

*We should still test T-cell based vaccines*

David I. Watkins

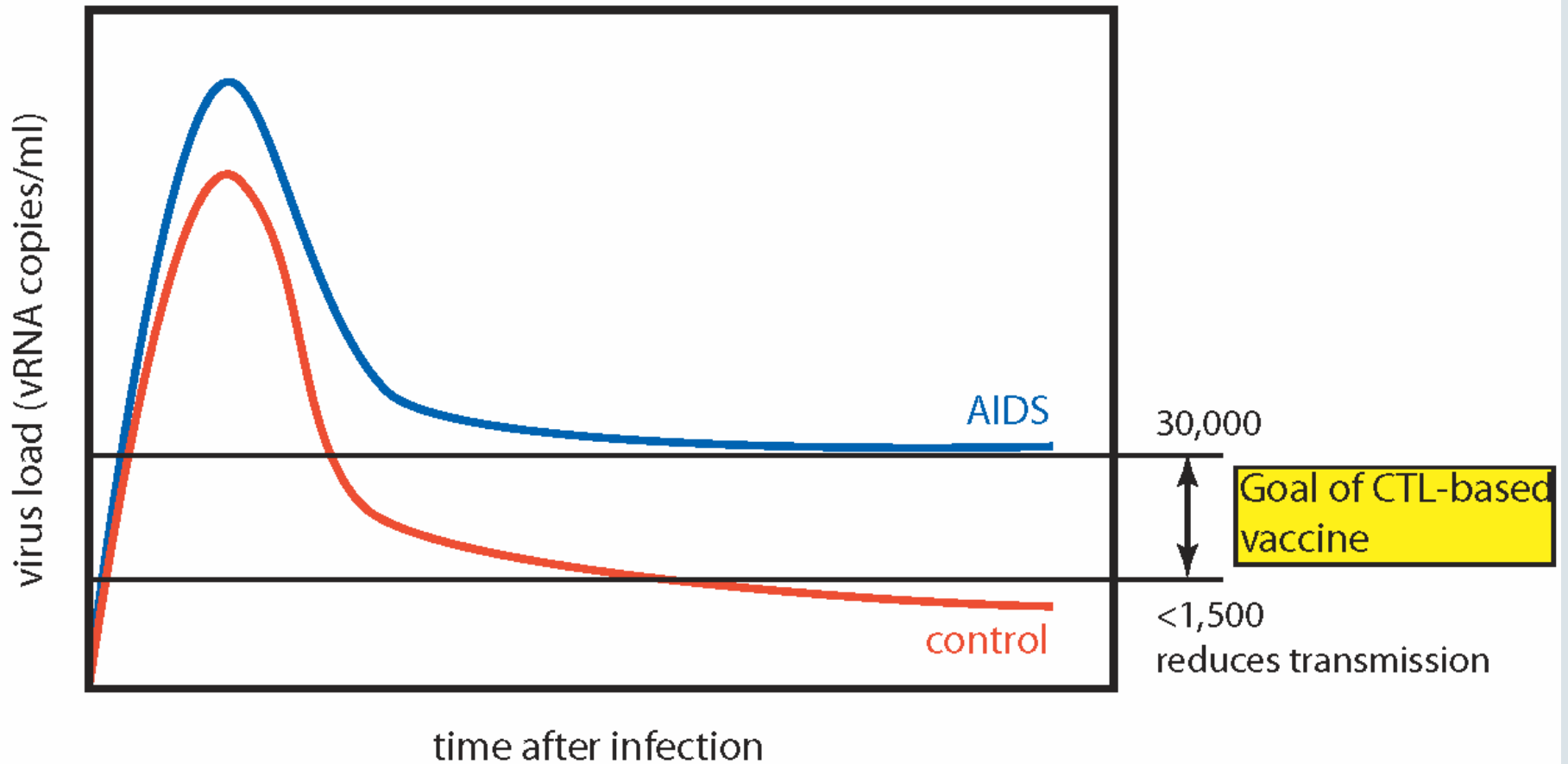
“The T cell concept is hanging by a thread.”

