

# Recent immunologic findings from the Step and related HIV vaccine clinical trials

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# Vaccine-induced immune responses in HIV-infected cases and matched controls



# Vaccine Immunogenicity in the Step Trial

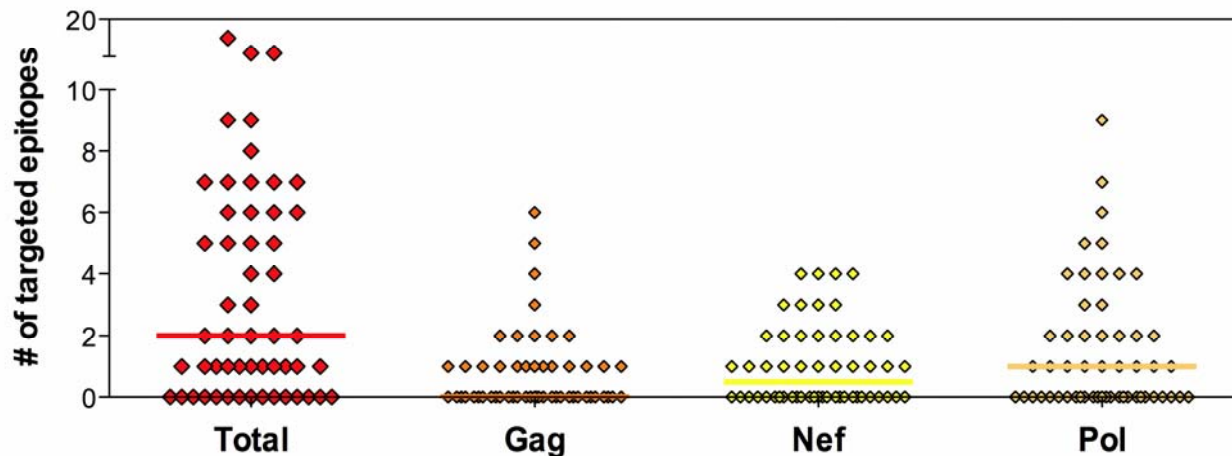
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- The rAd5 vector induces very high HIV-specific IFN- $\gamma$  secreting T-cell responses in humans:
  - 498 of 551 (90.4%) male vaccinees showed an HIV-specific T-cell response in ELISpot
  - Responses were predominantly mediated by CD8 T cells, but CD4 T-cell responses were also induced in 41% of vaccinees
  - Induced responses were polyfunctional,  $\frac{2}{3}$  of both CD4 and CD8 T cells produced more than one cytokine
  - There were no significant differences in immunogenicity between subjects who subsequently acquired HIV infection (cases) and those with matched baseline characteristics who did not become infected (matched controls)



# Step Immunogenicity cont'd

- The median number of targeted epitopes found by mapping responses to single 15mer peptides in Gag, Nef and Pol is **two** [the median number of targeted 15mers in responders (39/54, 72%) is 4]



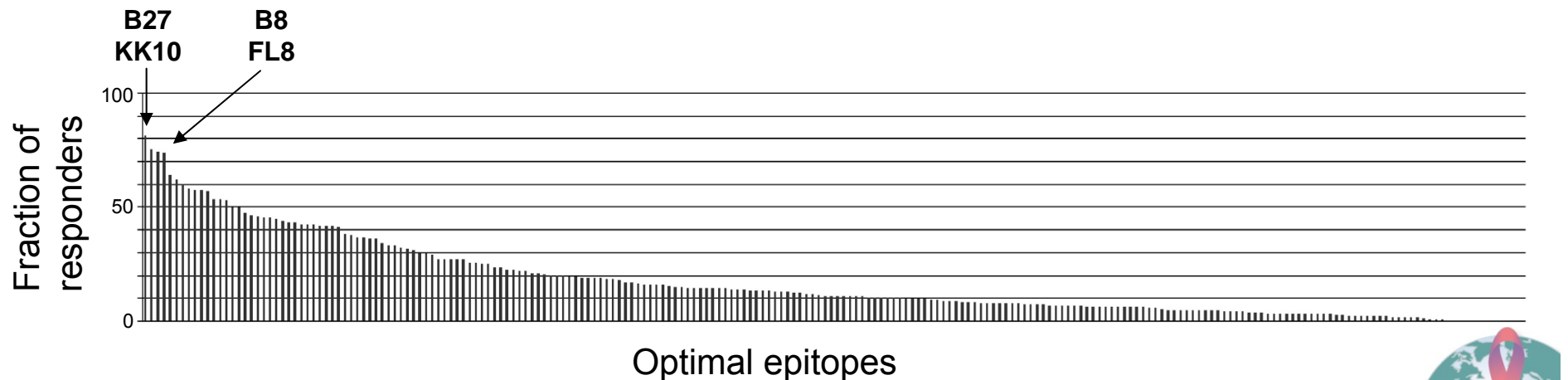
- In contrast, in macaques vaccinated with an Ad5 containing vaccine who are protected from heterologous SIV challenge, the median number of epitopes in Gag, Nef and Pol is 12.5 (Wilson *et al.* J Virol 09)



