We should still test T-cell based vaccines

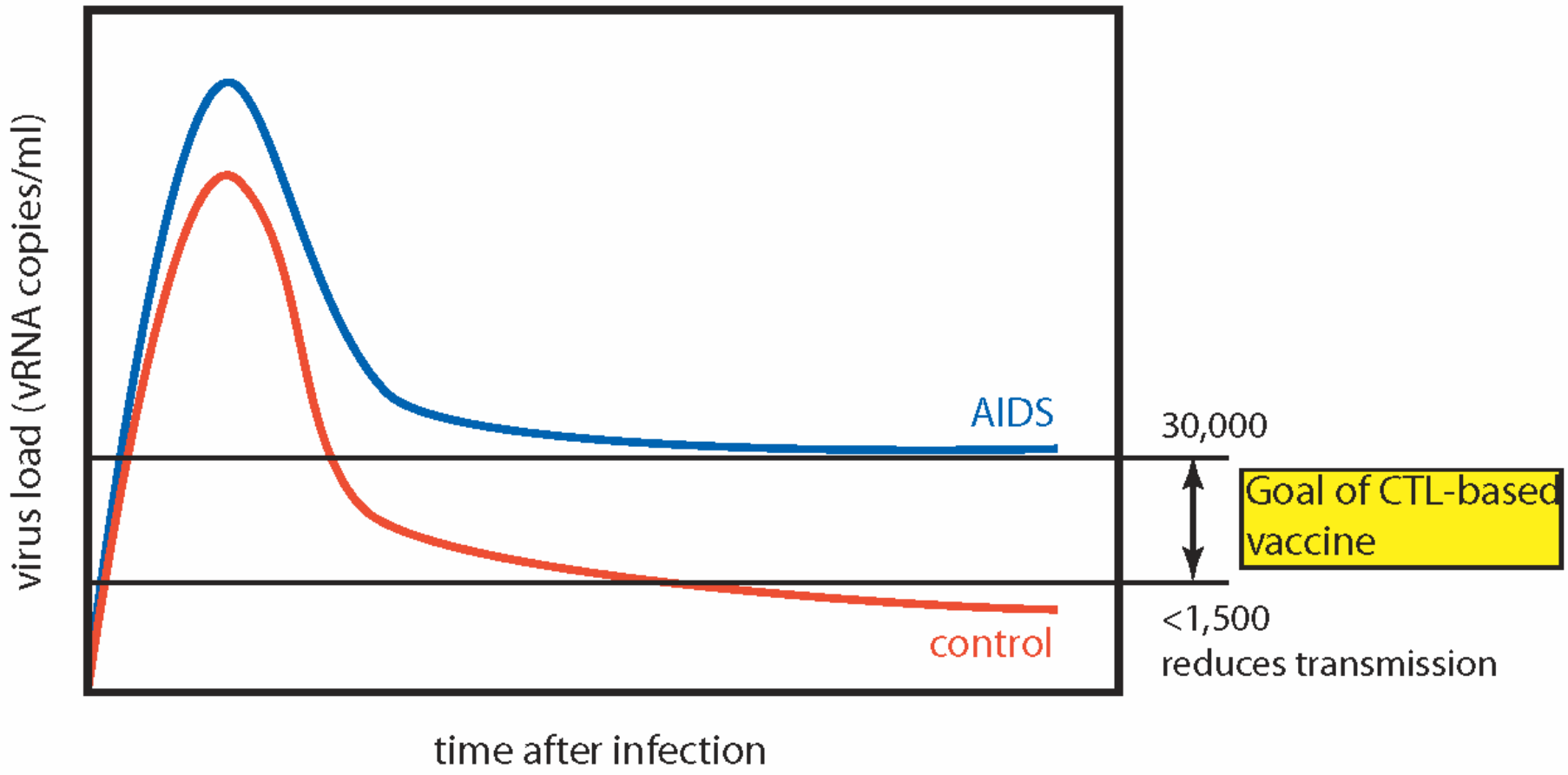
David I. Watkins

“The T cell concept is hanging by a thread.”

-Quote from an eminent HIV vaccine researcher at the AVRS meeting on 12/12/07

“Damocles was a courtier in the court of king Dionysius. He exclaimed that, as a great man of power and authority, Dionysius was truly fortunate. Dionysius offered to switch places with him for a day, so he could taste first hand that fortune. In the evening a banquet was held, where Damocles very much enjoyed being waited upon like a king. Only at the end of the meal did he look up and notice a sharpened sword hanging by a single piece of horsehair directly above his head. *Immediately, he lost all taste for the fine foods and other earthly pleasures and asked leave of the tyrant, saying he no longer wanted to be so fortunate.”*

The goal of a T-cell-based vaccine is to prevent transmission in the chronic phase.