-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.*

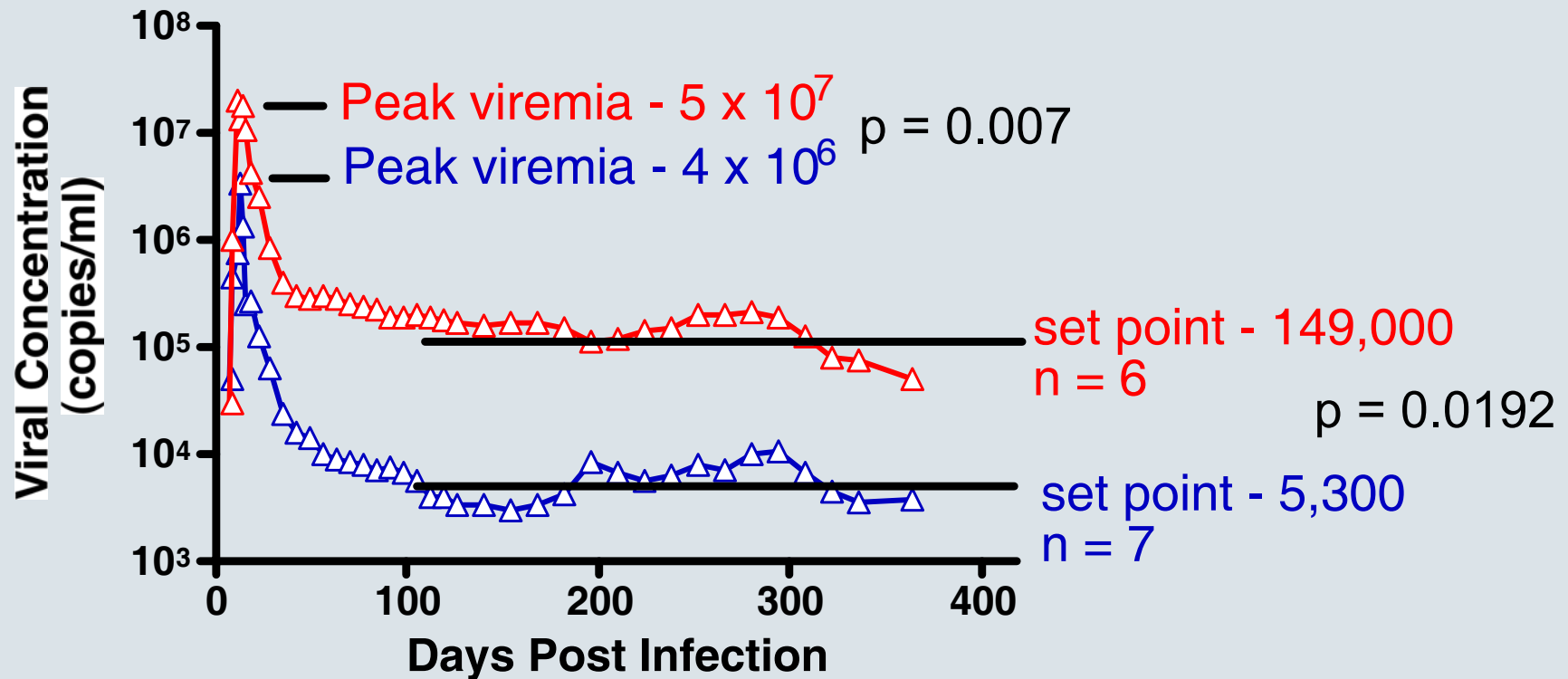


# *Monkey Testing of Vaccines : Homologous vs Heterologous Challenge*

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*



## *Conclusions*

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

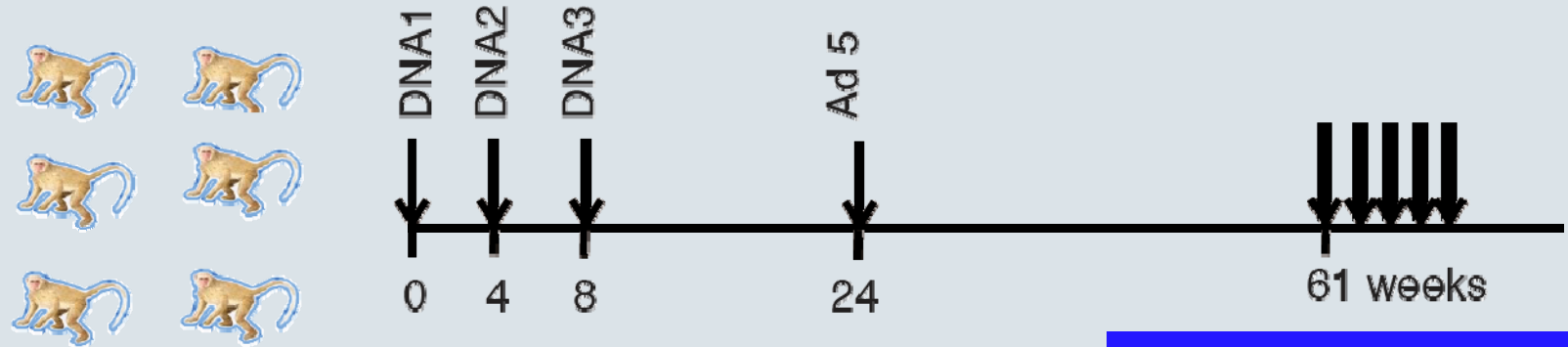
## *Caveats*

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

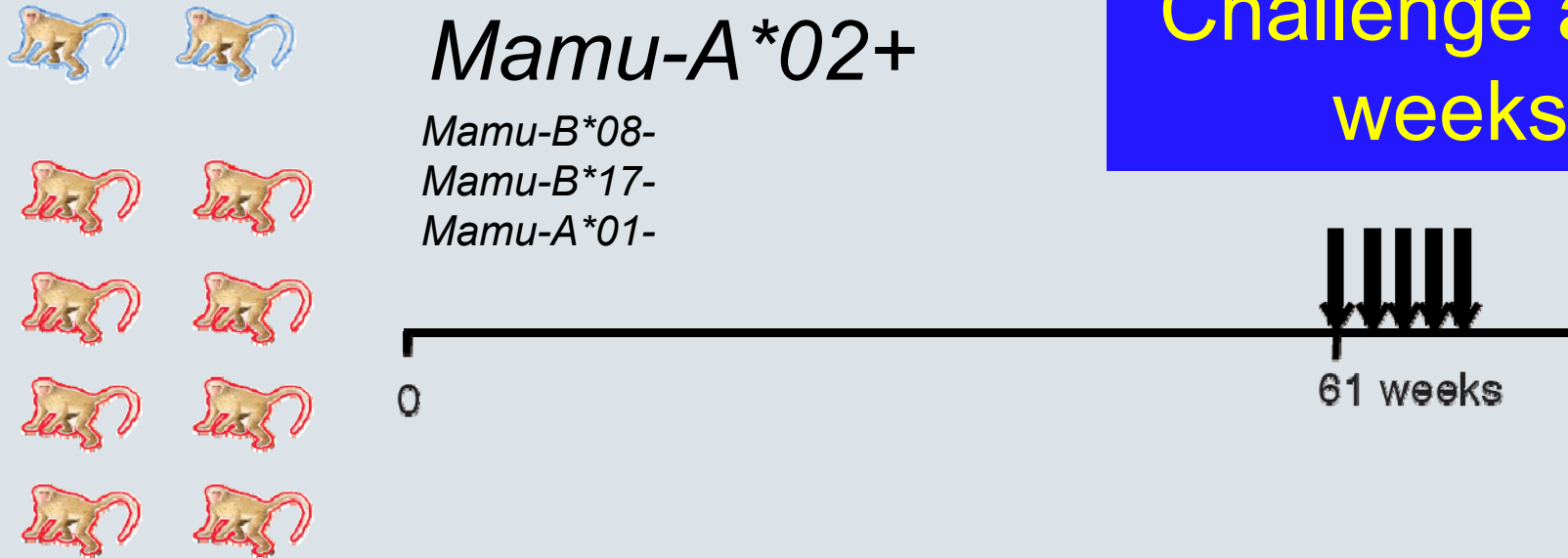
*DNA/Ad5 Encoding **All** SIV  
Proteins (except for Env) Induces  
High Frequency and Broad T-cell  
Responses*

*See Wilson et al, late breaker*

# Vaccination scheme

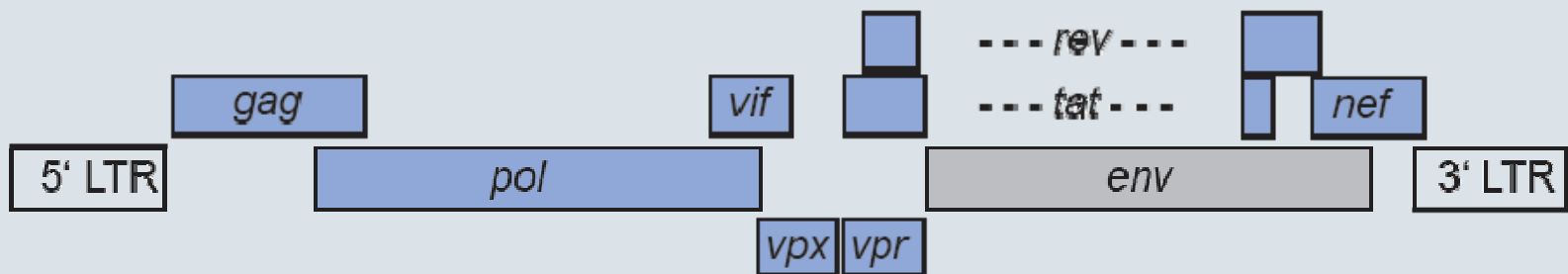


**Challenge at 61 weeks**



*Mamu-A\*02+*

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



SIVmac239 sequences

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

	<b>Gag</b>	<b>Nef</b>	<b>Tat</b>	<b>Rev</b>	<b>Vpr</b>	<b>Vpx</b>	<b>Vif</b>	<b>Env</b>	<b>Pol</b>	<b>Total</b>
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
<b>Average</b>	8	1	0	2	1	0	3	1	3	<b>20</b>

## *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-SIVmac239 $\Delta$ Nef.
- 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-SIVmac239 $\Delta$ Nef completely protects against replication of the highly pathogenic SIVmac239 and SIVmac251 during the ACUTE and chronic phases.)

