HVTN114: A Phase 1 Trial to Evaluate Late Boosts with AIDSVAX B/E of Participants Previously Vaccinated with MVA/HIV62B in DNA/MVA or MVA Regimens

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Introduction

The only HIV vaccine study that showed evidence of protection (RV144) induced antibodies directed against the V1V2 loop of gp120. The DNA recombinant MVA (HIV62B) developed by GeoVax induced antibodies that mainly dominated gp41 (**Figure 1**). While the latter response may also be beneficial in terms of protection, the current study was designed to determine whether boosting prior recipients of MVA/HIV62B given in DNA/MVA or MVA regimens with AIDSVAX B/E could broaden the antibody response to enhance targeting of gp120.

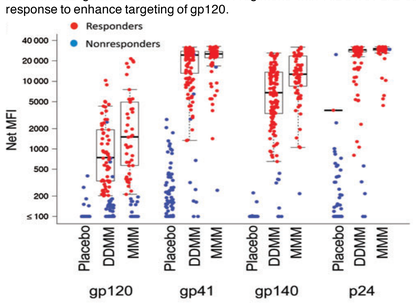
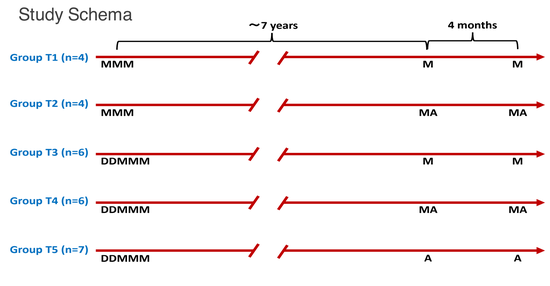


Figure 1: HIV62B induces antibodies that mainly target gp41. The net MFI of antibodies specific to the indicated HIV proteins is shown for vaccinees receiving HIV62B as DNA/MVA or MVA regimens in HVTN 205. *Goepfert et al. JID, 2014*

- **To evaluate the safety and tolerability of MVA/HIV62B and AIDSVAX B/E given separately or together as boost injections after prolonged immunologic rest**
- **To compare HIV-specific antibody responses elicited by MVA/HIV62B and AIDSVAX B/E given separately or together as boost injections after prolonged immunologic rest**

Methods

Study Schema



D= JS7 DNA plasmid; M=MVA/HIV62B; A=AIDSVAX B/E

- JS7 DNA and MVA/HIV62B express Env from the HIV-1 primary isolate ADA, Gag sequences from the HXB-2 strain of HIV-1-IIIB, and PR and RT sequences from the BH10 strain of HIV-1-IIIB
- AIDSVAX B/E is a bivalent HIV gp120 glycoprotein (MN gp120/HIV-1 and A244 gp120/HIV-1

Vaccine-Induced T cell Analysis

Flow cytometry was used to examine HIV-1-specific CD4+ and CD8+ T-cell responses using a validated ICS assay. A 17-color staining panel was used to stain for CD3, CD4, CD8, CD14, CD56, CXCR5, PD-1, ICOS, CD45RA, CCR7, IFN-γ, TNF-α, IL2, IL4, IL17a, CD40L, and granzyme B. PBMC were stimulated with PTE peptide pools comprised of Env-1-3, and Gag 1-2. Negative controls were not stimulated and positive controls were stimulated with SEB.

IgG Binding Antibodies Analysis

Serum HV-1-specific IgG responses against Con 6 gp120/B, Con Sgp140 CFI, and gp41 (B) were measured on a Bio-Plex instrument (Bio-Rad) using a standardized custom HIV-1 Luminex assay (Tomaras and Yates et al., J Virology 2008). The positive control was purified polyclonal IgG from HIV subjects (HIVIG) using a 10-point standard curve (4PL fit). The negative controls were NHS (HIV-1 sero-negative human sera) and blank beads.

Neutralizing Antibody Analysis

Neutralizing antibodies against HIV-1 were measured as a function of reductions in Tat-regulated luciferase (Luc) reporter gene expression in TZM-bl cells. The assay measured neutralization titers against the Env-pseudotyped vaccine strains (ADA, CM244.c01, and MN.3) and the heterologous matched Env-pseudotyped tier 1A neutralizing phenotype virus, TH023.6.