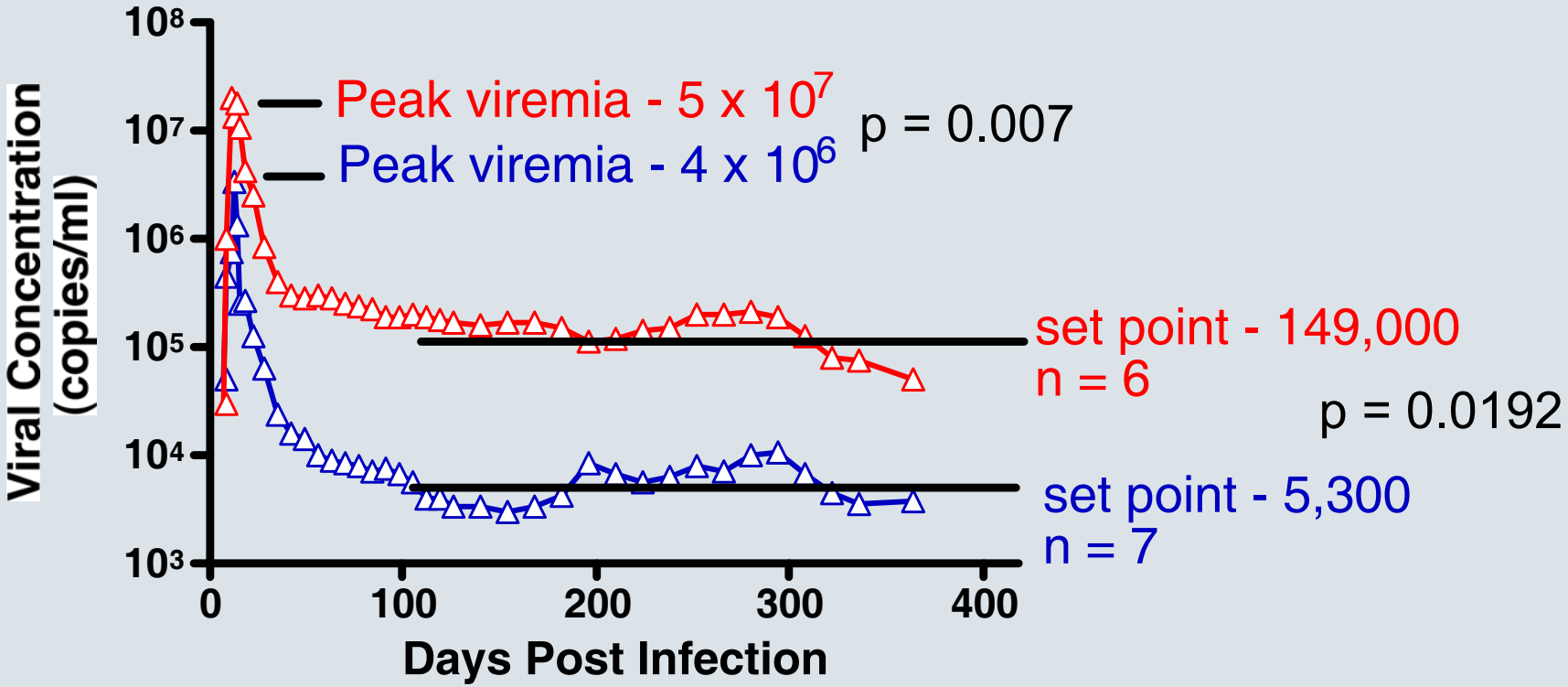


Monkey Testing of Vaccines : Homologous vs Heterologous Challenge

Almost all NHP SIV challenges use homologous viruses - never going to happen with HIV.

Homologous Challenge

DNA/Ad5 Gag/Tat/Nef/Rev, Challenge SIVmac239; Peak of 4 million and Set Point of 5,000



Wilson *et al., J.Virol*. 2006; 80 (12): 5875-85

Conclusions

- Vaccine-induced T-cell responses can control replication of SIV without neutralizing antibodies

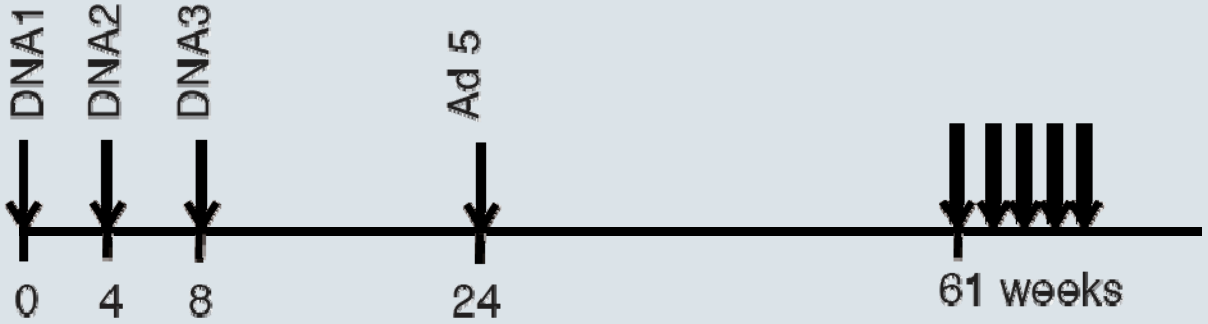
Caveats

- How much damage was inflicted by 10^6 copies/ml during acute phase?
- Vaccine and challenge virus exactly matched (homologous challenge).

DNA/Ad5 Encoding All SIV Proteins (except for Env) Induces High Frequency and Broad T-cell Responses

