



Abstract

Vaccine mediated induction of novel broad HIV-specific CD8⁺ cytotoxic T cells and binding antibodies (Ab) with effector function is a strategy for clearance of the HIV reservoir. Youth acquiring HIV in the perinatal period and initiated antiretroviral therapy (ART) in the first 6 months of life tend to have robust immune responses and small HIV reservoirs. The RV534 Phase 1 study was an open-label randomized proof-of-concept study to evaluate the safety and effects of prime-boost HIVIS DNA and MVA-CMDR vaccine regimens with or without Cervarix, containing AS04 adjuvant, a Toll-like receptor 4 agonist, on HIV reservoirs and their relationship to HIV-specific humoral and cellular immune responses in perinatally infected youth.

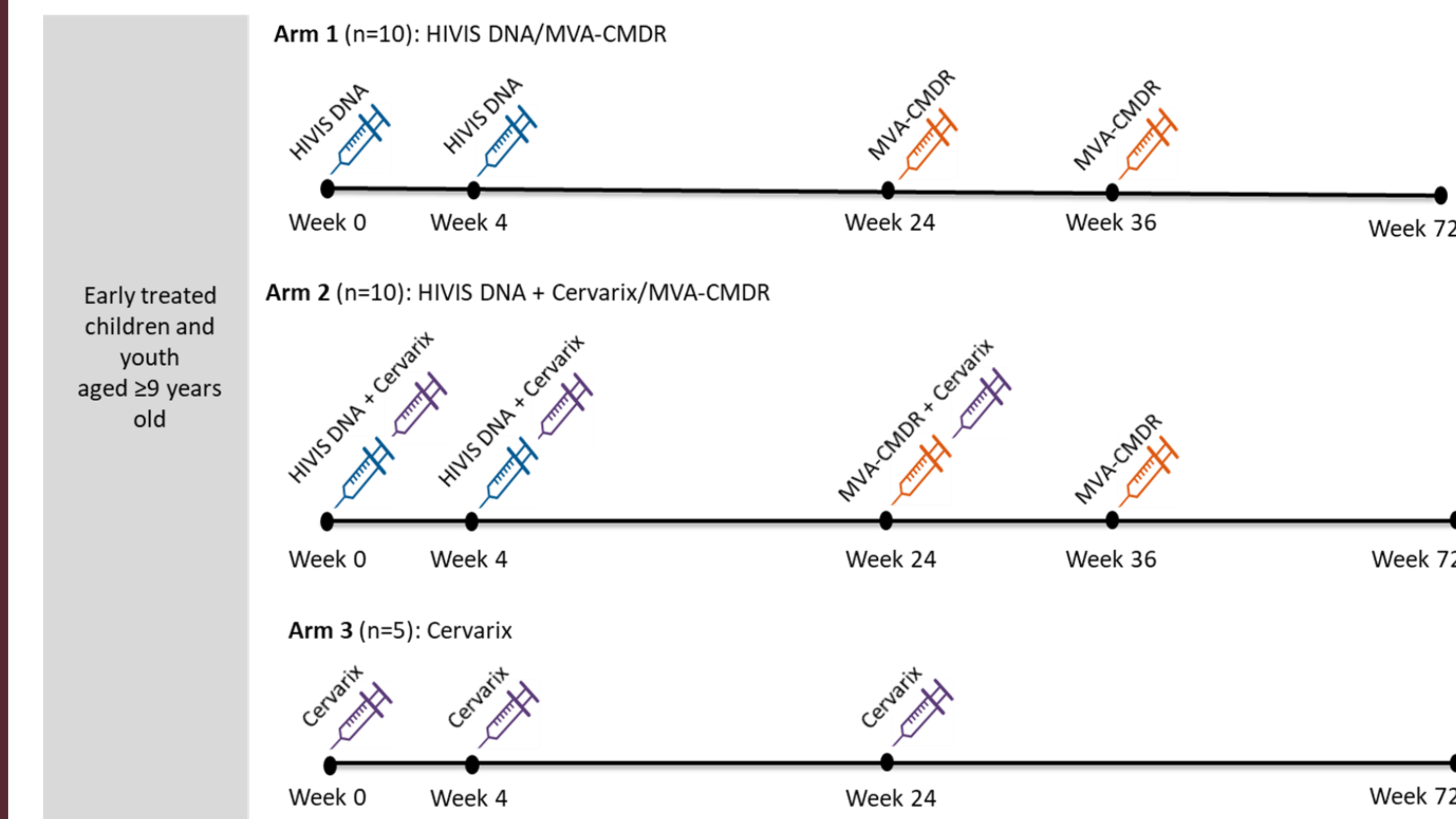
Perinatally HIV infected youth (n=25) median age 15 years, initiating ART in the first 6 months of life with consistent viral suppression, entry viral load <200 cps/ml and CD4 T cell count >400 cells/mm³ were enrolled at study site in Cape Town, South Africa. Participants were randomized and administered the vaccine HIVIS DNA (1500 µg, wks 0, 4) and MVA-CMDR (1x10⁸ IU, wks 24, 36), Arm 1 (n=10); the vaccines along with Cervarix, Arm 2 (n=10); and Cervarix alone (wks 0, 4, 24), Arm 3 (n=5). Antigen-specific IgG binding Ab against Env and Gag were measured at wks -2 (baseline), 8, 28, 40 and 60 by ELISA and/or multiplex Luminex®-based assay.

