CD8+ T-cell responses elicited by a novel recombinant adenovirus (Ad) serotype 35-vectored HIV-1 vaccine are reduced in healthy Ad5-seropositive, HIV-1 uninfected persons

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Background

- Preventive HIV vaccine candidates based on a replication defective adenovirus subtype 5 (rAd5) vector have advanced to efficacy trials (1, 2)
  - A phase IIB trial of the Vaccine Research Center's (VRC) multiclade, multigene DNA prime/Ad5 boost (HVTN 505) is currently enrolling
- High rates of background pre-existing humoral immunity to Ad5 may limit the immunogenicity and clinical utility of recombinant Ad5 (rAd5)-vectored vaccines
  - A recent seroepidemiologic survey suggests background Ad5 seroprevalence as high as 85-90% in South African adults (3)
- Novel vaccine candidates based on rare adenoviral serotypes, such as Ad35, are well tolerated and immunogenic in early phase trials (4, 5)
- Ad35-based vaccines may be able to circumvent pre-existing humoral immunity to Ad5 given its low global seroprevalence, unique receptor usage and tropism
- To evaluate the safety and immunogenicity of the VRC's rAd35 vaccine candidate compared to rAd5, we conducted a multisite, phase Ib trial within the NIAID-sponsored HIV Vaccine Trials Network

HVTN 077 Primary Objectives

To evaluate the safety and tolerability of the vaccine candidates and to compare immune responses between:

rAd35/rAd5 and DNA/rAd5

- How does rAd35 perform compared to DNA as a prime for rAd5?

DNA/rAd35 and DNA/rAd5

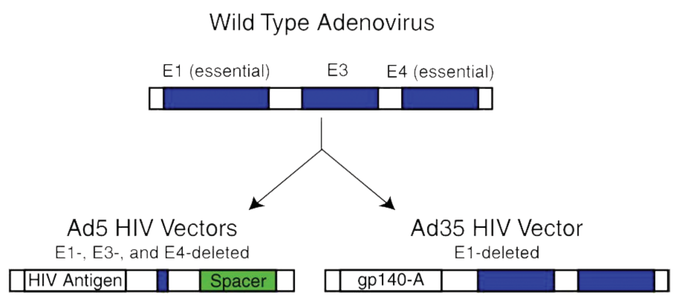
- How does rAd35 perform compared to rAd5 as a boost to DNA?

DNA/rAd35 in Ad5 neutralizing antibody titers ≥18

- What is the effect of Ad5 pre-existing humoral immunity on DNA prime/ rAd35 boost?

Methods

Study Products



- **rAd35:** recombinant adenoviral serotype 35 (1 x 1010 PU IM)
- **rAd5** (1 x 10^{10} PU IM)
- **DNA** (4 mg IM delivered via Biojector)
- All products encode HIV-1 **clade A Env** glycoprotein
  - gp140, truncated at the transmembrane domain of gp41, 92rw020 clade A strain
- Controls are final formulation buffer (FFB) and PBS

HVTN 077 Study Schema

			Injection schedule months (days)			
Group	Ad5 nAb*	N**	0 (0)	1 (28)	2 (56)	6 (168)
1	<18	34/6	rAd35	-	-	rAd5
2	<18	48/8	DNA	DNA	DNA	rAd5
3	<18	48/8	DNA	DNA	DNA	rAd35
4	≥18	34/6	DNA	DNA	DNA	rAd35
Total		192 164/28				

*Baseline neutralizing Ab titer to Ad5. For Ad35, all participants are Ad35 naïve (nAb <12).
**Number vaccine recipients/control recipients (PBS or FFB)

Outcomes

Safety

- Proportion with local and systemic reactogenicity are tabulated by study arm; adverse events and expedited adverse events are summarized

T cell immunogenicity

- **Ex vivo Intracellular Cytokine Staining:** IFN g and/or IL-2 in response to global PTE peptides 4 weeks after the boost (day 196)
- **% responders** and **magnitude of response** (% circulating CD4+/CD8+ T cells)

Results

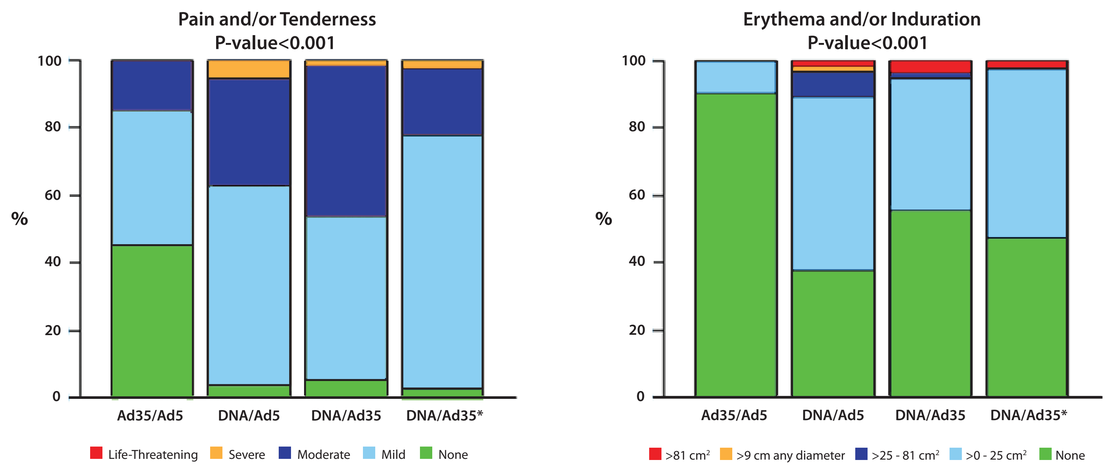
Cohort Demographics (N=192)

