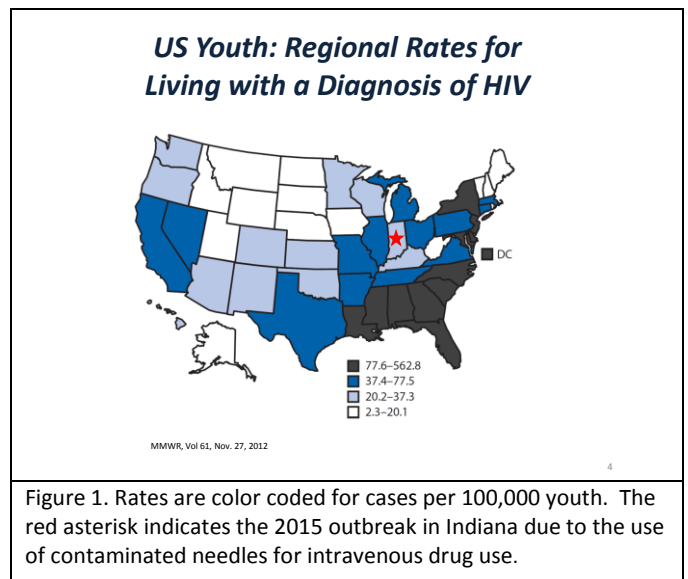


## GOVX-B11: A Clade B HIV Vaccine for the Developed World

**Executive summary:** GOVX-B11 is a Clade B HIV vaccine targeted for use in the Americas, Europe, Japan and Australia. The vaccine uses recombinant DNA and recombinant modified vaccinia Ankara (MVA) vaccines to express non-infectious virus-like particles in the person being vaccinated. It was developed by scientists at Emory University, the US National Institutes of Health and the US Centers for Disease Control and has been licensed by GeoVax, Inc. for commercialization. In Phase 1 and 2a clinical trials, conducted by the US National Institutes of Health sponsored HIV Vaccine Trials Network (HVTN), the vaccine has had consistent safety and reproducible immunogenicity. In preclinical challenge studies, the vaccine delays infection of monkeys during repeated rectal challenges. In comparison with the RV144 vaccine, which elicited antibody (Ab) responses that correlated with reduced risk for infection in the one partially successful AIDS vaccine trial, GOVX-B11 elicits a more favorable profile of Ab classes (isotypes), a broader specificity of Ab for the viral envelope protein (Env) and a more durable Ab response.

**Incidence of HIV in the United States:** Despite the advancements in drug treatments for HIV, AIDS remains a major health problem in the United States. About 1.2 million Americans are living with HIV, and about 50,000 new infections occur each year. HIV diagnosis rates are increasing in American youth faster than in any other age group in the US. In those aged 13 to 24, the incidence of HIV increased at an estimated average annual rate of 10.5% between 2002 and 2011 (Figure 1). With the increasing burden of the epidemic, health care costs are also growing. The US Government currently spends \$17.5 billion per year on the care of infections within the US, a 37.5% increase since 2005.



The public health “tool kit” for AIDS prevention includes several measures which can limit transmission: widespread education on HIV and AIDS, screening of donated blood before transfusion, and drug treatment to prevent mother-to-child transmission as well as person to person transmission. The use of condoms and clean needles can also prevent transmission. However, people at risk of transmitting or acquiring HIV have not proven reliable at using condoms, clean needles or antiretroviral drugs to control transmission. Of those who are infected in the United States, only 30% achieve successful control using drugs. The key tool, a vaccine, is still a missing tool.

