

**First-in-Human Phase 1 Safety and
Immunogenicity of an Adenovirus Serotype
26 HIV-1 Vaccine Vector**

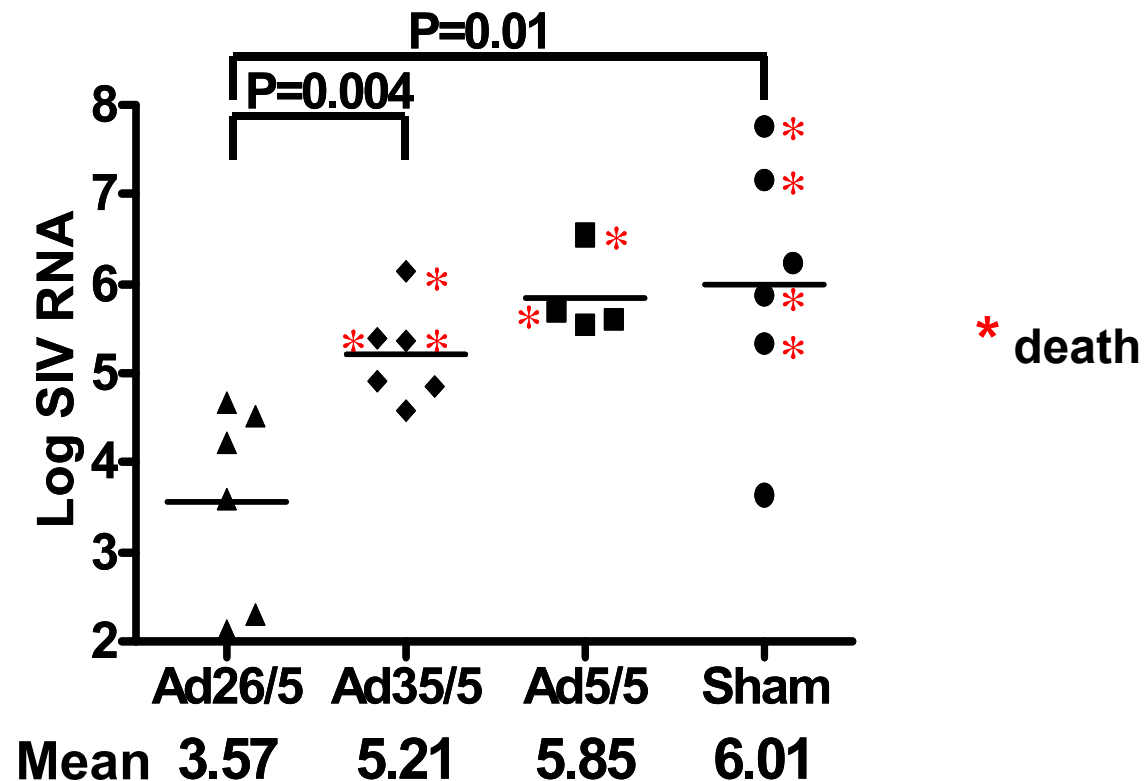
**Dan Barouch
October 21, 2009**

Adenovirus Serotype 26 (Ad26)

- **Ad26 is a rare Ad serotype that we selected for clinical studies following preclinical evaluation of group D (Ad26, Ad28, Ad48, Ad49) and group B (Ad11, Ad34, Ad35, Ad50) Ads**
- **Ad26 is substantially different than Ad5 in terms of:**
 - **Baseline seroprevalence (Abbink et al. J. Virol. 2007; 81:4654-4663; Thorner et al. J. Clin. Microbiol. 2006; 44:3781-3783)**
 - **Cellular receptors (Abbink et al. J. Virol. 2007; 81:4654-4663)**
 - **Tropism (Waddington et al. Cell 2008; 132:397-409)**
 - **Innate immune profile (Barouch et al., unpublished data)**
 - **Adaptive immune phenotype (Liu et al. J. Virol. 2008; 82:4844-4852)**
 - **Protective efficacy against SIV (Liu et al. Nature 2009; 457:87-91)**

Long-Term Significant 2.4 Log Decrease in Setpoint SIV RNA in rAd26/rAd5 Vaccinated Monkeys Post-Challenge

Setpoint SIV RNA Levels; Mean Day 112-500 Post-Challenge



HIV-1 Vaccine Clinical Development Strategy

- 1. Develop “prototype” novel rAd vectors expressing a single test antigen (VRC EnvA) for a rapid assessment of vector safety and immunogenicity in humans**
- 2. Develop “complete” vaccine products involving an optimal heterologous rAd prime-boost regimen expressing multiple HIV-1 antigens for further clinical development**

