V001: Phase I HIV-1 preventive Vaccine Trial

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4 IAVI Core Laboratory, London, UK
5 The EMMES Corporation, Rockville, USA
6 NIH Vaccine Research Center (VRC), Bethesda, USA
7 Emory University, Atlanta, Georgia, USA

Objectives

- To evaluate safety and immunogenicity of VRC recombinant multiclade HIV-1 adenoviral vector (Ad5) vaccine
  - Alone or
  - In a prime-boost combination with the VRC multiclade HIV-1 DNA plasmid vaccine in healthy African adults

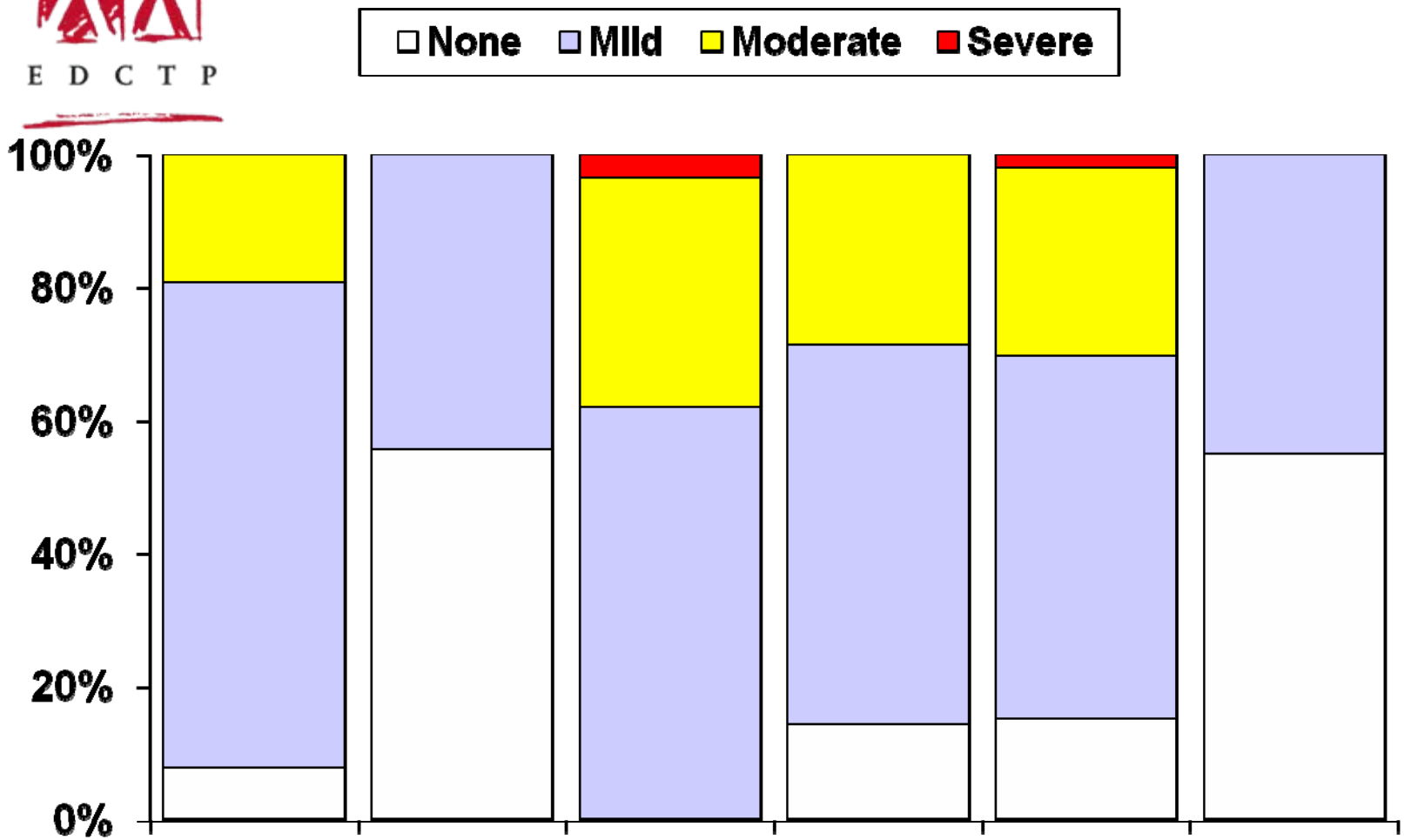
Methods (1)

