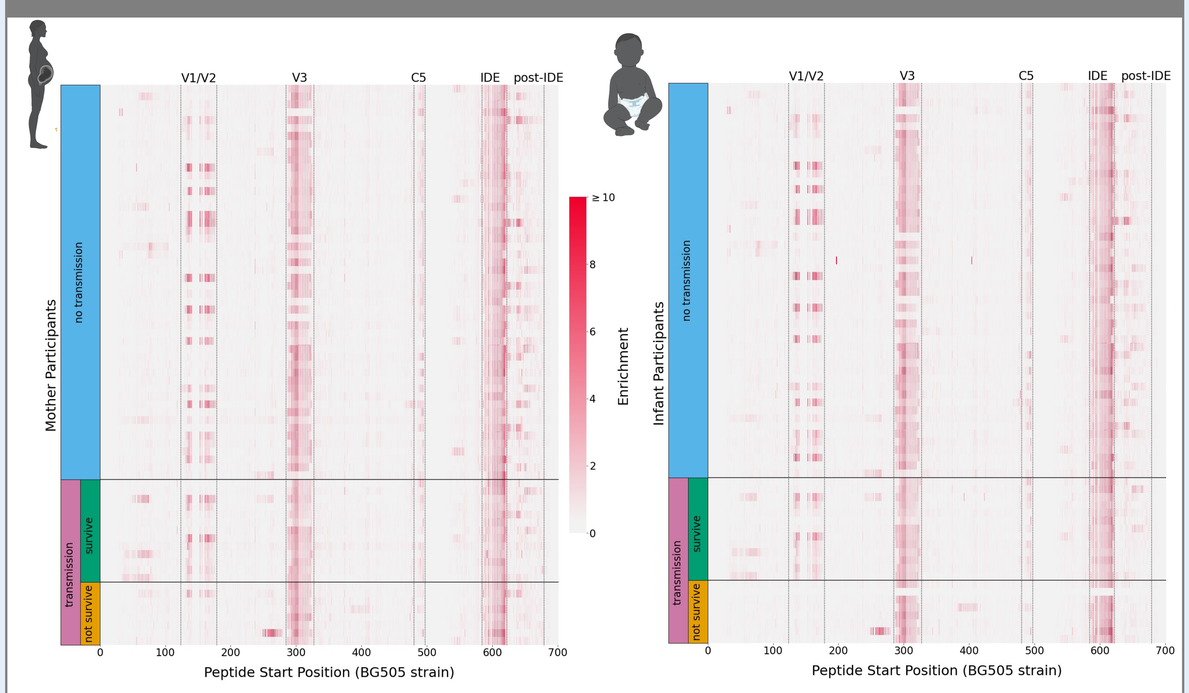




| Strain | Clade |
|---|---|
| **BG505.W6.C2 (BG505)** | A |
| **BF520.W14M.C2 (BF520)** | A |
| ZA1197.MB (ZA1197) | C |
| **BL035.W6M.C1 (BL035)** | A/D |

Phage Library Strains

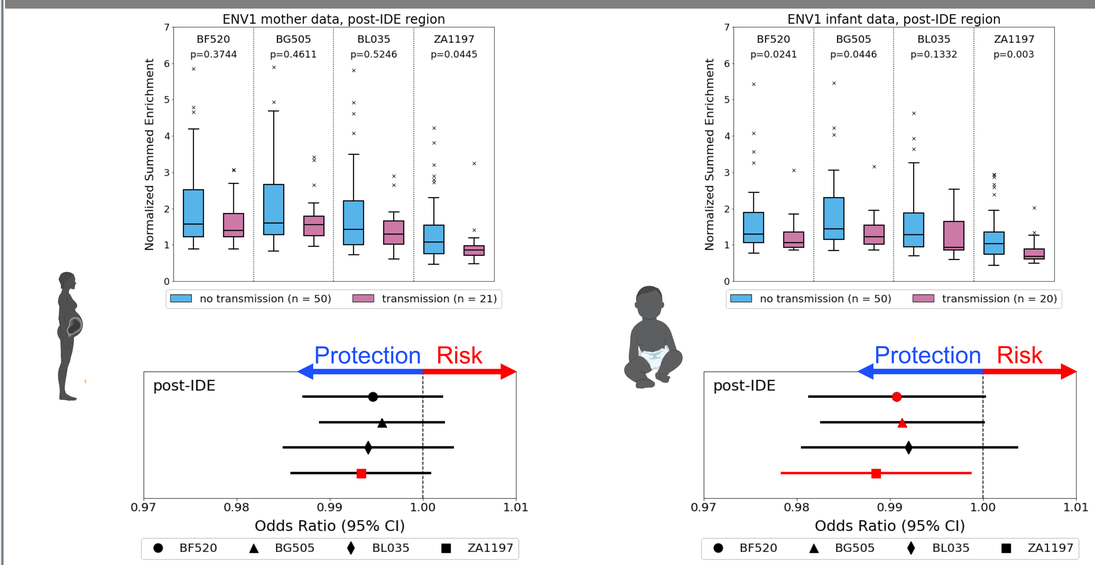
- Phage display immunoprecipitation sequencing **(PhIP-seq**) was used to evaluate the plasma Ab response to a peptide library spanning HIV Env
- Defined HIV Env epitopes with specific amino acid intervals indicated in the lower left panel
- Peptides from 4 HIV strains (lower right table) were included in the phage library, including 3 strains isolated from infants in the NBT cohort early during infection (bolded)
- Principal component analysis (**PCA**) was performed using strain-specific enrichment data for both mothers and infants to identify regions of high variance in enrichment within the cohort