A phase 1 randomized, double-blind, placebo controlled dose escalation clinical trial to evaluate the safety and immunogenicity of recombinant adenovirus serotype 26 HIV-1 vaccine (Ad26.ENVA.01**) in healthy, HIV-1 uninfected adults**

PI: Lindsey Baden, Brigham & Women's Hospital

Ad26.ENVA.01 (rAd26): Recombinant adenovirus serotype 26 vector vaccine is a recombinant product composed of an adenovirus serotype 26 vector (Δ E1/E3) that encodes a modified gp140 HIV-1 Clade A Env glycoprotein (strain 92rw020), manufactured in HER96 cells by Crucell

Protocol Schema and Study Objectives

			Schedule in Months (Days)		
Group	Number	Dose (vp)	0 (0)	1 (28)	6 (168)
1	10 2	10^9	rAd26 Placebo	rAd26 Placebo	rAd26 Placebo
2	10 2	10^{10}	rAd26 Placebo	rAd26 Placebo	rAd26 Placebo
3	10 2	10^{11}	rAd26 Placebo	rAd26 Placebo	rAd26 Placebo
4	10 2	10^*	rAd26 Placebo		rAd26 Placebo
Total	48 (40/8)				

- **Primary Objective:**
 - To evaluate the safety and tolerability of Ad26.ENVA.01

- **Secondary Objective:**
 - To evaluate the immunogenicity of Ad26.ENVA.01

Study Progress

- **Subjects Enrolled:** 36 (groups 1, 2, 3 fully enrolled)
 - **Gender:** 26 (72%) female
 - **Age:** 25 (69%) \leq 30 years (range 18-47 years)
 - **Race/Ethnicity:** 5 (14%) Black or Hispanic
 - **Ad26 Serologies:** 150 tested, 13 positive (8.6%), all low titers
-
- **1st vaccination:** 36 of 36 (100 %)
 - **2nd vaccination:** 34 of 36 (94 %)
 - **3rd vaccination:** 22 of 24 (92 %)
-
- **Prespecified interim safety and immunogenicity analysis of groups 1, 2, 3 after week 0 and week 4 immunizations; data remains blinded vaccine vs placebo**

Ad26.ENVA.01 Interim Safety Analysis

- **Prespecified safety analysis after week 0 and week 4 immunizations; data remains blinded vaccine vs placebo**
- **No serious adverse events (SAEs) and no pattern of vaccine-associated adverse events (AEs) in any group**
- **Minimal to no reactogenicity in the 10^9 vp and 10^{10} vp groups**
- **In the 10^{11} vp group, 7 subjects exhibited moderate (N=5) or severe (N=2) reactogenicity following initial vaccination**
 - **Fatigue, myalgia, chills**
 - **Mild fever of 100.5 F (38.0 C) in one subject**
 - **In all subjects, symptoms resolved within 24 hours**
 - **Did not recur after second vaccination**

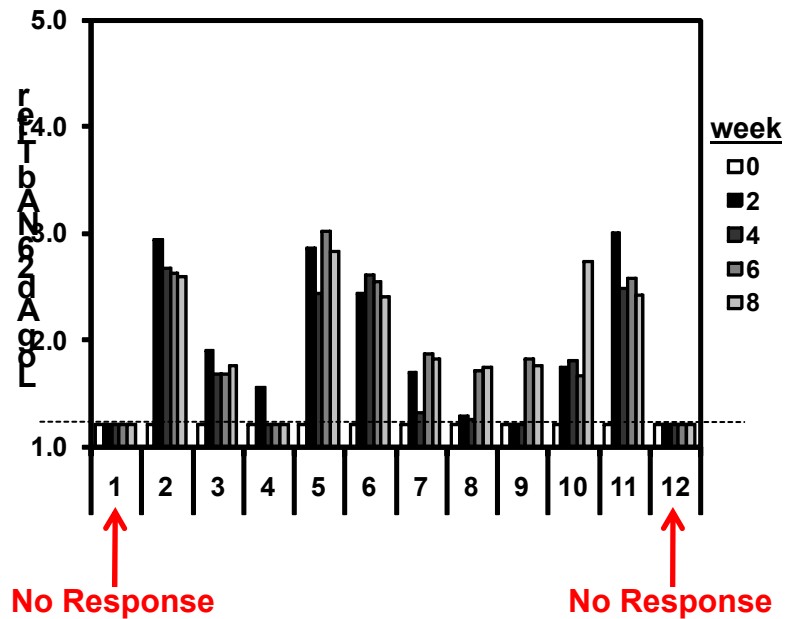
Ad26.ENVA.01 Interim Safety Analysis

- **Reactogenicity with 10^{11} vp Ad26 comparable with that reported with 10^{11} vp rAd5**
 - **Merck rAd5 (Priddy et al. CID 2008; 46:1769-1781)**
 - 58% HA, 42% chills, 47% fever
 - **VRC rAd5 (Cantanzaro et al. JID 2006; 194:1638-1649)**
 - 60% moderate reactogenicity, 40% fever
- **Ad26 vaccine safe and generally well tolerated to date at the three doses studied**