See Wilson et al, late breaker

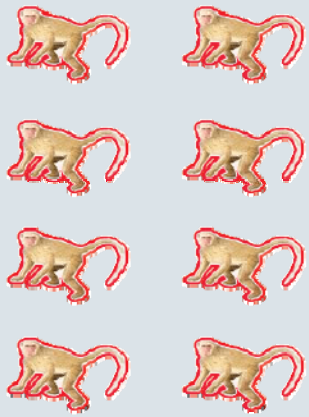
Vaccination scheme

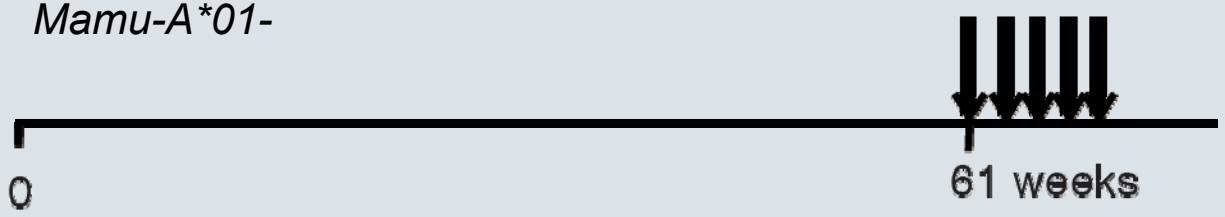


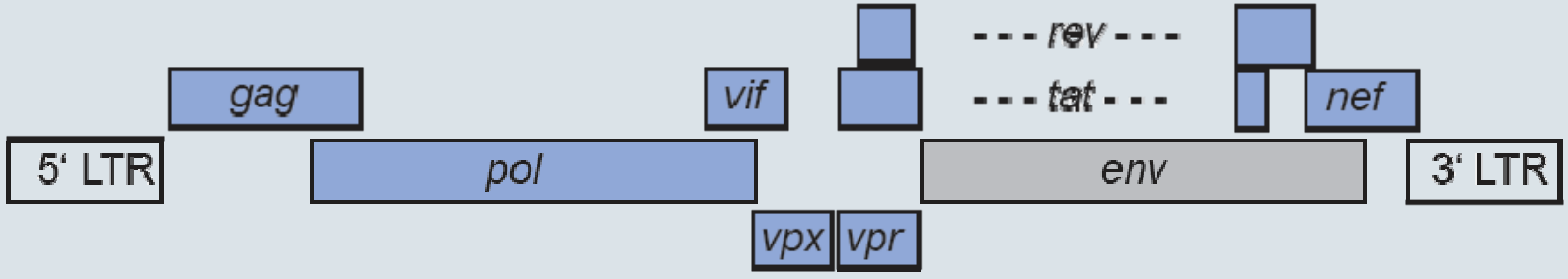
*Mamu-A*02+*

*Mamu-B*08-*
*Mamu-B*17-*
*Mamu-A*01-*

Challenge at 61 weeks







SIVmac239 sequences

Vaccinees Recognized 11 – 34 Epitopes (12,000 SFCs/million PBMC)

	Gag	Nef	Tat	Rev	Vpr	Vpx	Vif	Env	Pol	Total
r00061	7			2			2	1	1	13
r01099	9	2		2	2		3	1	3	22
r02089	13	1		4	1		5	1	9	34
r02103	9	2			2	1	4	1	2	21
r02114	11	2	1	2	1		4	2		23
r95116	5			3	1		2	1	1	13
r97112	8	2		3	1		5	1	4	24
r99063	4	2		1			1	1	2	11
Average	8	1	0	2	1	0	3	1	3	**20**

Challenge Choices

- SIVmac239- homologous, see Wilson *et al. J.Virol*. 80:5875, 2006
- SIVmac251- homologous, see Barouch *et al.*, Keystone 2008
- SHIV89.6- homologous except for Env- probably not the most stringent or realistic challenge for a T-cell-based vaccine
- SIVsmE660, heterologous swarm virus

SIVsmE660 Challenge

- Unlike cloned SIVmac239, different stocks of the uncloned, swarm viruses (SIVmac251, SIVsmE660) can have variable replicative and pathogenic potential.
- Depending on the stock of these viruses, control, naïve animals can have varying outcomes: some controlling viral replication without vaccination.

SIVsmE660 Challenge

- We made a stock of SIVsmE660 and used this to challenge 10 control, naïve animals and 10 animals vaccinated with our best vaccine-SIVmac239ΔNef.
- Would we see the characteristic variability of SIVsmE660 in our 10 control, naive animals?
- Would this stock of SIVsmE660 be easy to protect against? (Remember-SIVmac239ΔNef completely protects against replication of the highly pathogenic SIVmac239 and SIVmac251 during the ACUTE and chronic phases.)