The vaccine regimen was well tolerated with no vaccine related serious adverse events. Cervarix alone (Arm 3) did not induce HIV Env or Gag Ab responses. Binding IgG Abs against Env and Gag were present at baseline. HIVIS DNA alone did not induce HIV Env or Gag Ab responses. However, MVA-CMDR induced higher HIV Env Ab responses in Arms 1 and 2. HIV Env Ab responses were significantly higher (2-5 fold) than Cervarix alone (Arm 3) (p<0.05) across a multi-subtype antigen panel. Peak Env-specific Ab responses were observed at wk 40. MVA-CMDR boosts also significantly increased the Gag-specific Ab responses to subtype A and B by 3-5 fold (p<0.05) from baseline. Peak Gag-specific Ab responses were observed at wk 28 and subtype B Gag specific Abs were sustained through wk 60. The addition of Cervarix (Arm 2 vs Arm 1) did not increase Ab responses.

The HIVIS DNA and MVA-CMDR combination potentially induced antibody responses, against both HIV Env and Gag in perinatally infected youth. Correlation of vaccine induced Ab responses and their effect on the HIV reservoir are currently underway.

Background

The induction of CD8⁺ cytotoxic T cells and binding antibodies with effector functions is a strategy for clearance of the HIV reservoir. It is possible that youth who have initiated ART early will have smaller reservoirs. This Phase 1 Clinical Trial examines if the regimen below will affect the HIV reservoir. This work examines the induction of HIV-specific antibodies with this vaccine regimen.



Methods

Clinical Trial Participants – Perinatally infected youth (n=25) median age 15 years initiated ART in the first 6 months of life. Entry plasma viral load: <200 copies/mL and CD4 T cell count: >400 cells/mm³. The study was performed in Cape Town, South Africa.

Vaccine Components – HIVIS DNA (1500 µg) expresses HIV Env genes of subtypes A, B and C together with Gag subtypes A and B and RTmut/Rev of subtype B. MVA-CMDR (1x10⁸ IU) expresses HIV CM235 env/CM230 gag-pol. Cervarix is a bivalent Human Papillomavirus Bivalent (Types 16 and 18) vaccine containing the L1 protein and the AS04 adjuvant (a TLR4 agonist).

Antigen-specific IgG Measurements – HIV Envelope-specific IgG was measured either by Enzyme Linked Immunosorbent Assay (ELISA) or by multiplex Luminex-based assay. HIV Gag-specific IgG was measured by ELISA.