# Vaccine-induced epitopes correspond to those observed during acute HIV infection

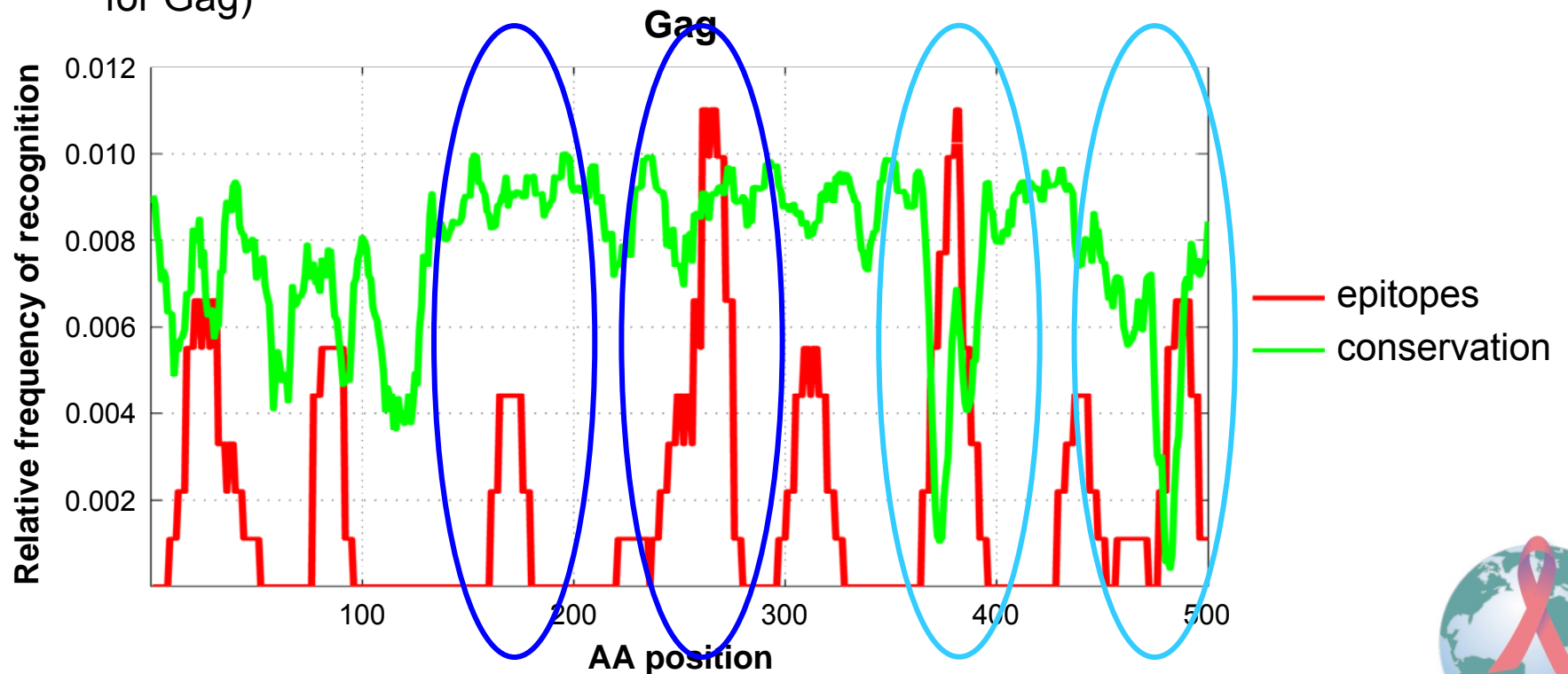
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- Some epitopes identified in responding vaccinees are immunodominant
  - e.g. 4/5 B\*27+ vaccinees mount responses to KK10, 2/3 B\*08+ vaccinees mount responses to FL8
- These match immunodominant epitopes found in acute infection (Streeck *et al.* J Virol 2009)



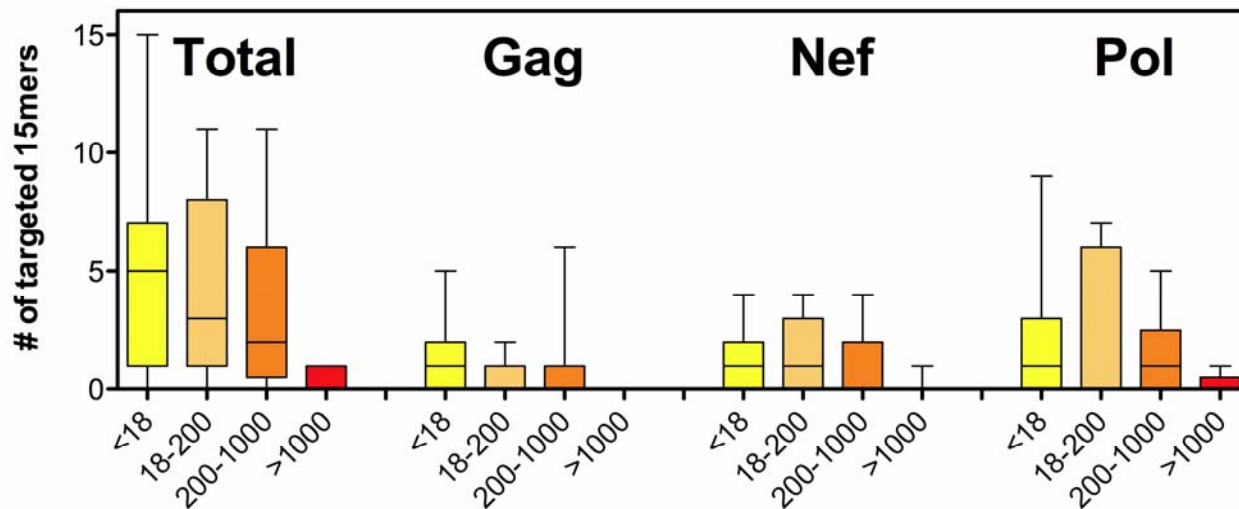
# Epitopes are found in conserved and variable regions

