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Scholarly Report Title: A Novel Approach to Understanding Vaccine-Induced Seropositivity (VISP) in HIV Vaccine Clinical Trial Participants

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A Novel Approach to Understanding Vaccine-Induced Seropositivity (VISP) in HIV Vaccine Clinical Trial Participants

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Vaccine-Induced Seropositivity (VISP) or Vaccine-Induced Seroreactivity (VISR) is emerging as a prominent cited reason for individuals declining participation in HIV vaccine clinical trials. As a result the progress towards an effective vaccine has been reduced. The VISP/VISR phenomenon refers to the appearance of seropositivity for HIV in individuals on screening enzyme immunoassays (ELISA) following receipt of the candidate HIV vaccine, although no patent HIV infection is present. This results in the individual being susceptible to social harms due to false positive HIV designation. This research endeavor introduces a continuous approach evaluating optical density values which will allow for a more informative way to view VISP/VISR.

We analyzed optical density values from HIV Vaccine Trials Network (HVTN) studies (Protocol 065, 078, 204, and 077). Through this quantitative approach, we attempted to answer three questions: 1) How do optical density values vary between participants who received candidate HIV vaccines and those who receive placebos 2) How do the optical density values in HIV clinical trials participants vary with a vaccine regimen or enzyme immunoassay utilized 3) Is there dynamics concerning optical density values that can be ascertained overtime? This research endeavor looked at optical density values related to VISP/VISR in a continuous manner, a departure from the present dichotomous standards for designating VISP/VISR. This new approach offers an alternative view of VISP and consequentially will aid in mitigating VISP/VISR induced social harms for HIV vaccine clinical trials participants and offer a novel metric of the potential immunogenicity of the candidate HIV vaccines.

Results: Analyses of the study protocols illustrate that there is a difference in optical density (OD) values between placebo and treatment groups in each study as expected (Wilcox signed-rank test: $p>.0001$-$.0096$). The OD values in placebo recipients demonstrated limited variability and clustered tightly around 0.1-0.2. A difference in optical density values between treatment groups within each protocol was identified (Wilcox signed-rank test: $p>.0001$). It was also seen that OD values could distinguish between different enzyme immunoassays (Wilcox signed-rank test $p>.0001$). Additionally, the OD could distinguish between different order in HIV vaccine candidate regimen ($p>.0001$). Finally, it was seen that there was a significant difference in

average OD ratios in a selected study participants between specific time intervals in selected study participants.

Introduction: There are estimated 7,000 incident HIV infections per day worldwide, there is an urgent need to develop an effective prophylactic HIV vaccine.[1] Despite the substantial advances in antiretroviral therapy, HIV infections and AIDS continue to have a substantial impact on developed and developing countries alike. Over the past twenty years, many potential vaccine candidates have been developed and assessed in over 30,000 individuals.[2] As HIV vaccine clinical trials increase in numbers and size (with efficacy trials), individuals that participate in HIV vaccine trials will significantly increase.[2] A predictable consequence of clinical studies with candidate HIV vaccines is the development of an immune response against HIV vaccine candidates which may cause routine antibody assays for HIV to be positive (when no HIV infection is present).[2] This phenomenon is called Vaccine Induced Seropositivity (VISP) or Vaccine Induced Seroreactivity (VISR). [3,10] This VISP/VISR designation is usually denoted at an optical density value above 1. The development of VISP is a result of both the immunogenicity of the vaccine construct and the antigen detection system of the enzyme immunoassay ulitilized.[4] This phenomenon can be seen in many of the HIV vaccine clinical trials conducted to date.[5–7,10] Although, eliciting a broadly-reactive, long-lasting antibody responses to HIV is generally viewed as desirable for HIV vaccine candidates. The VISP/VISR status result in social harms for HIV vaccine participants. These social harms include social exclusion, limited immigration, and the inappropriate use of-antiretrovirals.[5–7] These concerns have impacted many altruistic individuals from not participating in HIV vaccine clinical trials.[7] Because of these the potential social harms that can occur with those subjects who develop VISP/VISR there have been safety testing algorithms in place by HIV vaccine clinical trials organizations to better assesses if an individual is Vaccine-Induced Seropositive or HIV positive.[8] Furthermore, the HIV immunoassay industry has also attempted to circumvent this problem with the development of immunoassays that is based on consensus and clade-specific HIV peptides that are omitted in many HIV vaccine.[12] However, currently these algorithms are expensive or time inefficient and these newly developed immunoassays are not widely used.[2, 12] Furthermore, the assessment of enzyme immunoassays

(EIAs) readings used to designate VISP is achieved in a dichotomous fashion in both novel and tradition immunoassays.[4] However, because the presence of VISP/VISR can be temporally dynamic there is an opportunity to look at the continuous optical density data generated when EIA tests are done. This can provide information that has not yet been evaluated. This study assessed HVTN protocols 065, 078, 204, and 077. Data gathered from these studies aided in initially assessing the EIAs characteristics, determining the dynamic changes in optical density data from EIAs, and evaluating differences between EIA in conferring VISP/VISR. By evaluation of the optical density from this novel continuous perspective, it illuminated that possibility of assessing the variability between kits and vaccine constructs quantitatively, and introduced a way to assess the difference between vaccine constructs and regimen.