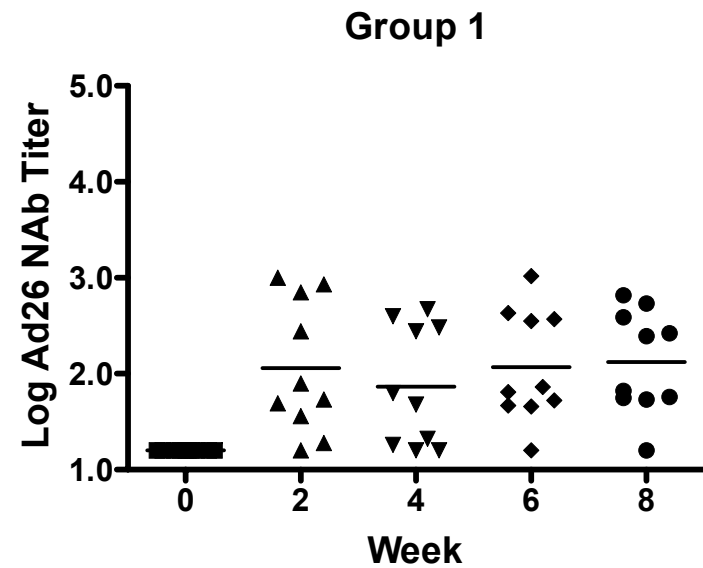
Ad26.ENVA.01 Interim Immunogenicity Analysis

- **Prespecified immunogenicity analysis after week 0 and week 4 immunizations; data remains blinded vaccine vs placebo**
- **36 subjects (10 vaccinees, 2 placebos per group):**
 - **Group 1: 10^9 vp**
 - **Group 2: 10^{10} vp**
 - **Group 3: 10^{11} vp**
- **Samples (laboratory coded to maintain blinding):**
 - **Weeks 0, 2, 4, 6, 8**
- **Immunologic Assays:**
 - **Ad26 NAb assay**
 - **EnvA ELISA assay**
 - **EnvA IFN- γ ELISPOT assay (validated)**

Ad26 NAb Responses – Group 1 (10⁹ vp)



No Response: samples #1 and #12



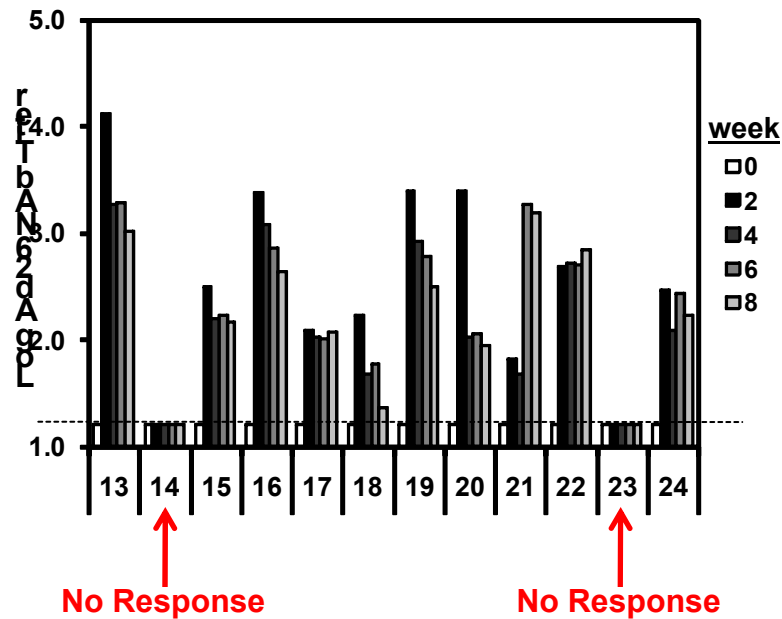
Log Ad26 NAb Titer (Week 8)