SIVmac239Δnef our Best Vaccine Study
Outline: Heterologous Challenge

Vaccine

A*01
A*02
A*11
B*08
B*17

6 months

SIVmac239Δnef

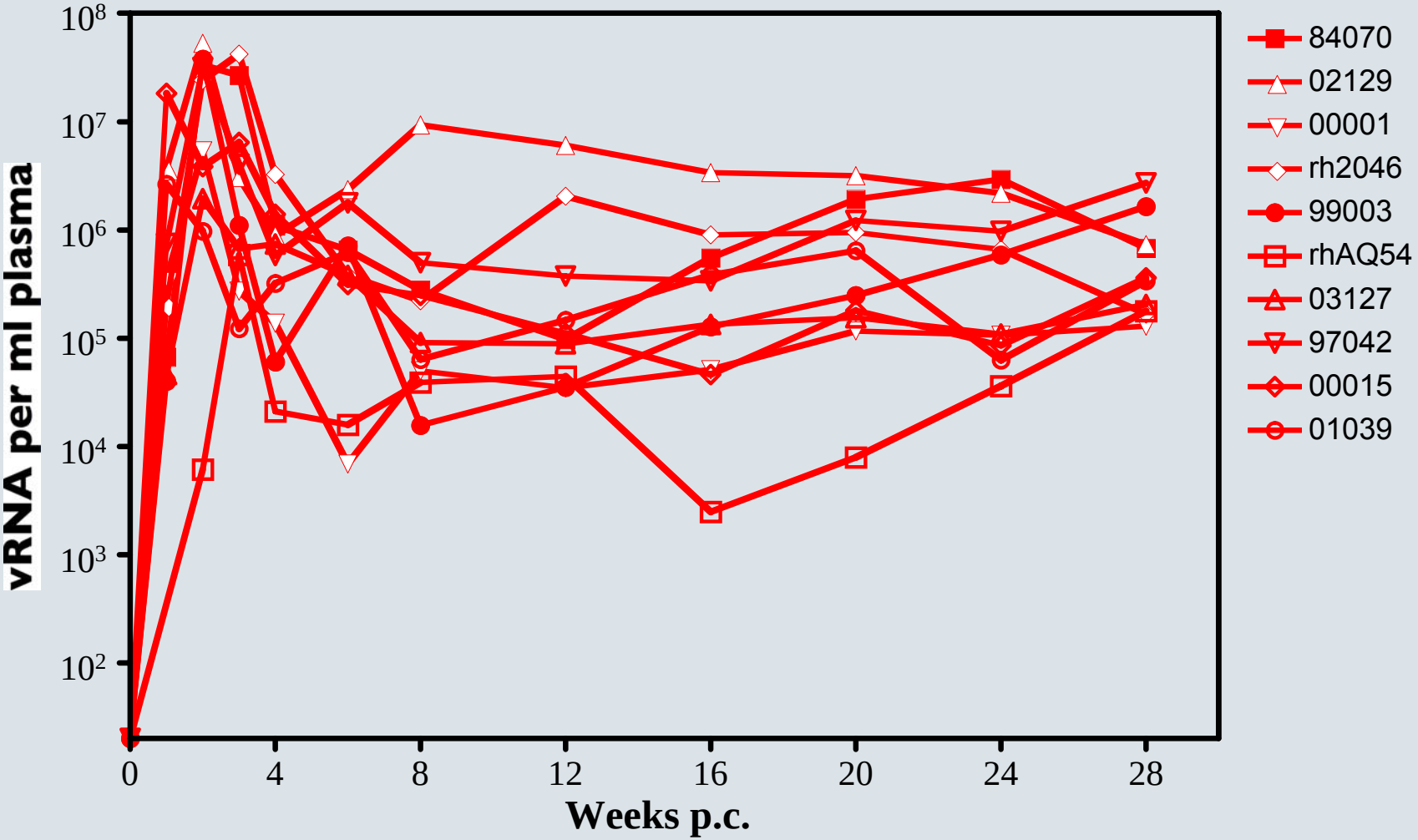
SIVsmE660 (i.v.)

Naïve

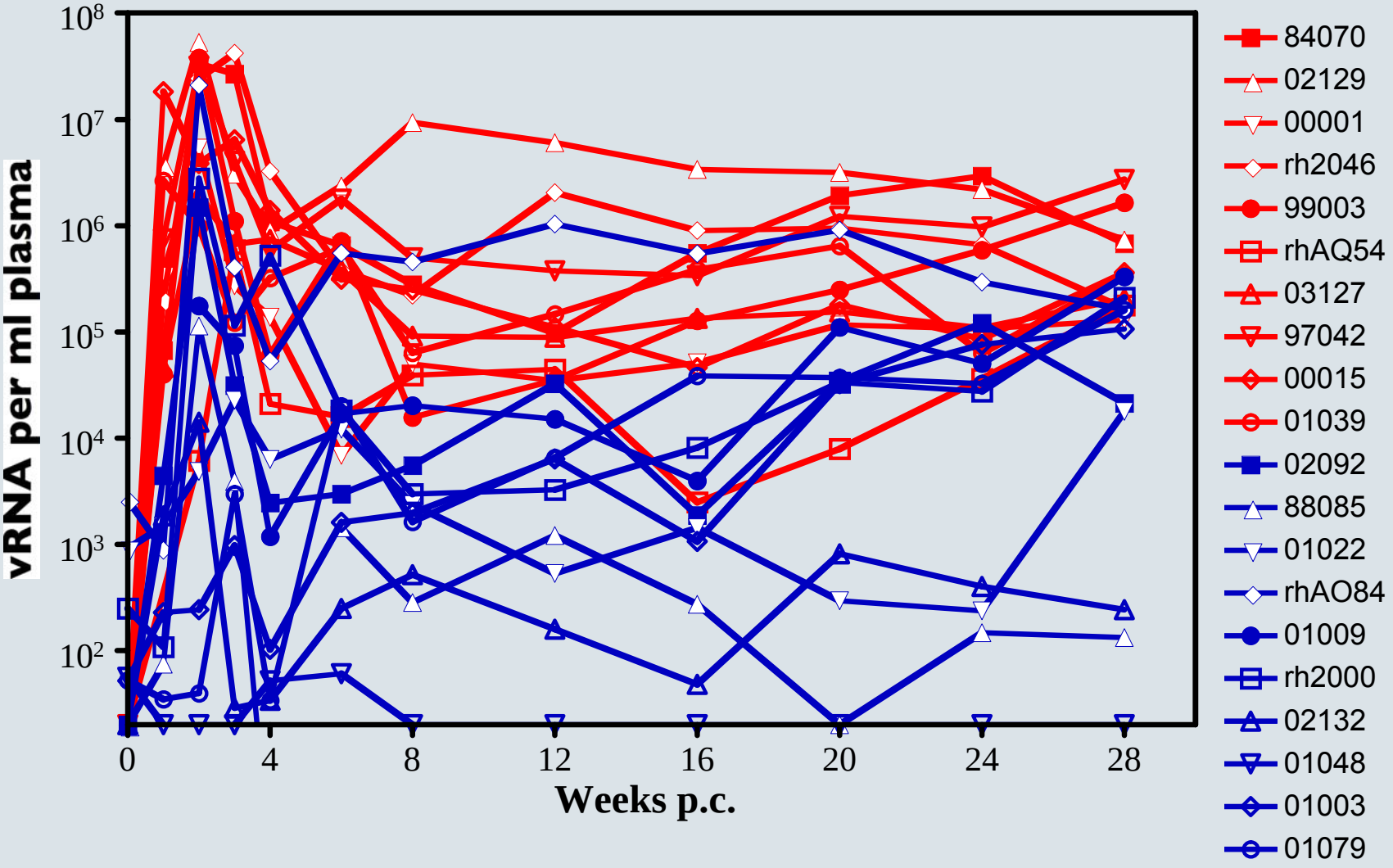
A*01
A*02
A*11
B*08
B*17

SIVsmE660 (i.v.)

