Vaccine Induced Seropositivity in non-infected HIV Vaccine Trial Volunteers

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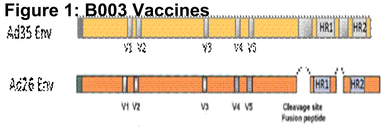
BACKGROUND

Phase 1 preventative HIV vaccine clinical trials enrol low risk HIV negative volunteers. Most HIV vaccine immunogens encode proteins mainly from the *env, gag, pol,* and *nef* regions. The HIV vaccines are designed to induce the production of protective antibodies, which may be detectable on standard serologic tests. The elicited HIV-specific antibodies, as a result of an immune response to the candidate HIV vaccine in the absence of HIV infection, can confound the interpretation of standard HIV test kits' results. Delineation of these seropositive results among vaccine recipients has resulted in the use of more complicated HIV testing algorithms and laboratory techniques, such as HIV-1 RNA detection. Determining the best suited HIV testing algorithm for a particular product/trial is crucial in distinguishing vaccine-induced sero-positivity (VISP) from true HIV infection.

METHODS

Kenya AIDS Vaccine Initiative (KAVI) enrolled 105 volunteers in three different phase 1 HIV vaccine trials (B002, B003 and B004). Volunteers were randomized to receive either the vaccine or placebo. All trial participants were healthy, HIV seronegative individuals, aged 18–60 years, generally assessed to be at low risk for HIV exposure. Protocol B002 evaluated an HIV fusion protein (F4/AS01) and Ad35-GRIN, Protocol B003/IPCAVD004/HVTN091 evaluated Ad26-ENVA and Ad35-ENV HIV vaccines, and the B004 protocol evaluated a Multiantigen HIV (HIV-MAG) plasmid DNA (pDNA) vaccine co-administered with recombinant human IL-12 pDNA (GENEVAX® IL-12) followed or preceded by recombinant Ad35-GRIN/ENV HIV Vaccine. The vaccine constructs in both the B003 trial and B004 trial **(Figure 1 and 2)** contained the envelope genes while none of the B002 vaccine immunogens **(Figure 3)** had envelope genes. Using a standardized HIV testing algorithm (Figure 4), samples from the 105 volunteers who had received at least two doses of the vaccine regimen were tested using a 4th Generation BioMerieux Vironostika HIV Ag/Ab Elisa kits at several study visits. This Elisa kits detects antibodies to HIV-1 gp160 and p24 antigens. Any positive results were confirmed with HIV-1 RNA PCR.

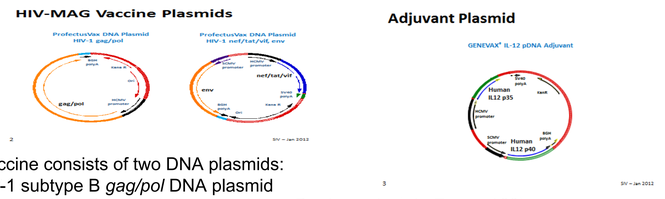
Figure 1: B003 Vaccines



Ad35-ENV: Recombinant adenovirus serotype 35 vector vaccine is a recombinant replication-incompetent product that encodes the HIV-1 subtype A gp140 *env* gene. (**Figure 1)**

Ad26.ENV.01 (rAd26): Recombinant adenovirus serotype 26 vector vaccine is a recombinant replication-deficient product composed of an adenovirus serotype 26 vector that encodes the HIV-1 Clade A Env glycoprotein 140 (strain 92rw020) (**Figure 1)**

Figure 2 :B004 Vaccine (HIVMAG



The HIV-MAG vaccine consists of two DNA plasmids:
ProfectusVax HIV-1 subtype B *gag/pol* DNA plasmid
ProfectusVax HIV-1 subtype B *nef/tat/vif, env* (subtype B primary isolate Env gp160) DNA plasmid (**Figure 1**).

Figure 3: B002 Vaccines

Ad35-GRIN (Clade A) vector

F4 adjuvanted with AS01 - GSK Biologicals' proprietary liposome-based Adjuvant System containing:

- QS-21: *Quillaja Saponaria* Molina, fraction 21*
- MPL: 3-*O*-desacyl-4'- monophosphoryl lipid A
- 50 or 25 µg each in $AS01_B$ and $AS01_E$ respectively

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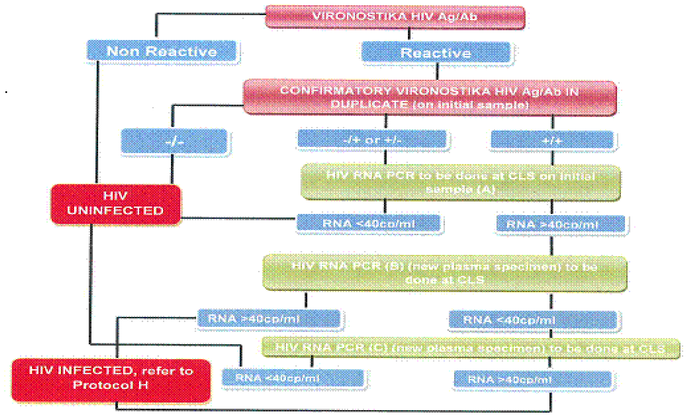
Figure 4: On study HIV testing Algorithm



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RESULTS

At final study visit, 97% (31/32) vaccine recipients from the B003 trial and 35% (7/20) vaccine recipients from the B004 trial tested HIV positive due to vaccine induced antibodies, without being infected with HIV, while none (0/32) of B002 vaccine recipients showed any VISP **(Table 1).** All the volunteers that received the investigational product and expressed VISP had HIV-1RNA-PCR confirmatory tests conducted and all test results were undetectable for HIV-1infection. However there was one volunteer in B002 who had detectable HIV -1 RNA PCR.

Table 1. VISP Results

STUDY NAME	VISP RESULTS	PERCENTAGE OVERALL	HIV-1 RNA PCR RESULTS	LAST VISIT TIME POINT
B002	0/32	0%	1/32	WEEK 64
B003	31/32	97%	0/32	WEEK 52
B004	7/20	35%	0/32	WEEK 48

Vaccine recipients in B003 and B004 trials had a high percentage of VISP because both investigational products contained envelope genes, while none of the B002 vaccine recipients had a positive HIV test result by EIA at any time point. No placebo recipients had a false positive HIV test result.

CONCLUSION

The occurrence of VISP is dependent on the HIV gene inserts. The HIV vaccines that contain the envelope genes tend to produce VISP especially when tested with a 4th Generation BioMerieux Vironostika HIV Ag/Ab Elisa because both the B003 and B004 vaccines contained envelopes genes gp 140 and gp 160 and the antibodies to these genes are detectable by this particular Elisa test kit .The VISP (B003) samples were tested with HIV rapid Kits ((Alere Determine HIV ½ and Trinity Uni-Gold), and the results showed significant reduction of VISP (9.4% and 3.1% respectively) when compared with 4th generation HIV Elisa kits[1] .

All study participants must be given information during the consent process that describes the effects of vaccines, the possibility of VISP. Volunteers with VISP must be provided with appropriate counseling and testing. It is important that appropriate follow-up testing be conducted, including HIV-1 RNA testing, to minimize potential misinterpretation of HIV test results. Testing for VISP at the end of the study to assess the VISP status of the study participants is critically important to prevent incorrect HIV diagnosis and social harm.

Development of a rapid and accurate serological HIV test that is unlikely to cross-react with vaccine–induced antibodies would be a useful approach to differentiate VISP from HIV infection.

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