# *SIVmac239 $\Delta$ nef* our Best Vaccine Study

## Outline: *Heterologous* Challenge

### Vaccine

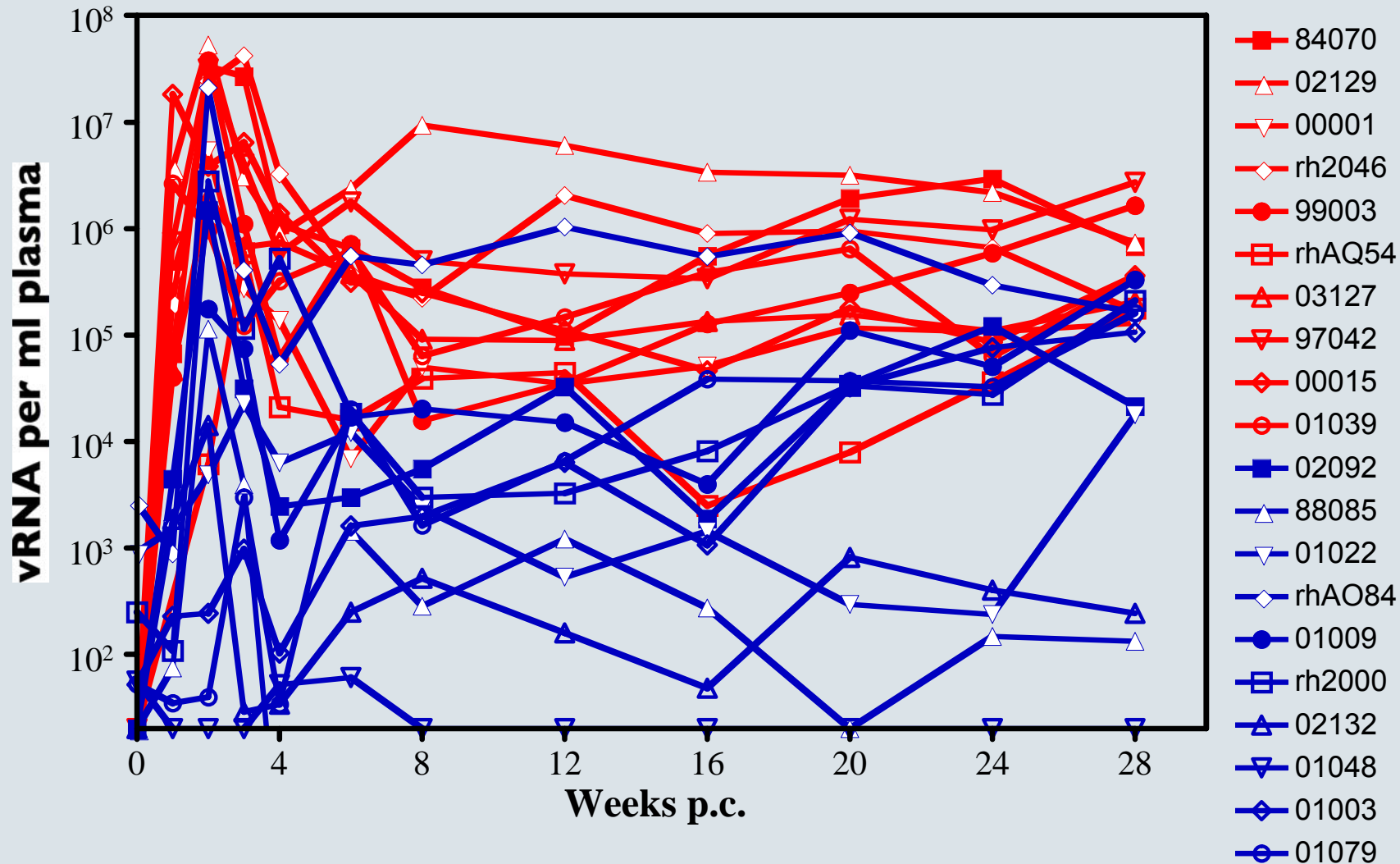


### Naïve

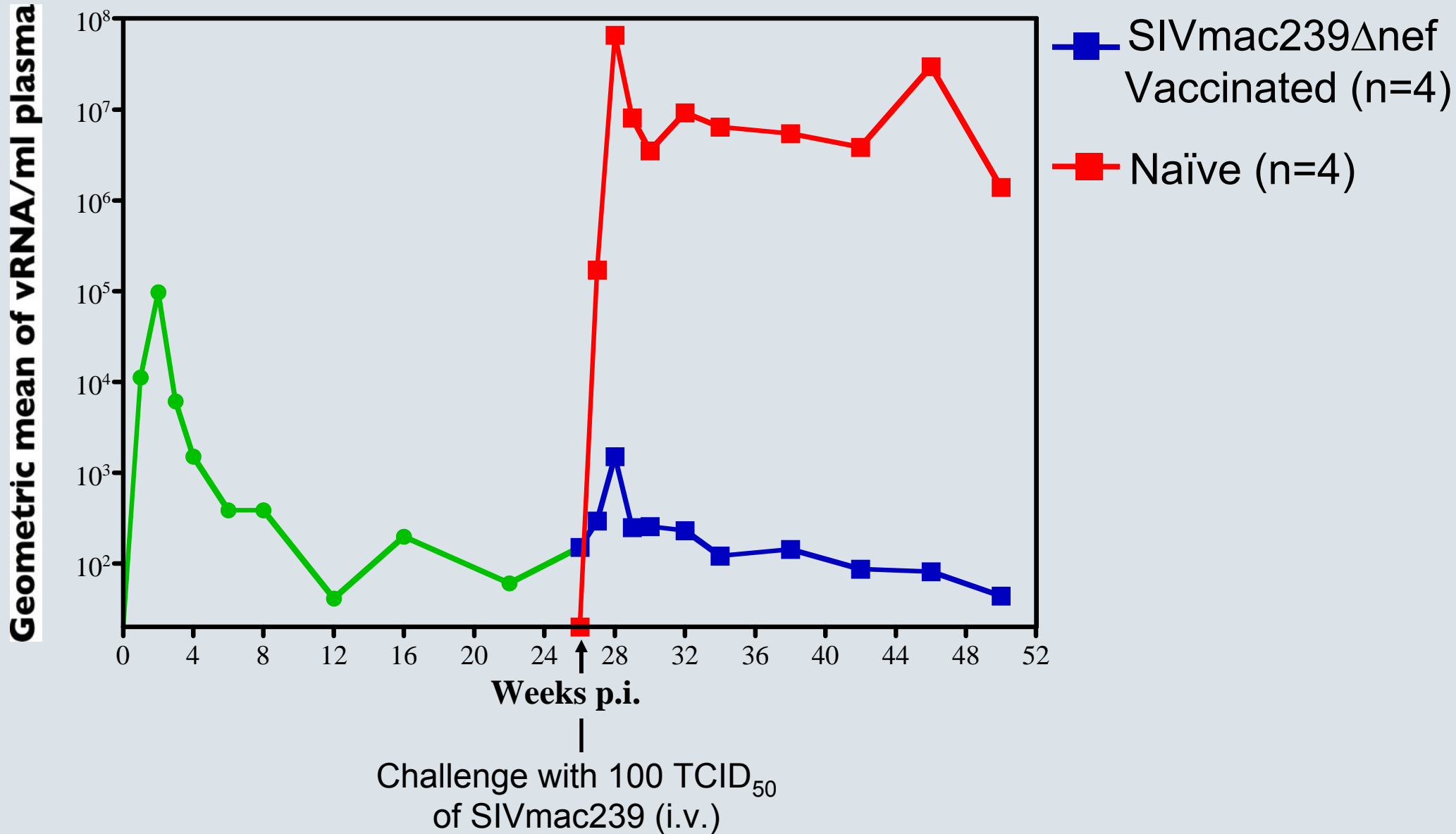




*Heterologous Challenge-Vaccinees 5/10 Above 