Student Role: During June 1st, 2013- February 4th, 2014 I initially worked on garnering data from multiple HVTN sites. This endeavor included setting up conference calls and receiving permission from the protocol leadership. Once the data was acquired I worked closely with Barbara Metch, a head statistician at the HVTN, on data analysis which is further described in the method section. After the data analysis was concluded I created graphs, and charts via PRISM and presented the findings at multiple conferences. These include, HVTN Group Meeting, and Soma Weiss Conference at Harvard School of Medicine.

Methods: These data was gathered from protocol 065, 078, 204, and 077. These four protocols can be characterized as completed HIV vaccine clinical trials evaluating for safety and immunogenicity potential. These clinical trials were chosen because they employed different vaccine constructs, and different EIAs. Analysis was carried out by SAS Enterprise 9.1, which included, Wilcox signed-rank tests, and logistical regression.

Results:

A total of 782 optical density readings derived from volunteers who received placebos and approximately 782 optical density readings from individuals who received candidate vaccinations (Figure 1). These data were all derived from individuals who had End of Study testing. Individuals were not included in analysis if they were loss to follow up, or were HIV-1 infected or had vaccine related issues. All the participant's data were compiled from protocol

204, 065, 78 and 204. Optical density values were derived from the Biorad Genetic Systems HIV ½ plus O EIA, Biorad Genetic Systems Rlav, bioMerieux Vironostika HIV-1, and Abbott HIV AB ½ (rDNA) (Table 1). This difference in enzyme immunoassays utilized is a result of the HVTN End of Study testing algorithm consistently implemented in HVTN vaccine clinical trials.

Protocol 065 evaluated the safety and immunogencity of PGA2/JS7 (D) vaccine and recombinant modified vaccine Ankara/HIV62 (M) vaccine in healthy, HIV-1 uninfected adult participants. At End of Study for Protocol 065 the optical density values of participants who received different candidate vaccines and regimens varied significantly within each enzyme immunoassay utilized six month after the last candidate vaccination given (Figure 1). Notably, the Abbott HIV AB HIV ½ EIA has a total 85 optical density observations and employing the Wilcox signed rank text indicated a significant difference in optical density values between treatment groups (p=.0014) (Figure 2). Furthermore, at the End of Study for Protocol 065 these data also showed that between Abbott HIV AB HIV ½ (N=24) and Biorad GS HIV ½ Plus O (N=24) there is a significant difference between the enzyme immunoassays' elicited optical density readings (p=.0050) (Figure 3).

Protocol 077 evaluated the immunogencity and safety of the recombinant adenoviral serotype 35 (rAd35) and serotype 5 (Ad 5) HIV-1 vaccine constructs with a heterologous prime-boost regimen in healthy, Ad5-naïve, and Ad5-exposed, low risk, HIV uninfected individuals. Protocol 077 has a total of 69 optical density observations analyzed at End of Study. These data illustrated that between the optical density values elicited by the Biorad GS HIV ½ Plus O and the Abbott HIV AB ½ there was a significant difference (p=0.0001) (Figure 4).

Protocol 78 evaluated the safety and immunogencity of heterologous prime/boost vaccine regimens (NYVAC-Br/rAd5) and (rAd5/NYVAC-B) in healthy, HIV-1 uninfected, Ad5 seronegative adult participants. These data derived from the participants at the end of study graphically depicted a difference between optical density values between the different vaccine regimen of a full dose of NYVAC/ rAd5 (n=26) and rAd5/NYVAC (n=23) (Figure 5). The optical density values were elicited exclusively from the Biorad GS HIV ½ Plus O enzyme immunoassay.

Utilizing logistical regression of the optical density ratio and following patients who solely received MMM full dose (N=24) in protocol 065 (Figure 6). These data indicated a significant difference between 6.5 month and 9 months (p=0.0001) and 9 and 12 months (p=.0009) in optical density ratios (Figure 6). The Biorad GS HIV ½ Plus elicted the optical density data for these data.

Discussion & Conclusions:

This study illustrates a stark departure for viewing optical density values as simply below and above a threshold of 1.00 (which designated VISR/VISP). Due to this novel perspective, the following conclusions were determined:

First**,** the FDA approved EIAs behaved as expected. 100% of the optical density values in the placebo group did not reach the VISP threshold of 1.00. This is seen in figure 6. These results are supported by the literature and practices which suppose that there should be no reactivity in individual who receive placebos whereas participants who receive candidate vaccines will have some reactivity [1-5, 10]. These data support that vaccine induced reactivity is not solely a function of the enzyme immunoassay used but a reaction to the candidate vaccine given. If this was not true, the use of enzyme immunoassays in screening for vaccine induced seropositive would be obsolete. These tools were developed to screen for patent HIV infection, and thus their lack of ability to discern from an immune response evoked by a candidate vaccination from a patent HIV infection is not surprising. However, these data support that these screening immunoassays behave as they were developed to perform.

