

HVTN 094:
GeoVax DNA/MVA HIV Vaccine

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Recombinant DNA Advisory Committee

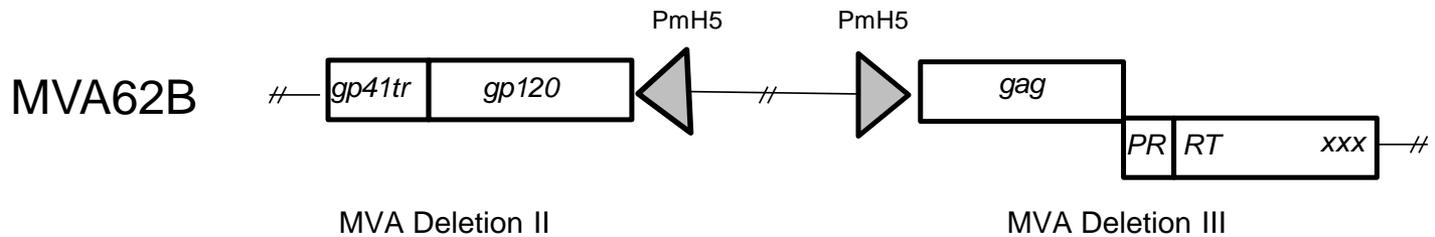
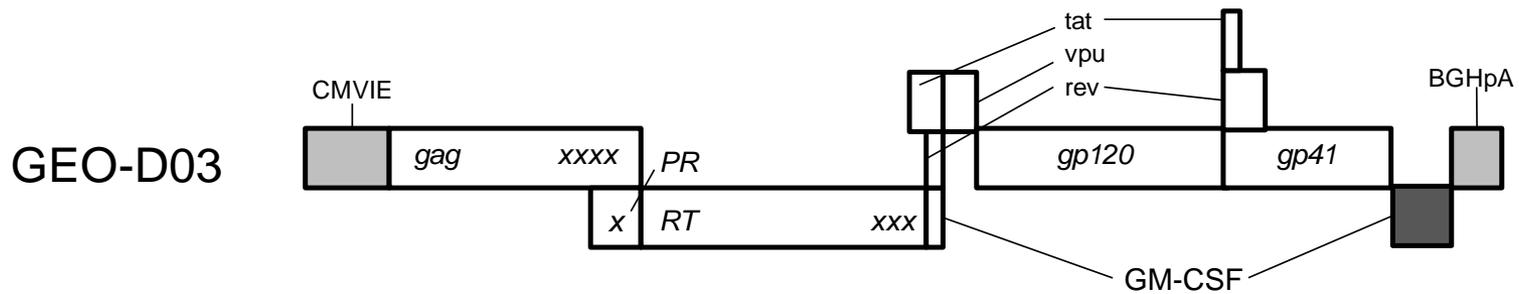
Bethesda, MD

June 7, 2011

***Use of GM-CSF
as a Vaccine Adjuvant for a
DNA/MVA HIV Vaccine***

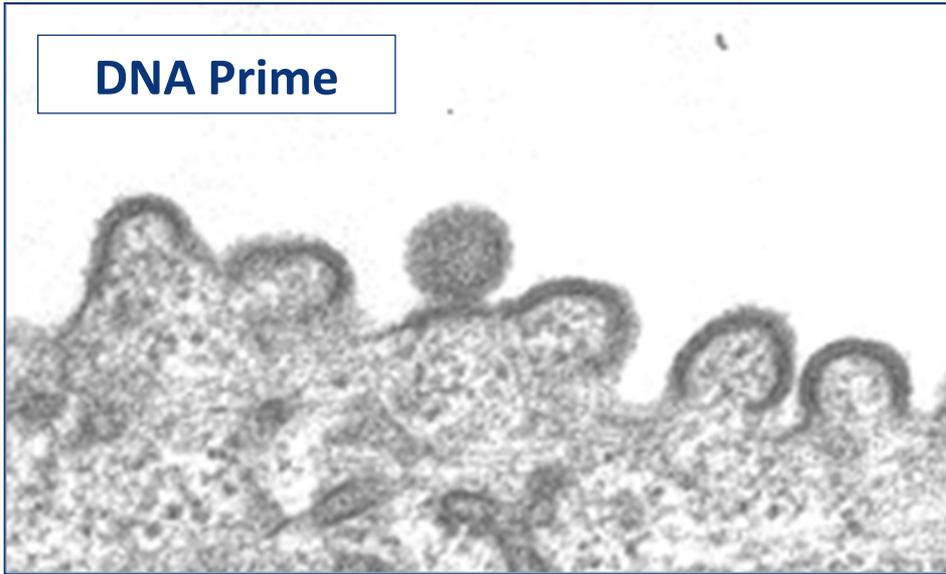
***Co-expressed with HIV VLP
in the DNA prime for an MVA boost***

Immunogens

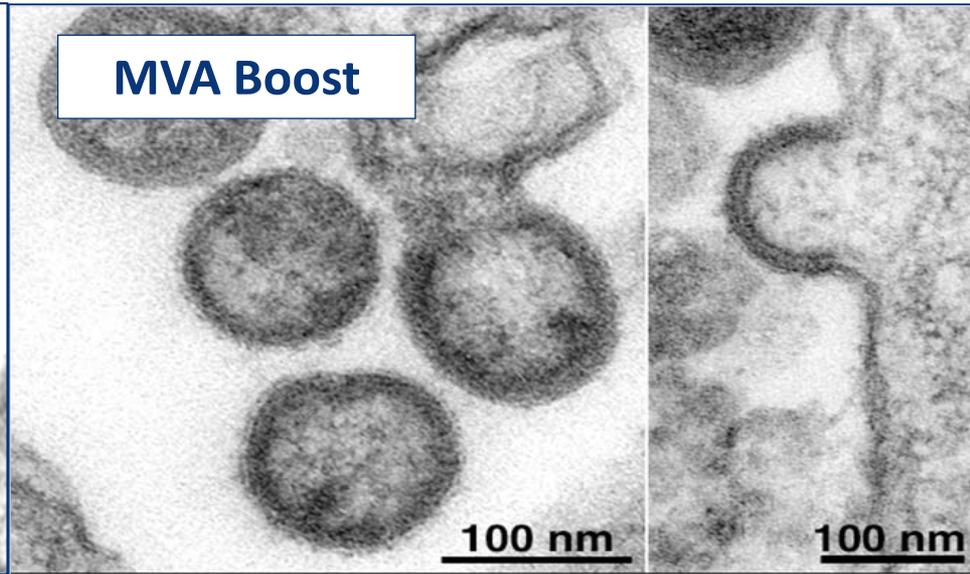


Both DNA and MVA Vaccines Express Virus-Like-Particles (VLPs)