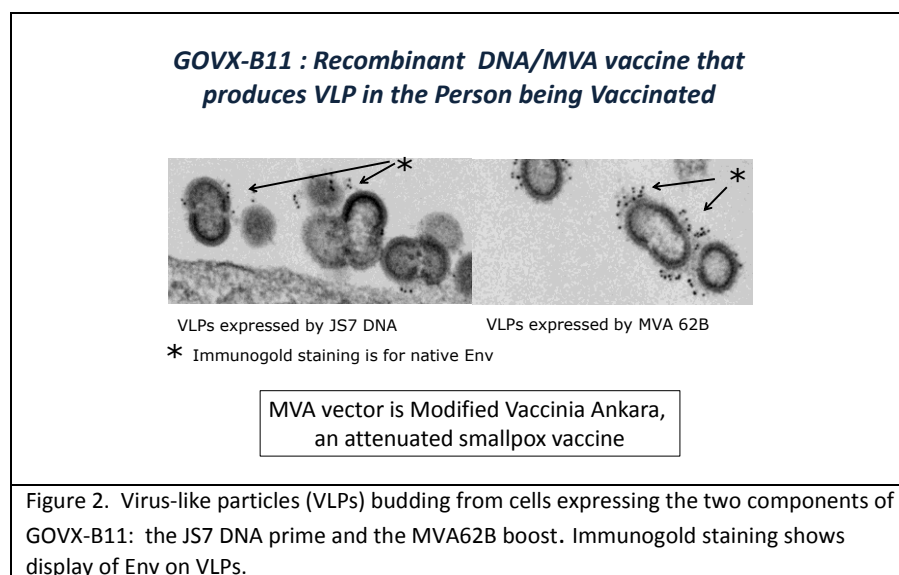
**History of HIV Vaccines:** Since the recognition of HIV as the cause of AIDS in 1983, six efficacy trials have been conducted for candidate AIDS vaccines. Out of these, only one has shown protection. This trial,

termed RV144 and conducted in Thailand, achieved 60% efficacy in the initial six months post vaccination. By 12 months, efficacy was declining, and the vaccine was only 31% efficacious through 36 months post vaccination. RV144 was a community-based trial, involving 16,000 Thais. An in-depth analysis of this trial led to the hypotheses that

- (i) Antibody (Ab) to the V1V2 region of the Envelope protein (Env) could directly block infection (Env mediates HIV entry into cells).
- (ii) Ab to several regions in Env could tag infected cells or virus for destruction by natural killer cells, macrophages, neutrophils and complement (C').
  - a. This killing was particularly effective for Ab of the IgG3 subgroup.
  - b. This killing activity could be blocked by Ab of the IgA isotype in serum.

**GOVX-B11 vaccine:** Given these hypotheses and considering prior results from the GeoVax vaccines in non-human primate studies and human trials, the GeoVax GOVX-B11 vaccine is ready for a pivotal efficacy trial.

The GOVX-B11 vaccine consists of a recombinant DNA vaccine used to prime immune responses and a recombinant MVA vaccine used to boost the primed responses. Both the DNA and MVA vaccines produce non-infectious virus-like particles in the cells of the vaccinated person (Figure 2). The proposed regimen for the Phase 2b efficacy trial consists of DNA delivered into the muscle with a needle and syringe at 0 and 2 months and MVA delivered into the muscle with a needle and syringe at 4, 6 and 10 months (DDMM\_M regimen).



**Phase 1 and 2a clinical trials of GOVX-B11:** The GOVX-B11 vaccine has been tested at various doses and regimens by the HVTN in trials involving approximately 500 participants. In these trials, the vaccine has been extremely well tolerated. In terms of pain and tenderness at the site of inoculation, DNA inoculations have been indistinguishable from placebo inoculations. Following MVA inoculations, about 70% of participants have transient mild pain, and 25% transient moderate pain at the site of injection.

Systemic symptoms (most frequently malaise, fatigue, myalgia, headache and nausea) have been similar to those in placebo recipients.

Figure 3 compares the overall immune responses elicited by the GOVX-B11 vaccine (green bars) and the partially protective RV144 vaccine (gray bars).

These data show that both vaccines had overall similar response rates for CD4+ T cells, the helper cells for immune responses; that GOVX-B11 elicited a higher CD8+ T cell response rate than was elicited in RV144; and that both vaccines had similarly high response rates for antibody (Ab) to the Env of HIV.