In addition, this study illustrated vaccine constructs regimen and enzyme immunoassays kits behave differently as indicated by the varying optical density values elicited. Cooper et al illustrates that different vaccine constructs have varied in the amounts of participants who develop vaccine induced seropositivity.[2] The Cooper et al study builds upon other studies that illustrated that different vaccine constructs and immunoassays have varying amount of participants that develop vaccine induced seropositivity.[2, 10] The results in this study extend the significance further by illustrating that looking beyond the dichotomous view of vaccine seroreactivity and examining closely the optical density values allows one to see that in fact there

is a difference in magnitude in the optical density values elicited by the vaccine construct coupled with the antibody detection system used. This finding not only supports the conclusions of past study findings that VISP or VISR rates differed based on vaccine constructs and enzyme immunoassays used, but also mirrored studies that have more formally analyzed the antibody induced response of these HIV vaccine constructs.[11,13]

The importance of this departure from viewing the optical density from the traditional dichotomy to the continuous view is underscored by the figure 5. This finding illustrates that screening immunoassays developed to screen for patent HIV infection can also discern small differences between administrations of vaccine regimens with closer analysis of optical density values (e.g. NYVAC/rAd5 vs. NYVAC-B/rAd5). These results suggest that the optical density values magnitude difference can be a metric of immunogenicity denoting that vaccine regimen that causes a higher magnitude of optical density could signify a more effective neutralizing antibody response against HIV-1. This could be further substantiated if properly assessed with tools that were designed to evaluate for such immunogenicity of vaccine constructs regimen. This assertion is supported by findings by Bart P et al which found that indeed rAd5/NYVAC is superior to NYVAC-B/rAd5 and is dependent on rAd5 dose for neutralizing antibody responses against HIV-1.[9] These findings was established with a method that is appropriate in assessing the neutralizing antibody elicitation capability of a vaccine regimen. However, such a method is expensive, time consuming, and requires appropriate technical expertise. This is especially true when comparing it to the ease of deriving such information from optical density values which are routinely gathered during use of EIAs during phase 1 of HIV vaccine clinical trials. The continuous look at this data may inform which vaccine constructs would most likely be immunogenetic and subsequently give credence to further testing and evaluation with more sensitive and expensive assays. Currently, such data are underutilized.

Lastly, there appears to be a decay associated with optical density ratio supporting the notion that quantitative assessment will render a better view of the dynamics of optical density values (Figure 6). Although these changes in data shown in figure 6 are significant in only particular intervals it demonstrates the utility of viewing the data derived from enzyme immunoassays as a continuum. These data show that there was a decay over time associated with the optical

density values, which is also substantiated by findings that have shown some participants in HIV vaccine clinical trials become seronegative on enzyme immunoassays although the participants were shown to have VISP/VISR at the End of Study.[10] At the current moment, there are no ways to predict what individuals will develop VISR/VISP or will no longer be seropositive at End of Study.[5-7,9] However, these data illustrate that it may be possible to extrapolate what individuals will have changes in their vaccine induced seropositive status.

Limitations: Although these data examined span multiple studies, the sample size is still limited and more power would allow for conclusions to be more expansive and substantiated. There are multiple HIV studies that have been completed and are currently underway that could help support the findings here. Furthermore, the development of an equation with the variables shown to be associated with VISP/VISR would allow us to predict which patients would become and remain reactive. However, because of our limited sample size and lack of transparency of the manufacturers of the enzyme immunoassay kits analyzed such an equation could not be appreciated. Nevertheless, with partnership with many of the companies that design these kits we will able to gain better information concerning what specific antigens these kits detect. Lastly, the length of the long-term follow up was approximately 12 months (after last vaccination), to more fully examine the dynamics of the optical density it will be necessary to continue to enroll patients in long-term follow up.

Future work: In future studies we hope to examine how optical density values can help inform End of Study testing algorithms conducted at the HVTN. Furthermore, we hope to expand to this systematic review of optical density readings to HVTN protocols 983, 085, and 094. This will allow us to see how different vaccine constructs and regimens elicit different responses in optical density. Also, when gathering more data we will encourage participants whom optical density values we have already gathered to enroll in long-term follow-up. In addition, the social harms experienced by the patients has never been fully documented and quantified thus, it would be prudent to do so because it would allow a fuller understanding of VISR/VISP and the importance of understanding its inherent link to HIV vaccine clinical trials. Lastly, we hope to further elucidate the possibility of an immunogenic link between optical density ratios readings and the possible effectiveness of vaccine candidates. It is possible that these optical density

readings can aid in directing research to which vaccine constructs would be best to further evaluate and develop.