DNA Prime



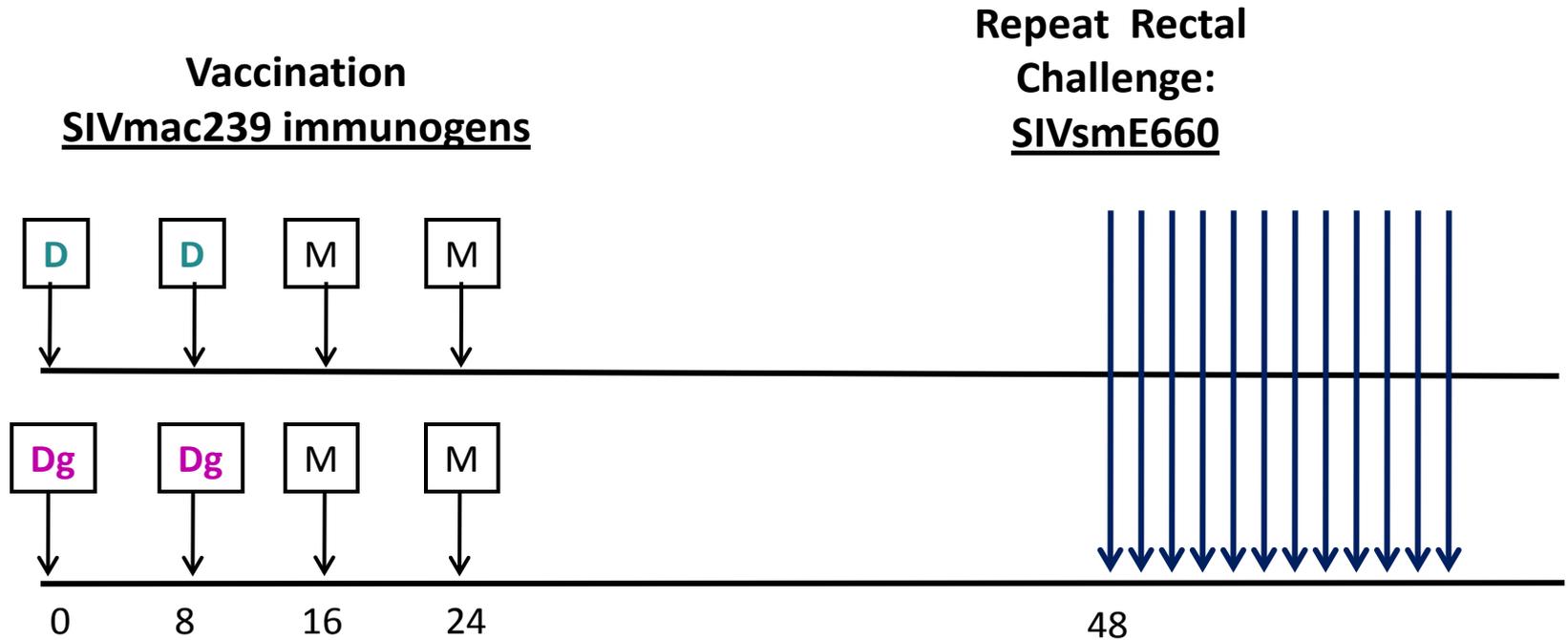
MVA Boost



Rationale for co-expressing GM-CSF in the DNA Prime

Enhanced Prevention of Infection in SIV/Non-Human Primate

Non-Human Primate Trial Regimen



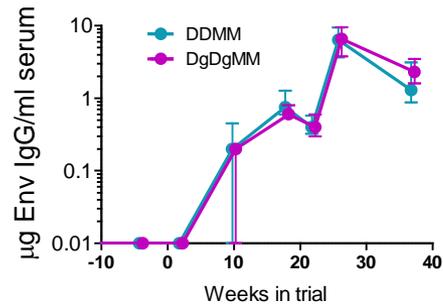
D, DNA expressing SIV VLP

Dg, DNA co-expressing SIV VLP and GM-CSF

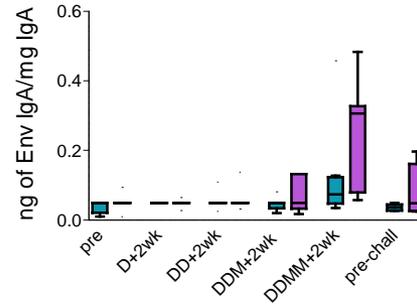
M, MVA expressing SIV VLP

GM-CSF Enhanced Env Antibody Responses