100,000 Copies/ml at 28 Weeks Post Challenge  
(note: 3/5 Controllers were A\*01,B\*08 or B\*17)*



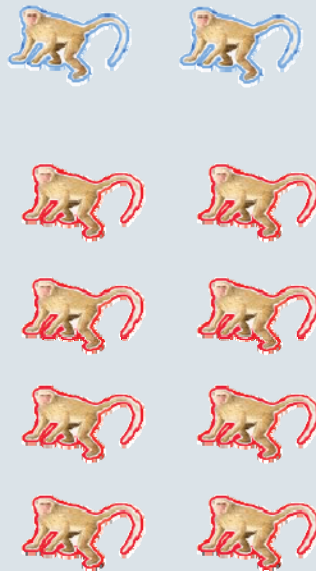
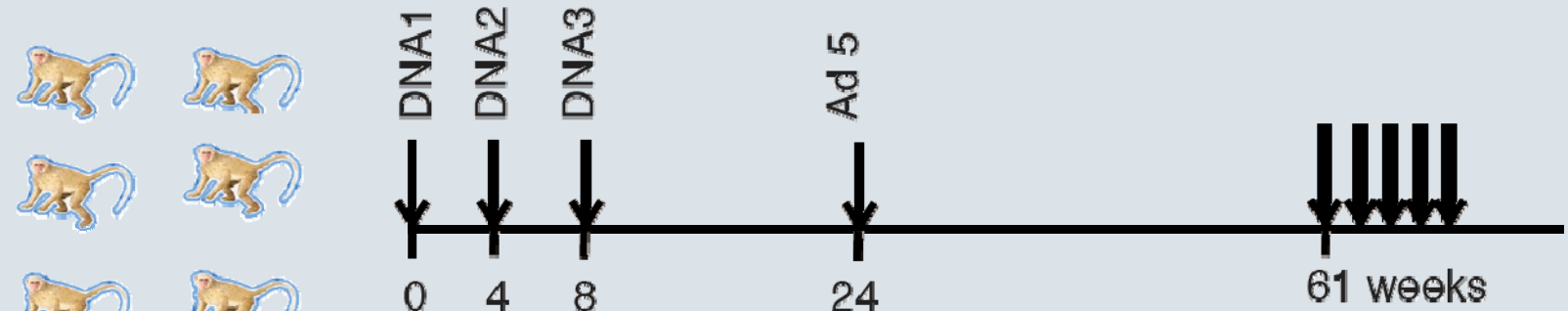
# Homologous Challenge with SIVmac239- Complete Control