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Tables and Figures

Enzyme Immunoassays (EIAs)	Inserts
Biorad Genetic Systems HIV ½ plus O EIA*	"**gp160, p24 , gp36** and a synthetic polypeptide mimicking an artificial HIV-1 group O specific epitope."
Biorad Genetic Systems rLAV	**"gp41** and **HIV-1 viral lysate"**
bioMerieux Vironostika HIV-1	**"p24 core HIV-1"**
Abbott HIV AB HIV ½ (rDNA)	"**HIV-1 gag** and **env** together with **HIV-2 env Recombinant proteins**"

Table 1: These are the selected enzyme immunoassays (EIAS) implemented in the HVTN protocol 077, 078, 065, and 204. The insert was ascertained from the product package.

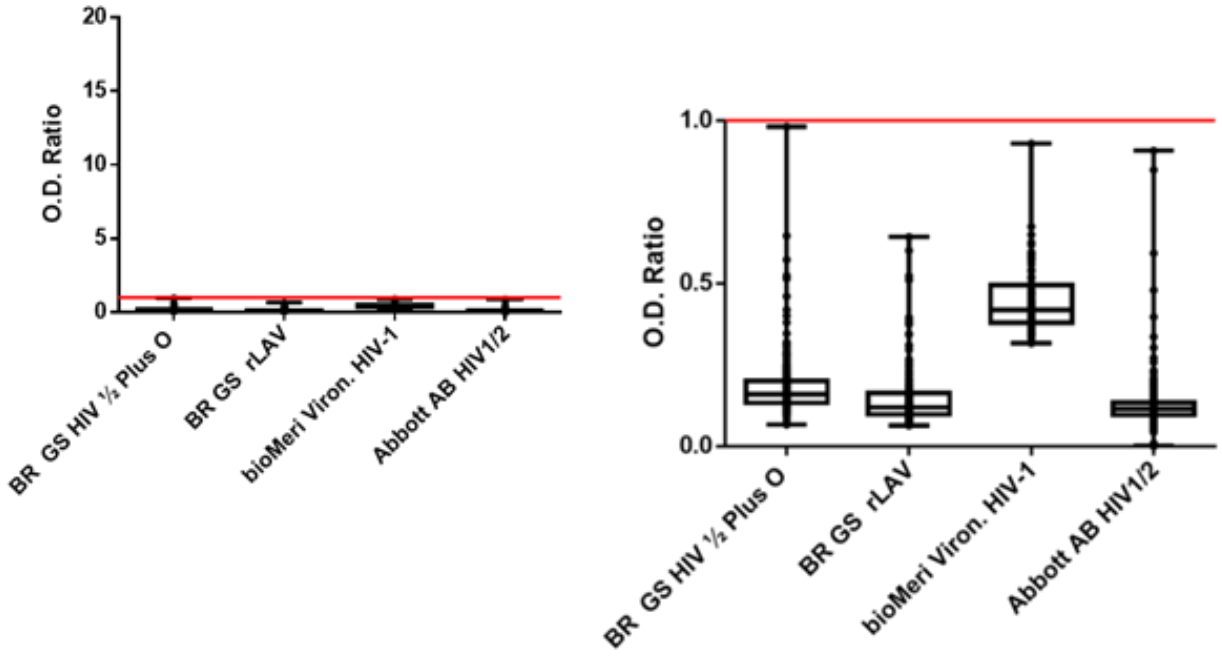


Figure 1: The left box graph indicates the optical density values of the placebo group (N=782), and the right box graph represents optical density values from the treatment group (N=782). Optical density ratio readings were compiled from protocol 065, 077, 078, and 204. Note: The red line denotes the VISP/VISR threshold of 1.00.

