

TOWARDS AN HIV VACCINE

why is it so hard to make an HIV vaccine and where are we now?

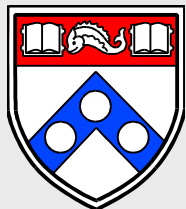
Neal Nathanson, MD

Emeritus Professor

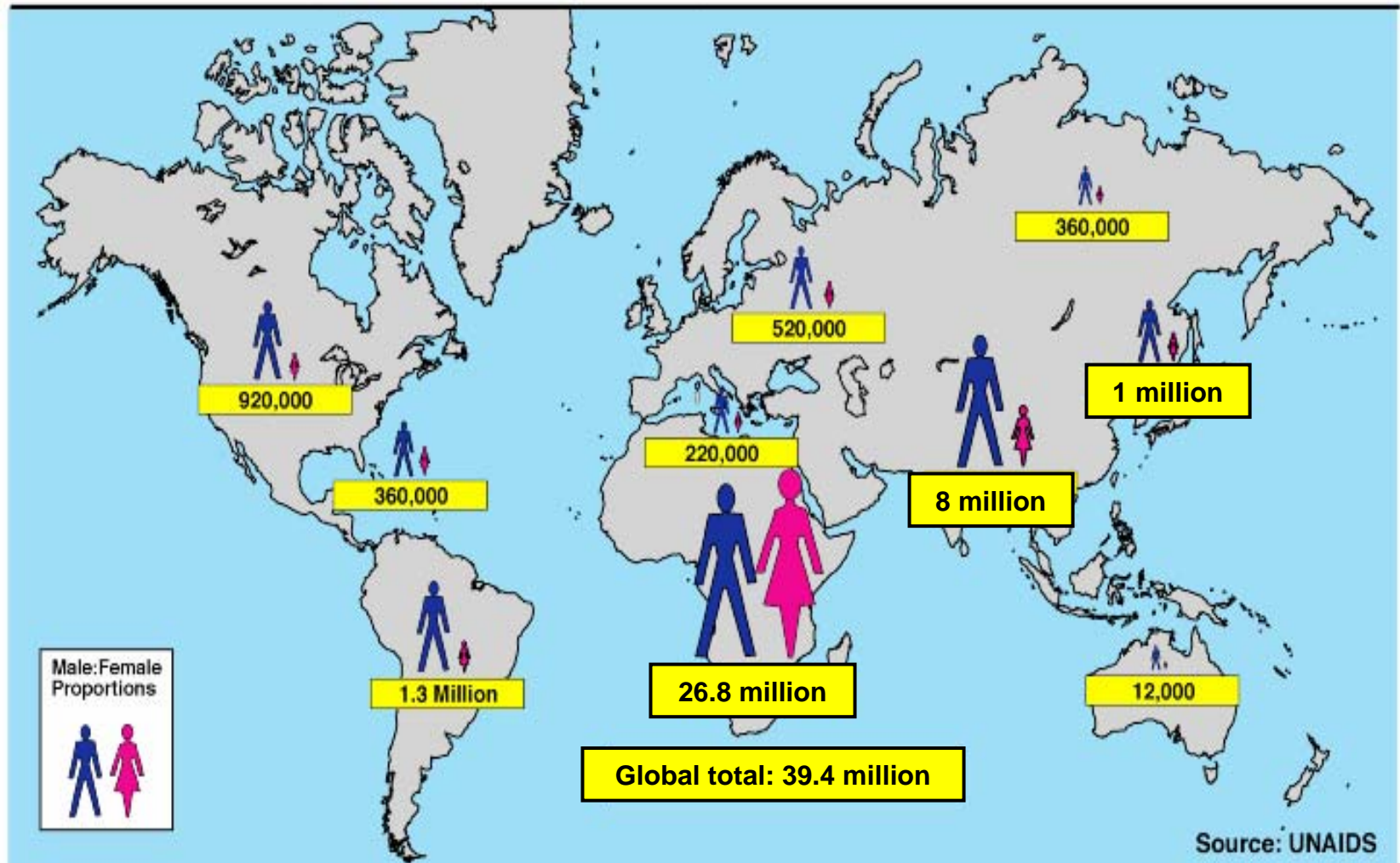
Department of Microbiology

University of Pennsylvania

School of Medicine



Estimated number of persons living with HIV/AIDS, December, 2004



TOWARDS AN HIV VACCINE

- **Why is it so hard to make an AIDS vaccine?**
- **‘Sterilizing’ or ‘partial’ immunity?**
- **Immune correlate of protection?**
- **Cellular immunity: provides protection?**
- **Neutralizing antibody: a daunting challenge**
- **Cross-clade immunity?**
- **Current status of AIDS vaccines?**