- Most targeted 15mer peptides are recognized by multiple participants
- While some targeted regions are **conserved**, several dominantly targeted regions are relatively **variable**, leading to an overall **inverse** correlation between conservation score and frequency of recognition ( $r = -0.11$ ,  $p = 0.01$  for Gag)



# Influence of Ad5 serostatus on vaccine-induced T-cell responses

- The presence of neutralizing antibodies (nAb) to the vector prior to the first vaccination is associated with a reduction in response rates to peptide pools (McElrath *et al.* Lancet 2008; Priddy *et al.* CID 2008)
- Epitope mapping data shows that this effect is especially pronounced in subjects with Ad5 nAb titers >1000 (p = 0.004 for total responses in <18 vs >1000)



# Vector-specific T-cell responses

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- Ad5-specific T-cell responses were not correlated with Ad5 nAb titers – 54% of placebo recipients with Ad5 nAb titers  $\leq 18$  had Ad5-specific CD4 T cells (22% had Ad5-specific CD8 T cells)
- In Ad5 seronegative participants, administration of the Step vaccine led to significant increases in Ad5-specific CD4 and CD8 T-cell responses
- In Ad5 seropositive participants, Ad5-specific CD8 T-cell responses increase after vaccination, while CD4 T-cell responses are maintained at levels comparable to those in placebo recipients
- Epitopes targeted by Ad5-specific T cells are conserved across multiple adenoviruses within and outside of group C, suggesting broad cross-reactivity with other adenoviruses used as vaccine vectors





# Ad5 hexon-specific T-cell responses are in regions conserved across multiple serotypes

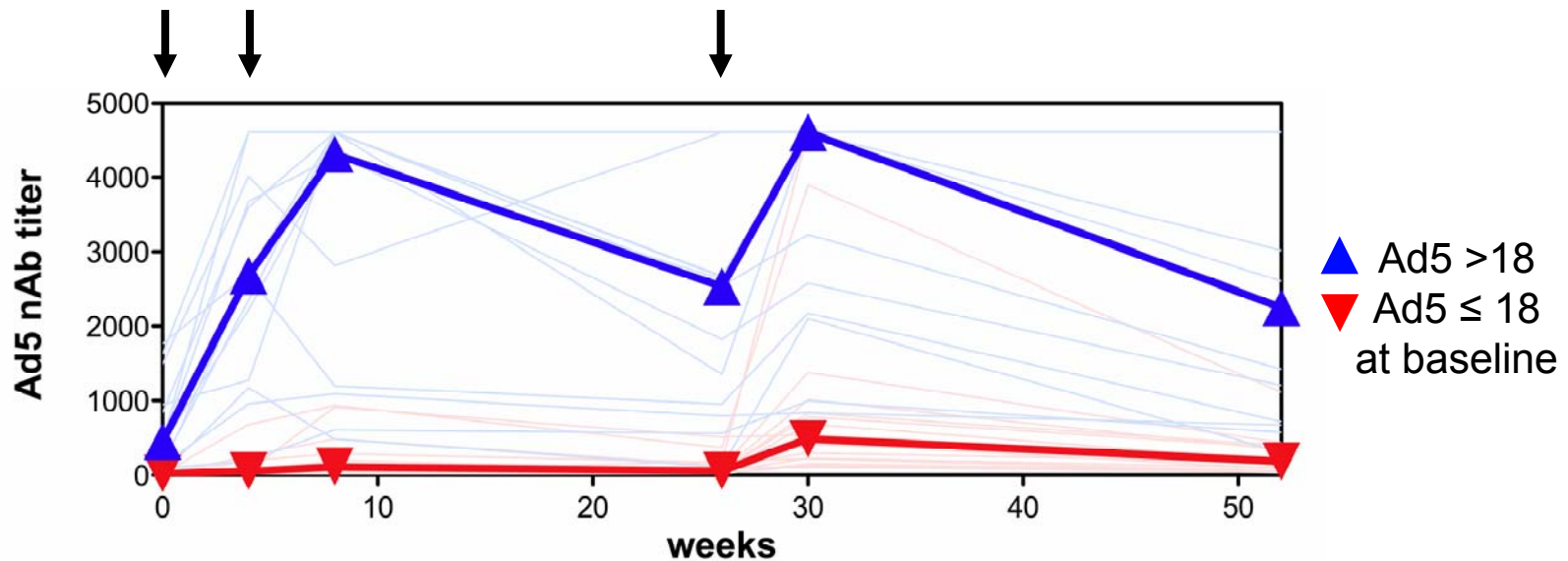
	250	260	270	280	290	300	310	320	
Ad5 Hexon	VLKKTTPMKP	CYGSYAKPTN	ENGGQGILVK	QQNG--KLES	QVEMQFFSTT	E---ATAGNG	--DNLTPKVV	LYSEDVDIET	295
Ad1 Hexon	.....	.....R...	K.....A	NNQ--A...	K.....APS	G---TAMNER	--NAVQ.SI.	.....NM..	307