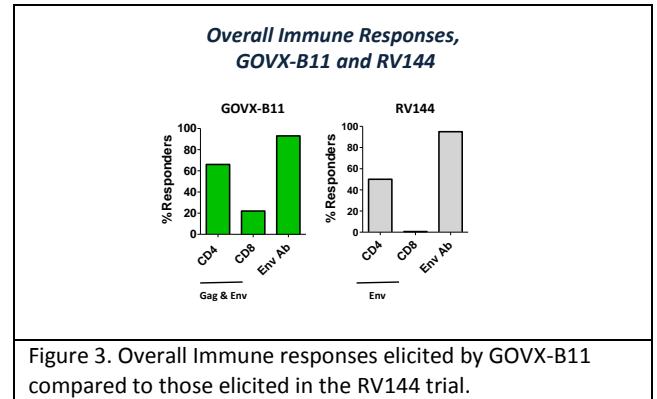


Figure 3. Overall Immune responses elicited by GOVX-B11 compared to those elicited in the RV144 trial.

The forms of Env used for eliciting Ab in the GOVX-B11 and RV144 vaccines are very different (Figure 4). The Env displayed by the GOVX-B11 prime is a native trimer of the complete Env glycoprotein (gp160). The gp160 form of Env consists of a gp120 receptor binding subunit and a gp41 stalk subunit that anchors Env in the viral membrane. The gp120 subunit has high sequence variability, whereas gp41 is relatively conserved. In RV144, the Env displayed in the prime consists of the gp120 subunit fused to the transmembrane region of the stalk subunit. Both GOVX-B11 and the RV144 vaccine elicit responses to protective specificities in gp120, designated V1V2, V3 and C1 (Figure 4). However, RV144 elicited higher response rates to the V1V2 region of Env than elicited by GOVX-B11. In contrast, only GOVX-B11 elicited anti-gp41 Ab. This Ab to gp41 included a high response rate to the conserved immunodominant region of gp41, which is a known target for protective antibody-dependent cell-mediated killing.

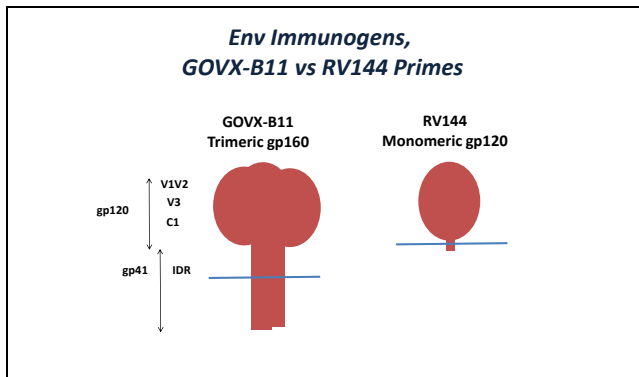


Figure 4. Forms of Env expressed by the priming vaccines in GOVX-B11 and RV144.