TOWARDS AN HIV VACCINE

**WHY IS IT SO HARD TO
MAKE AN AIDS VACCINE?**

TOWARDS AN HIV VACCINE

RESEARCH EXPERIENCE

- HIV env protein fails to induce neutralizing Ab
- Live attenuated SIVs protect but cause AIDS

BIOLOGICAL ISSUES

- First HIV infection may not attenuate a second HIV infection?
- Persistence of HIV and progression to AIDS

IMPLICATION

- Immunobiological questions must be addressed
- Mechanisms of vaccine protection?

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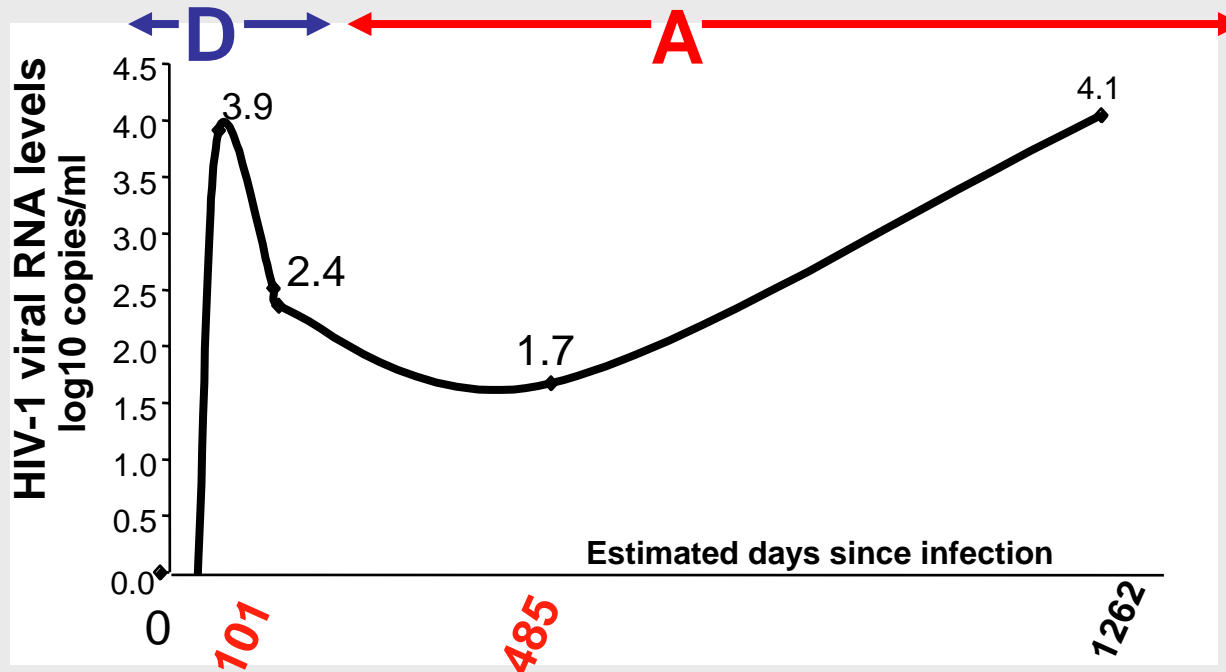
VAXGEN TRIAL OF rgp120
multiple immunizations, 3 year cumulative infection percentage
Science 2003, 299: 1290