- Phase I, randomized, double blind, placebo-controlled clinical trial
- 114 healthy volunteers at low risk for HIV enrolled
- 4 active arms:
  - A and B: 1 x 10^{10} rAd5 or 10^{11} rAd5
  - C and D: 3 x 4mg DNA followed by rAd5 boost either at 10^{10} or 10^{11}

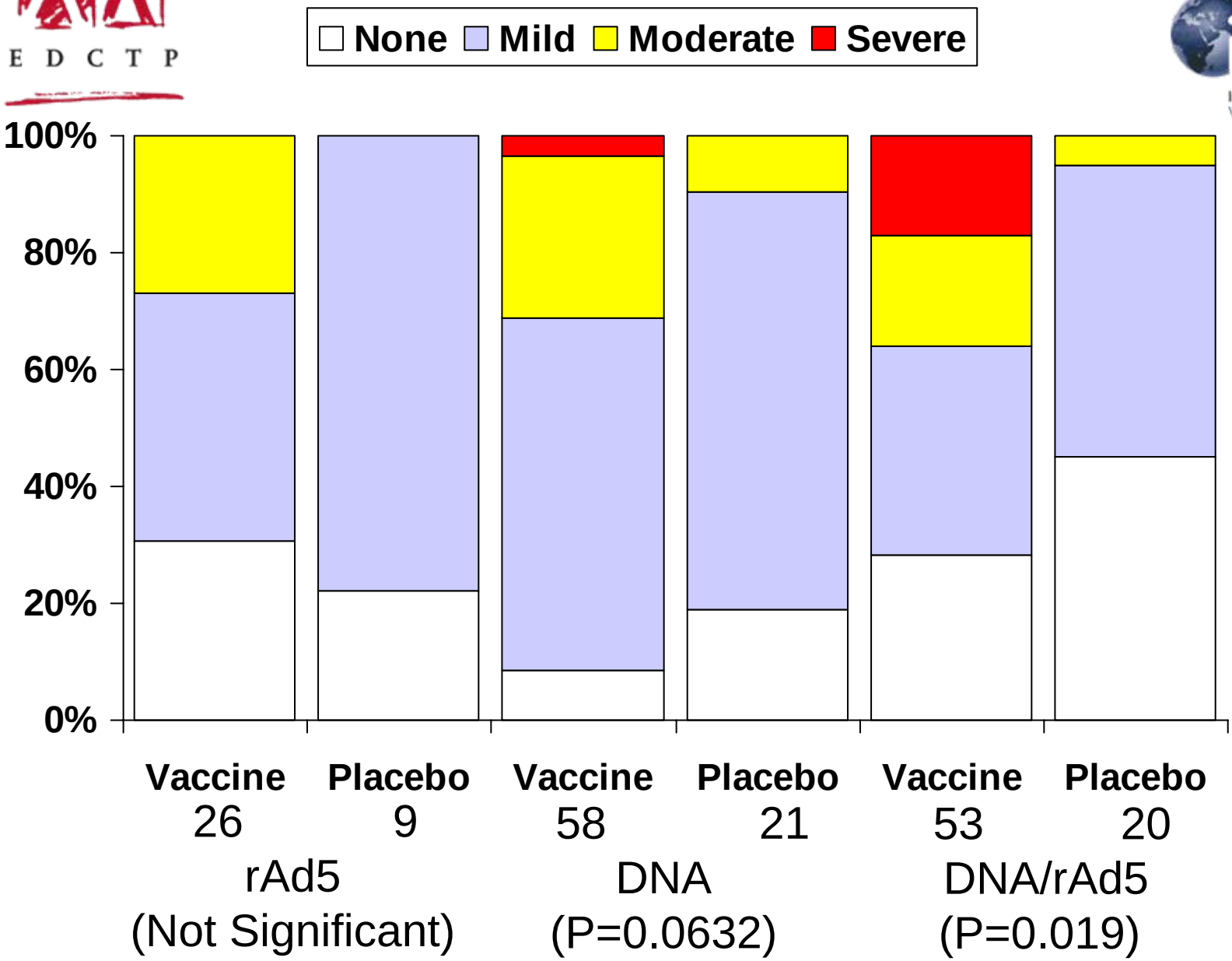
Methods (2)