Statistical Analysis

T cells: To assess positivity for a peptide pool within a T-cell subset, a two-by-two contingency table was constructed comparing the HIV-1 peptide stimulated and negative control data. The four entries in each table were the number of cells positive for IL-2 and/or IFN-γ and the number of cells negative for IL-2 and IFN-γ, for both the stimulated and the negative control data. If both negative control replicates were included, then the average number of total cells and the average number of positive cells were used. A one-sided Fisher's exact test was applied to the table, testing whether the number of cytokine-producing cells for the stimulated data was equal to that for the negative control data. Since multiple individual tests (for each peptide pool) were conducted simultaneously, a multiplicity adjustment was made to the individual peptide pool p-values using the Bonferroni-Holm adjustment method. If the adjusted p-value for a peptide pool was ≤0.00001, the response to the peptide pool for the T-cell subset was considered positive. Because the sample sizes (i.e., total cell counts for the T-cell subset) were large, e.g., as high as 100,000 cells, the Fisher's exact test has high power to reject the null hypothesis for very small differences. Therefore, the adjusted p-value significance threshold was chosen stringently (≤ 0.00001). If at least one peptide pool for a specific HIV-1 protein was positive, then the overall response to the protein was considered positive. If any peptide pool was positive for a T-cell subset, then the overall response for that T-cell subset was considered positive.
Binding antibody: Samples from post-enrollment visits were declared to have positive responses if they met three conditions: (1) the MFI minus Blank values were ≥ antigen-specific cutoff at the 1:50 dilution level (based on the 95th percentile of the baseline visit serum samples and at least 100 MFI), (2) the MFI minus Blank values were greater than 3 times the baseline (day 0) MFI minus Blank values, and (3) the MFI values were greater than 3 times the baseline MFI values. In this report, HVTN 205 baseline, instead of HVTN114 baseline was used for the positive response calls. The MFI minus blank responses at the 1:50 dilution level were used to summarize the magnitude at a given time-point.
Neutralizing antibody: Response to a virus/isolate in the TZM-bl assay is considered positive if the neutralization titer is above a pre-specified cutoff (one-half the lowest dilution tested). A titer is defined as the serum dilution that reduces relative luminescence units (RLUs) by 50% relative to the RLUs in virus control wells (cells + virus only) after subtraction of background RLU (cells only). The pre-specified cutoff is 10 for TZM-bl cells. Tables show the response rates and corresponding 95% confidence intervals calculated by the Wilson score method.

Results: Boosting with MVA/HIV62B and/or AIDSVAX B/E appears safe and well tolerated

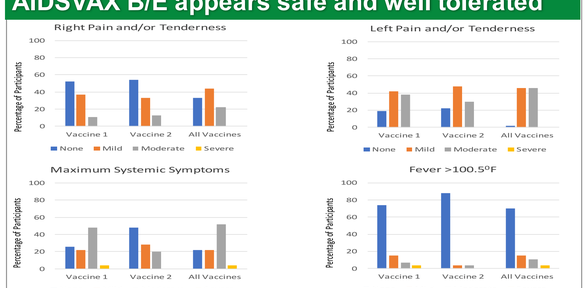


Figure 1: Local and systemic symptoms in 27 vaccinees.
Note that the study remains blinded in terms of safety, but all 27 participants received some form of boost with 24 receiving a second boost. Right and left pain and/or tenderness as well as maximum systemic symptoms and fever.

Results: Modest boosting of CD4 T cell responses with MVA/HIV62B and/or AIDSVAX B/E