Ad2 Hexon	.....	.....R...	PF...SV..P	DEK.--VPLP	K.DL....N.	----TSLNDR	QGNATK....	.....NM..	307
Ad6 Hexon	.....	.....R...	S.....VM.E	.N----....	.....S	T---NATNEV	--N.IQ.T..	.....NM..	303
Ad26 Hexon	A...D.K...	....F.R...	.K...AKFKP	VNE.EQPKDL	DIDFAY.DVP	GGSPAG.S.	--EEYKADII	.T.N.NL..	292
Ad35 Hexon	A..P..N...	.....	LK...AKPKN	SEPSSE.I.Y	DID.E..DNS	S-----QR	--T.FS..I.	M.A.N.GL..	296
	330	340	350	360	370	380	390	400	
Ad5 Hexon	PDTHISYMP	IKEGNSRELM	GQQSMPNRP	YIAFRDNFIG	LMYYNSTGNM	GVLAGQASQL	NAVVDLQDRN	TELSYQLLLD	375
Ad1 Hexon	.....K.S	KTDE..KAML	...A.....	.....	.....	.....	.....	.....	387
Ad2 Hexon	....L..K.G	KGDE..KAML	.....	.....	.....	.....	.....	.....	387
Ad6 Hexon	....L..K.K	MGDK.AKVML	...A.....	.....	.....	.....	.....	.....	383
Ad26 Hexon	....VV.K.G	TSDNS.EINL	V.....	..G...V.	.....	.....	.....	.....	372
Ad35 Hexon	....VV.K.G	TEDTS.EANL	.....	..G.....	.....	.....	.....	.....	376
	410	420	430	440	450	460	470	480	
Ad5 Hexon	SIGDRTRYFS	MWNQAVDSYD	PDVRIIENHG	TEDELPNYCF	PLGGVINTET	LTKVKP--KT	GQENG---W	EKDATEFSDK	449
Ad1 Hexon	.....	.....	.....	.....	...IGV.D.	YQGI.S-NGN	.NPQN----	T.ND-D.AAR	461
Ad2 Hexon	.....	.....	.....	.....	...IGV.D.	YQAI.A-NGN	.SGDNGDTT.	T..E-T.ATR	465
Ad6 Hexon	.....	.....	.....	.....	...IGI.D.	FQA..TTAAN	.DQGN--TT.	Q..S-T.AER	460
Ad26 Hexon	.L.....	..S.....	.....	V.....	..N.TGTNS.	YQG..ITNGN	DGAEE--SE.	..D-AI.RQ	449
Ad35 Hexon	.L.....	.....	...V.....	V.....	..D.IGVPT.	SY.SIVPNGE	D---N--NN.	K-EP-.VNGT	449
	490	500	510	520	530	540	550	560	
Ad5 Hexon	NEIRVGNNFA	MEINLNANLW	RNFLYSNIAL	YLPDKLKYSP	SNVKISDNPN	TYDYMNKRVV	APGLVDCYIN	LGARWSLDYM	529
Ad1 Hexon	...G.....	L.....	.....	.....	..T..E..P...	S.....	.....	.....	541
Ad2 Hexon	...G.....	.....	.....	.....	..N..T..E.....	.....	.....	.....	545
Ad6 Hexon	...G.....	.....	.....	.....	..N..T..E.....	.....	.....	.....E..	540
Ad26 Hexon	.Q.CK..VY.	....Q....	KS....V..	...SY..T.	A...LPA.T.	.E...G...	..S...A..H	I.....P.	529
Ad35 Hexon	S..GQ..L.	....Q....	.S....V..	...SY..T.	...TLPE.K.	.....G...	P.S...T.V.	I.....A.	529