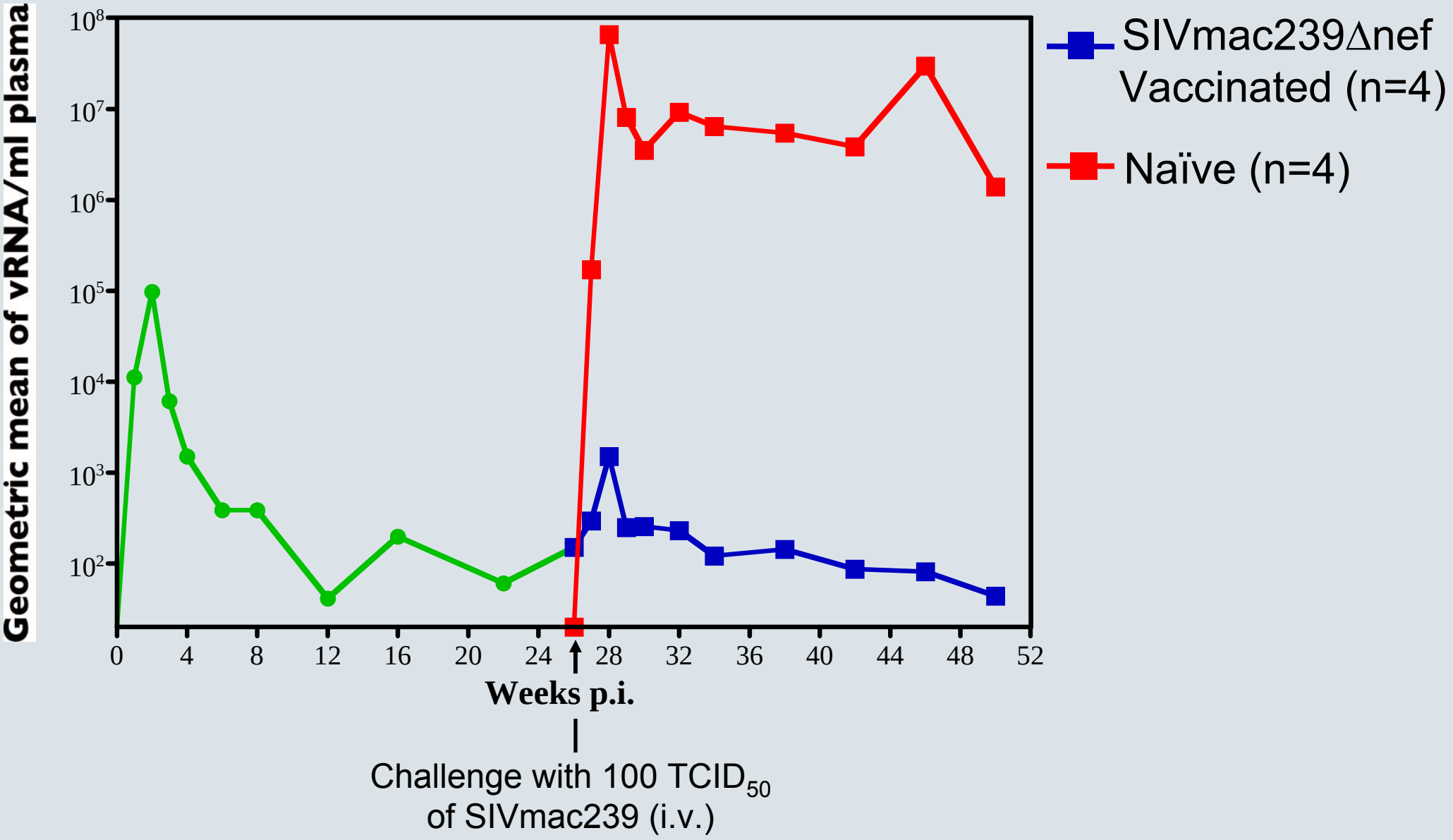
*SIVsmE660-Control, Naïve Animals; 10/10 Above 100,000 copies/ml at 28 Weeks Post Challenge (note: 6/10 are A*01, B*08 or B*17)*



*Heterologous Challenge-Vaccinees 5/10 Above 100,000 Copies/ml at 28 Weeks Post Challenge (note: 3/5 Controllers were A*01,B*08 or B*17)*