## BG505 Enrichment Profiles in NBT Mothers and Infants



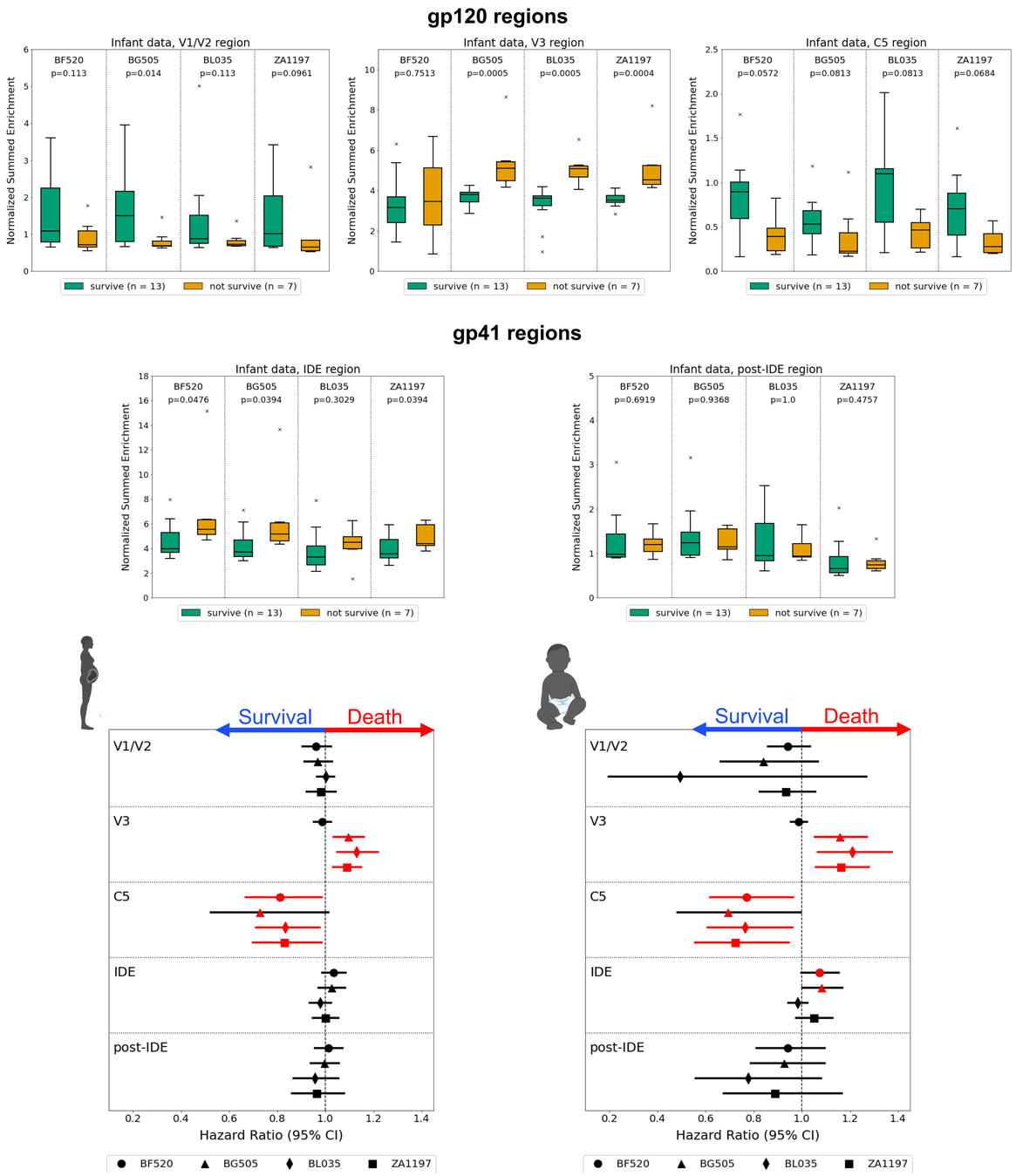

Fold-enrichment of BG505 strain peptides compared to input phage library for maternal (left) and infant (right) plasma samples (indicated by row). Individuals are grouped by MTCT status and HIV+ infant survival during study follow-up period. Non-transmitting pairs are ordered by maternal viral load. Bordered regions were identified as explaining high variance via PCA.

## Transmission Analysis




Post-IDE summed enrichment for non-transmitting and transmitting individuals was compared via Mann-Whitney U test (upper panels) or binomial logistic regression, adjusted for maternal viral load during late pregnancy (lower panel). Forest plots report odds ratios with 95% confidence intervals. Red data points indicate predictors with p-values < 0.1; red points and lines indicate p < 0.05. No other regions were significant predictors of MTCT risk.

## Survival Analysis




Surviving and non-surviving infant summed enrichment for gp120 (upper panels) and gp41 (middle panels) regions were compared via Mann-Whitney U test. Region enrichment for both mothers and infants was also compared based on infant survival status using Cox proportional-hazards models of infant mortality and survival time. Forest plots report hazard ratios with 95% confidence intervals. Red data points indicate predictors with p-values < 0.1; red points and lines indicate p < 0.05.

## Conclusions

- PhIP-seq identifies Ab responses to Env epitopes of several HIV strains
- Targeting of post-IDE peptides may be associated with reduced MTCT risk
- Ab responses to immunodominant epitopes (V3 and IDE) are significantly higher in non-surviving infants
- Passively-acquired Ab responses to sub-dominant epitopes (V1/V2, C5, Post-IDE) are associated with improved clinical outcome in HIV+ infants

## Acknowledgments

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