Mean: 2.12

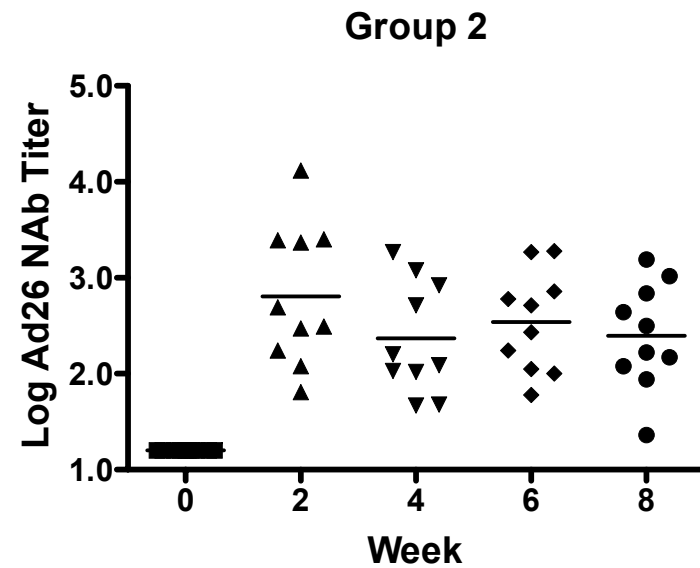
Median: 2.11

IQR: 1.75-2.59

Ad26 NAb Responses – Group 2 (10¹⁰ vp)



No Response: samples #14 and #23



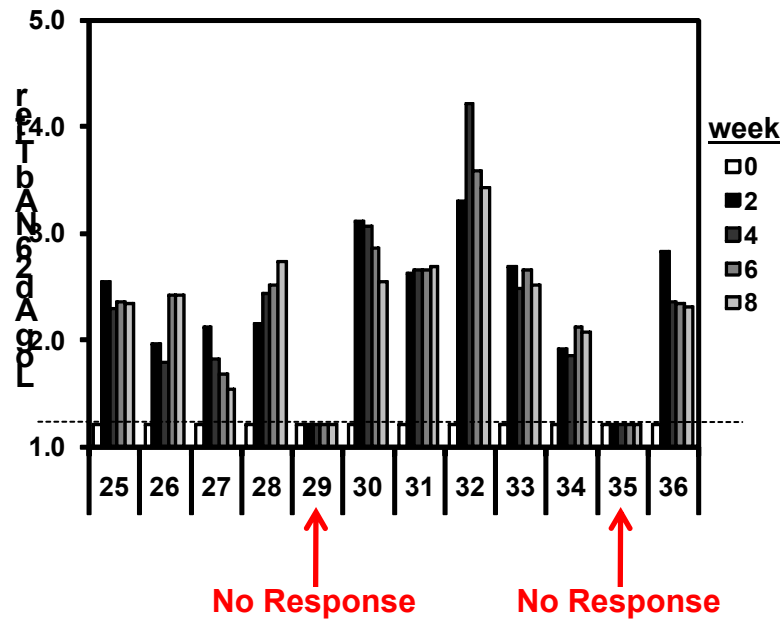
Log Ad26 NAb Titer (Week 8)

Mean: 2.40

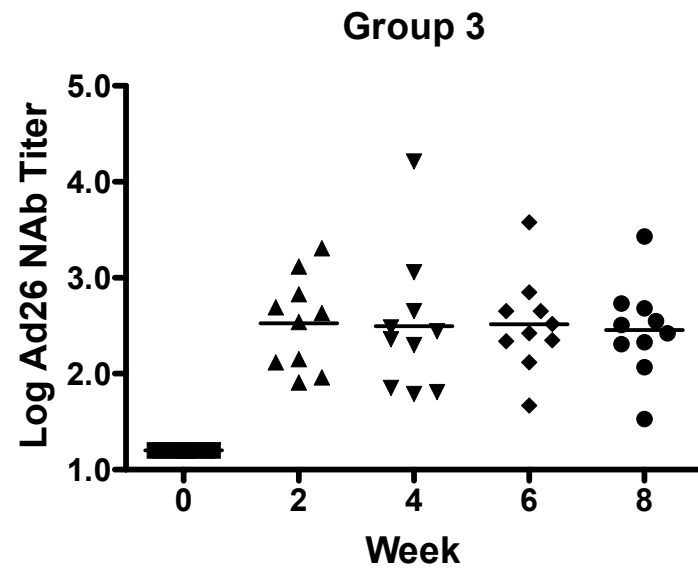
Median: 2.36

IQR: 2.08-2.84

Ad26 NAb Responses – Group 3 (10¹¹ vp)