## *SIVsmE660 Challenge*

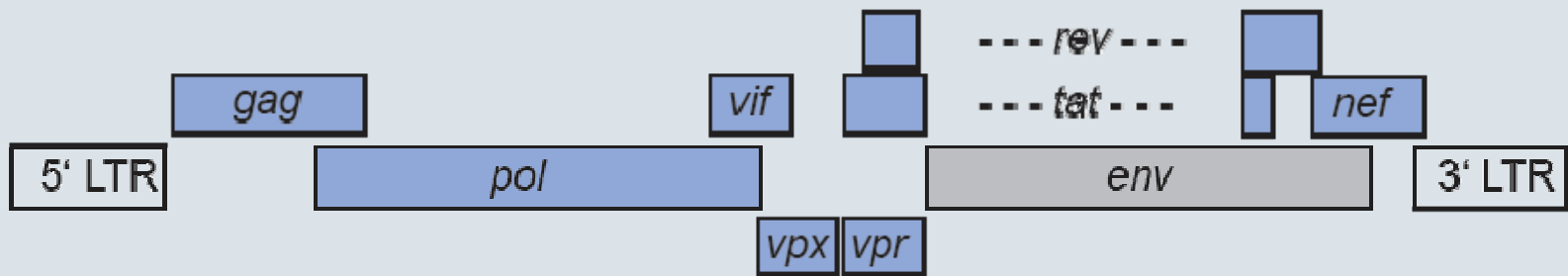
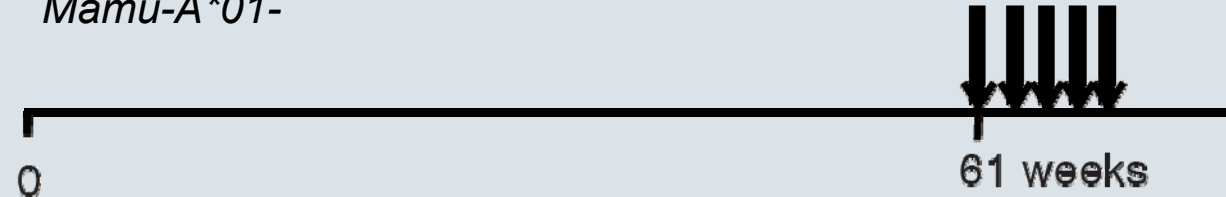
- Our stock of SIVsmE660 replicates well in control, naïve animals (even Mamu-A\*01, B\*08 and B\*17 positive animals) and does not appear to exhibit the variability characteristic of some SIVsmE660 stocks.
- This stock of SIVsmE660 was difficult to protect against using our best vaccine (after i.v.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

# Vaccination scheme



*Mamu-A\*02+*  
*Mamu-B\*08-*  
*Mamu-B\*17-*  
*Mamu-A\*01-*

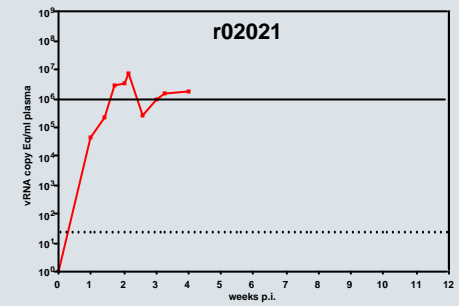
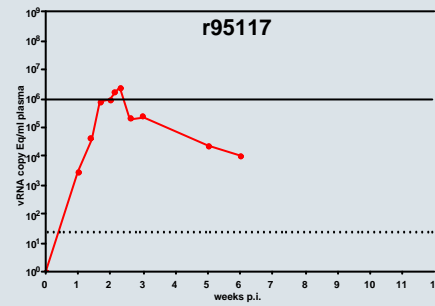
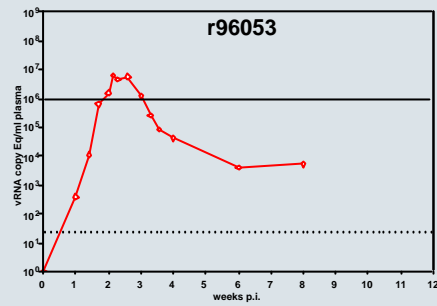
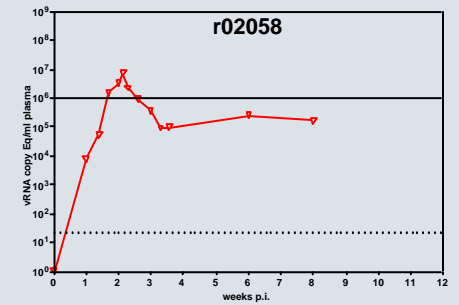
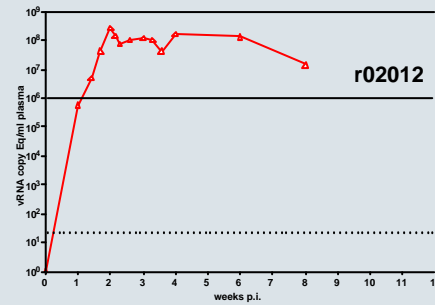
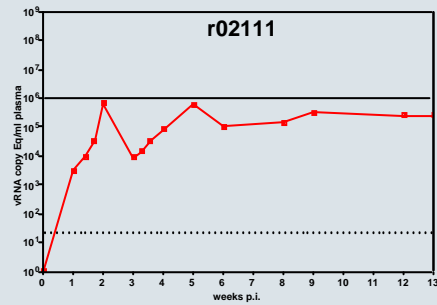
Challenge with repeated low dose SIVsmE660 at 61 weeks