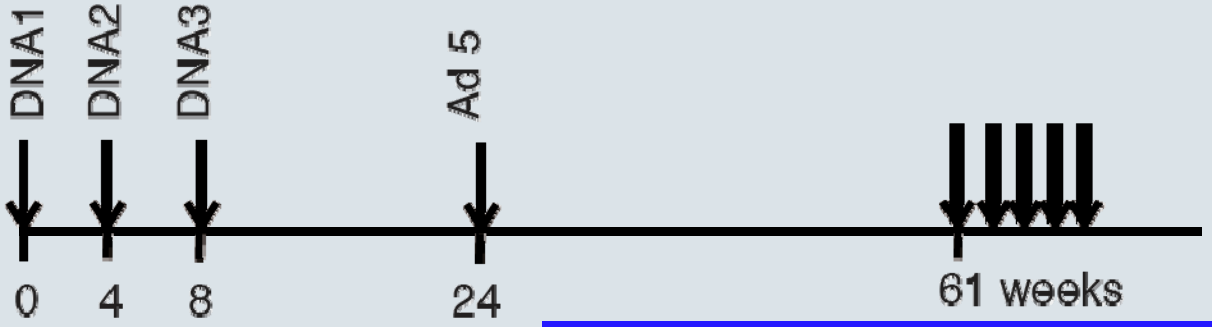
Homologous Challenge with SIVmac239- Complete Control



SIVsmE660 Challenge

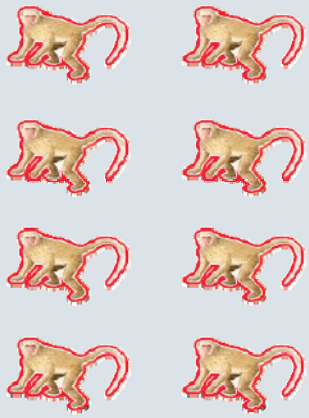
- Our stock of SIVsmE660 replicates well in control, naïve animals (even Mamu-A*01, B*08 and B*17 positive animals) and does not appear to exhibit the variability characteristic of some SIVsmE660 stocks.
- This stock of SIVsmE660 was difficult to protect against using our best vaccine (after i.v. challenge).

Vaccination scheme

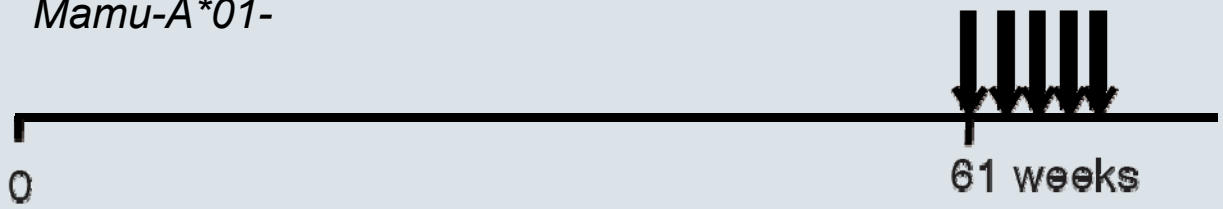


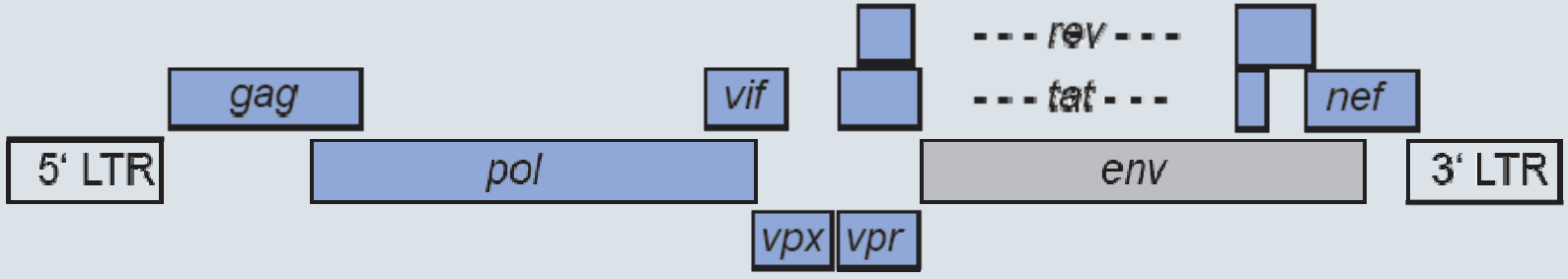
*Mamu-A*02+*

*Mamu-B*08-*
*Mamu-B*17-*
*Mamu-A*01-*



Challenge with repeated low dose SIVsmE660 at 61 weeks

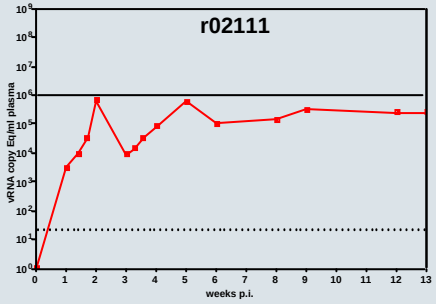


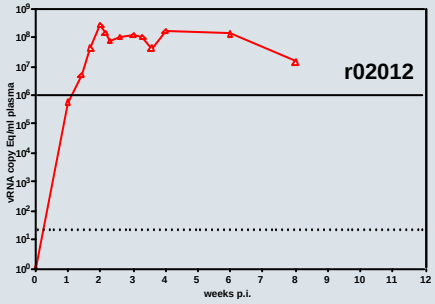


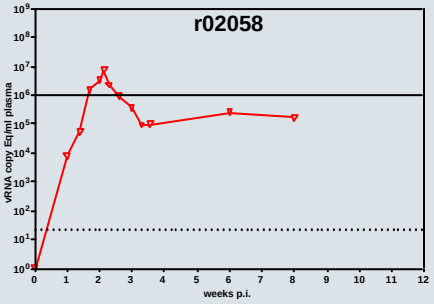
SIVmac239 sequences

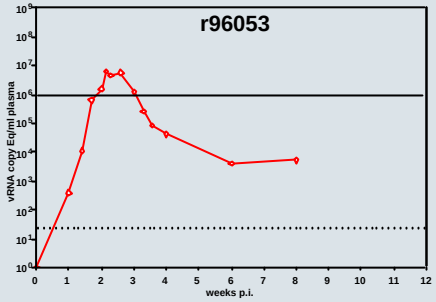
Acute Phase Viral Replication of SIVsmE660 Challenge Virus After Repeated Low Dose Mucosal Challenge