GROUP	TREATMENT	SUBJECTS	INFECTIONS	PERCENT
TOTAL	PLACEBO	1679	98	5.8%
	VACCINE	3330	191	5.7%
WHITE,	PLACEBO	1508	81	5.4%
HISPANIC	VACCINE	3003	179	6.0%
BLACK,	PLACEBO	171	17	9.9%
ASIAN, OTHER	VACCINE	327	12	3.7%

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FIRST HIV INFECTION MAY NOT PROTECT AGAINST SECOND INFECTION?

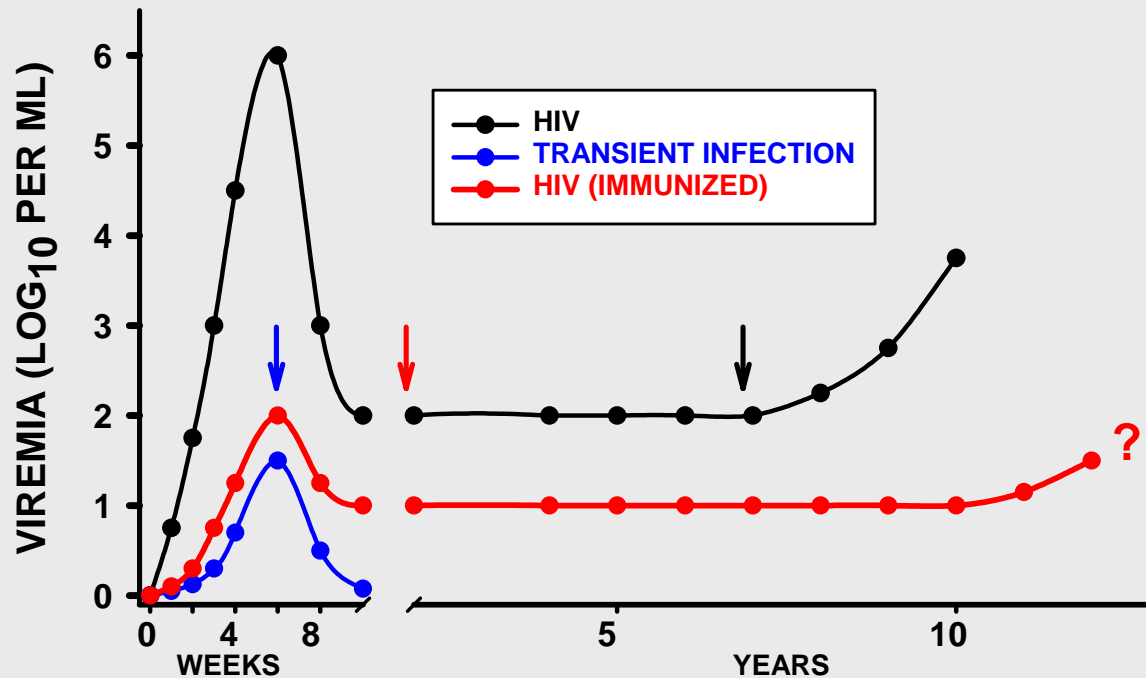
HIV INFECTION IN SEX WORKERS, NAIROBI, KENYA
CASE # 3
OVERBAUGH ET AL, 2005, UNPUBLISHED



TOWARDS AN HIV VACCINE

THE DAUNTING TRIAD: FAILURE TO PREVENT INFECTION;
PERSISTENCE; LOSS OF CD4 T CELLS

*DYNAMICS OF HIV INFECTION ILLUSTRATING
PROBLEMS IN PRE-EXPOSURE IMMUNIZATION*



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**“STERILIZING” OR
“PARTIAL” IMMUNITY?**