- Safety and tolerability:
  - assessed clinically and by routine laboratory tests
- Immunogenicity:
  - Ad5-specific neutralization assay (NT)
  - IFN-gamma ELISpot assay
    - frozen PBMC (fresh PBMC in Kenya)
    - matched peptides
    - reported as spot forming cells (SFC)/million PBMC

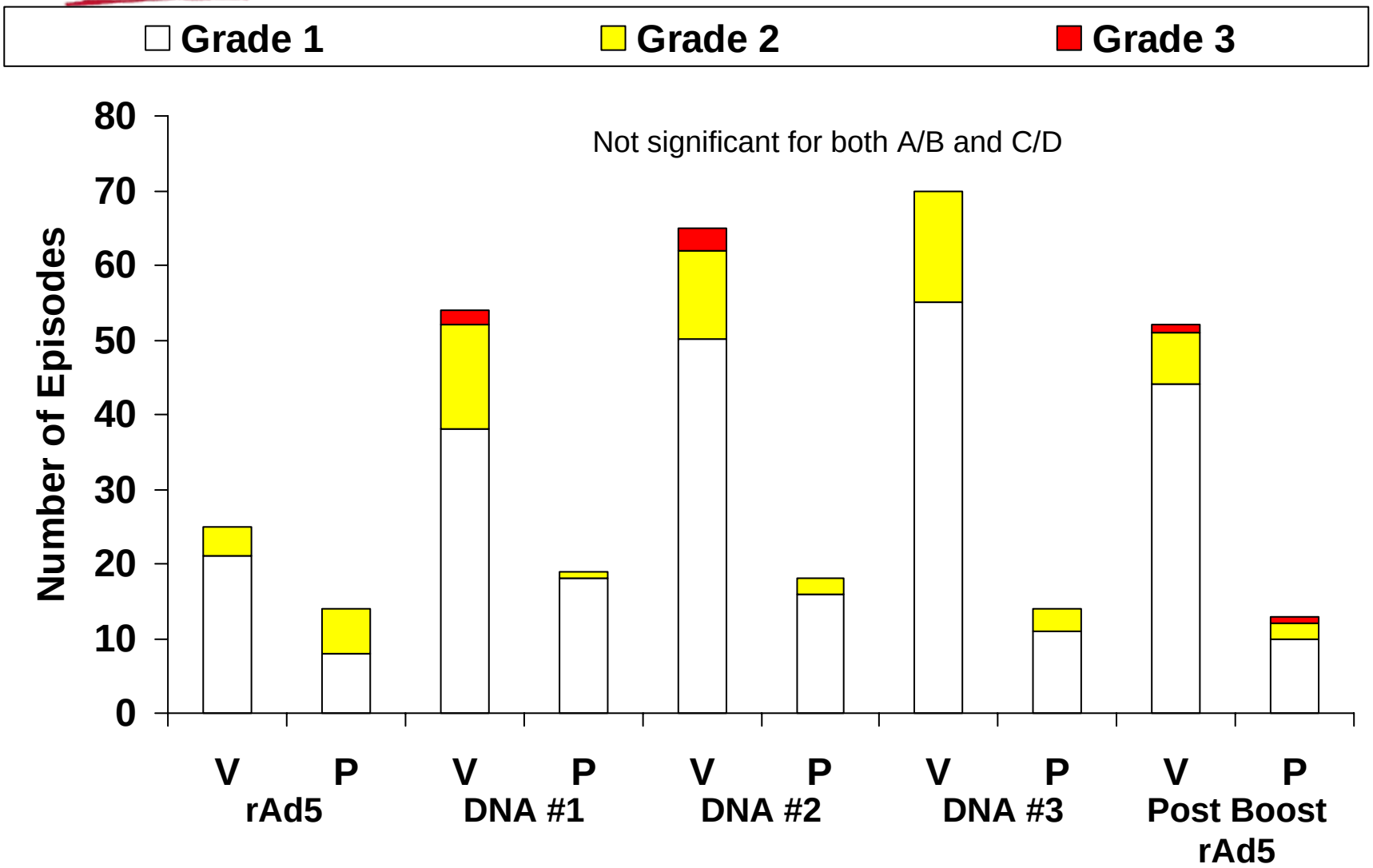
Max Local Reactogenicity(3d)



