HARNESSING ORIGINAL ANTIGENIC SIN FOR PREVENTING MTCT OF HIV

Ashley N. Nelson[a], Maria Dennis[a], Jesse F. Mangold[a], Katherine Li[a], Riley J. Mangan[b], George M. Shaw[c], Katharine Bar[c], Barton Haynes[a], M. Anthony Moody[a], Justin Pollara[a], Koen K.A. Van Rompay[d], Kristina De Paris[e], and Sallie R. Permar

[a]Human Vaccine Institute, Duke University Medical Center, Durham, NC, [b]Molecular Genetics and Microbiology, Duke University School of Medicine, Durham, NC, [c]Department of Medicine, University of Pennsylvania, Philadelphia, PA, [d]California National Primate Research Center, University of California, Davis, CA, [e]Department of Microbiology and Immunology and Center for AIDS Research, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

00294

INTRODUCTION

- Inconsistencies in adherence and implementation of ART hinder progress towards the elimination of pediatric HIV infection, thus maternal vaccination strategies that can complement current ART regimens are needed.
- Both maternal autologous virus neutralization and the magnitude of maternal HIV envelope (Env) V3 -specific antibody responses have been implicated in decreased MTCT risk of HIV.
- The ideal universal therapeutic vaccine for the prevention of MTCT of HIV would boost maternal antibody responses specific to the original antigen, which varies widely among individuals and across geographical regions.
- Hypothesis: An HIV immunization regimen, utilizing immunogens closely related to the maternal circulating virus populations will boost autologous antibodies through the phenomenon of original antigenic sin.

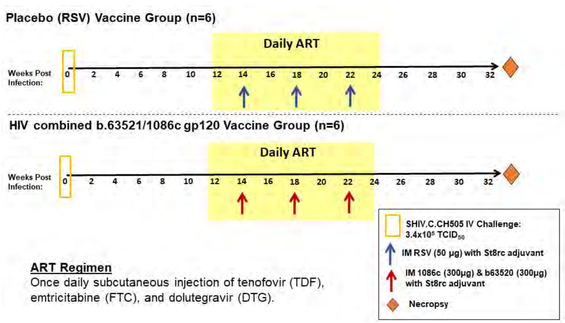
Study Goals

Evaluate the immunogenicity of a heterologous vaccine regimen in SHIV-infected, ART-suppressed, non-pregnant female rhesus macaques to:

1. **Boost antibodies that target maternal autologous virus pools through the phenomenon of original antigenic sin.**
2. **Elicit humoral immune responses previously associated with reduced MTCT risk in human cohorts**

METHODS

A. Study Design



ART Regimen
Once daily subcutaneous injection of tenofovir (TDF), emtricitabine (FTC), and dolutegravir (DTG).

B. Plasma Viral Load

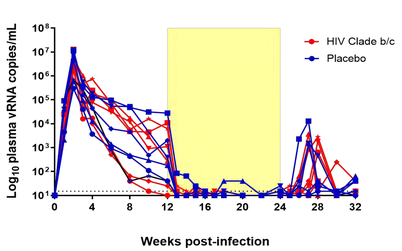


Figure 1. (A)Schematic of infection, treatment, and vaccination of rhesus macaques. (B) Plasma viral load kinetics. Viral loads declined to below the limit of detection within 2-3 wks of ART initiation. Upon treatment interruption, 50% of RMs in the placebo group rebounded within 2-3 wks and 83% of vaccinated RMs had viral rebound within 3-4 wks.

Vaccination of SHIV-infected, ART-treated RMs with heterologous HIV Envs augments functional antibody response against the original virus, suggesting that original antigenic sin can be exploited for maternal HIV vaccination

RESULTS

Vaccination during ART boosted plasma Env gp120 and V3-specific IgG antibody binding responses against vaccine and challenge antigens.

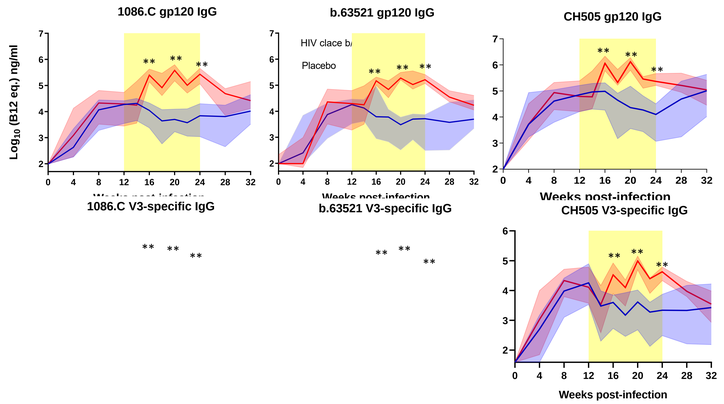


Figure 2. Plasma gp120- and V3-specific IgG binding responses were measured by ELISA. Both vaccine-(A), and challenge antigen-specific (B) responses were increased in the vaccinated RMs compared to the placebo cohort. Bold lines represent the median, and the range is depicted by the shaded area. Mann Whitney U test was used to compare antibody binding responses between the vaccine and placebo groups 2 wks after each immunization (14, 20, and 24 wpi). *p<0.05; ** p< 0.01

Antibody avidity against vaccine and challenge antigens increased after HIV Env vaccination.