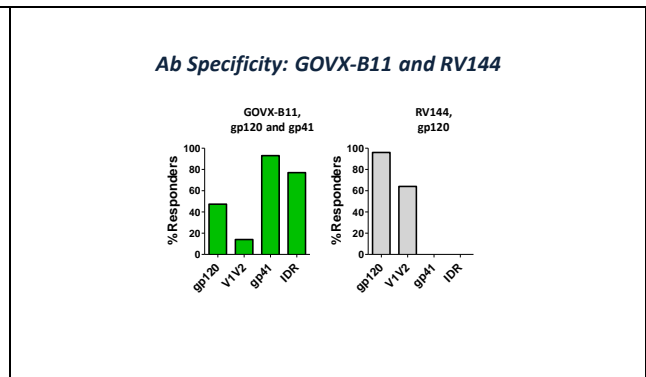
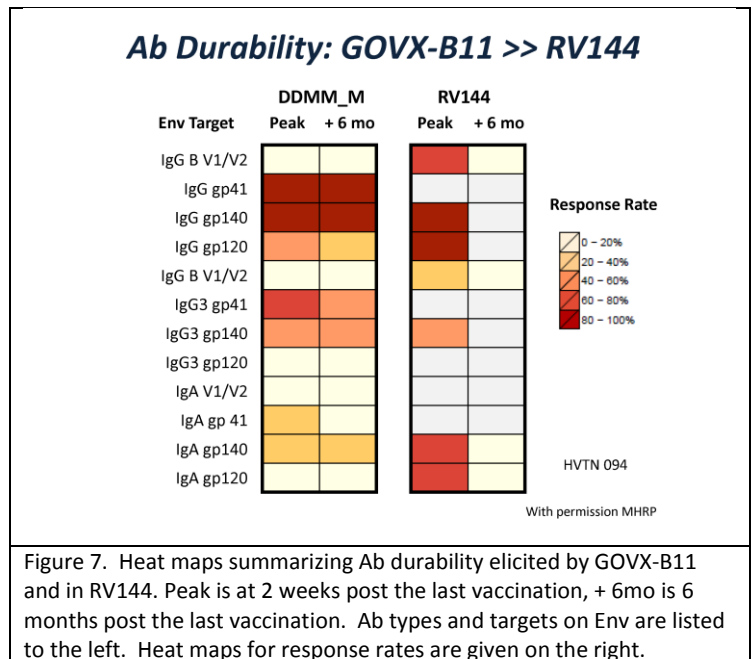
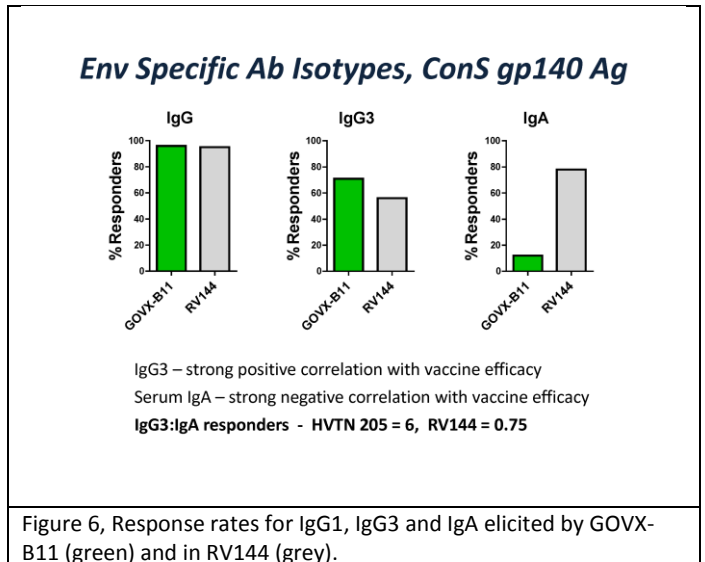


Figure 5. Note high response rate to gp41 elicited by GOVX-B11 (green). Note the higher response rates for gp120 and the V1V2 region of gp120 elicited in the RV144 trial (grey).