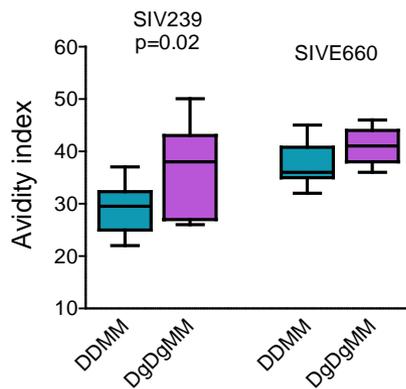
Serum IgG



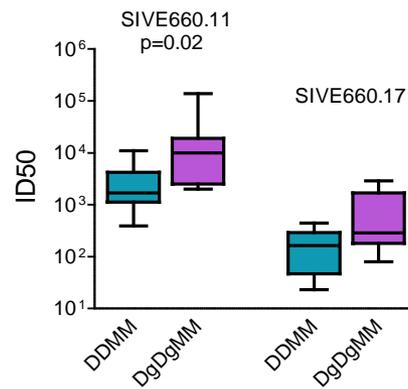
Rectal IgA



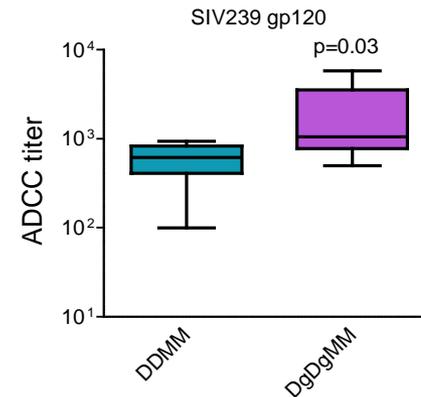
Avidity, IgG



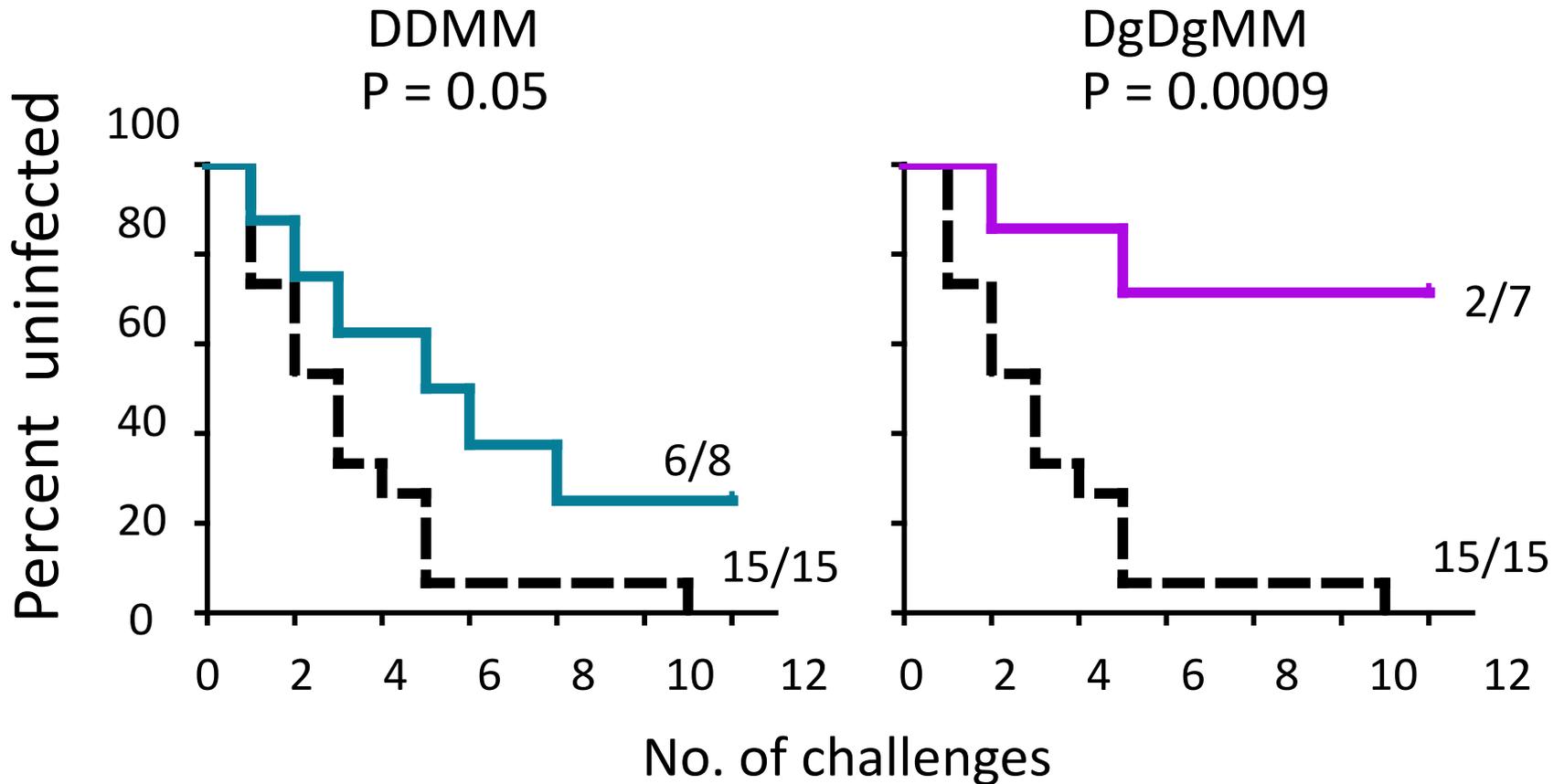
Neutralizing



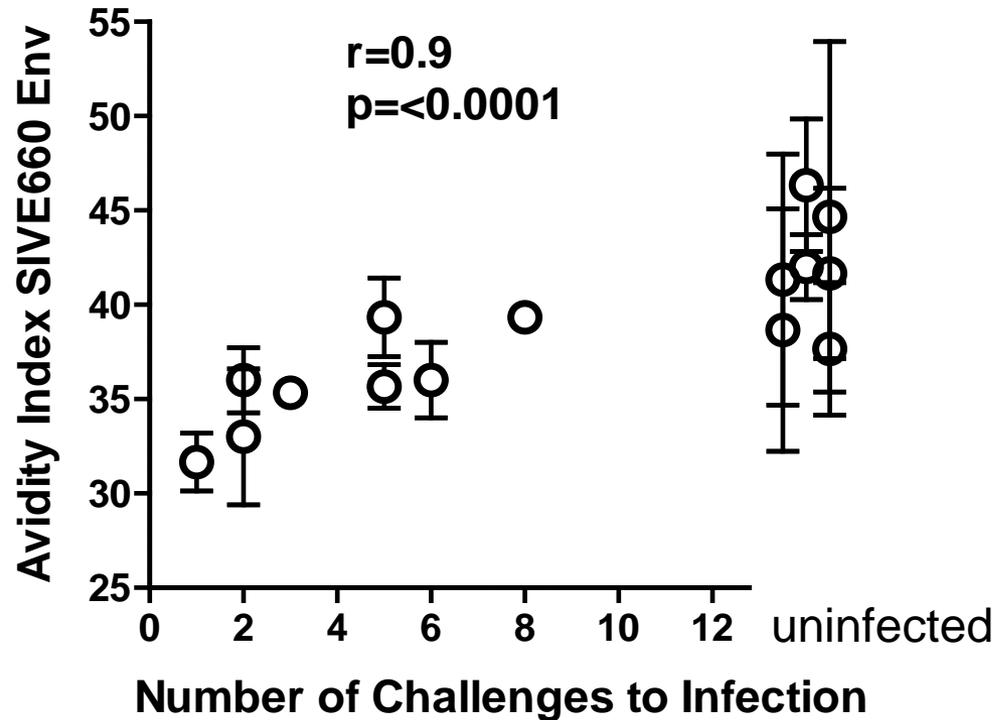
ADCC



GM-CSF: Improved Protection against Acquisition from 25% to 70%



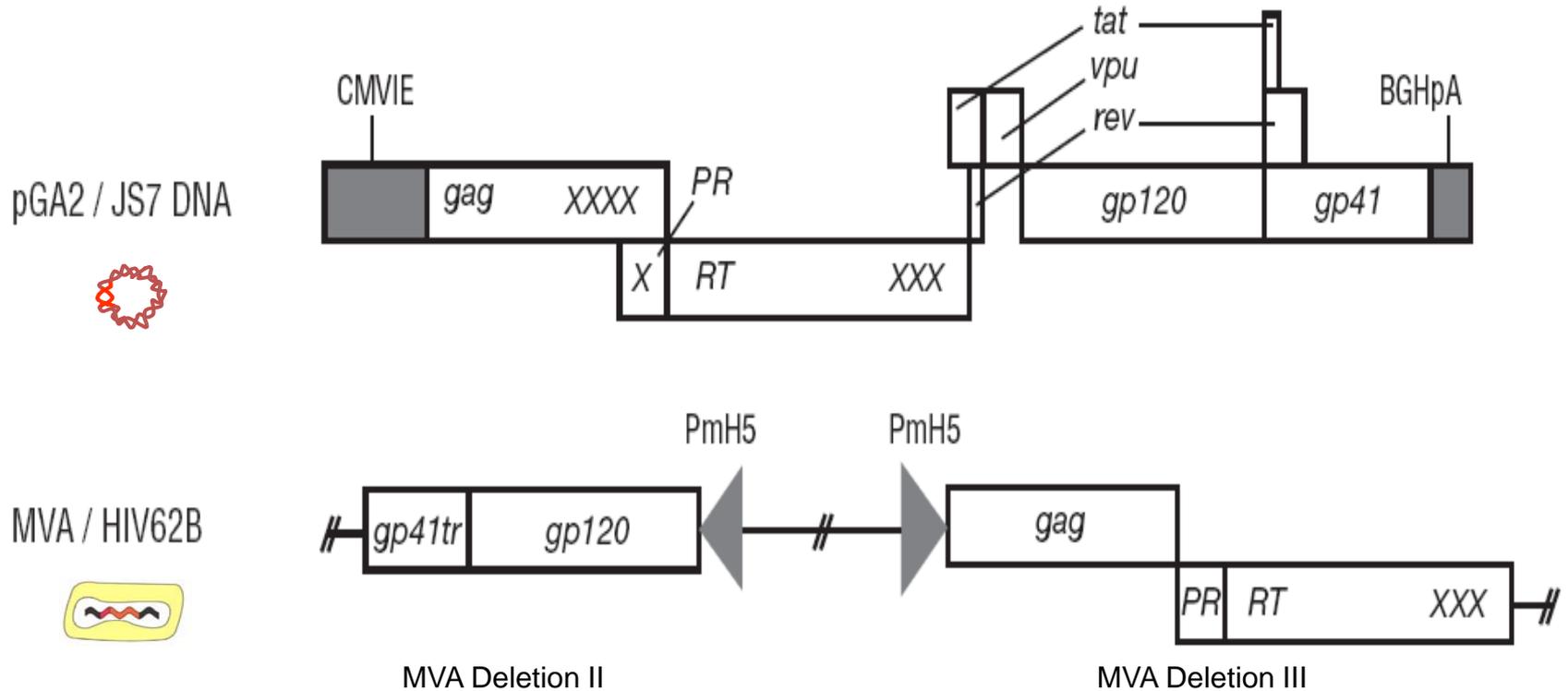
Avidity Index for E660 Env Correlates with Number of Challenges to Infection