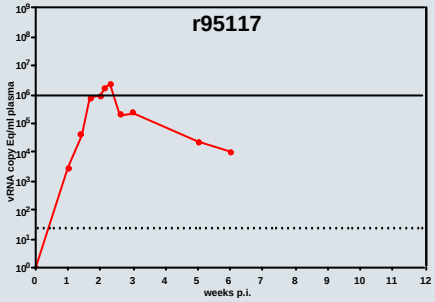
Controls

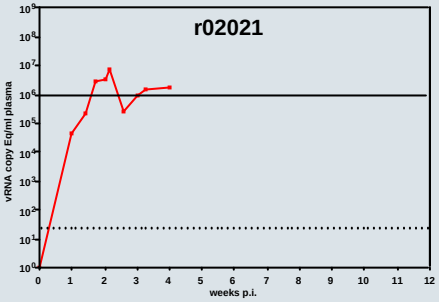






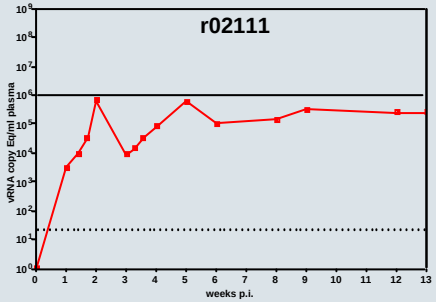


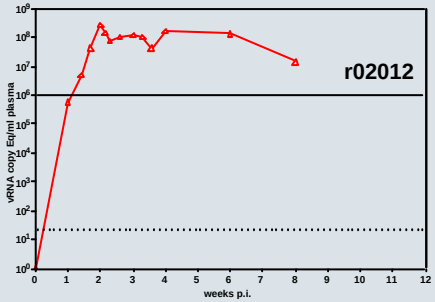


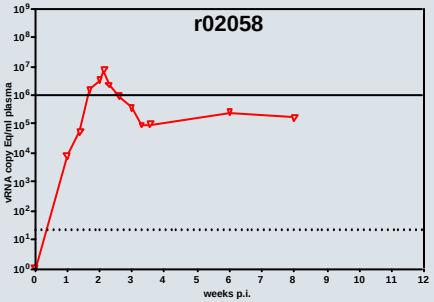


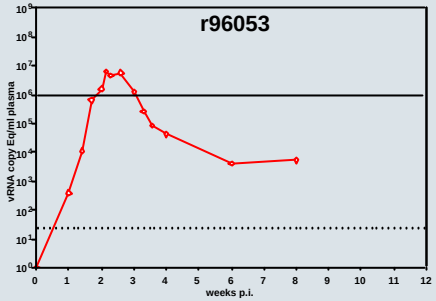
Vaccinees Control Acute Phase Viral Replication of Heterologous Challenge Virus