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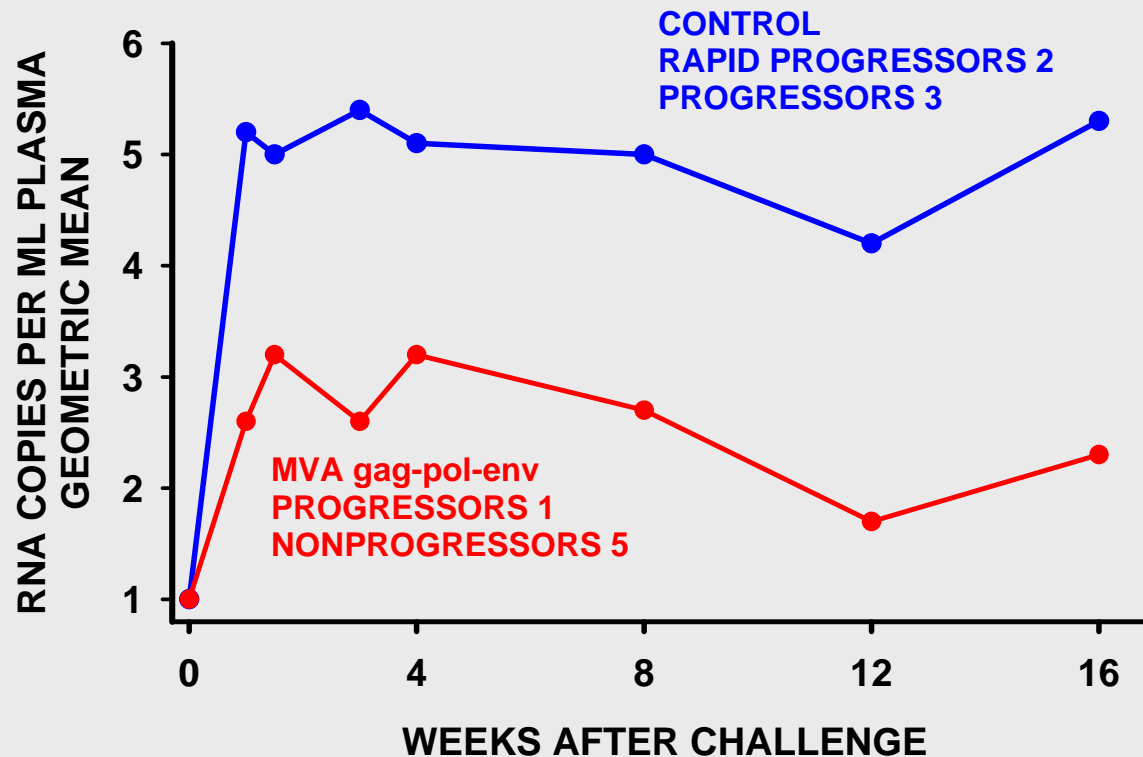
“STERILIZING” OR “PARTIAL” IMMUNITY?

For viruses causing acute infections, subjects who have been adequately immunized usually undergo an abortive infection when exposed to a potentially virulent wildtype virus

- **Will such ‘partial’ protection confer adequate resistance to an HIV challenge or is ‘absolute’ protection (‘sterilizing’ immunity) needed?**
- **Do studies of immunized monkeys challenged with SIV provide a useful reference?**
- **Do studies of viral set points and survival curves in HIV-infected humans provide a useful predictor?**