Results

Figure 1. HIVIS DNA/MVA-CMDR Regimen Induces HIV Env-Specific Antibodies (ELISA)

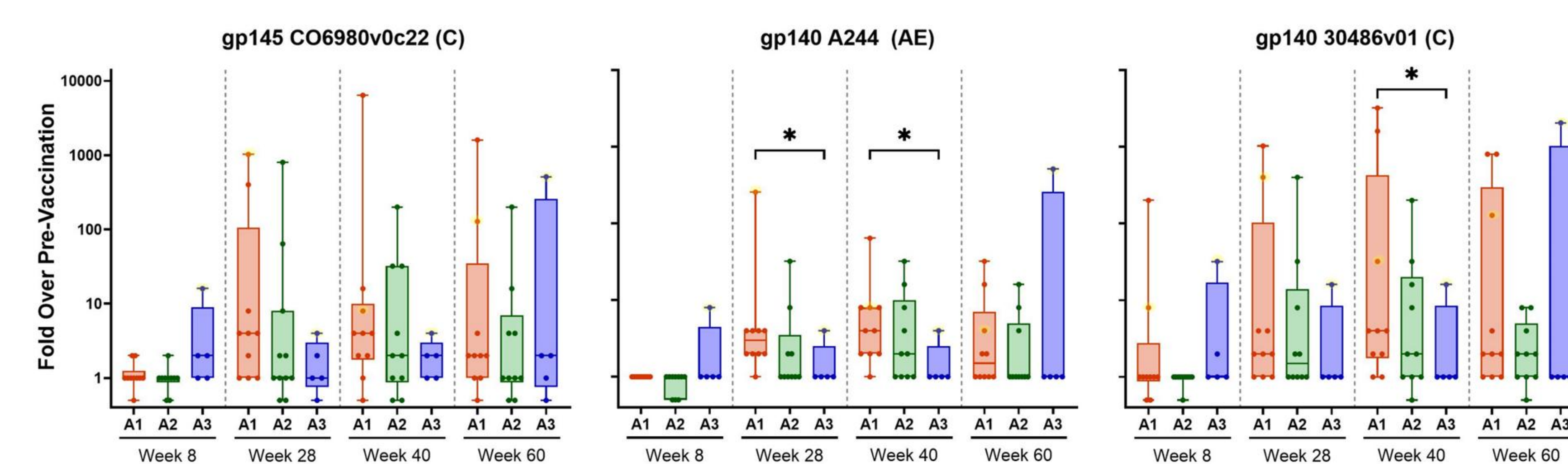


Figure 2. HIVIS DNA/MVA-CMDR Regimen Induces HIV Gag-Specific Antibodies (ELISA)