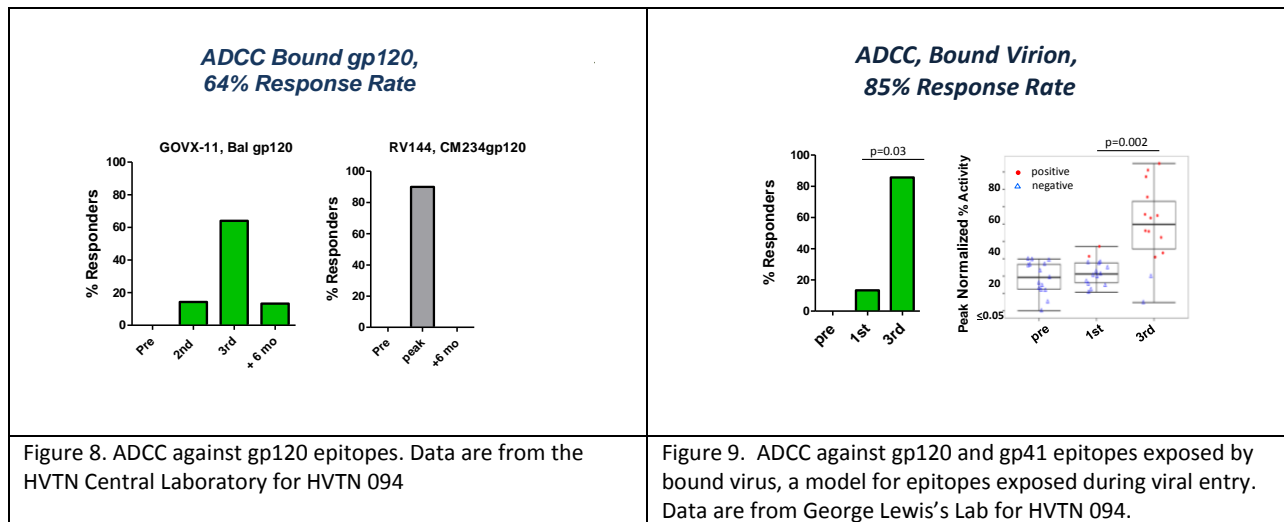
Antibodies belong to different classes (isotypes) and subgroups within isotypes. These isotypes and subgroups determine how Ab binds lytic factors (C') in serum and signals white blood cells for the engulfment or killing of a virus or infected cell. GOVX-B11 and RV144 both elicited essentially 100% response rates for Env-specific Ab of the IgG1 subgroup of IgGs (Figure 6). IgG1 is a favorable subgroup for initiating cell-mediated killing. GOVX-B11 elicited slightly higher response rates than RV144 for IgG3, the most favorable IgG subgroup for protection. However, more importantly, GOVX-B11 elicited a

much lower serum IgA response rate than elicited in RV144 (15% as opposed to 80% response rate). In RV144, Serum IgA showed a strong negative correlation with vaccine efficacy. In RV144, the ratio of IgG3 to IgA in plasma was a strong correlate for reduced risk of infection. The ratio of these response rates is almost 10 times more favorable for GOVX-B11 than RV144 (6.0 as opposed to 0.75).

In RV144, protection waned as the levels of Ab contracted. Encouragingly, GOVX-B11 elicited much more durable Ab than RV144 (Figure 7). In Figure 7, Ab response rates are presented as heat maps. Different regions of Env are listed to the left of the heat maps. The heat maps compare response rates at peak vaccine response with those present 6 months later. Data for GOVX-B11 are presented in the left panels and data for RV144 in the right panels. Reduction in antibody response, indicated by reduction in intensity of color in a given row, is much greater for RV144 than for GOVX-B11. For GOVX-B11, deep rust holds and other colors drop by only one category in the first six-months post vaccination. For RV144, all colors drop by more than one category in this same time period. This difference, in part, reflects the fact that Ab responses to gp41, a major target for Ab elicited by GOVX-B11, were much more durable than Ab responses to gp120, the only Env target for Ab in RV144 (see Figure 5, for differences in the specificity of the elicited Ab). However, responses for gp120 were also more durable for GOVX-B11 than in RV144 (see 4<sup>th</sup> row from top, Figure 7).