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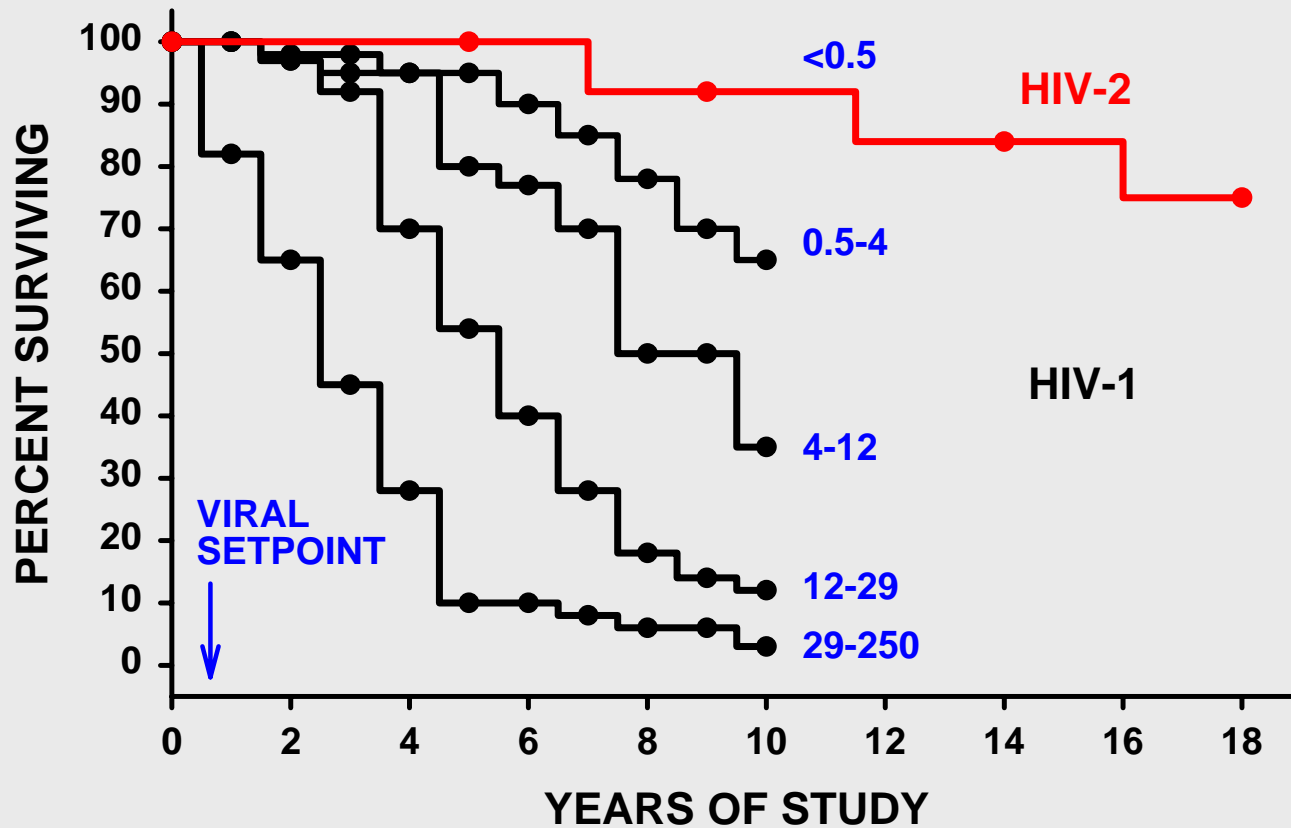
**PROTECTION OF RHESUS MACAQUES
AGAINST SIV SM E660 IV CHALLENGE
BY RECOMBINANT VACCINIA (MVA) IMMUNIZATION**
Ourmanov, J Virology, 2000, 74: 2740



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VIRUS SETPOINT DETERMINES THE COURSE OF THE INFECTION

Mellors et al, Science, 1996, 272: 1167; Whittle et al, COI, 1998, 10: 382.



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**IMMUNE CORRELATES
OF PROTECTION?**

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CORRELATE HYPOTHESIS?

- **Does protection correlate with a specific immune response parameter, such as antibody, CTL killing, or CD4+ proliferation?**

BARRIER HYPOTHESIS?