vaccinees  
 unvaccinated controls  
 both vaccinees and unvaccinated controls



# Vector-specific antibody responses

Vaccination with an Ad5 vector induces nAb responses in all tested subjects



- Nonetheless, no increase in the number of HIV infections in vaccinees who were seronegative at baseline was observed
- Ad5 nAb titers are not increased prior to HIV infection in cases compared to controls (see Spies *et al.* poster P19-48, 10/21)



# Human genetic variation influences vaccine-induced T-cell responses

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- The influence of human genetic variation on the induction of T-cell responses by vaccination has been assessed in all male vaccinees.
- The locus most prominently associated with the magnitude of vaccine-induced responses (although not genome-wide significant) is the locus encompassing the HLA-B and HLA-C genes (see Fellay *et al.* poster LB-173424 on 10/20)

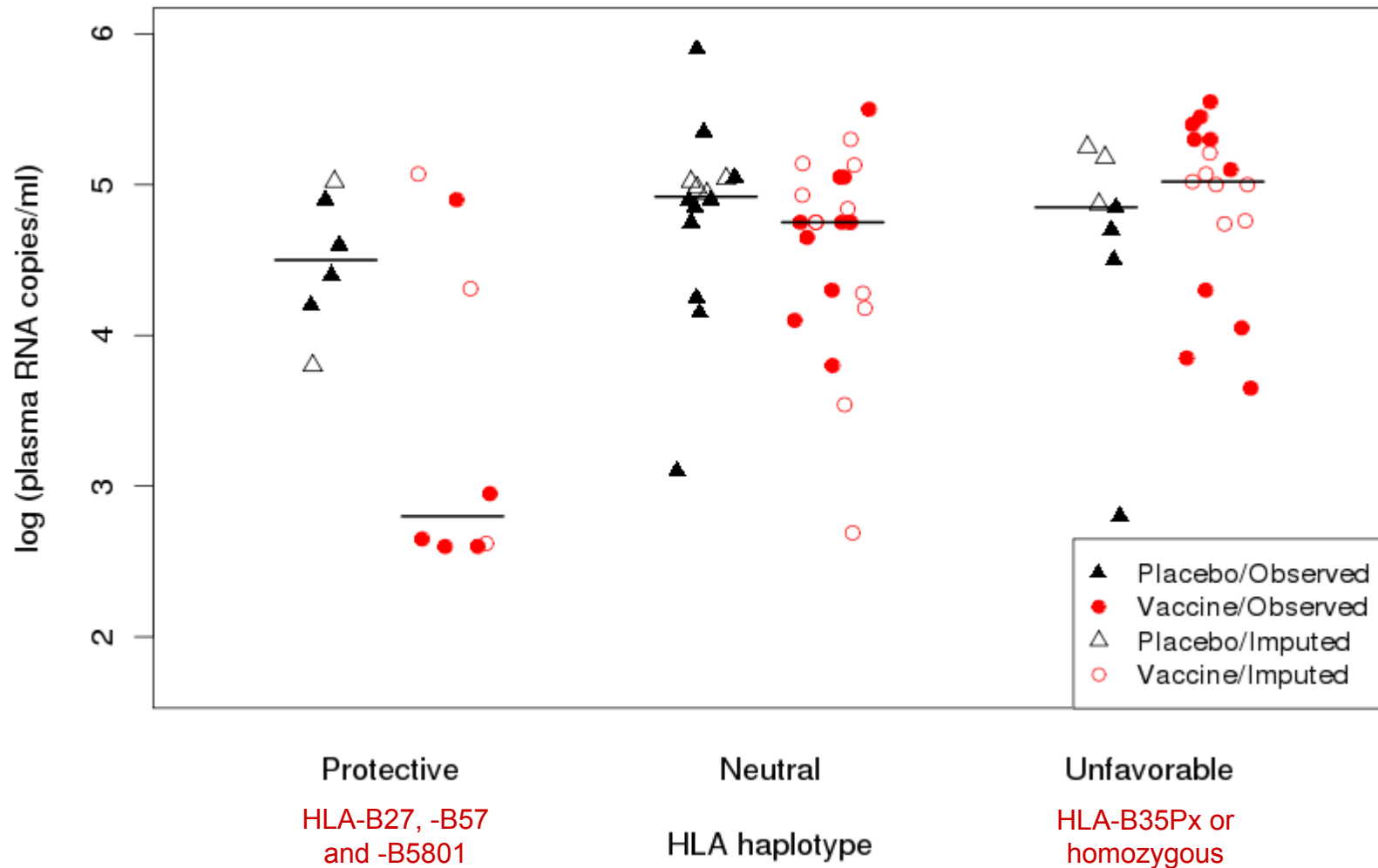


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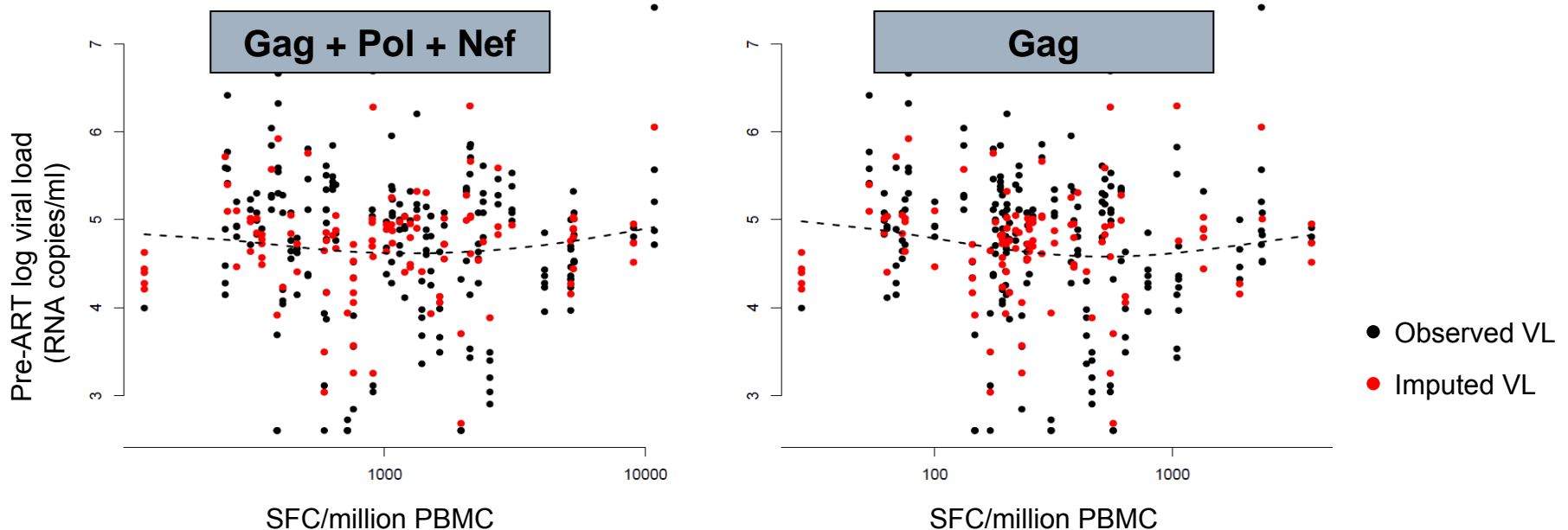
HIV-infected cases: pre- and post-  
infection immune responses and other  
factors influencing viral load