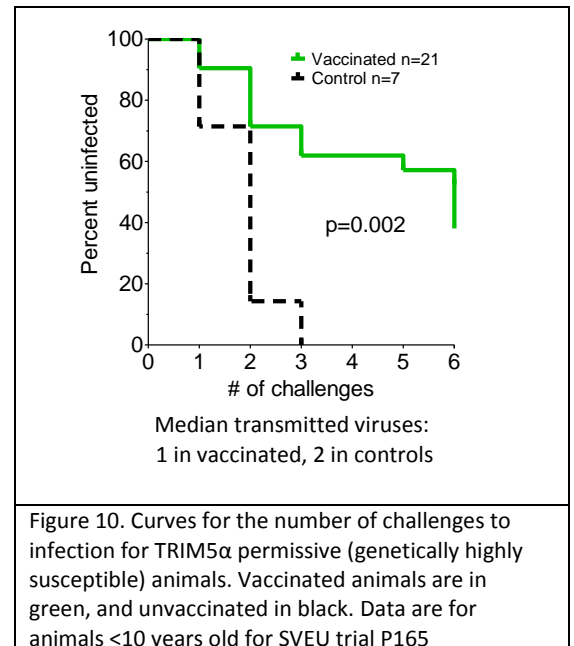


Figures 8 and 9 depict the excellent response rates for antibody dependent cellular cytotoxicity (ADCC) elicited by the GOVX-B11 vaccine. In Figure 8, ADCC is measured for gp120. Note the increase in the response rate with the third MVA boost. The 64% response rate observed here is lower than the 70-90% response rate observed in RV144. However, the GOVX-B11 elicited response was still scoring at 6 months post the peak vaccine response, whereas the response elicited in RV144 had declined to undetectable levels by this time (Figure 8). Figure 9 shows an assay where responses score both gp120 and gp41 epitopes exposed during viral entry. Again, the response is highest after the third MVA boost. The 85% response rate is also higher than the 64% response rate seen for gp120 alone.




**Preclinical Protection Studies using the SIV/maquette**

**model:** Protection studies have been carried out in rhesus macaques vaccinated with simian immunodeficiency virus 239 (SIVmac239) homologs of GOVX-B11. In these trials, vaccinated animals are challenged with simian immunodeficiency virus E660 (SIVsmE660 virus), using weekly rectal exposures (Figure 10). The Envs in SIVmac239 (the vaccine) and SIVsmE660 (the challenge virus) are 83% identical, a level of homology similar to that between the Env in GOVX-B11 and the Envs in circulating strains of clade B HIV. This trial showed age-dependent protection with vaccinated animals < 10 years old having an 81% reduction in per exposure risk of infection (Figure 10). Furthermore, when animals became infected, the median number of transmitted viruses in unvaccinated animals was two, whereas it was only one in vaccinated animals. Most heterosexual human infections are with one transmitted virus, whereas 40% of transmissions in men who have sex with men involve two viruses. Thus the preclinical challenge was a rigorous challenge, potentially even more rigorous than occurs in most transmissions among homosexual partners.



**Summary:** GOVX-B11 is a VLP-expressing DNA/MVA vaccine that elicits a broad-based Ab and T cell response capable of providing preclinical protection against a heterologous challenge. Based on the partially successful RV144 trial, the Ab responses elicited by GOVX-B11 have strong features for reducing the risk of infection. These features include excellent IgG3 to IgA ratios, outstanding durability, multiple target specificities including the highly conserved immunodominant region of gp41 and excellent activity in assays for antibody-dependent cellular cytotoxicity. Testing of this vaccine in a pivotal efficacy trial provides a unique opportunity to identify a vaccine capable of ending the persistence of HIV in the United States (Figure 11).

<b>GOVX-B11: Ready for Pivotal Efficacy Trial</b>
<ul style="list-style-type: none"><li>• Two component vaccine</li><li>• DDMM_M regimen</li><li>• MSM, ages 18-40</li><li>• Americas</li><li>• ~3000 participants, equally divided between treatment and placebo</li><li>• Seeking funding to initiate trial</li><li>• Opportunity to successfully end the persistence of HIV in the U.S.</li></ul>
 <p>Figure 11. GeoVax plans for a Phase 2b trial with GOVX-B11. DDMM_M, DNA inoculations at months 0 and 2 followed by MVA inoculations at months 4, 6 and 10. MSM, men who have sex with men.</p>