Characteristic	N	%
Female	81	42
Race/ethnicity		
White	125	65
Hispanic	16	8
Black	31	16
Multiracial/Other	9	5
Asian	10	5
Native American	0	0

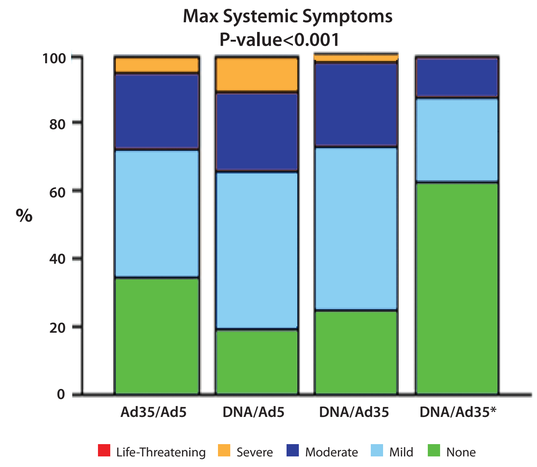
Median age = 28 years

Local and Systemic Reactogenicity

Max Local Reactogenicity by Treatment Group



Max Systemic Reactogenicity by Treatment Group

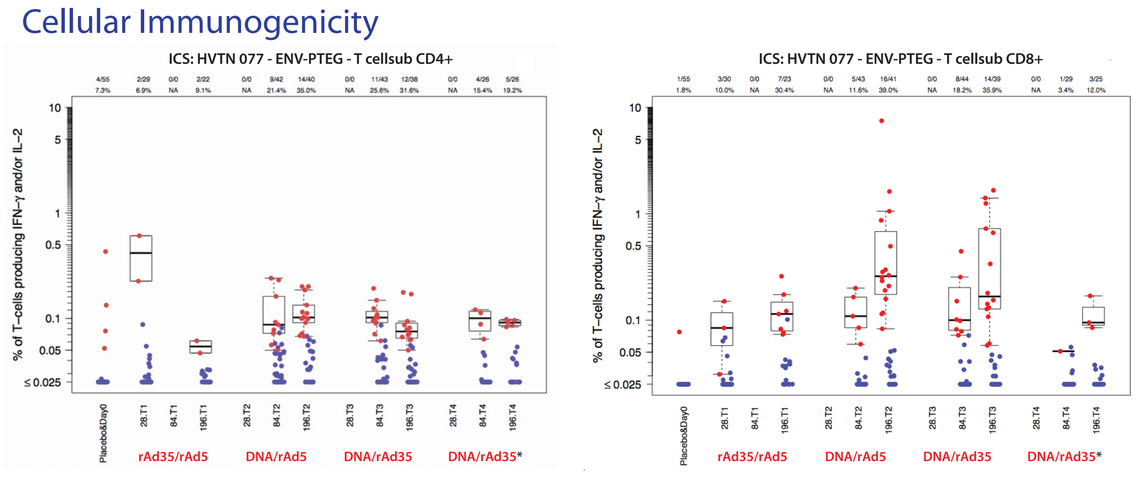


Adverse Events

- Preliminary analysis suggests similar rates of adverse events across groups. Three expedited adverse events were observed:

  Unrelated (2): Motor vehicle accident associated trauma; rectal bleeding
  Probably not related (1): upper extremity DVT in young woman with history of migraines on OCPs shortly after a viral URI

Cellular Immunogenicity



Conclusions

- rAd35 as a prime to rAd5 and as a boost to DNA is **safe and well tolerated**
  - DNA/rAd35 **similar reactogenicity profile** to DNA/rAd5
  - **rAd35/rAd5 less reactogenic** than DNA/adenovector
  - prior Ad5 seropositivity associated with **fewer systemic symptoms to DNA/rAd35**
- We observed a trend toward a **better HIV-specific CD4+ T-cell response with a 3 DNA prime vs. a rAd35 prime of rAd5**
- We found **comparable CD4+/CD8+ T-cell response rates** with DNA/rAd5 vs. DNA/rAd35
- **Interestingly, we observed that HIV-specific CD8+ T-cell responses to DNA/rAd35** (but not CD4+) were **reduced in the setting of prior Ad5 nAb**
  - Studies to probe possible cellular and humoral mechanisms for this effect are currently underway
- Analyses of **antibody responses** from peripheral blood on all volunteers and **immunohistochemistry** from rectal biopsy samples on a subset are forthcoming
- Further exploration of recombinant Ad35-vectored HIV vaccines is warranted

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