Max Systemic Symptoms(3d)



Adverse Events (28D) Severity



V001 Safety summary

- 108 volunteers completed the trial
- Study unblinded
- Local reactogenicity: mostly mild and transient
- Systemic reactogenicity: self limited and slightly more severe after rAd5 boost.
- Adverse events: no vaccine-related serious adverse events
- No intercurrent HIV infection

V001 Immunogenicity

Arm (12/4)	W0	W4	W8	W24	W6	W36	W48
A	rAd5 10^{10}						
B	rAd5 10^{11}				W12	W30	W36 W48
C	DNA 4mg	DNA 4mg	DNA 4mg	rAd5 10^{10}			
D	DNA 4mg	DNA 4mg	DNA 4mg	rAd5 10^{11}			

IFN-γ ELISPOT response rates at single post vaccination timepoints

6 weeks post single Ad5		$1x10^{10}$	$1x10^{11}$	Placebo
Ad5	(n)	6/13	7/13	0/9
	%	46%	54%	0%
	95% CI	19-75%	25-81%	0-34%
4 weeks post 3XDNA		$1x10^{10}$	$1x10^{11}$	Placebo
DNA	(n)	11/28	14/27	1/20
	%	39%	52%	5%
	95% CI	22-59%	32-71%	0-25%
6 weeks post Ad5 boost (W30, d210)		$1x10^{10}$	$1x10^{11}$	Placebo
DNA+Ad5	(n)	19/26	18/26	0/18
	%	73%	69%	0%
	95% CI	52-88%	48-86%	0-19%

Frequency of responses 6 wks post Ad5 boost

Antigen	Responses (%: 95% C.I.)	
Env*	33/52	(63%: 50% - 76%)
Env A	30/52	(58%: 44% - 70%)
Env B	27/52	(52%: 34% - 62%)
Gag	21/52	(40%: 45% - 73%)
Pol	12/52	(23%: 30% - 56%)
Nef**	6/52	(12%: 5% - 23%)
Any	37/52	(71%: 58% - 82%)