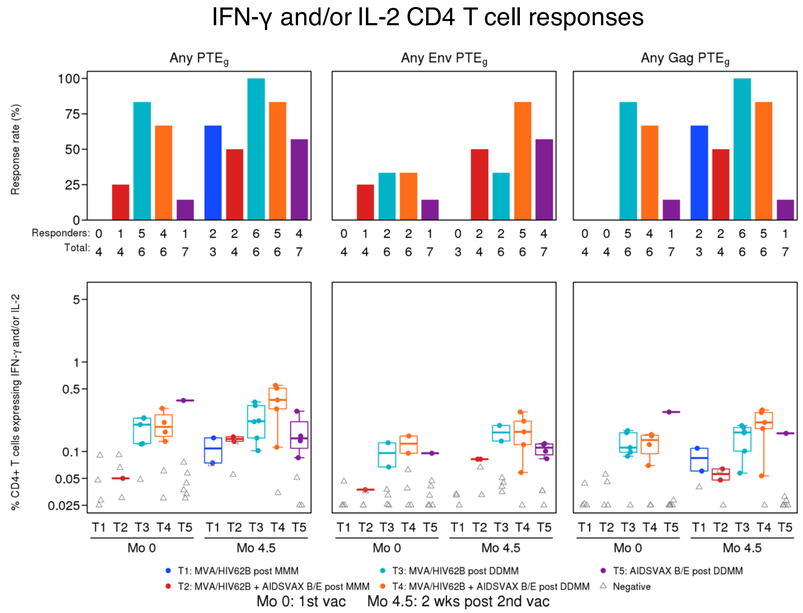


Figure 2: CD4 T cell responses directed against Env or Gag PTE pools.
Vaccine PBMC were stimulated with Env and Gag PTE pools, stained with a 17 color panel, and analyzed by flow cytometry. CD4 T cells producing IFN-γ and/or IL-2 are shown. AIDSVAX B/E recipients demonstrated increased responses to Env PTE (23.5% at month 0 vs. 64.7% at month 4.5; p=0.02). The magnitude of responses was boosted to Env in all groups (p≤0.02) and to Gag in those receiving MVA/HIV62B (p=0.004). CD8 T cell responses were minimally induced (not shown).

Results: AIDSVAX B/E with or without MVA/HIV62B induces a higher magnitude of vaccine and tier 1 neutralizing antibodies

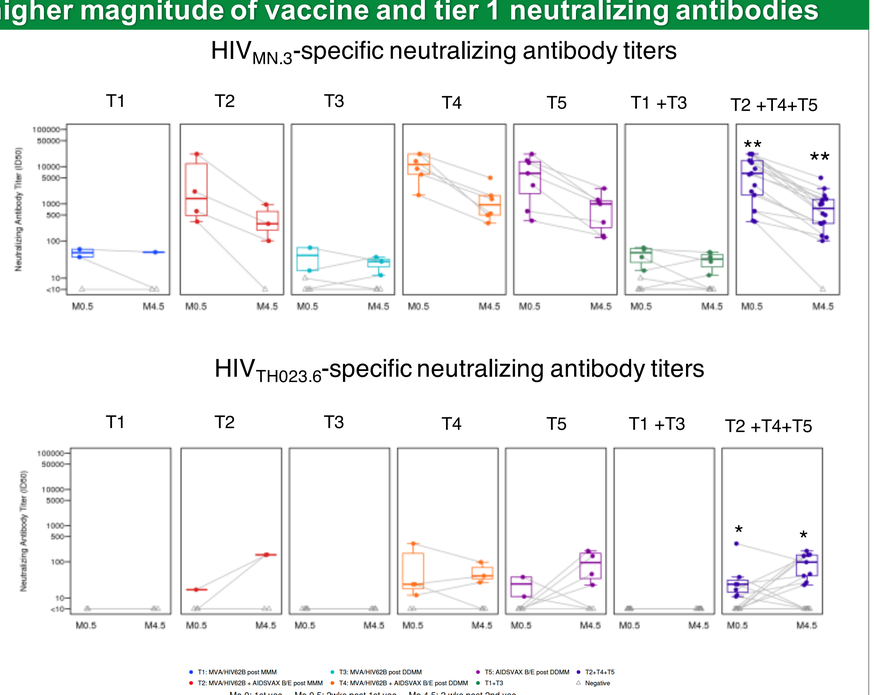


Figure 3: Neutralizing antibodies main seen against HIV$_{MN.3}$.
Neutralizing antibodies were measured using the TZM-bl cells. Vaccinees boosted with AIDSVAX B/E containing regimen also demonstrated a higher response frequency of neutralizing antibodies against HIV strains MN.3 compared to MVA/HIVB alone (100% vs 44.4% at month 0; p=0.0005 and 94.1% vs 44.4% at month 4.5, respectively; p=0.005) and TH023.6 (41.2% vs 0% at month 0; p=0.03 and 52.9% vs 0% at month 4.5, respectively; p=0.006. Similar differences although weaker overall responses were seen against HIV strain TH023.6. No responses detected against ADA or CM244.c01 (data not shown). ***p<0.05; **p<0.001 compared to T1+T3**