# Protective HLA alleles are associated with lower setpoint viral load, especially in vaccine recipients



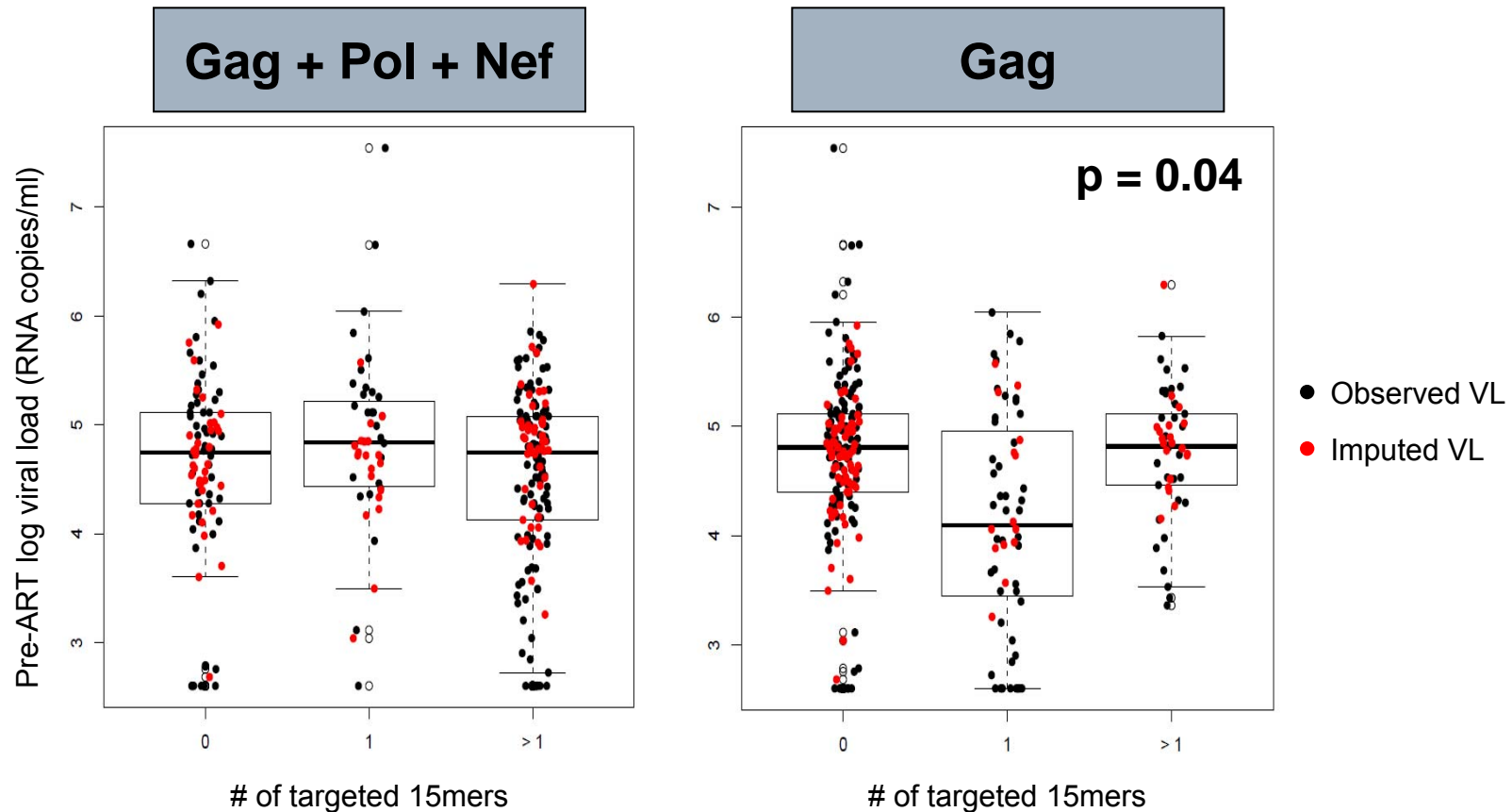
# No correlation of the magnitude of vaccine-induced responses (pre-infection) and viral load



- The magnitude of vaccine-induced T-cell responses to peptide pools was assessed by ELISpot in 52 vaccinees at week 8
- Although the magnitude of Gag-specific T-cell responses has been associated with reduction of viral load in non-vaccinated subjects (Edwards *et al.* J Virol 02), this effect is not apparent in Step trial vaccinees