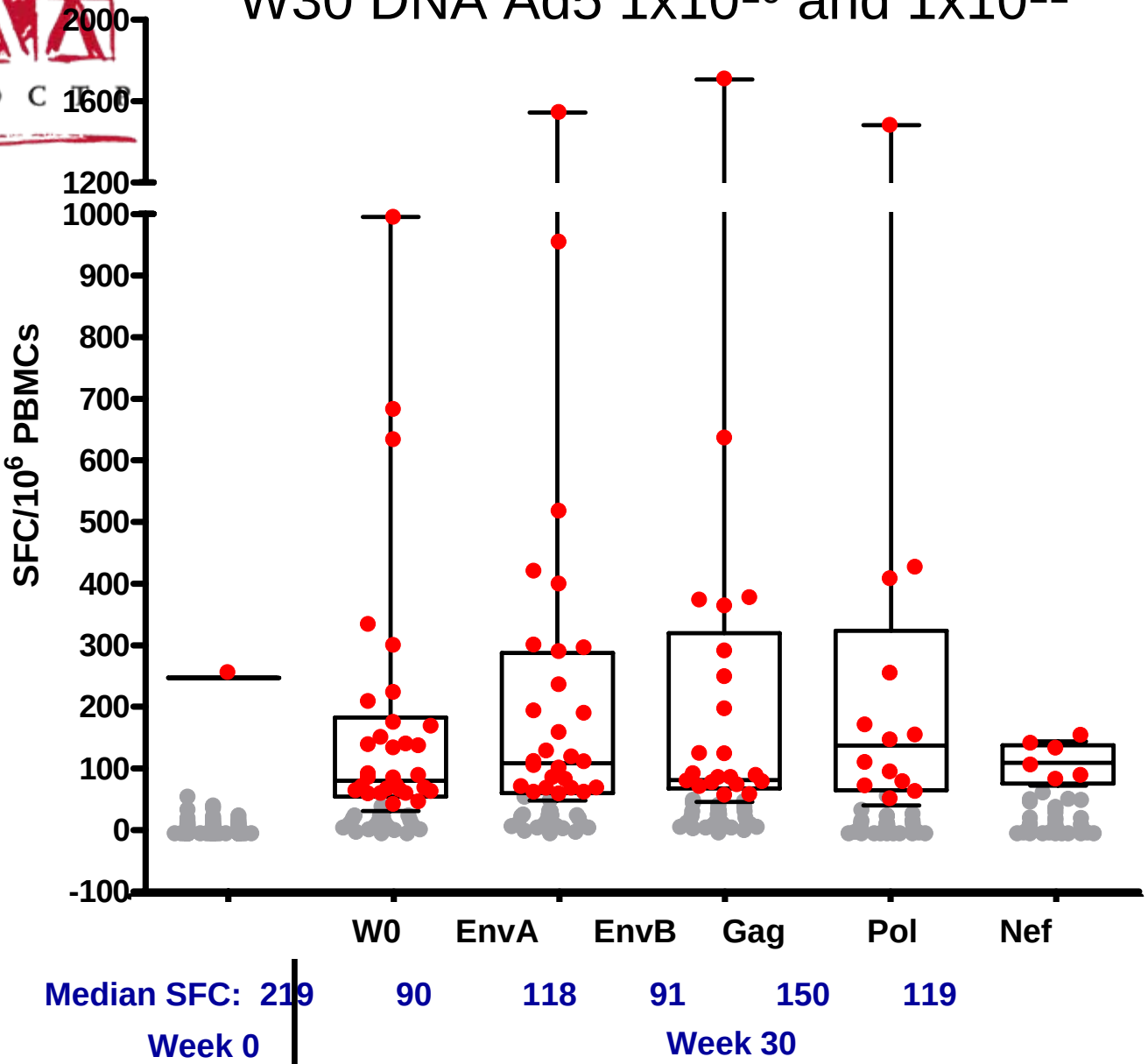
IFN-g ELISPOT responses in DNA primed Ad5 10^{10} and DNA primed Ad5 10^{11} vaccinated individuals 6 weeks after Ad5 boost