Acknowledgements

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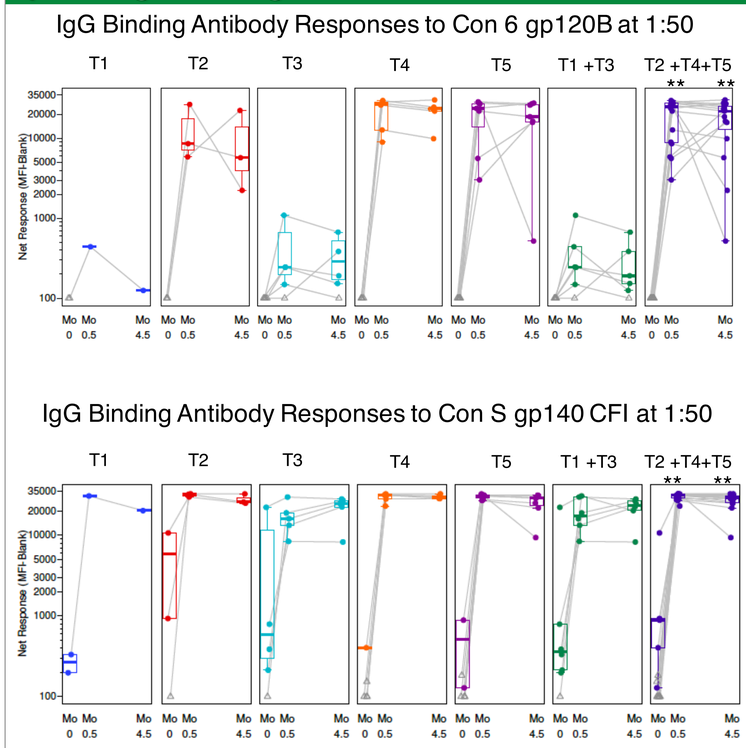
Results: Boosting with AIDSVAX B/E broadens gp120-specific IgG binding antibodies



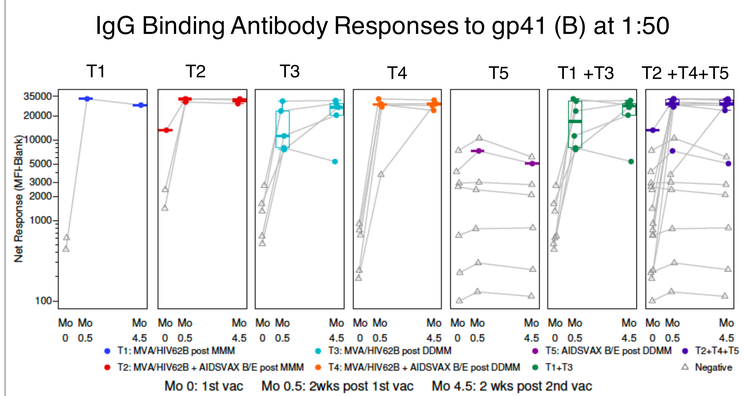


Figure 4: Envelope-specific IgG binding antibody responses Serum HIV-1-specific IgG responses against Con 6 gp120/B, Con Sgp140 CFI, and gp41 (B) were measured on a Bio-Plex instrument using a standardized custom HIV-1 Luminex assay. ****p<0.008**

Summary

1. Boosting a DNA with or without MVA vaccine regimen after a prolonged rest (~7 years with MVA/HIV62B and/or AIDSVAX B/E appears safe and well tolerated although the safety data are still blinded.
2. CD4 T cell and Ab responses to gp140 were detectable in ~50% of the vaccinees following the ~7 year rest
3. AIDSVAX B/E containing boost induced a higher magnitude of vaccine strain (MN.3) and tier 1 strain (TH023.6) neutralizing antibodies.
4. AIDSVAX B/E containing boost induced a higher magnitude of gp120 and gp140 specific IgG binding antibody responses in all recipients while responses to gp41 were similar amongst all groups.
5. Boosting of CD4 T cell responses was observed in most vaccinees with a higher frequency and magnitude of Env-specific responses seen with AIDSVAX containing boosts and higher magnitude of Gag-specific responses in those receiving MVA/HIV62B boosts alone.
6. CD8 T cell responses were induced in a minority of vaccinees regardless of boost type.

Significance for vaccine design

These data indicate that a broadened antibody response can be induced in vaccinees who previously received a DNA/MVA vaccine regimen when boosted with AIDSVAX B/E. While the correlates of vaccine-induced protection against HIV infection are poorly understood, it seems reasonable to expect that a broadening of antibody responses is a useful feature for a vaccine designed to prevent HIV infection.