# Gag-specific T-cell responses are associated with lower viral load

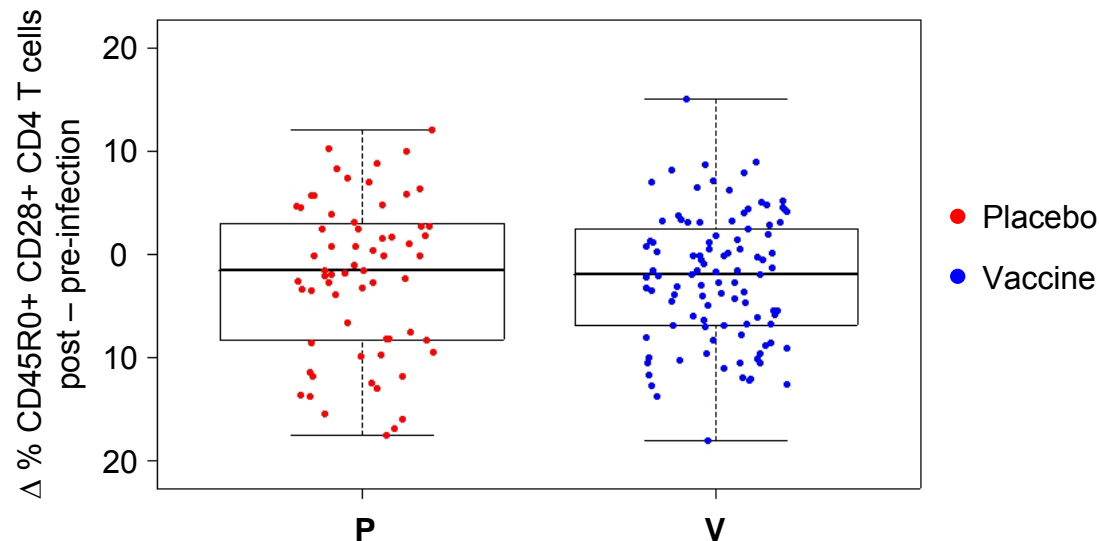


- Elispot breadth to single 15mer peptides was assessed in 48 vaccinees at week 8



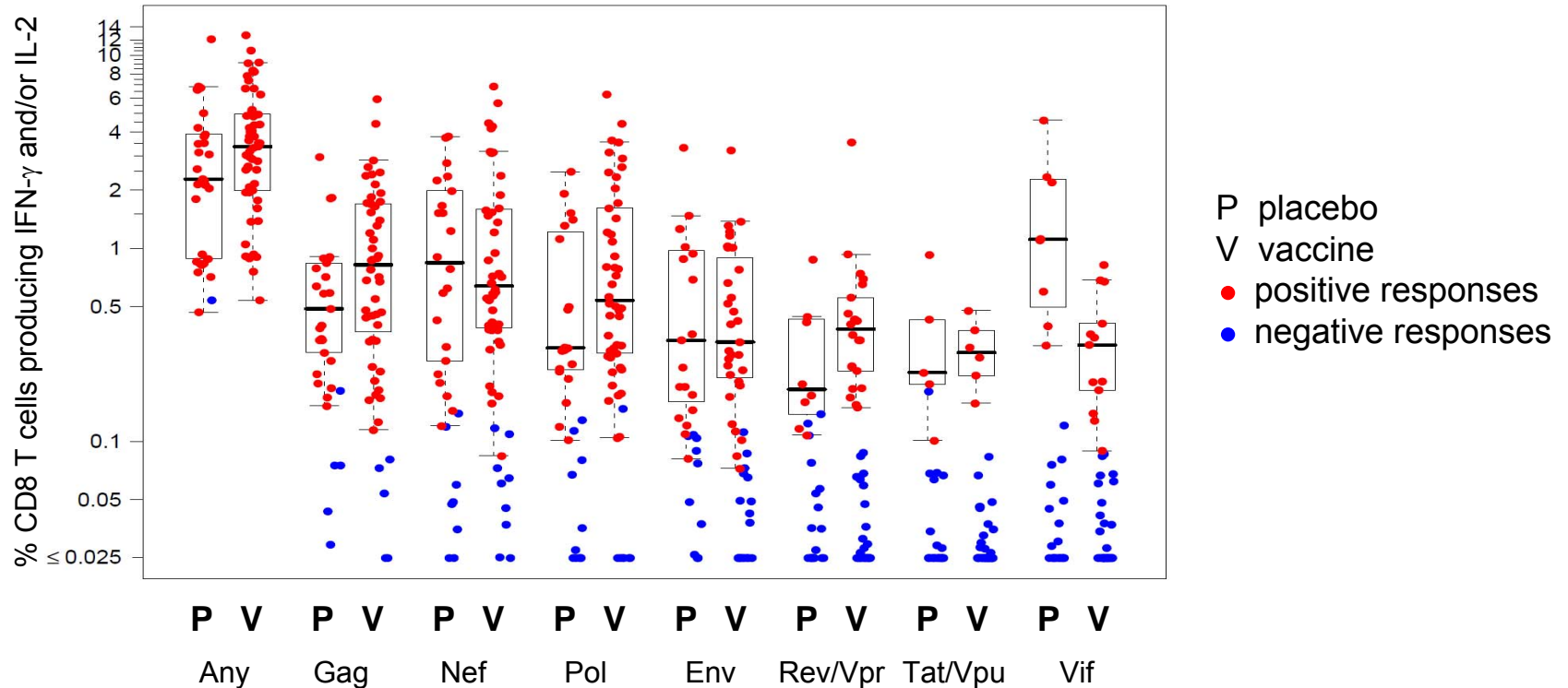
# Vaccination does not impact the relative abundance of Central Memory CD4 T cells early after HIV infection

- Vaccination using an rAd5 containing regimen followed by pathogenic SIV infection showed an increased preservation of Central Memory (CM) CD4 T cells that was associated with increased survival (although not prolonged reduction of viral load) in rhesus macaques (Letvin *et al.* Science 2006)
- However, comparison of the percentage of pre- and post-infection CM (CD45R0+ CD28+) CD4 T cells in 83 Step cases 1-2 weeks after diagnosis of HIV infection showed no significant difference between vaccine and placebo recipients