SIVmac239 sequences

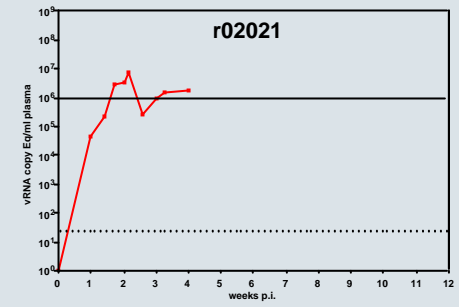
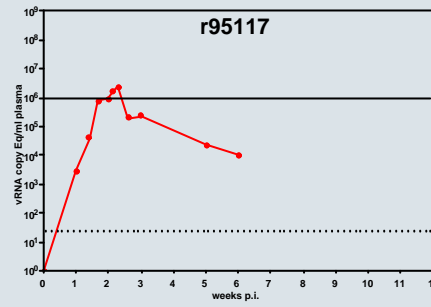
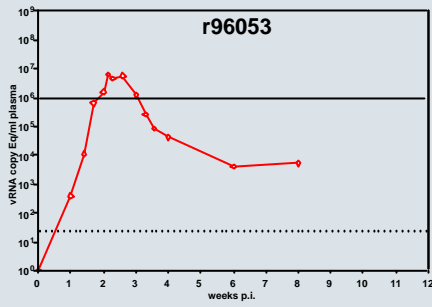
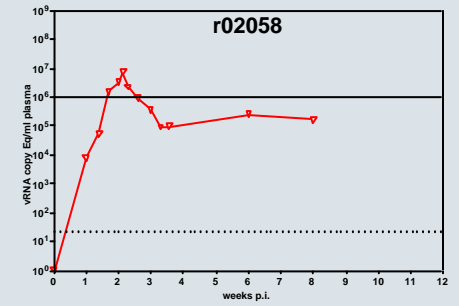
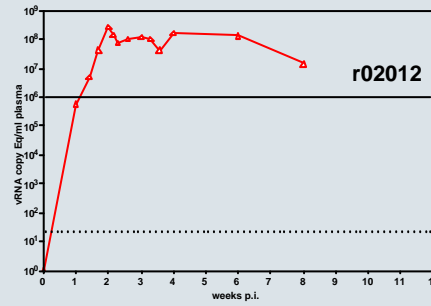
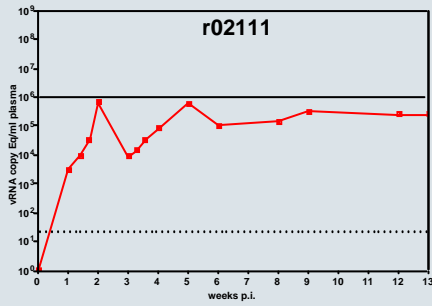
# Acute Phase Viral Replication of SIVsmE660 Challenge Virus After Repeated Low Dose Mucosal Challenge

Controls

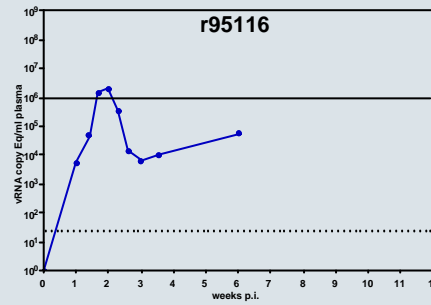
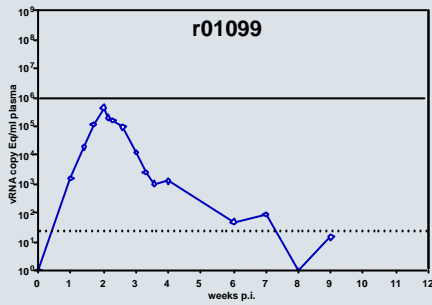
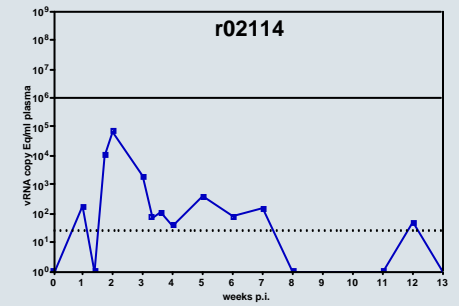
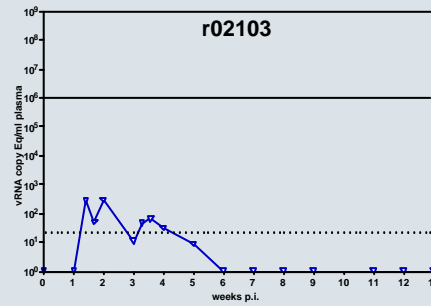
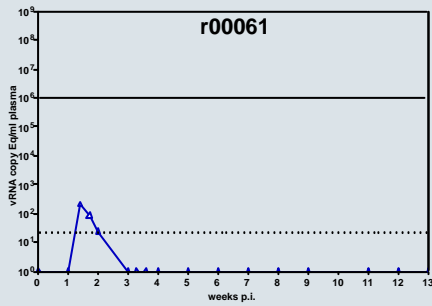