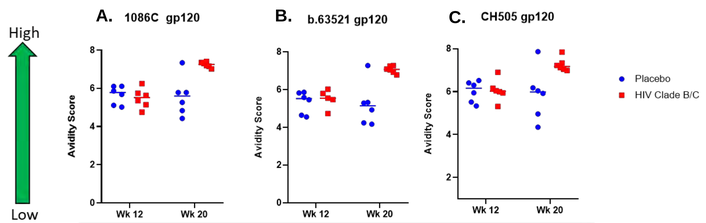


Figure 3. Plasma gp120-specific IgG antibody avidity was measured by Surface Plasmon Resonance at 12 and 20wpi. Avidity scores were calculated as the ratio of the binding response units/dissociation rate (k_d). Avidity scores increased in the HIV Env vaccinated RMs against vaccine (A and B) and challenge (C) antigens.

ADCC antibodies are enhanced with vaccination, yet autologous neutralization was similar between the two groups.

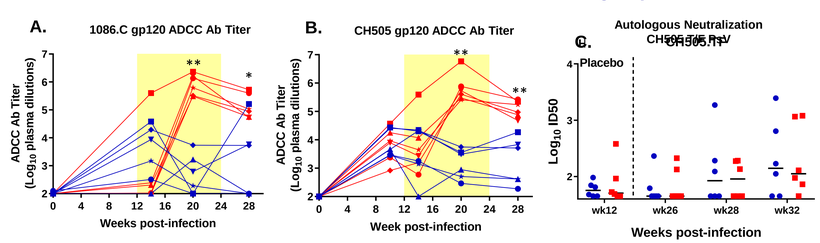


Figure 4. Antibodies capable of mediating ADCC were measured against 1086.C (A) and CH505 (B) gp120-coated target cells. Plasma HIV-1 neutralization was assayed in TZM-bl cells against the autologous, CH505.TF (C) virus. Mann Whitney U test was used to compare ADCC Ab titers between the vaccine and placebo groups. *p<0.05; ** p< 0.01

HIV Env vaccinated RMs exhibited V1V2 responses of greater magnitude and breadth.

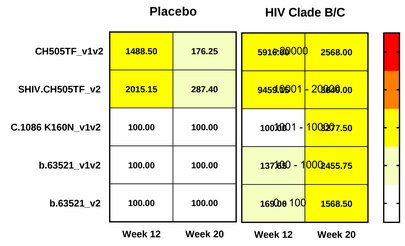


Figure 5. A binding antibody multiplex assay was used to assess antibody binding specificity to various HIV Env V1V2 epitopes at 12 and 20 wpi.

Increased plasma CH505-specific gp120 IgG antibody binding and avidity responses among HIV Env vaccinees

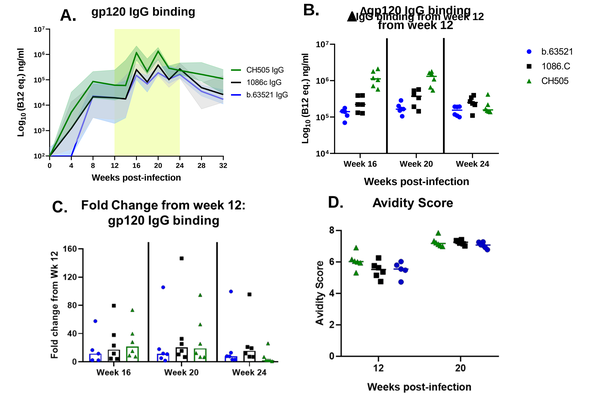


Figure 6. IgG binding responses across all three antigens were compared among vaccinees (A). To evaluate changes in IgG binding responses among the vaccinated cohort across all three antigens, the difference (B) and fold change (C) from week 12 (pre-ART/immunization) were compared for each antigen at 16, 20, and 24 wpi. Antibody avidity score across was also compared among vaccinees (D).

SUMMARY AND CONCLUSION

- HIV Env vaccinated RMs exhibited enhanced IgG binding and avidity responses against the vaccine immunogens and the challenge virus Env, SHIV.C.CH505.
- The HIV Env vaccinated cohort exhibited enhanced V3-specific IgG responses, a previously identified predictor of decreased MTCT risk.
- Plasma autologous virus (CH505.TF) neutralization was similar between the two groups upon treatment interruption, while ADCC responses were markedly boosted in Env vaccinated animals.

Our results suggest that a maternal HIV vaccination regimen can be developed to boost autologous antibody responses and previously identified humoral immune responses associated with decreased MTCT risk. Future work will determine whether these responses can be boosted in SHIV-infected, ART-suppressed, pregnant RMs.

ACKNOWLEDGEMENTS

This research is being supported by the NIAID award# 5P01AI117915 and the NIH TL1 Training Grant #TR002555.