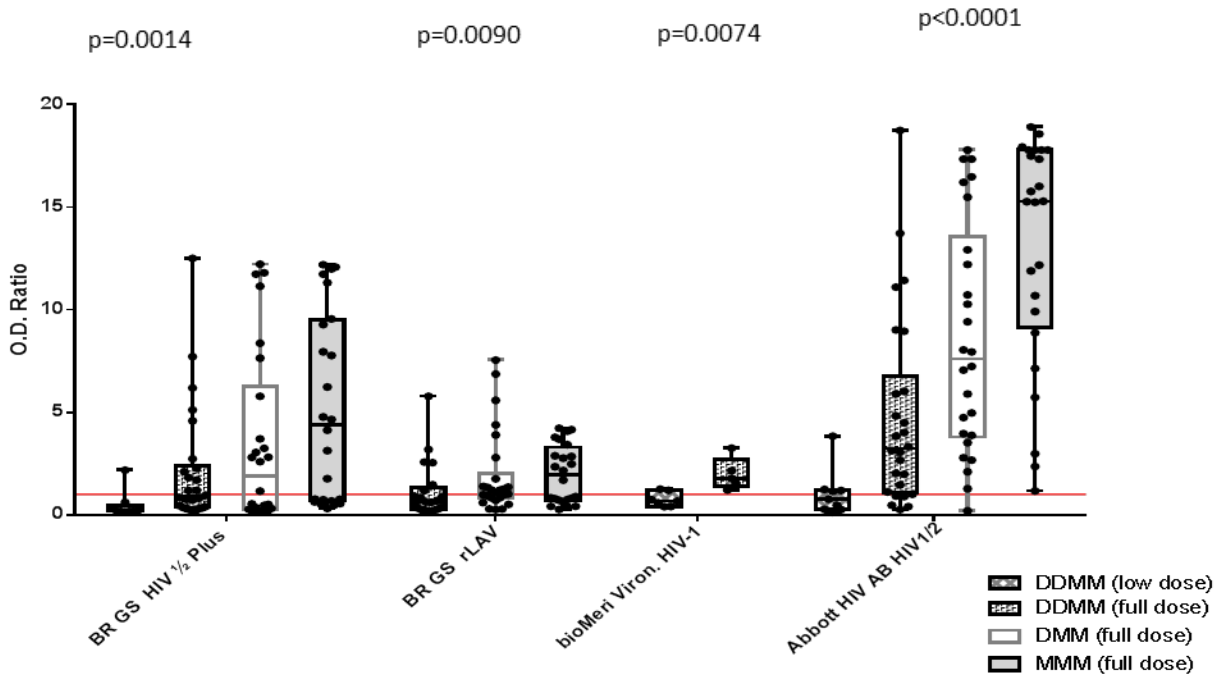


Figure 2: Optical density observations derived from protocol 065. Box plot illustrated a difference of optical density values elicited by different vaccine constructs and regimen given. The p values are denoted above the respective EIAs. Note: The red line denotes the VISP/VISR optical density threshold of 1.00. (N=85)

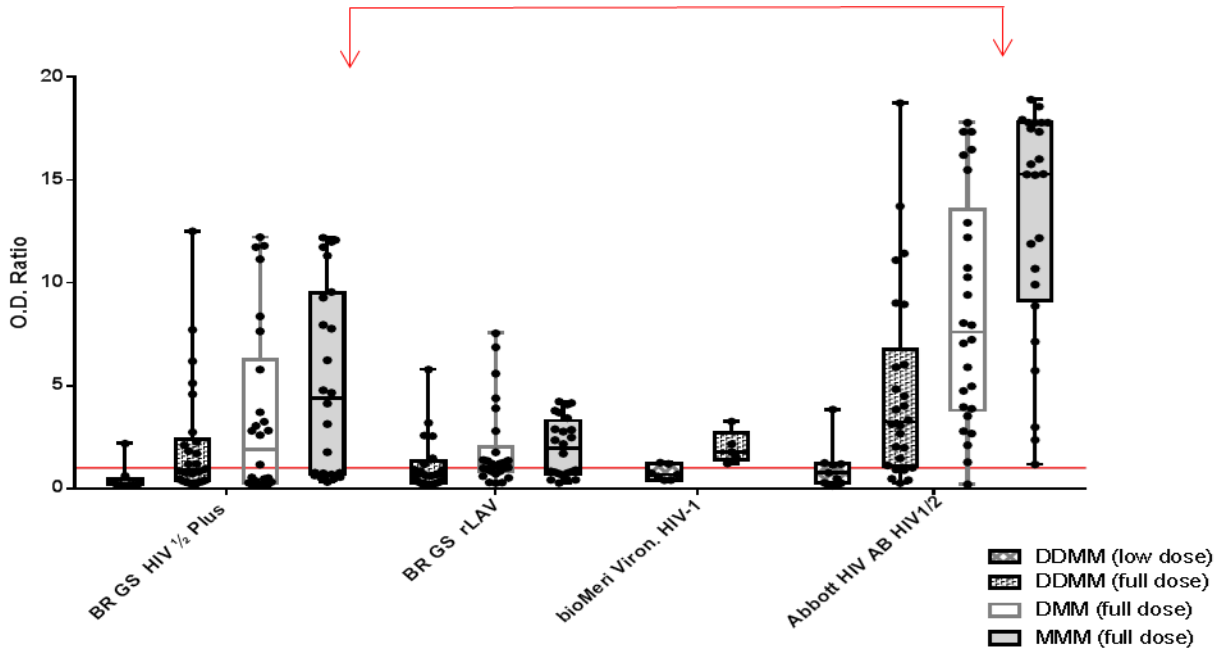


Figure 3: Optical density observations derived from protocol 065. Illustrated a significant difference between Abbott HIV AB HIV ½ kit and the Biorad GS HIV ½ Plus Kit (p=0.0050). Note: The red line denotes the VISP/VISR optical density threshold of 1.00. (N=85)