# Vaccinees Control Acute Phase Viral Replication of Heterologous Challenge Virus

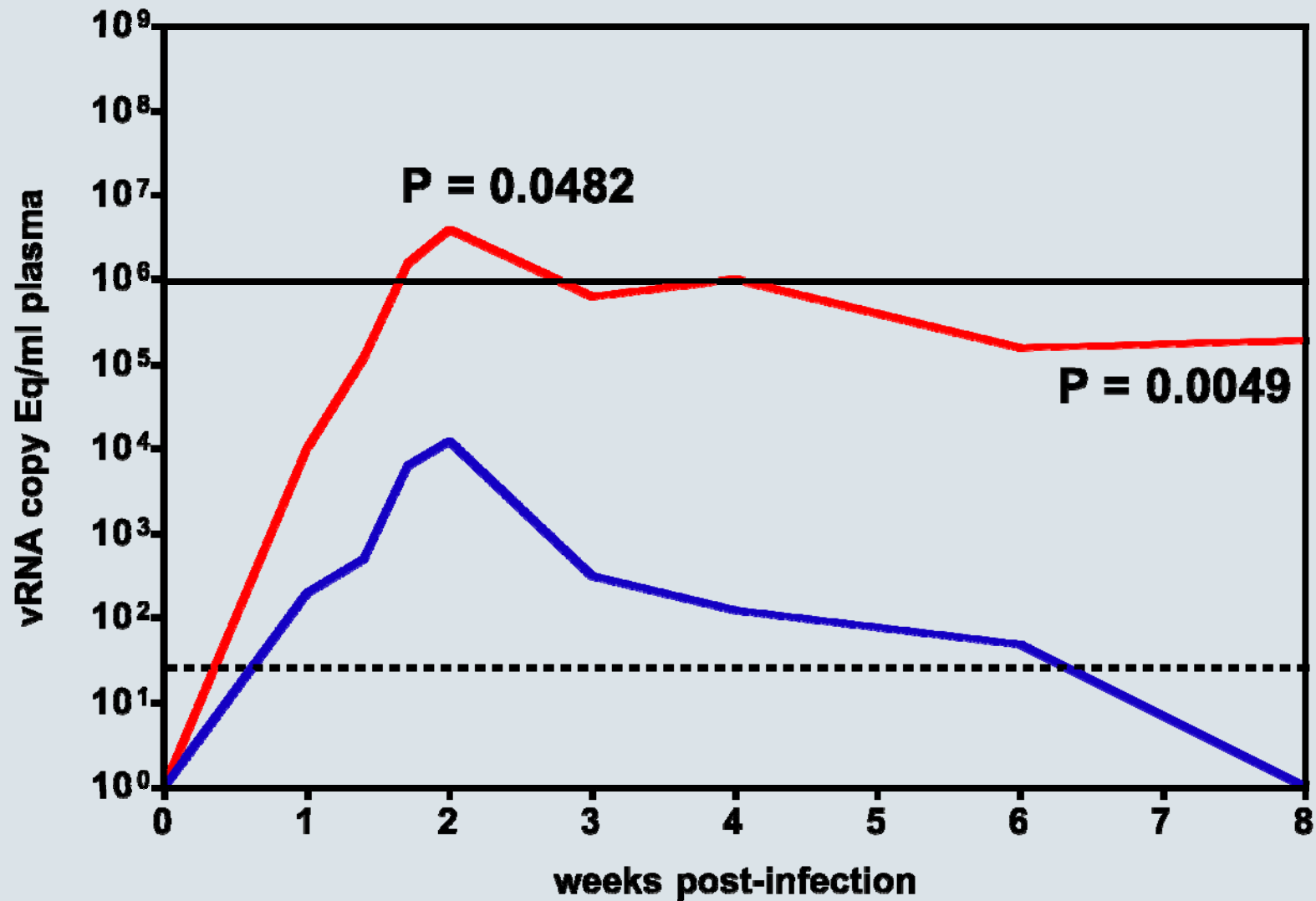
Controls



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**