* Env response includes number of volunteers positive to either EnvA or EnvB

** Nef not included in boost

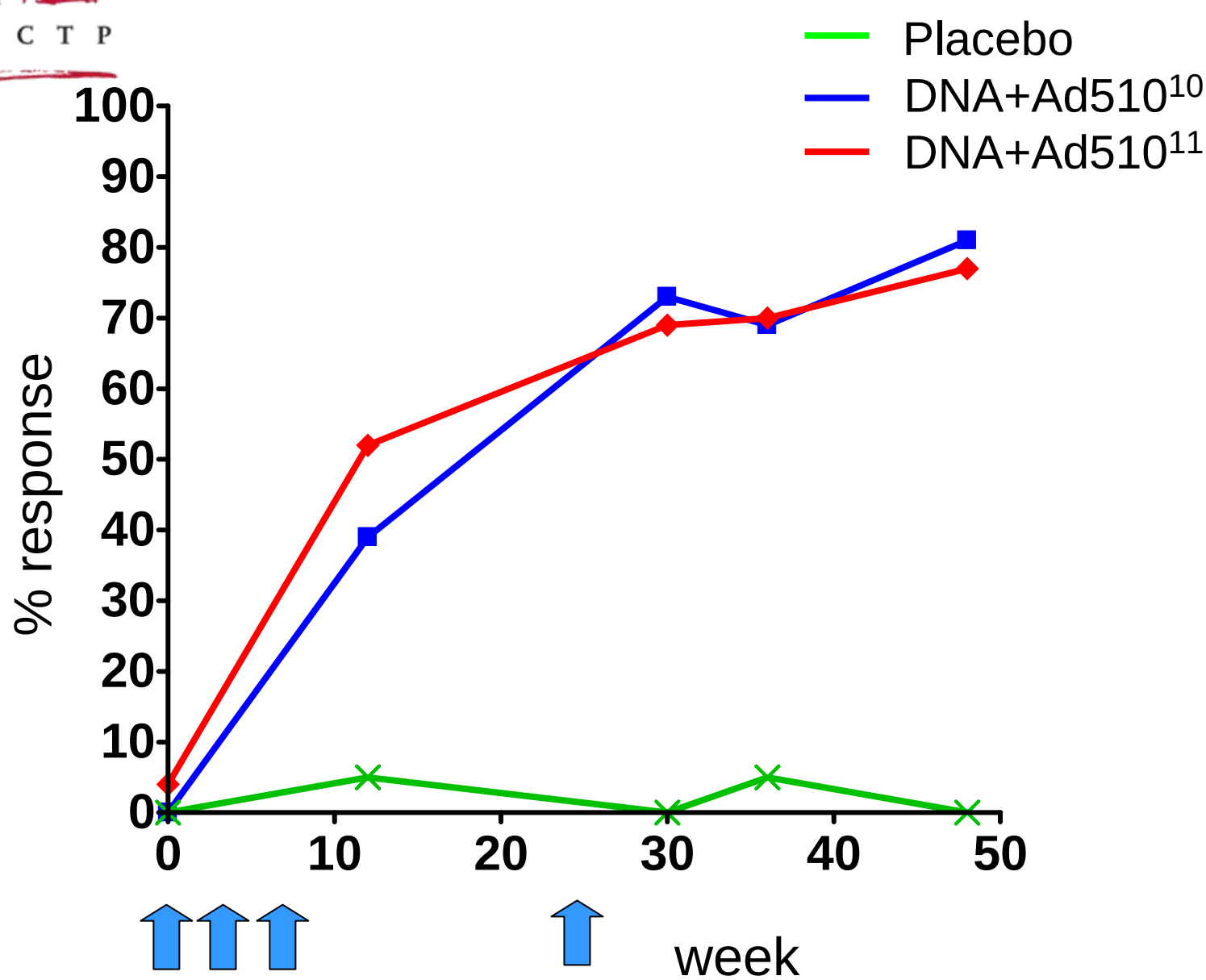
IFN-γ ELISPOT response magnitude

W30 DNA Ad5 $1x10^{10}$ and $1x10^{11}$



Responses in vaccinees, Day 0 peptide pool responses shown in one column, median SFC for positive responses

IFN-γ ELISPOT response duration



V001 Immunogenicity summary

- After either rAd5 alone or three 4mg DNA injections: IFN-gamma ELISpot responses were detected in ~50% of subjects, with median SFC ~80/million PBMCs
- IFN-gamma ELISpot responses detected in >70% of subjects primed with DNA and boosted with rAd5, with median SFC ~ 105/million PBMCs

Discussion & Conclusions

- At baseline, 74% of volunteers had neutralizing antibodies (NAbs) against Ad5
- Impact of NAbs upon immunogenicity was modest
- Data comparable to VRC 004, 006, 007
- Both vaccines safe and well tolerated

Next steps

pending ethics and regulatory review

- V002: Phase II clinical trial to assess safety and immunogenicity of 3 x 4mg DNA injection boosted by rAd5 in 300 volunteers at risk for HIV infection
- PAVE 100:Phase IIb TOC clinical trial to assess efficacy for preventing HIV-1 acquisition and/or reducing viral load (n~8500).