No Response: samples #29 and #35



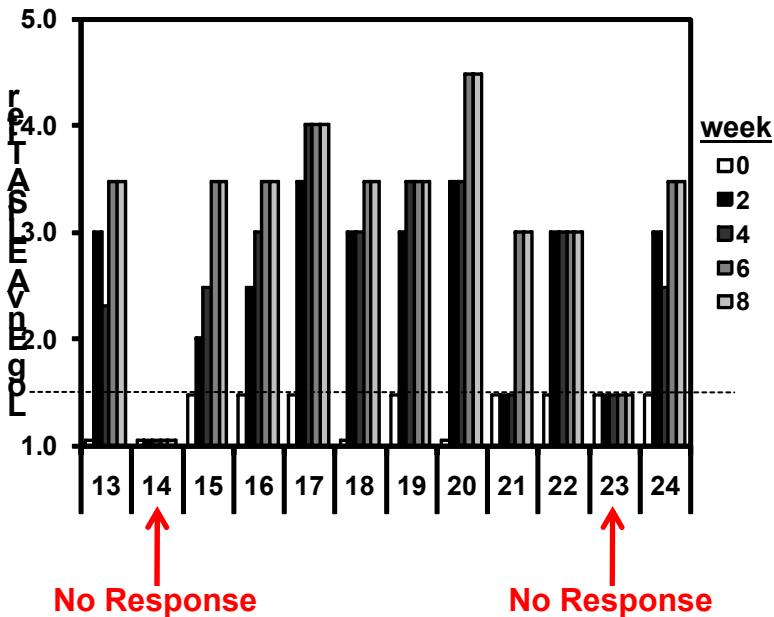
Log Ad26 NAb Titer (Week 8)

Mean: 2.46

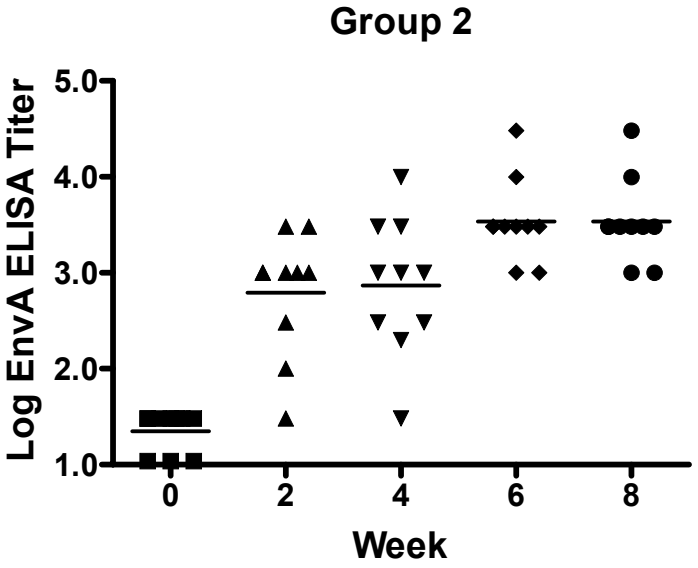
Median: 2.46

IQR: 2.31-2.68

EnvA ELISA Responses – Group 2 (10¹⁰ vp)



No Response: samples #14 and #23



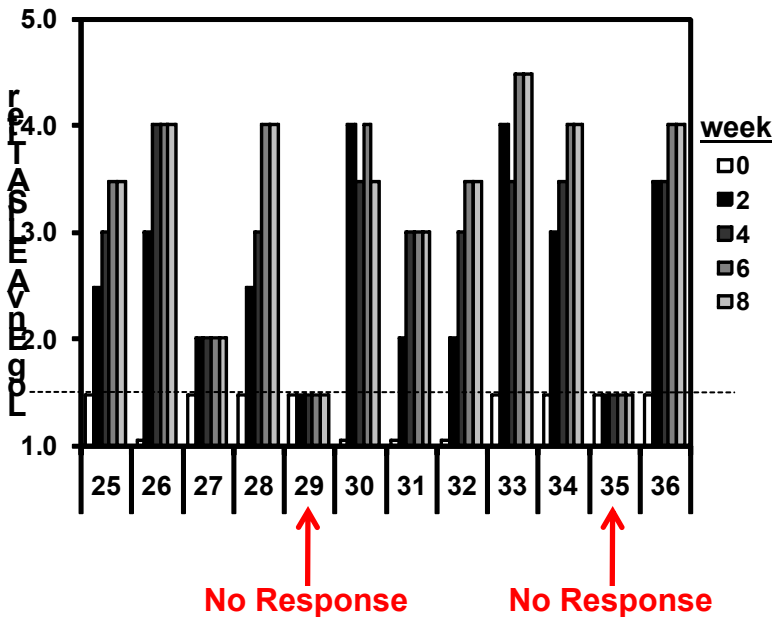
Log EnvA ELISA Titer (Week 8)