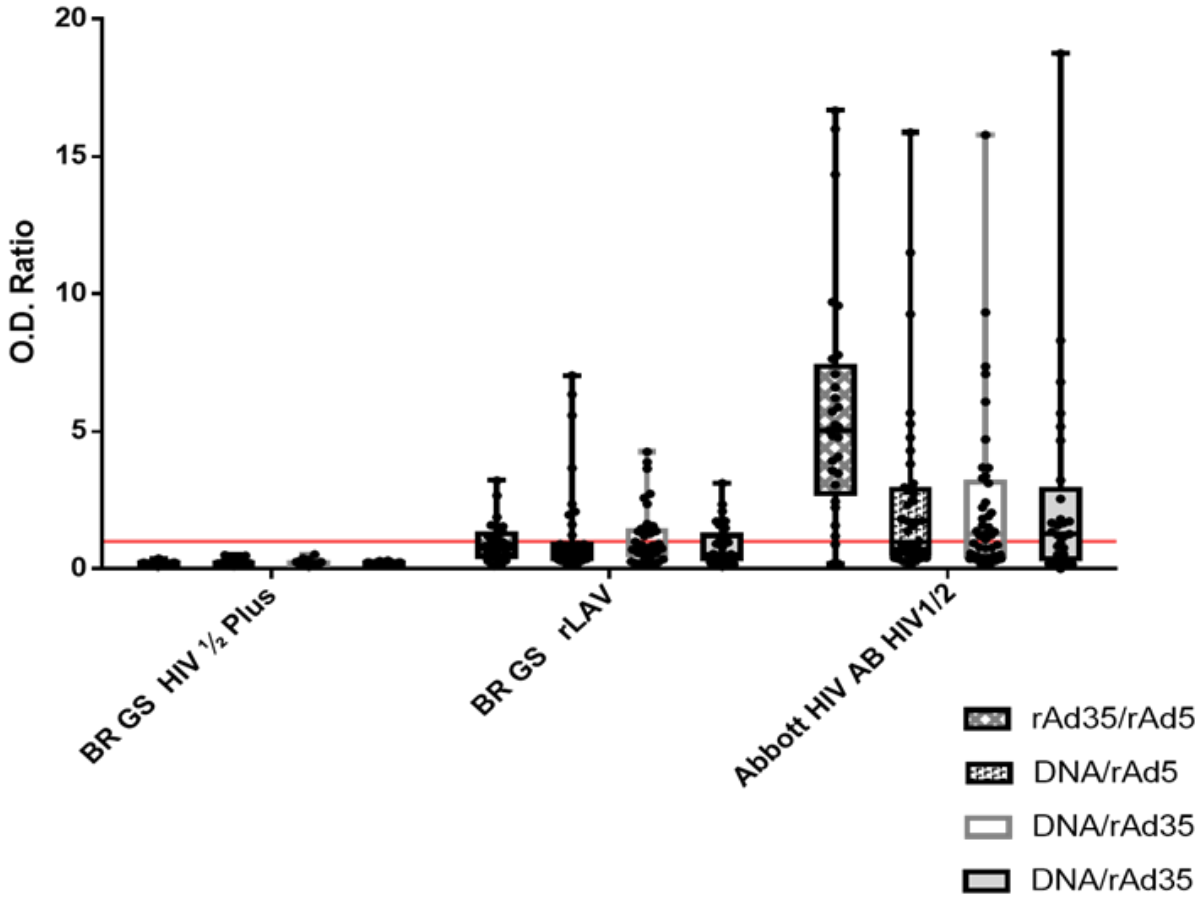


Figure 4: Theese optical density values are derived from HVTN protocol 077. The boxplots illustrate a significant difference between Abbott HIV AB HIV ½ kit and the Biorad GS HIV ½ Plus Kit (p=0.0001). Note: The red line denotes the VISP/VISR optical density threshold of 1.00. (N=69)