V002 proposed Sites

PSF, Kigali Rwanda

UVRI, Entebbe Uganda

KAVI, Nairobi Kenya

CGCMRC,Mtwapa Kenya

ZEHRP, Lusaka Zambia

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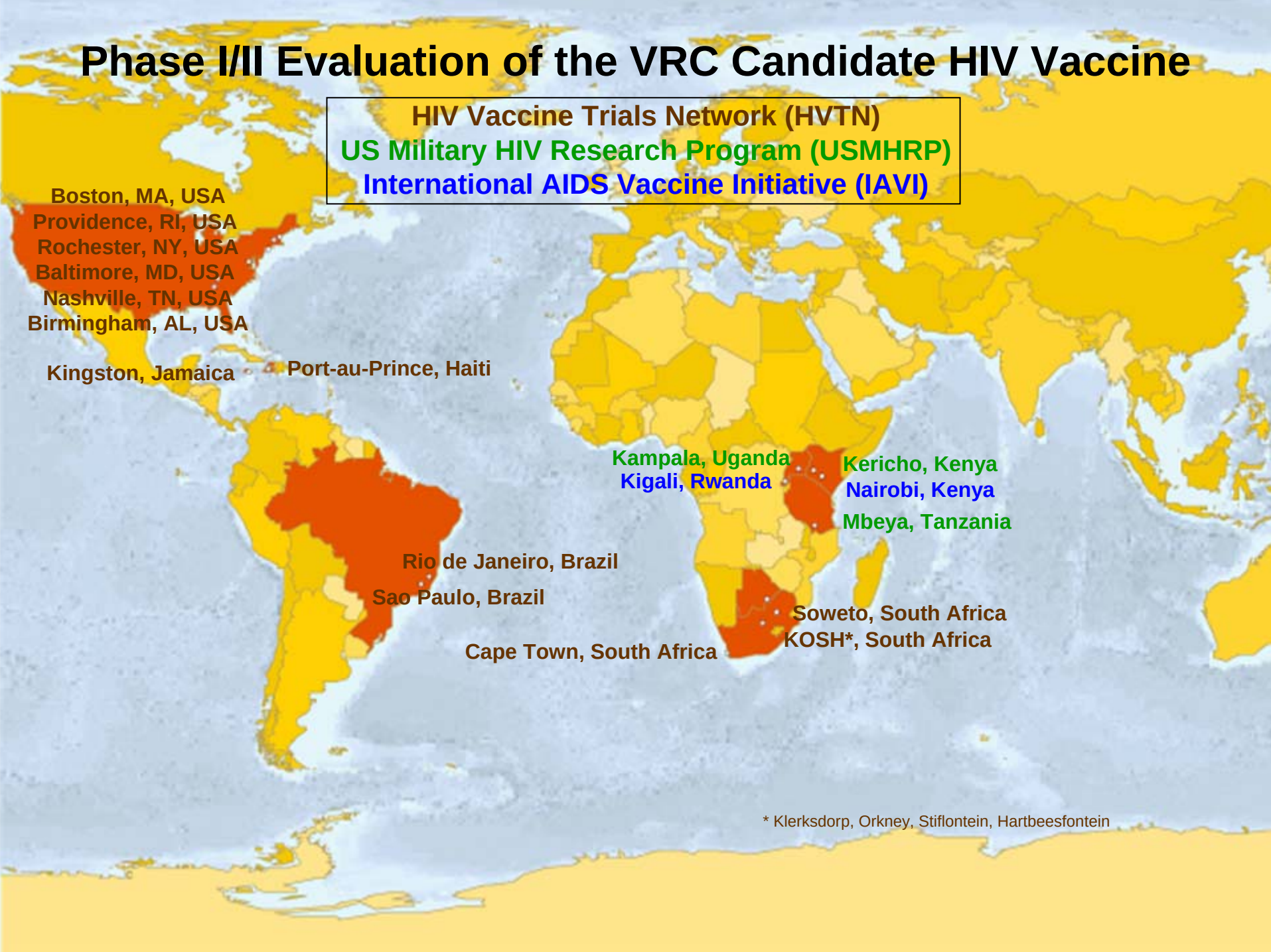
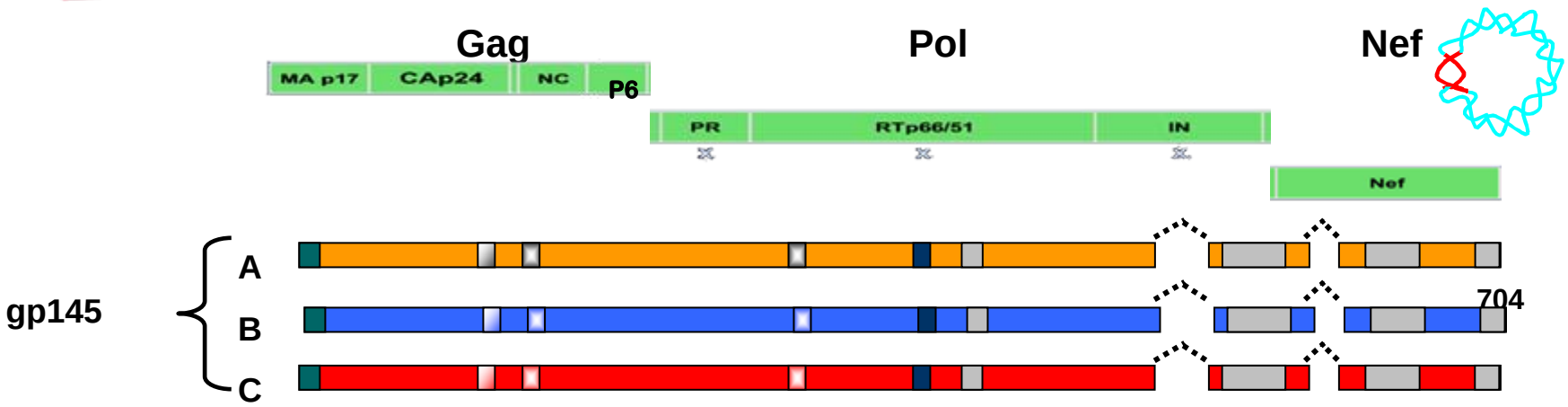
* As of 11/06