Mean: 3.53

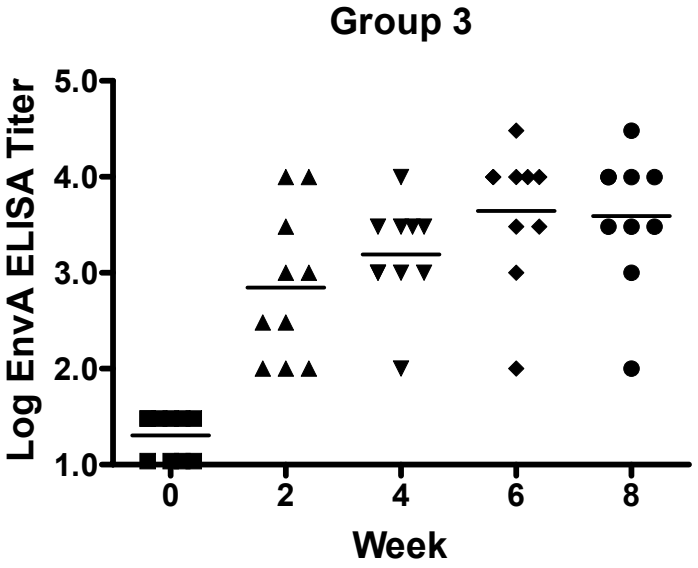
Median: 3.50

IQR: 3.50-3.50

EnvA ELISA Responses – Group 3 (10¹¹ vp)

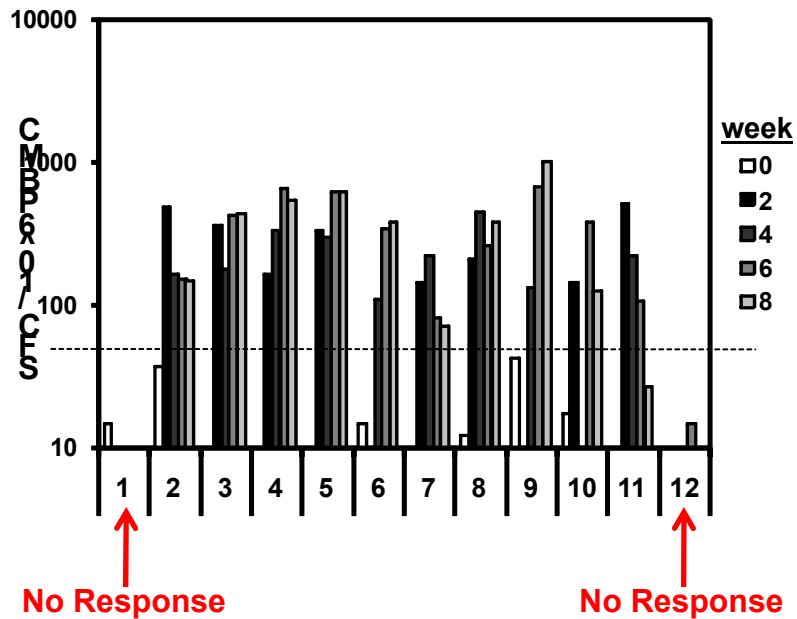


No Response: samples #29 and #35

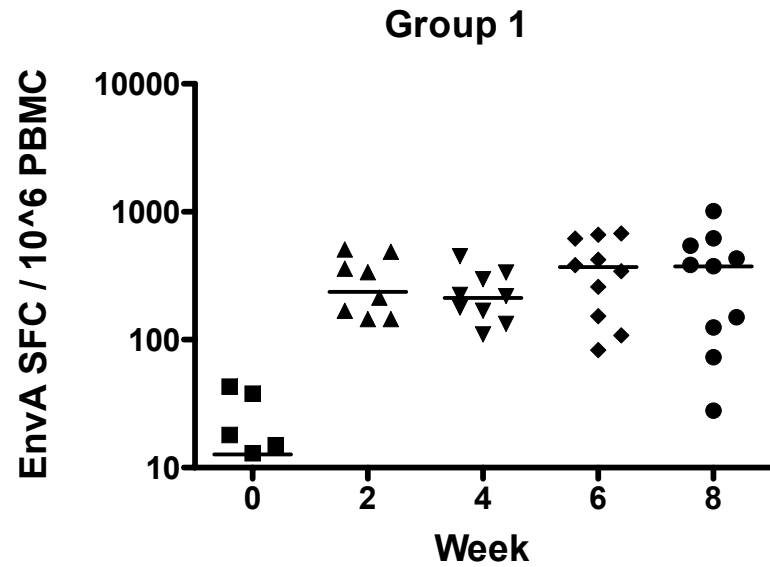


Log EnvA ELISA Titer (Week 8)
 Mean: 3.59
 Median: 3.75
 IQR: 3.50-4.00

EnvA ELISPOT Responses – Group 1 (10⁹ vp)