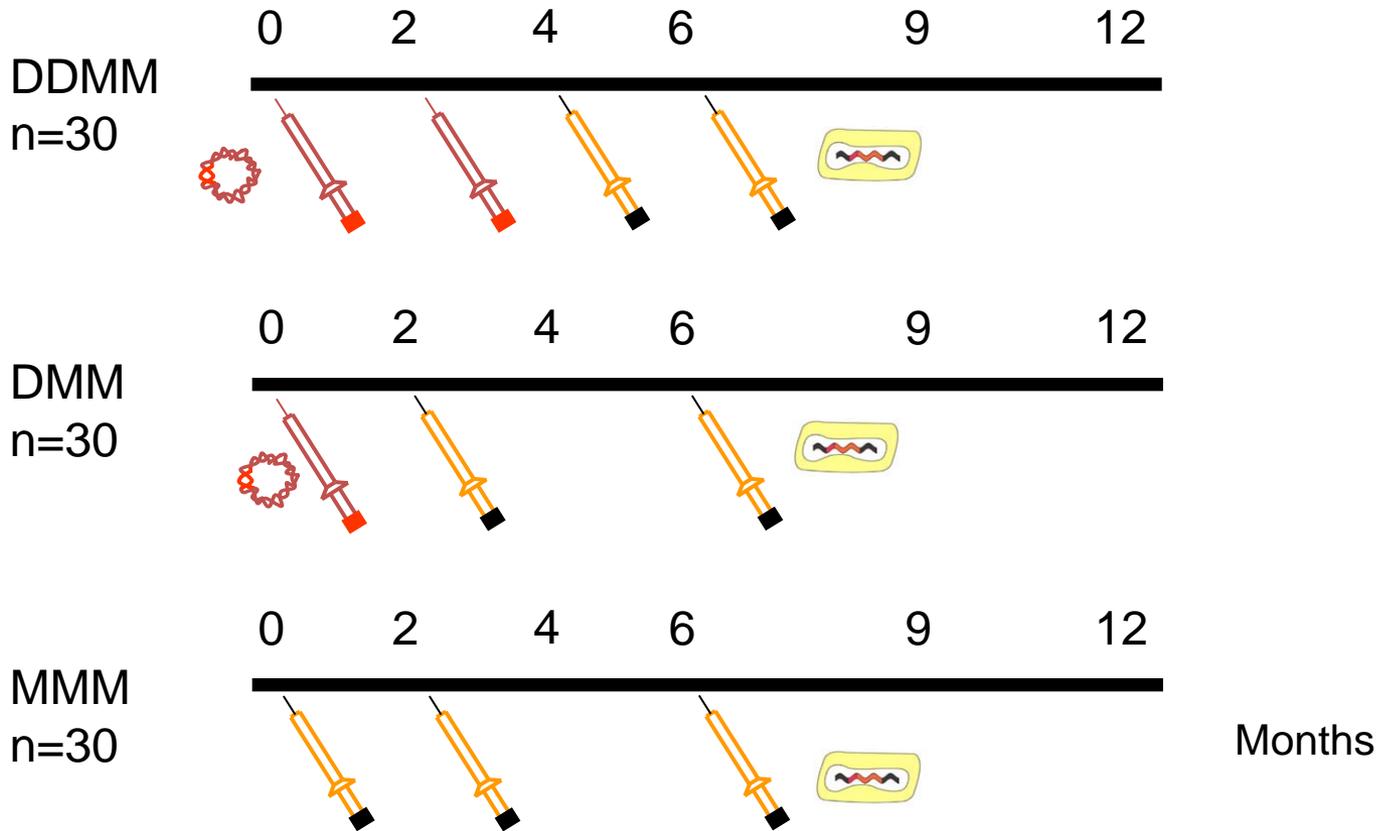
Prior Clinical Experience with Unadjuvanted Vaccine