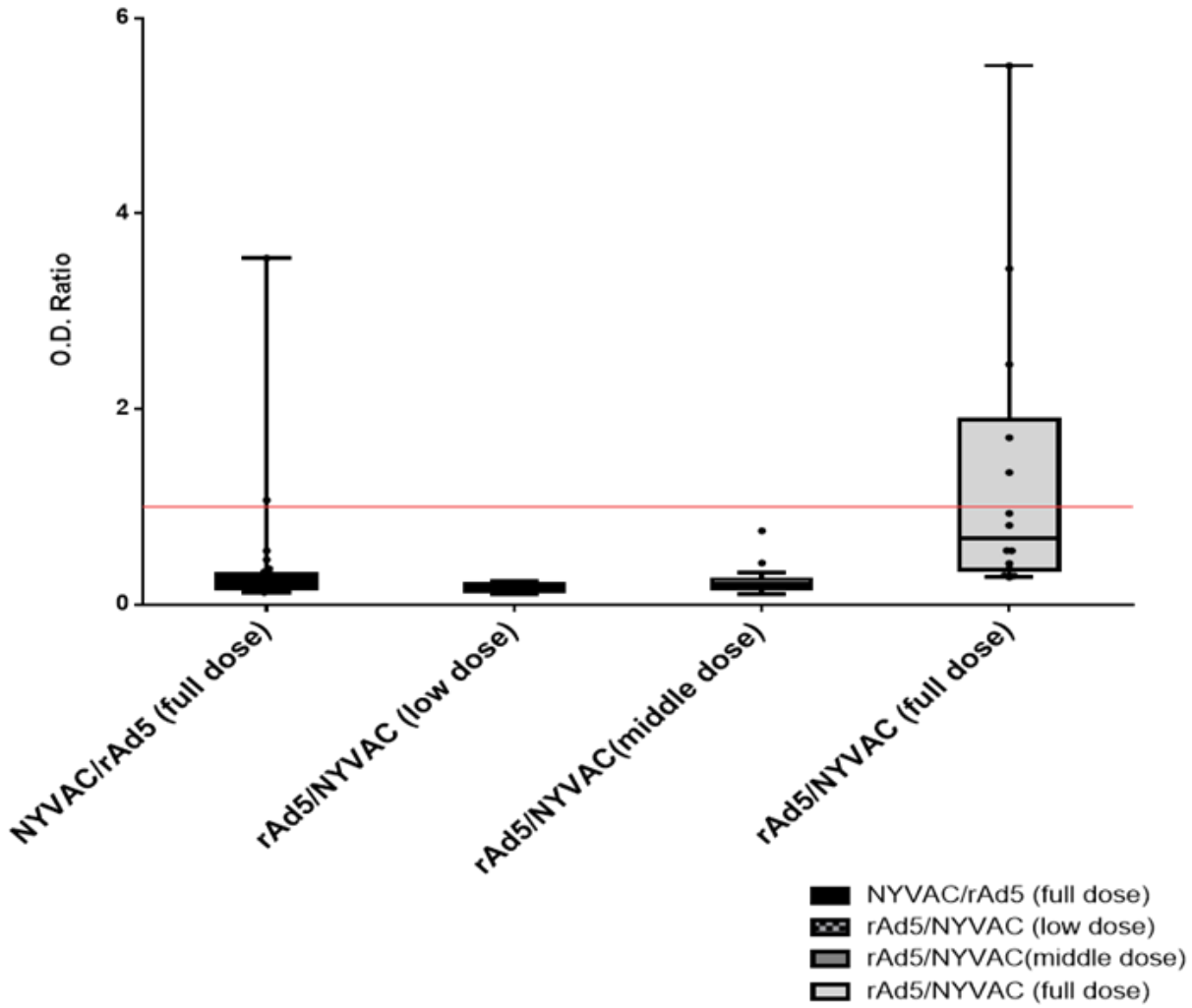


Figure 5: These optical density values are derived from HVTN protocol 078. These were elicited exclusively from the Biorad GS HIV ½ Plus O enzyme immunoassay (N=83).