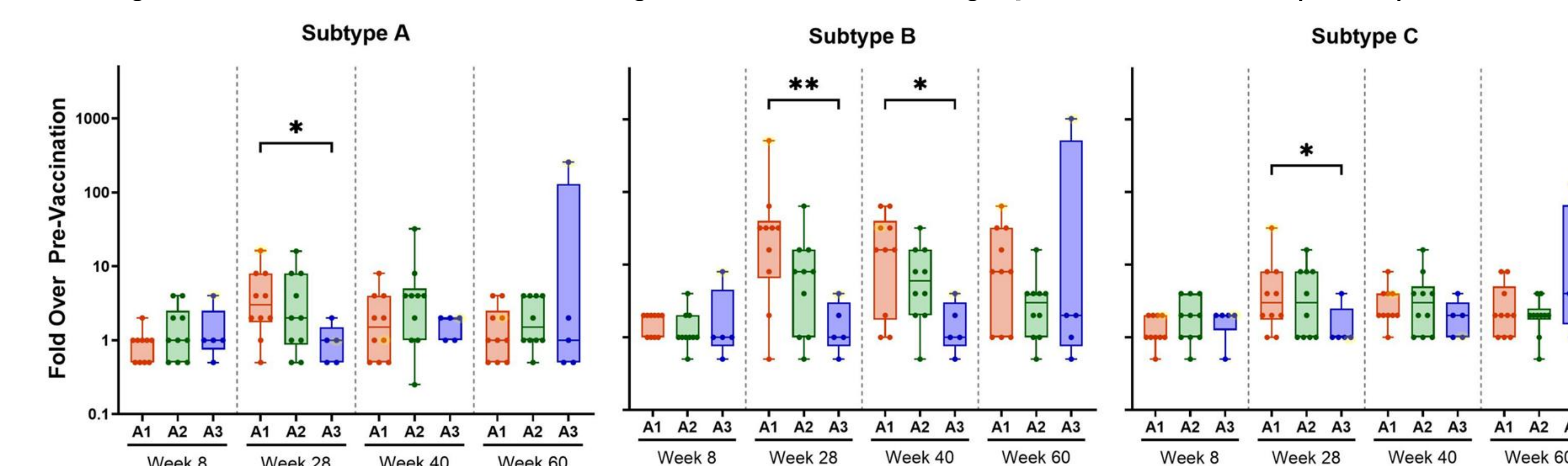
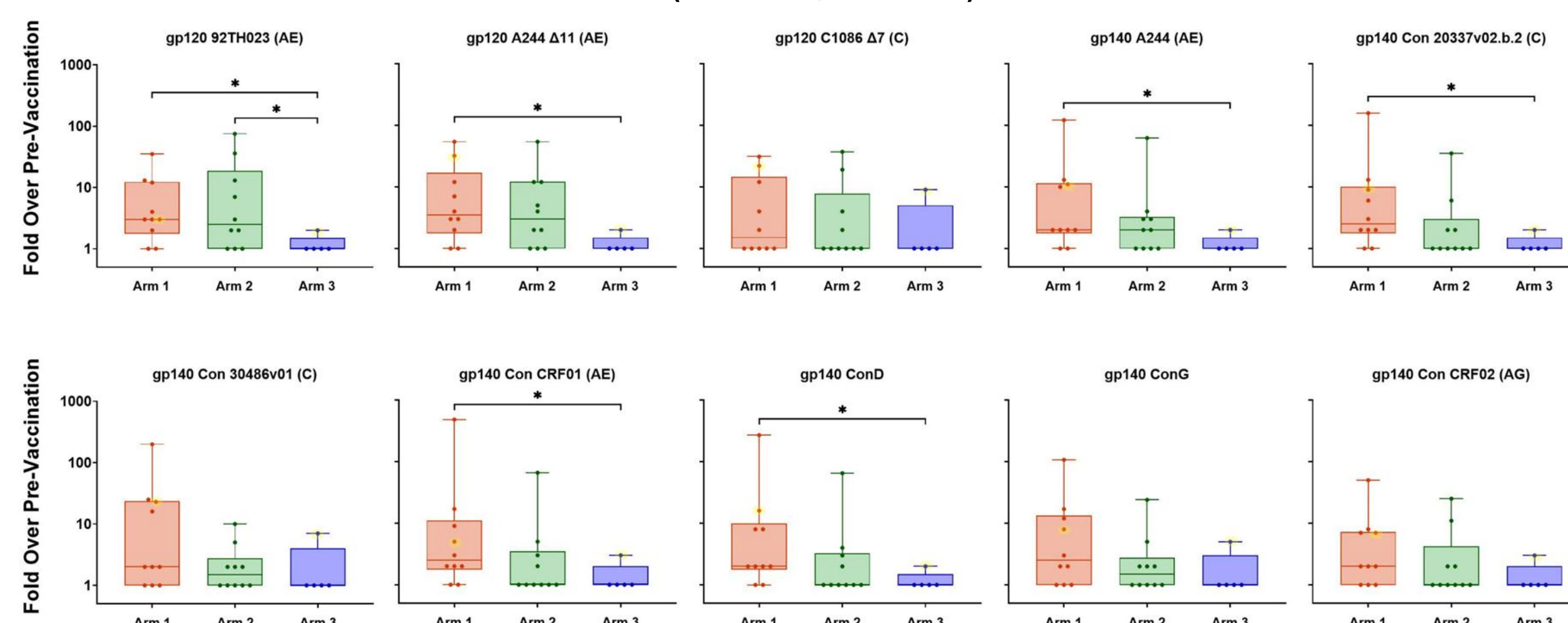


Figure 3. HIVIS DNA/MVA-CMDR Regimen Induces Antibodies Against Several HIV Env Subtypes (Luminex, Week 40)



Acknowledgements

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Figure 4. Longitudinal Analyses of the Presence of HIV Env-Specific Antibodies (ELISA)

