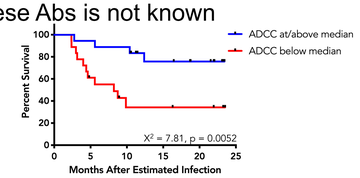
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# *Epitopes Associated with Altered Pathogenesis in Vertical HIV-1 Transmission*

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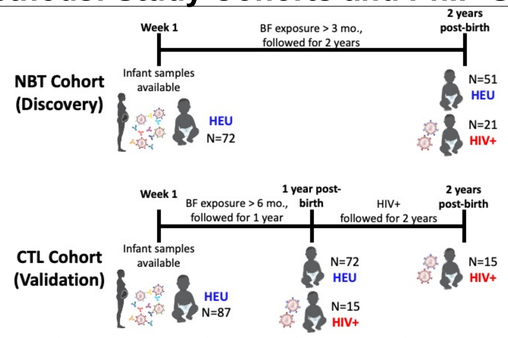
## Introduction

- Identifying correlates of protection from HIV acquisition and pathogenesis in humans is key to optimizing preventative approaches
- Infants receive HIV-specific antibodies (**Abs**) from their mothers via passive-antibody transfer
- Studying mother to child transmission allows for determination of whether HIV-specific antibodies present during HIV exposure influence HIV pathogenesis
- Plasma ADCC mediated by passively-transferred Abs is associated with improved survival in HIV+ infants, but the epitope of these Abs is not known

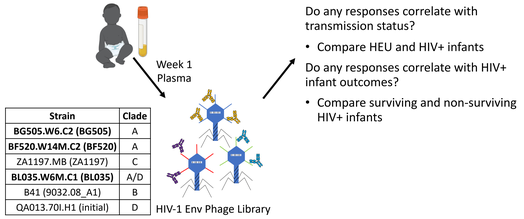



**Hypothesis**: Abs targeting specific Envelope (**Env**) epitopes are associated with improved clinical outcome

## Methods: Study Cohorts and PhIP-Seq




Samples from two Kenyan cohorts of breastfeeding infants were included: the Nairobi Breastfeeding Trial (**NBT**; 1992-1998) and the Cytotoxic T Lymphocyte (**CTL;** 1999-2002). Mothers tested HIV+ at enrollment in late pregnancy. Infants tested HIV-negative at birth, with some acquiring HIV during follow-up (HIV+). All infants breastfed at least until HIV acquisition. Both studies were carried out before the widespread availability of ART, but most mothers in CTL started a short course of zidovudine in the third trimester of pregnancy.

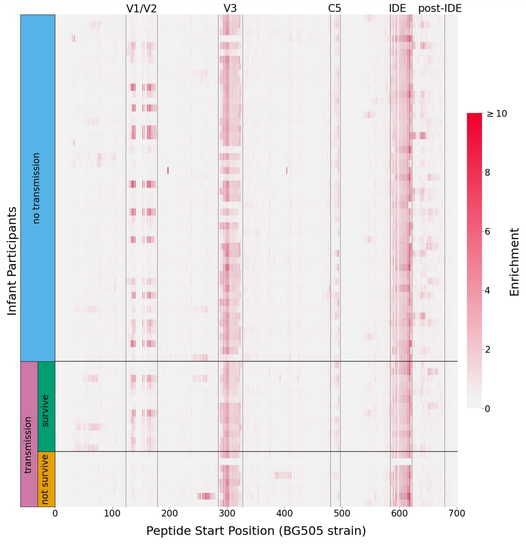



| Strain | Clade |
|---|---|
| BG505.W6.C2 (BG505) | A |
| BF520.W14M.C2 (BF520) | A |
| ZA1197.MB (ZA1197) | C |
| BL035.W6M.C1 (BL035) | A/D |
| B41 (9032.08_A1) | B |
| QA013.70I.H1 (initial) | D |

Infant samples from the first week of life were tested for HIV Env peptide binding via phage immunoprecipitation sequencing (PhIP-Seq). The phage library presents 38 amino acid long peptides spanning the Env ectodomain (1772 peptides total) of six strains (indicated in table). Adjacent peptides overlap by 36 amino acids. Bolded strains were isolated from infants in the NBT cohort.