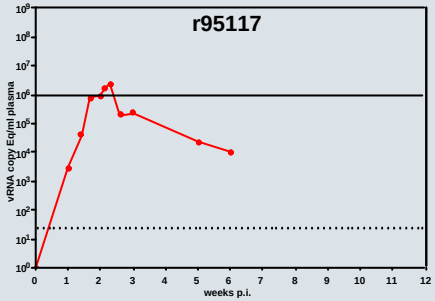
Controls

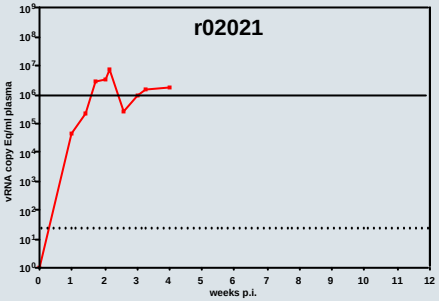




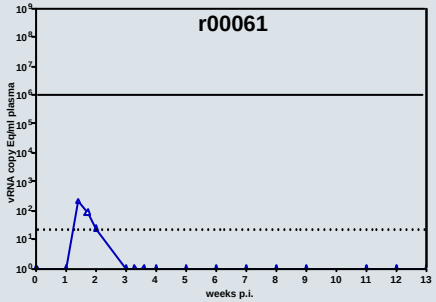


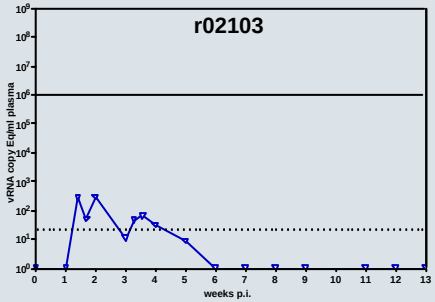


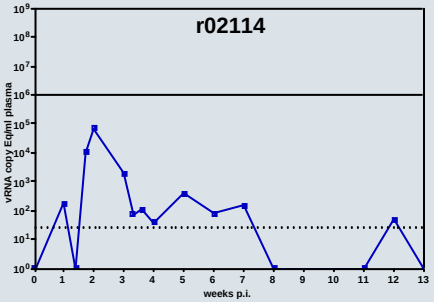


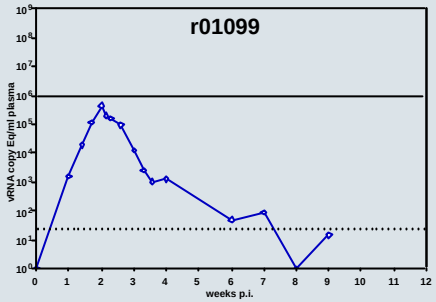


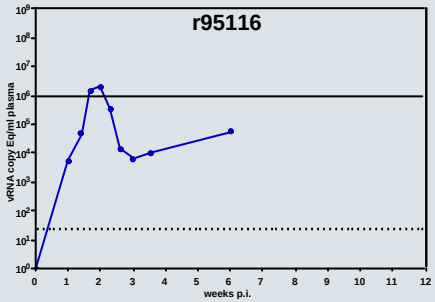
Vaccinees



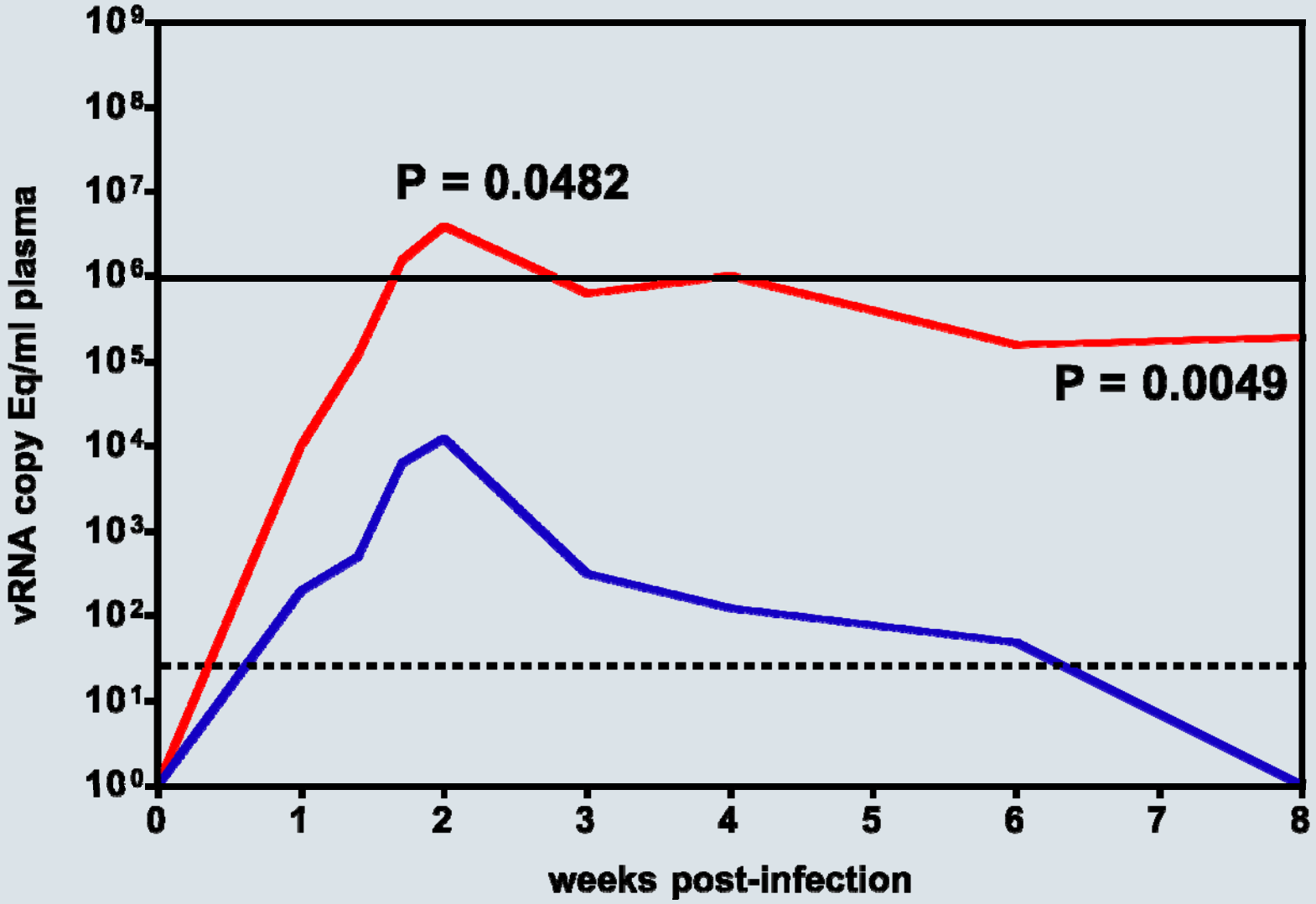








Vaccinees Control Acute Phase Viral Replication of Heterologous SIVsmE660



Mucosal Low Dose E660 Challenge

- After five low dose mucosal challenges, 5 vaccinees and 6 controls were infected.
- The five vaccinees averaged 12,600 copies/ml at peak and the six controls averaged 4,000,000 copies/ml at peak.

We should still test T-cell-based vaccines

- First, of course it would be ideal to induce neutralizing antibodies. A combination of both vaccine-induced antibodies and T-cells would be optimal

BUT WE DO NOT HAVE ANY CANDIDATE ANTIBODY-BASED VACCINES YET

- Macaque vaccine regimens (no Env) based only on the induction of T-cell responses can control viral replication in both the acute and the chronic phase in outbred macaques (not A*01, B*08,or B*17 positive), even after stringent homologous or heterologous SIV challenge

SO T-CELL RESPONSES ALONE CAN CONTROL VIRAL REPLICATION IN THE COMPLETE ABSENCE OF NEUTRALIZING ANTIBODIES