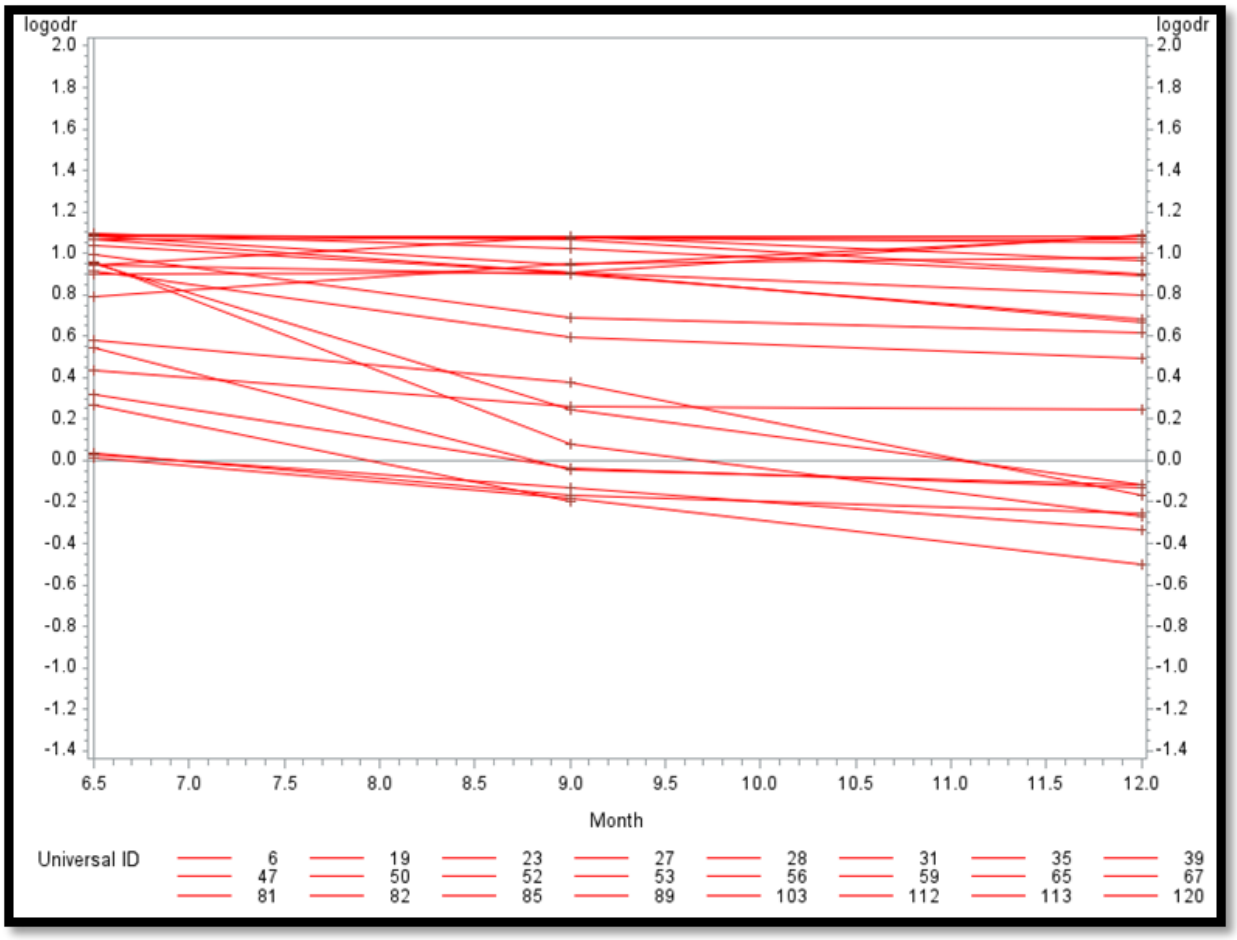


Figure 6: Optical density values complied from participants who received the MMM vaccine construct (N=24) over a 12 month period. The enzyme immunoassay used was Biorad GS HIV ½ Plus. Significant difference between 6.5 month and 9 months (p=0.0001) and 9 and 12 months (p=.0009) in optical density ratios. Note: The logodr of 0.0 indicates VISP/VISR threshold.

Appendix

This appendix includes the vaccine regimens of the protocols included in this study.

Protocol 065:

Treatment	Vaccination	Regimen	Interval	Inserts
DDMM (low dose)	JS7 DNA (0.3 mg) / MVA (1×10^7)	2 DNA & 2 MVA	Every 2 months (DNA first)	JS7 DNA: Gag. PR, RT, Env, Tat, Rev, and Vpu MVA: gag, pol, and Env genes
DDMM (full dose)	JS7 DNA (3 mg) /MVA (1×10^8)	2 DNA & 2 MVA	Every 2 months (DNA first)	
DMM (full dose)	JS7 DNA (3 mg) /MVA (1×10^8)	1 DNA & 2 MVA	Every 2 months exclude 4th month (DNA first)	
MMM (full dose)	MVA (1×10^8)	3 MVA	Every 2 months exclude 4th month (DNA first)	

Protocol 077:

Treatment	Vaccinations	Regimen	Interval (months)	Inserts
rAd35/rAd5	rAd35 and rAd5	2	0- rAd35 6- rAd5	rAd5: HIV-1 clade A Env DNA: HIV-1 clade A Env glycoprotein rAd35: HIV-1 clade A Env
DNA/rAd5	3 DNA And rAd5	4	0- DNA 1-DNA 2-DNA 6-rAd5	
DNA/rAd35	3 DNA and rAd35	4	0- DNA 1-DNA 2-DNA 6-rAd35	
DNA/rAd35	3 DNA and rAd35	4	0- DNA 1-DNA 2-DNA 6-rAd35	

Protocol 078:

Treatment	Vaccinations	Regimen	Interval (months)	Inserts
NYVAC/rAd5 (full dose)	Two NYVAC-B and rAd5 ($1x10^{10}$)	2 NYVAC & rAd5	0- NYAC 1-NYAC 5-Placebo 6- rAd5	rAd5: clade B Gag-Pol fusion; clades A, B, C Env NYVAC-B: HIV-1_{BX08} gp120 and HIV-1_{IIIB} gag-pol-nef
rAd5/NYVAC (low dose)	Two NYVAC-B and rAd5 ($1x10^8$)	2 NYVAC & rAd5	0- rAd5 1-Placebo 5- NYVAC 6- NYVAC	
rAd5/NYVAC (middle dose)	Two NYVAC-B and rAd5 ($1x10^9$)	2 NYVAC & rAd5	0- rAd5 1-Placebo 5- NYVAC 6- NYVAC	
rAd5/NYVAC (full dose)	Two NYVAC-B and rAd5 ($1x10^{10}$)	2 NYVAC & rAd5	0- rAd5 1-Placebo 5- NYVAC 6- NYVAC	