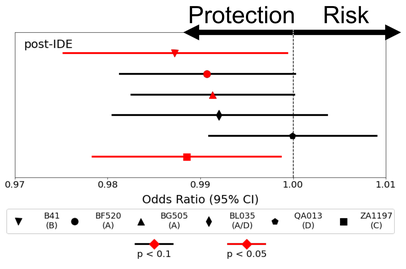
## *Passively-acquired antibodies* targeting the *gp41 IDE* were associated with *decreased survival* in Kenyan infants that acquired HIV

## Results: PhIP-Seq Identifies Env Ab Epitopes in NBT Infant Plasma

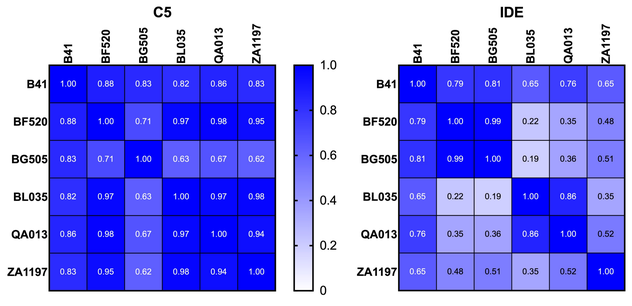



Left panel: **Representative heatmap showing BG505 PhIP-Seq data for NBT infants**. Red coloring indicates fold-enrichment for plasma samples compared to input phage. Individuals are grouped by HIV acquisition status and HIV+ infant survival during study follow-up period. Epitopes regions explaining high variance in principal component analysis (PCA) are indicated above.

Right panel: **Forest plot of infant HIV acquisition risk by post-IDE enrichment.** Post-IDE summed enrichment for HEU vs. HIV+ infants was compared via binomial logistic regression, adjusted for maternal viral load. Plots report odds ratios with 95% CI. No other regions were significant predictors of MTCT risk.

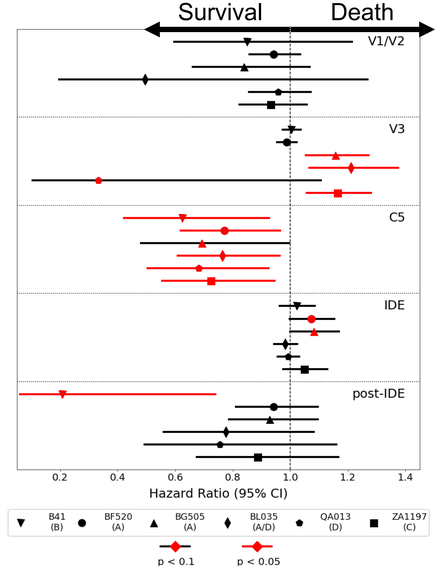



## Results: Multiple Epitopes Associated with HIV+ Infant Survival




Left panels: **Heatmaps of C5 and IDE enrichment correlation between strains.** For HIV+ infants, the strain-specific responses to peptides spanning the C5 (left) and IDE (right) regions were compared via Pearson correlation. Heatmaps report Pearson r, with more highly correlated values colored darker blue.

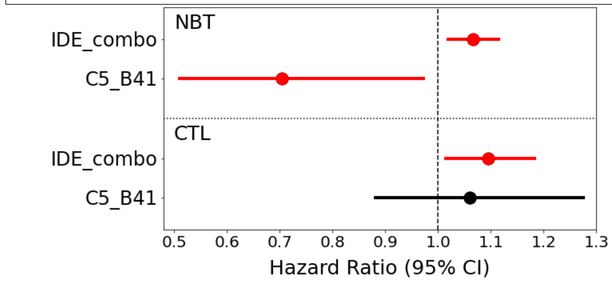
Right panel: **Forest plot of Ab epitope association with HIV+ infant survival.** Enrichment was compared using Cox proportional-hazards models of mortality and survival time. Forest plots report strain-specific hazard ratios for regions as predictors of infant survival with 95% confidence intervals. Strains are indicated with different symbols (see legend below).




## Survival Analysis Refinement

- Exploratory, univariate survival analysis imposes a high multiple-testing burden
- Within some regions (e.g. C5), there is high sequence identity across strains and the enrichment data is often highly correlated between strains
- Predictors of highly correlated strains (r > 0.90) were consolidated by taking their average enrichment
- In refined univariate analysis, IDE_combo (BG505 + BF520) and C5_B41 were the most significant predictors of HIV+ infant survival

## Results: IDE Responses Are Associated with Survival in Two Cohorts




**Forest plots of multivariate Cox-proportional hazards models of HIV+ infant survival in the NBT and CTL cohorts using IDE_combo and C5_B41 as predictors**. Plots report hazard ratios of two-predictor models of infant survival with 95% confidence intervals. Red predictors have a p value less than 0.05 for the indicated cohort.

## Conclusions

- PhIP-seq identifies Ab responses to Env epitopes of several HIV strains
- Targeting of post-IDE peptides may be associated with reduced HIV acquisition risk
- Ab responses to immunodominant epitopes (V3 and IDE) were associated with decreased survival of HIV+ infants in the NBT cohort, whereas responses to C5 were associated with improved survival
- Passively-acquired Ab responses to the gp41 IDE correlated with decreased survival of HIV+ infants in both the NBT and CTL cohorts

## Acknowledgments

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