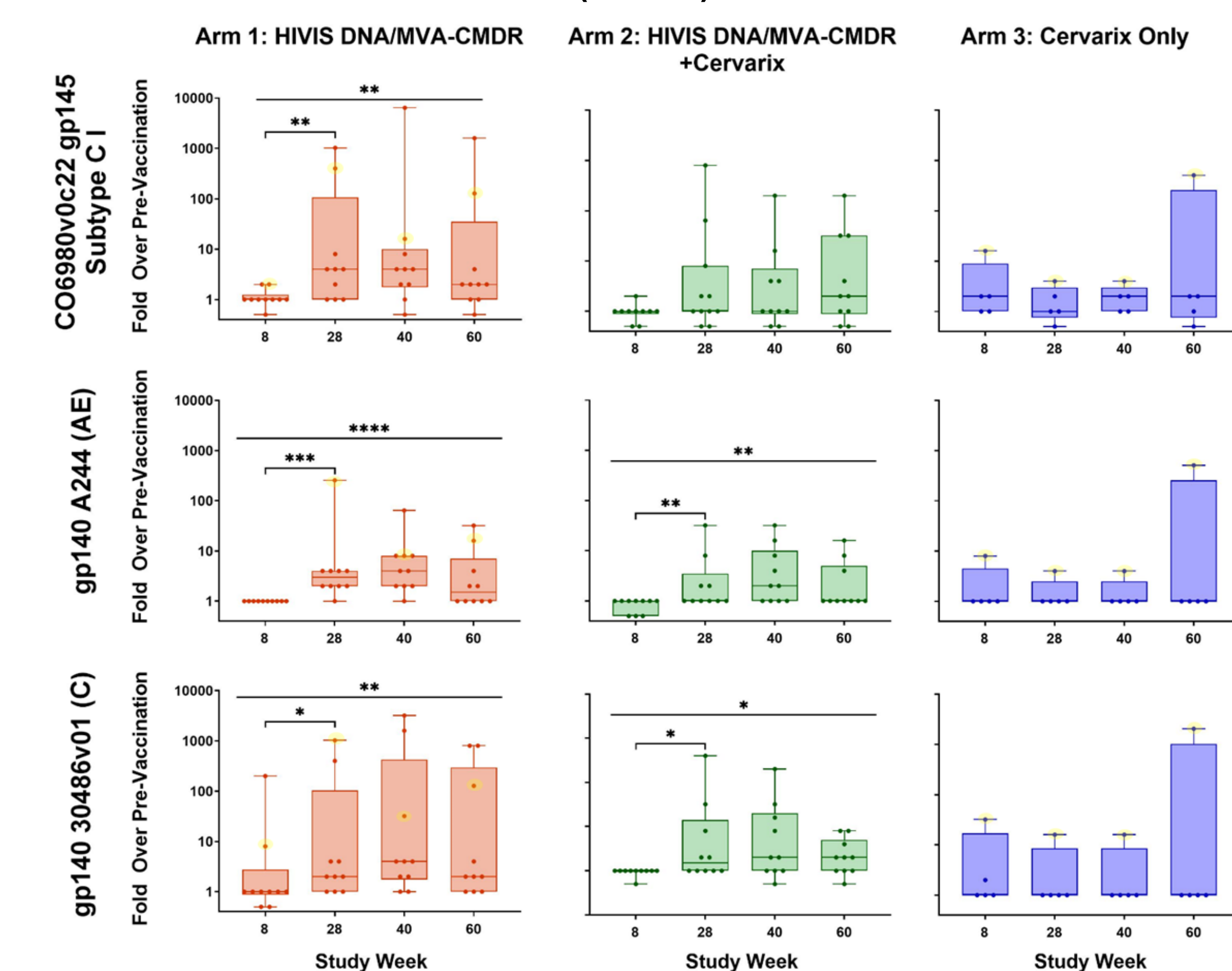
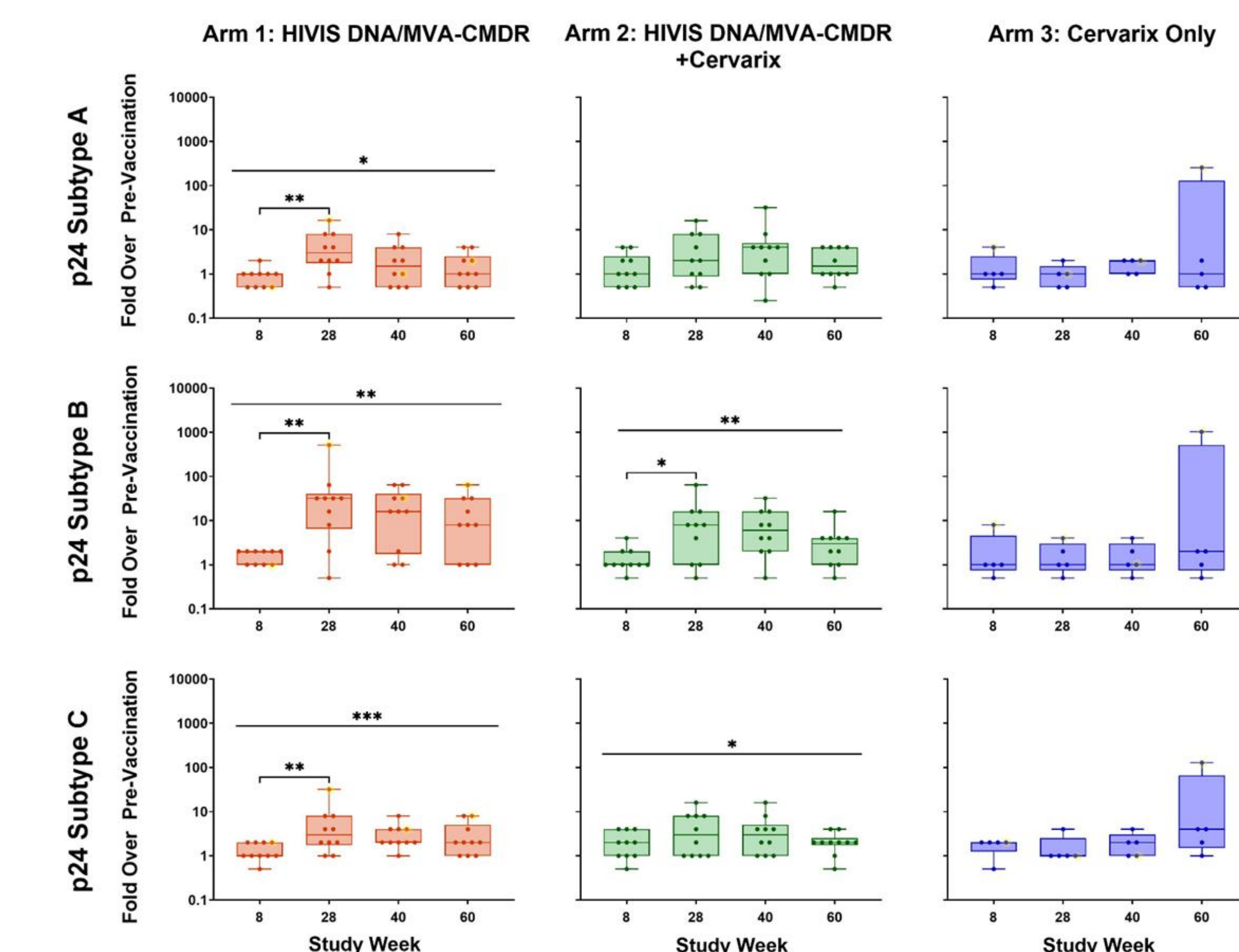


Figure 5. Longitudinal Analyses of the Presence of HIV Gag-Specific Antibodies



Conclusions

- The combination of HIVIS DNA and MVA-CMDR induced significantly higher HIV Env-specific Ab responses.
- The regimen also induced significantly higher HIV Gag-specific Ab responses. The responses were sustained through week 60.
- Inclusion of Cervarix (Arm 2 vs Arm 1) did not increase the Ab responses.