Phase I/II Evaluation of the VRC Candidate HIV Vaccine

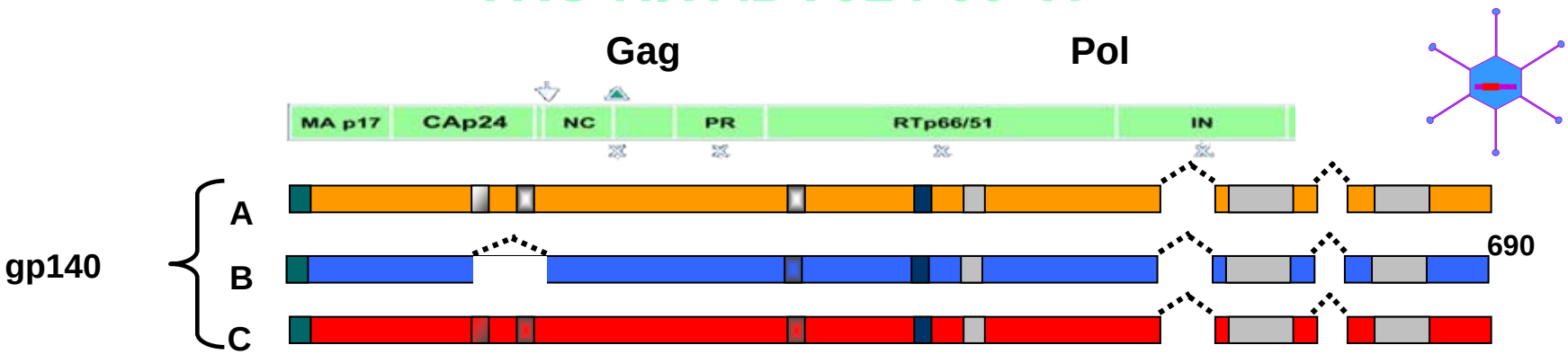


Study Vaccines

VRC-HIVDNA016-00-VP



VRC-HIVADV014-00-VP



V001 Trial Design

Arm	M0	M1	M2	M6
A (13/5)	rAd5 10^{10}			
B (13/4)	rAd5 10^{11}			
C (29/11)	DNA 4mg	DNA 4mg	DNA 4mg	rAd5 10^{10}
D (29/10)	DNA 4mg	DNA 4mg	DNA 4mg	rAd5 10^{11}

Sites: PSF Kigali, Rwanda
KAVI, Nairobi, Kenya

Route of injection: DNA biojector
rAd5 needle/syringe