***Clinical Trials Conducted
by HIV Vaccine Trials Network
(HVTN)***

JS7 DNA with HIV62B MVA



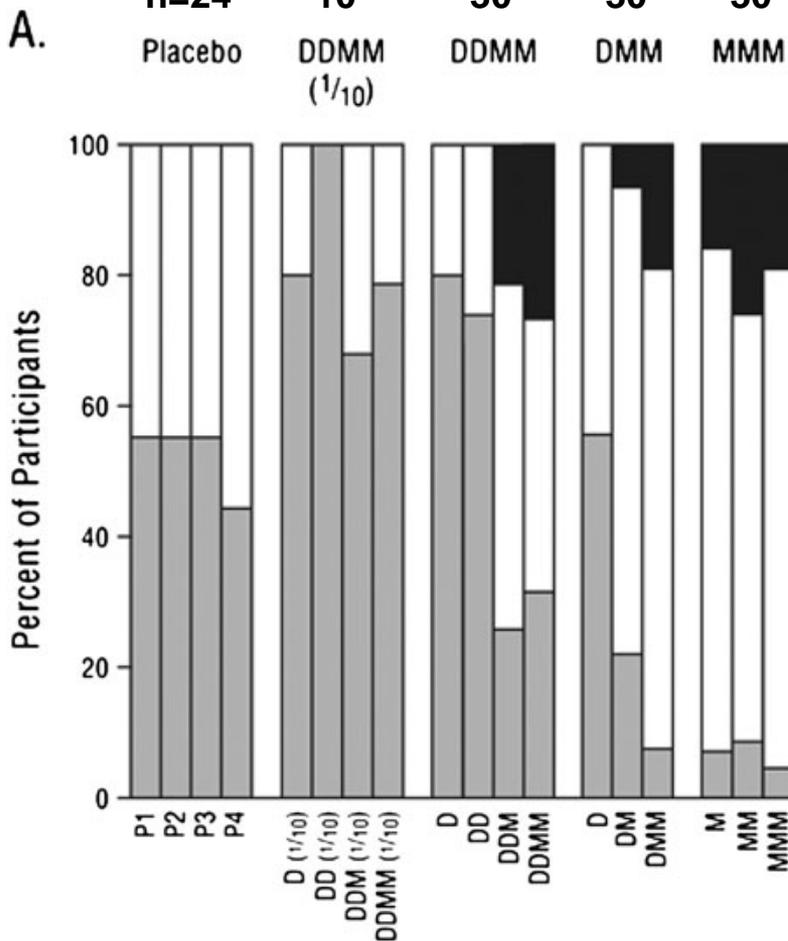
Phase 1: HVTN 065



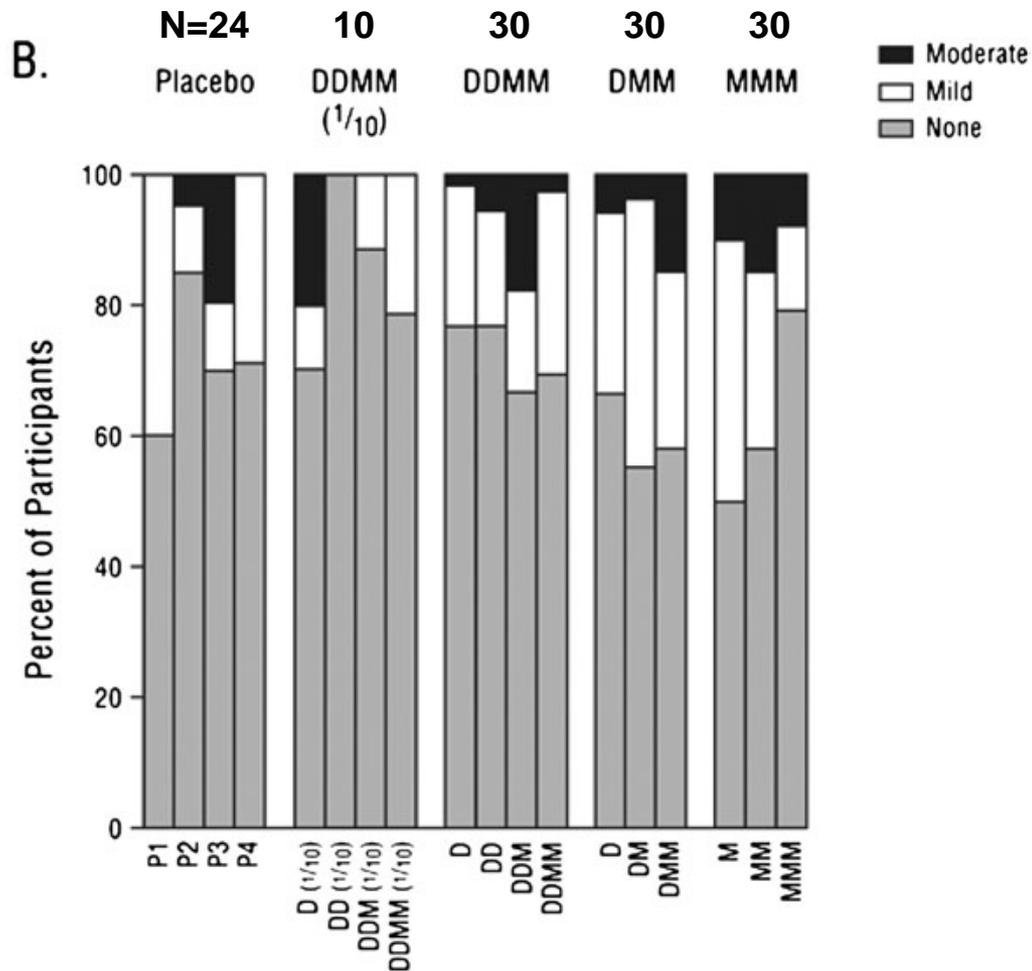
24 placebos

HVTN 065 Safety

Local pain and/or tenderness



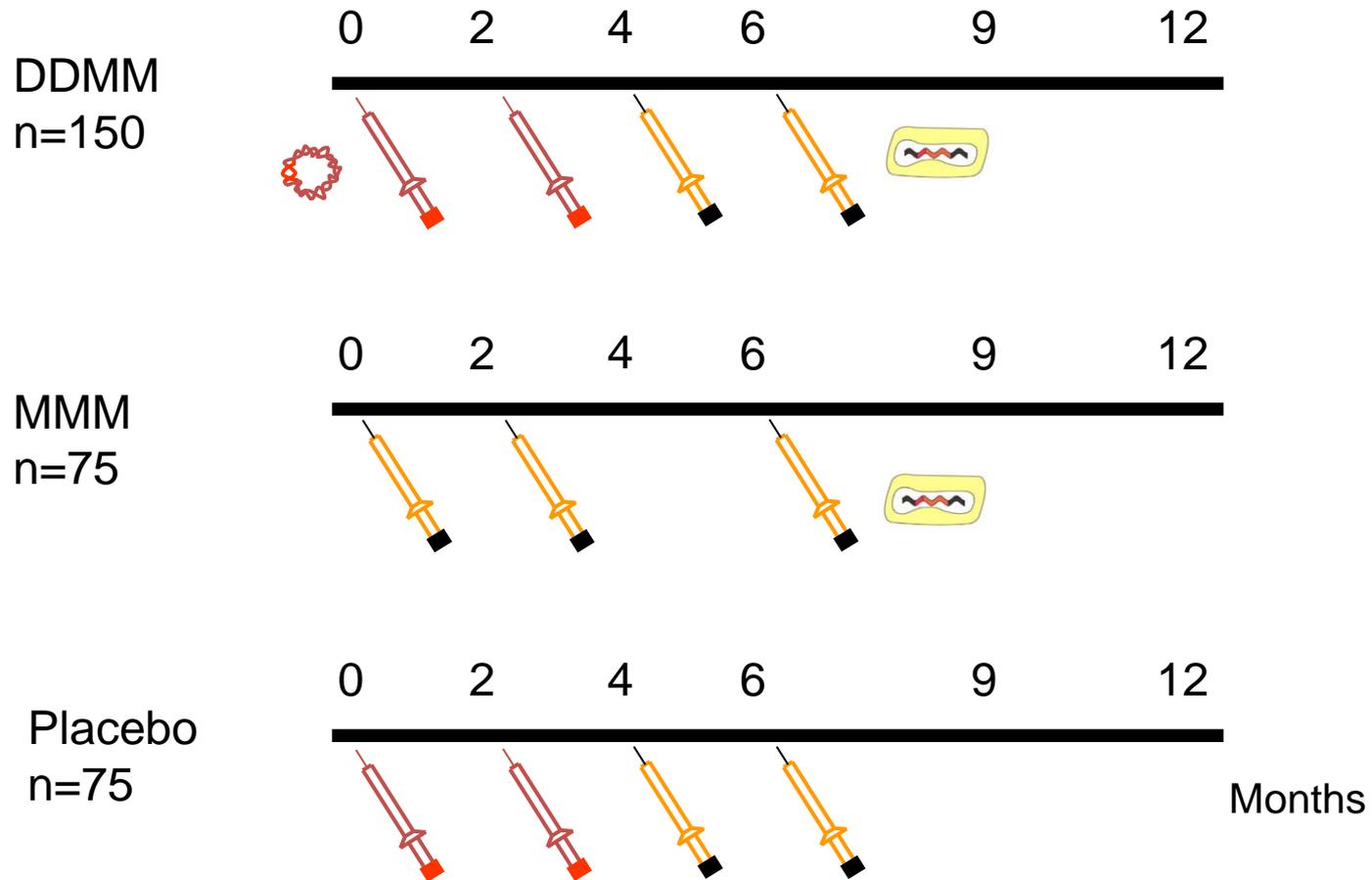
Any systemic symptoms



Summary of HVTN 065 Findings

- Excellent safety and tolerability
- DNA/MVA elicits highest T cell responses
 - Rates of response and breadth of epitopes
 - Two DNA primes better than one
- MVA/MVA elicits highest Ab responses
 - Titers of Env Ab and breadth of neutralizing Ab
 - Three MVA deliveries better than two