No Response: samples #1 and #12



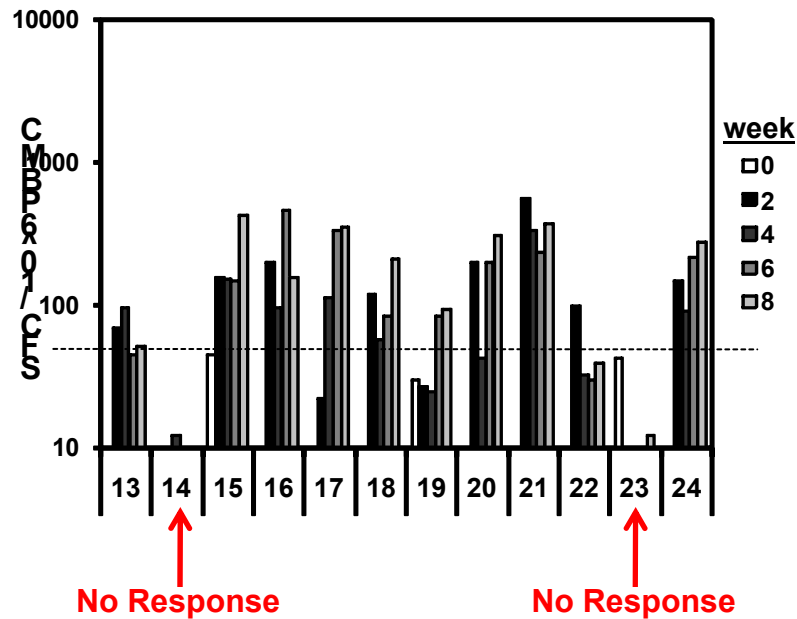
EnvA ELISPOT Response (Week 8)

Mean: 375

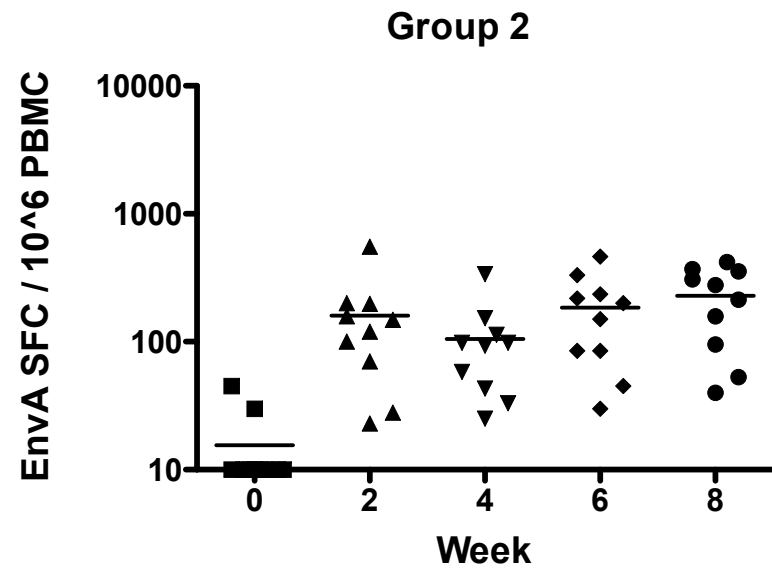
Median: 381

IQR: 125-545

EnvA ELISPOT Responses – Group 2 (10¹⁰ vp)



No Response: samples #14 and #23



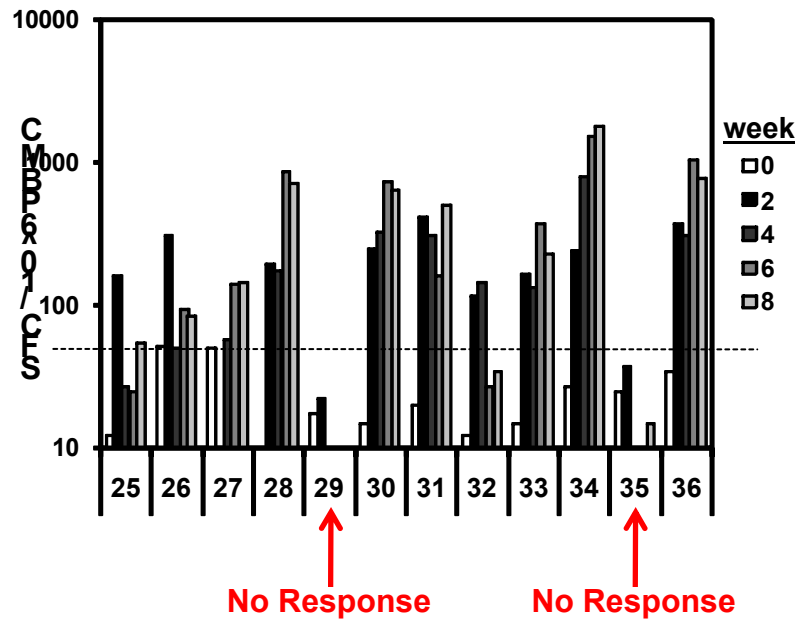
EnvA ELISPOT Response (Week 8)