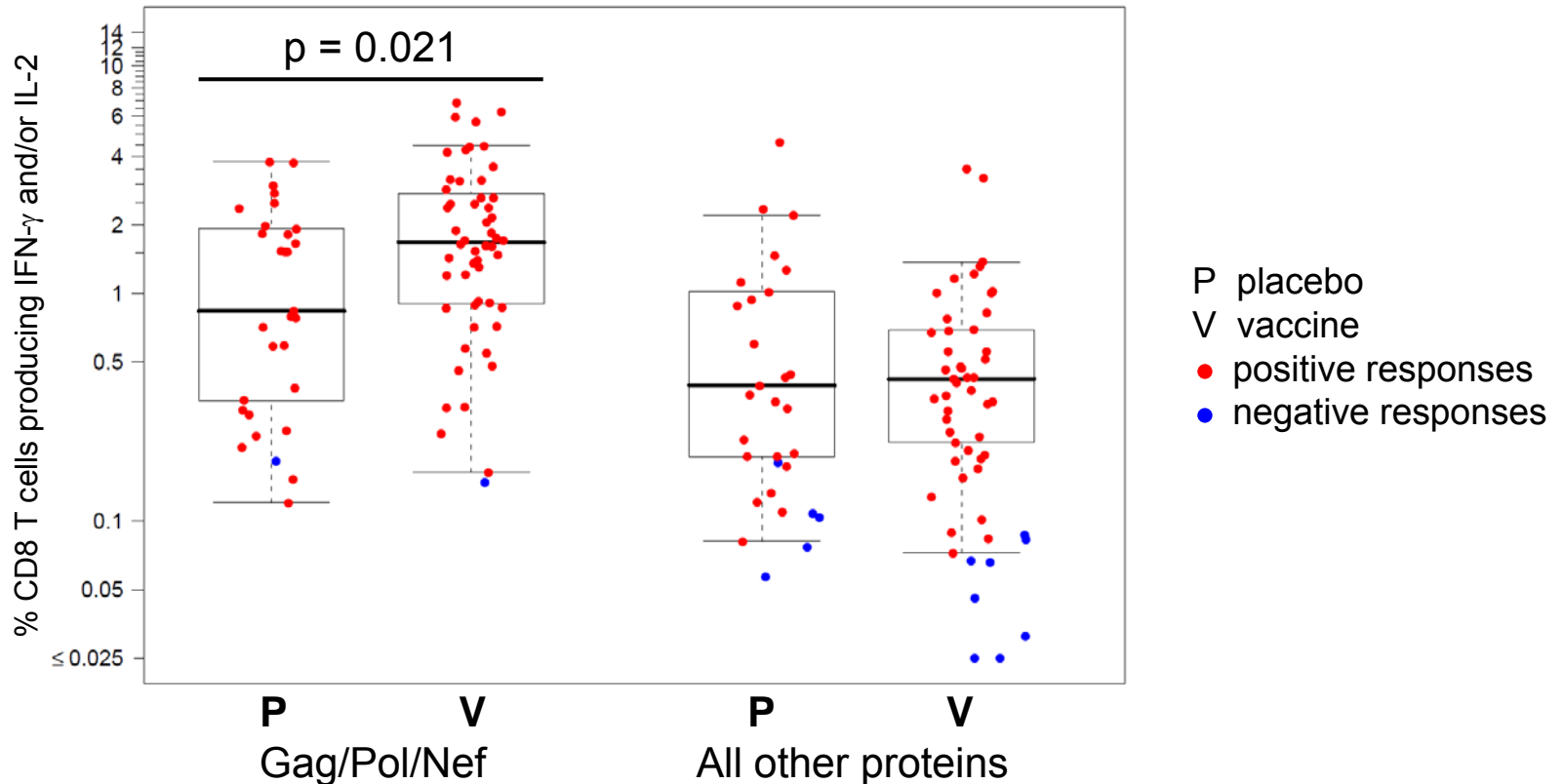
# HIV infection induces CD8 responses to all HIV proteins in Step trial cases



- CD8 T-cell responses were measured by ICS in 87 participants (33 placebo and 54 vaccine recipients)
- Samples were obtained 1 week (8 participants) and 2 weeks (79 participants) post HIV diagnosis



# Post-infection CD8 T-cell responses to proteins contained in the vaccine are stronger in vaccinees



- CD8 T-cell responses were measured by ICS in 87 participants (33 placebo and 54 vaccine recipients)
- Samples were obtained 1 week (8 participants) and 2 weeks (79 participants) post HIV diagnosis



# Summary

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- The MRKAd5 HIV-1 gag/pol/nef vaccine was highly immunogenic and induced similar humoral and cellular immune responses in cases and controls
- While the cellular immune responses seem to be functionally competent, the breadth of responses as well as the epitopes targeted by the induced T cells may have been suboptimal
- While there is no indication that vector-specific T-cell responses are responsible for increased risk of HIV acquisition, the extensive cross-reactivity of Ad5-specific T cells may have implications for other Ad-based vectors



# Summary cont'd

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- Vaccination did not lead to the preservation of Central Memory CD4 T cells upon HIV infection, although anamnestic T-cell responses in vaccinees led to a significantly higher magnitude of post-infection responses to the proteins contained in the vaccine
  
- While no immune correlate for HIV acquisition has been defined for Step to date, correlations with setpoint viral load can be exploited to inform next generation vaccines
  - HLA associations
  - Targeting of specific regions in Gag



# Conclusions

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- Know thy vector
- Epitopes recognized: is more always better, or is it the right ones that matter?
- Effector cells: “Union gives strength”

*Aesop, The Bundle of Sticks*



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