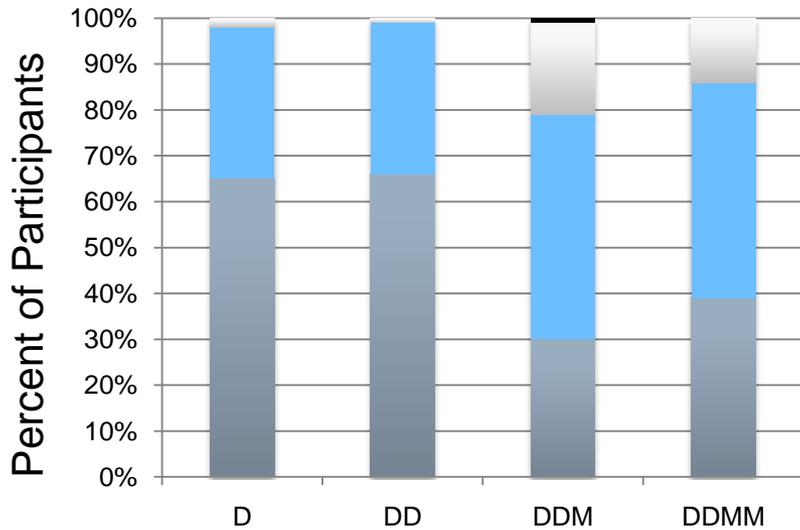
Phase 2a: HVTN 205



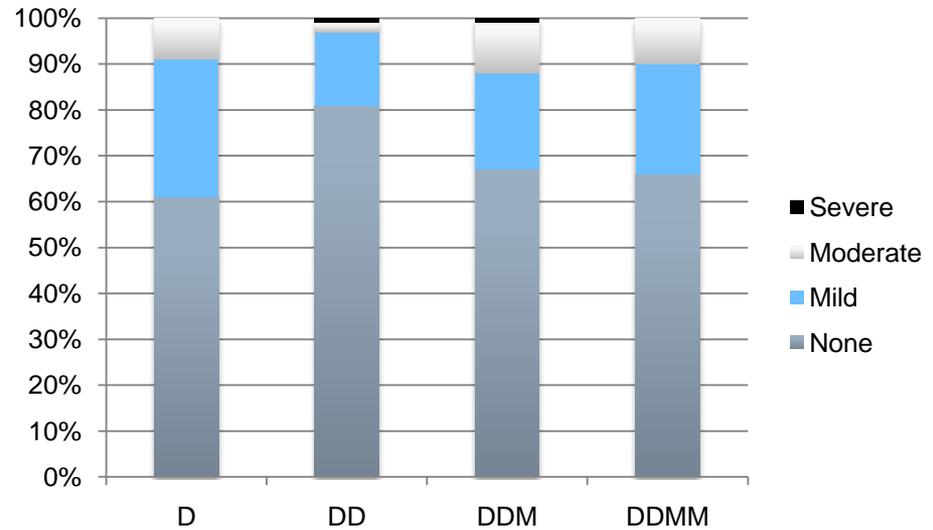
HVTN 205: Blinded Safety

Part A: 120 DDMM; 60 placebo

Pain and Tenderness



Systemic Symptoms



Summary of HVTN 205, to date

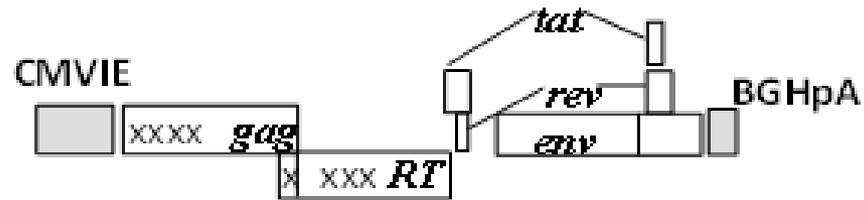
- Part A: DDMM (120), placebo (60)
 - All data remain blinded
 - Safe and tolerable, ongoing monitoring
 - Reproducible T cell responses
 - Expected response rates
 - Magnitude
 - Specificity: Gag>Env
- Part B: DDMM (30), MMM (75), placebo (15)
 - Completing enrollment

HVTN 094

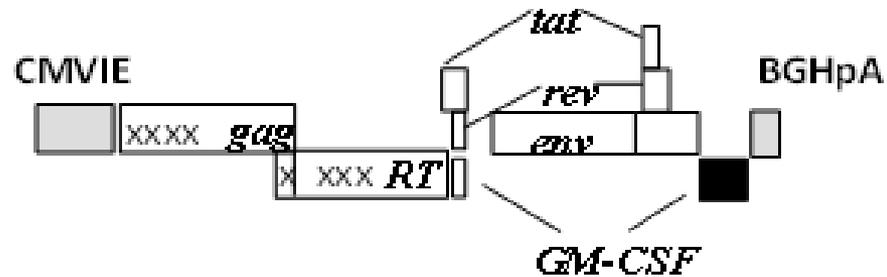
A phase I placebo controlled clinical trial to evaluate the safety and immunogenicity of a prime-boost vaccine regimen of GEO-D03 DNA and MVA/HIV62B vaccines in healthy HIV-1-uninfected vaccinia naïve adult participants