Mean: 229

Median: 245

IQR: 95-355

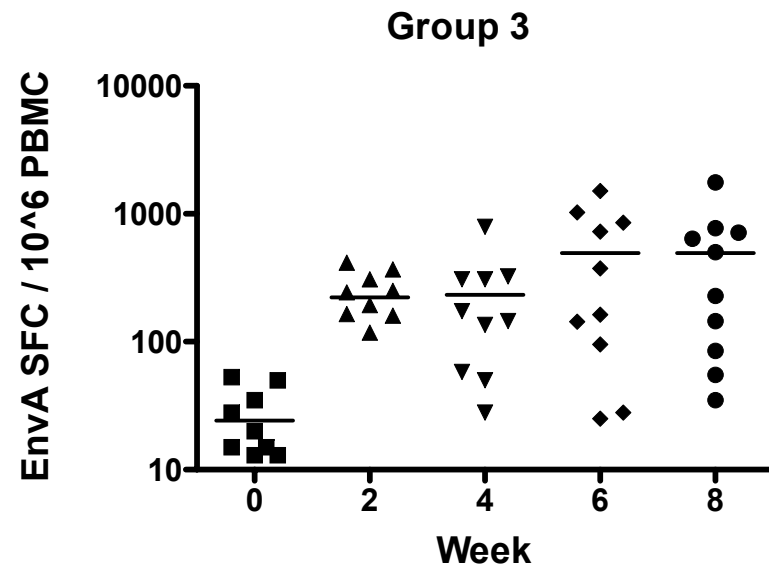
EnvA ELISPOT Responses – Group 3 (10¹¹ vp)



No Response

No Response

No Response: samples #29 and #35



EnvA ELISPOT Response (Week 8)

Mean: 494

Median: 365

IQR: 85-715

Ad26.ENVA.01 Interim Immunogenicity Analysis

- **Ad26 vaccine was immunogenic at all three doses tested**
 - 10 vaccinees, 2 placebos per group
 - 10 subjects/group: Ad26 NAb, EnvA ELISA, EnvA ELISPOT responses
 - 2 subjects/group: no vector- or insert-specific immune responses
- **Effect of homologous boost immunization**
 - Ad26 NAb titers: minimal effect
 - EnvA ELISA titers: modest augmentation by approx 0.5 log
 - EnvA ELISPOT responses: modest augmentation by approx 2-fold
- **Effect of increasing vaccine dose**
 - Ad26 NAb responses: $10^9 < 10^{10} \sim 10^{11}$ vp
 - EnvA ELISA responses: $10^9 < 10^{10} \sim 10^{11}$ vp
 - EnvA ELISPOT responses: $10^9 \sim 10^{10} \sim 10^{11}$ vp
- **2 log dose range between immunogenicity (10^9 vp) and reactogenicity (10^{11} vp)**

Ad26.ENVA.01 Interim Analysis – Conclusions

- **Multiple ongoing and planned studies:**
 - **EnvA-specific multiparameter ICS assays**
 - **Ad26-specific multiparameter ICS assays**
 - **Epitope mapping studies**
 - **Tier 1 clade A/B/C NAb assays**
 - **ADCC and ADCVI assays**
 - **Later timepoints will assess the durability of responses and the utility of the month 6 boost immunization**
- **Ad26 is safe and immunogenic in humans at doses of 10^9 , 10^{10} , and 10^{11} vp**
- **Immunogenicity at 10^9 vp unexpected based on NHP studies**
- **Ad26 is a promising vector for further clinical development**

Proposed Next-Generation HIV-1 Vaccine Candidate

NIH IPCAVD U19 AI078526 Program

- Our IPCAVD program aims to develop a global HIV-1 vaccine candidate for clinical evaluation
 - Vectors that avoid pre-existing vector-specific NAbs and that can be combined into a heterologous prime-boost regimen
 - **Heterologous rare serotype rAd prime-boost regimen**
 - Antigens that improve cellular immune breadth and that optimize coverage of global virus diversity
 - **2-valent mosaic Gag/Pol/Env antigens (Symposium #6: Refining Immunogen Design this afternoon)**
- Rare serotype Ad vectors expressing mosaic HIV-1 antigens are currently being manufactured for clinical studies by Crucell

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