JS7 DNA vs GEO-D03 DNA

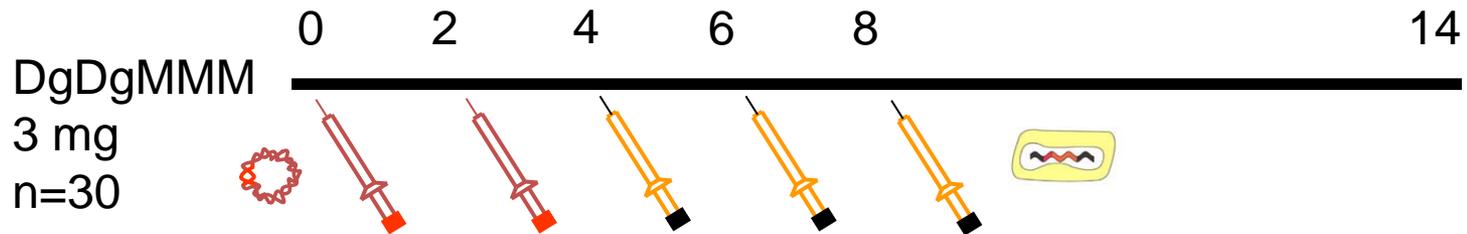
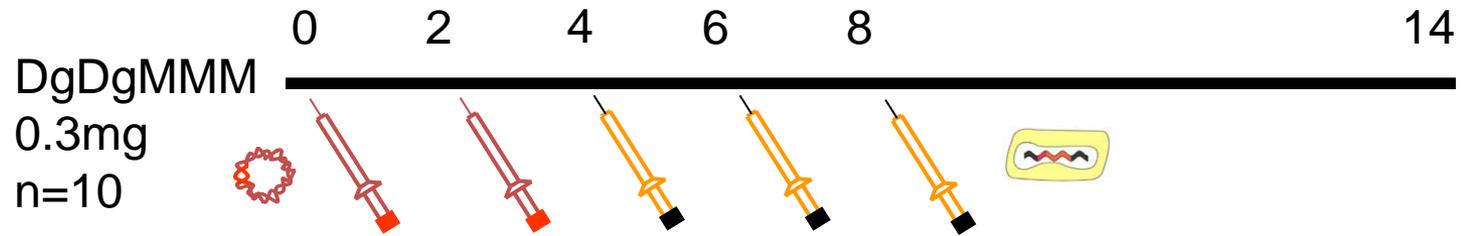
pGA2/JS7



GEO-D03



Phase 1: HVTN 094



8 placebos

Study Rationale

- DNA (JS7) prime w MVA (MVA62B) boost safe, immunogenic
- New DNA (GEO-D03) may have improved immunogenicity, and assoc with enhanced protection in NHP model
- Two DNA optimal for cellular response, 3 MVA optimal for antibody response in HVTN 065
 - Evaluate antibody response after 2nd vs. 3rd MVA dose to assess importance of 3rd dose in the context of DNA prime
 - **Comparison with 135 DDMM pts in HVTN 205 will be conducted as an ancillary protocol; sufficient power for safety and immunologic parameters**

HVTN 094 Study Objectives

Primary

- Evaluate safety and immunogenicity of DgDgMMM immunization series, with dose escalation of Dg vaccine
 - Low dose: 0.3 mg
 - Full dose 3.0 mg

Secondary

- Frequency and magnitude of anti-Env binding Ab
- Proportion vaccinees w/ neutralizing Ab after 2nd vs. 3rd MVA dose
 - Among those with NAb, magnitude and breadth of response
- Frequency and magnitude of T-cell response after 2nd vs. 3rd MVA dose

Immunogenicity Assays

Humoral

- Total binding IgG and IgA to Env
- Neutralizing antibody
 - Systematic assessment of neutralization sensitivity of panel of 109 geographically and genetically diverse isolates (Seaman 2010 JVI)
 - **Primary analysis using 11 isolates from Tiers 1 and 2; if positive, additional isolates tested**

Cellular

- Flow cytometry to examine vaccine-specific CD4+ and CD8+ T cell responses; validated assay (Horton 2007 JIM)
- **False positive rate ($\approx 4\%$) taken into account in power calculations and statistical analysis**

Informed Consent Process

- Extensive discussions with HVTN staff
 - Clinicians
 - Counselors
- Detailed, standardized educational materials
 - Frequently Asked Questions (FAQ)
 - Slide decks
- Test of understanding
- Written informed consent
- Ongoing education after enrollment
 - Includes notification of relevant information from other trials

Informed Consent Form (ICF)

Required forms	# of pages
Protocol specific ICF	16
Approved contraception	1
HVTN “VISP” (Vaccine-Induced Sero-Positivity) registry	3
HIPAA (Health Insurance Portability and Accountability Act)	3
Participant Bill of Rights and Responsibilities	1
Total	24

Informed Consent

GM-CSF

- **Anti-GM-CSF tested at baseline, 2 weeks after first and 2nd DNA doses, 2.5 months after 2nd DNA vaccination**
- Prior experience with GM-CSF in vaccines
 - Protein adjuvant : HIV, hepatitis B and cancer vaccines
 - Cells expressing GM-CSF: cancer vaccines
 - DNA vaccines: malaria and melanoma vaccines
- **Potential AEs discussed in ICF; history of GM-CSF in other vaccines to be included in standardized educational materials**

Informed Consent

HIV testing

Protocol-specific consent form

- **“The study vaccines may cause you to test positive on some types of HIV tests.** This means that after you get the study vaccines, a routine HIV test done outside this clinic may say you have HIV, even if you don’t... Our tests can tell the difference between true HIV infection and a positive result that is caused by the study vaccines.”
- **“If you receive a positive test result caused by the study vaccines at any time, we can provide you with free HIV testing for as long as you need it.** If this happens, we do not know how long you will test positive due to the study vaccines...”
- **“If someone believes you are HIV infected and you are not, you could face discrimination and other problems.** For example, you could be denied medical or dental care, employment, **insurance**, a visa, or entry into the military. You **might not be allowed to donate blood** or other organs....”

VISP (vaccine-induced seropositivity) consent

- **VISP test results may cause problems in several areas like insurance**, job applications, the military, prison, visa applications, emigration/immigration, and **blood** and tissue **donation**.

Informed Consent

Compensation

- Reimbursement amounts set by site in collaboration with CAB, approved by local IRB
- Usual amount at US sites is
 - \$100 for each injection visit (longer visits)
 - \$50 for each non-injection visit
- **Amounts vary based on local cost-of-living, transportation costs, community norms**