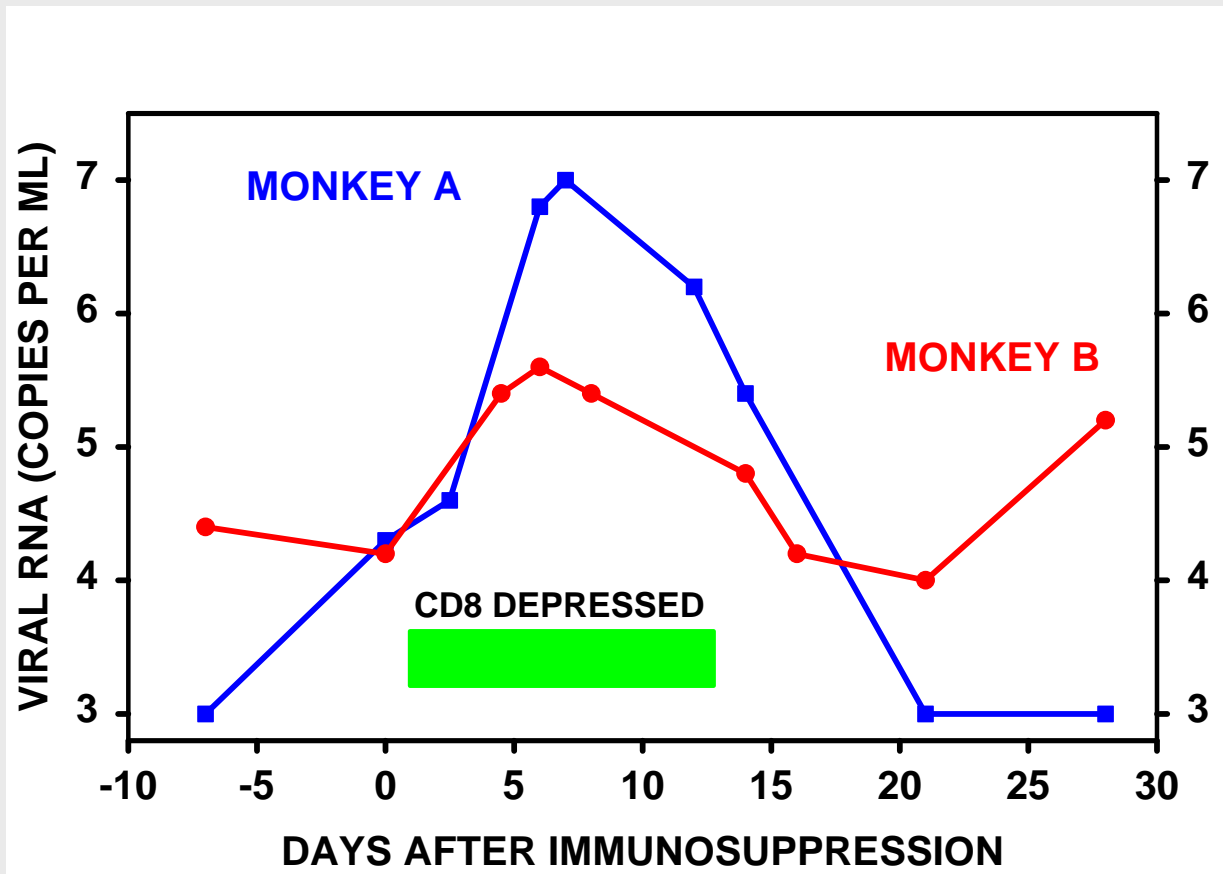
- **Might a combination of antibody plus CTLs plus associated cytokine responses act in concert to constitute a sufficient barrier?**
- **Could different immunizing protocols protect by a different mix of immune defenses?**

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**CELLULAR IMMUNITY
PROVIDES PARTIAL
PROTECTION**

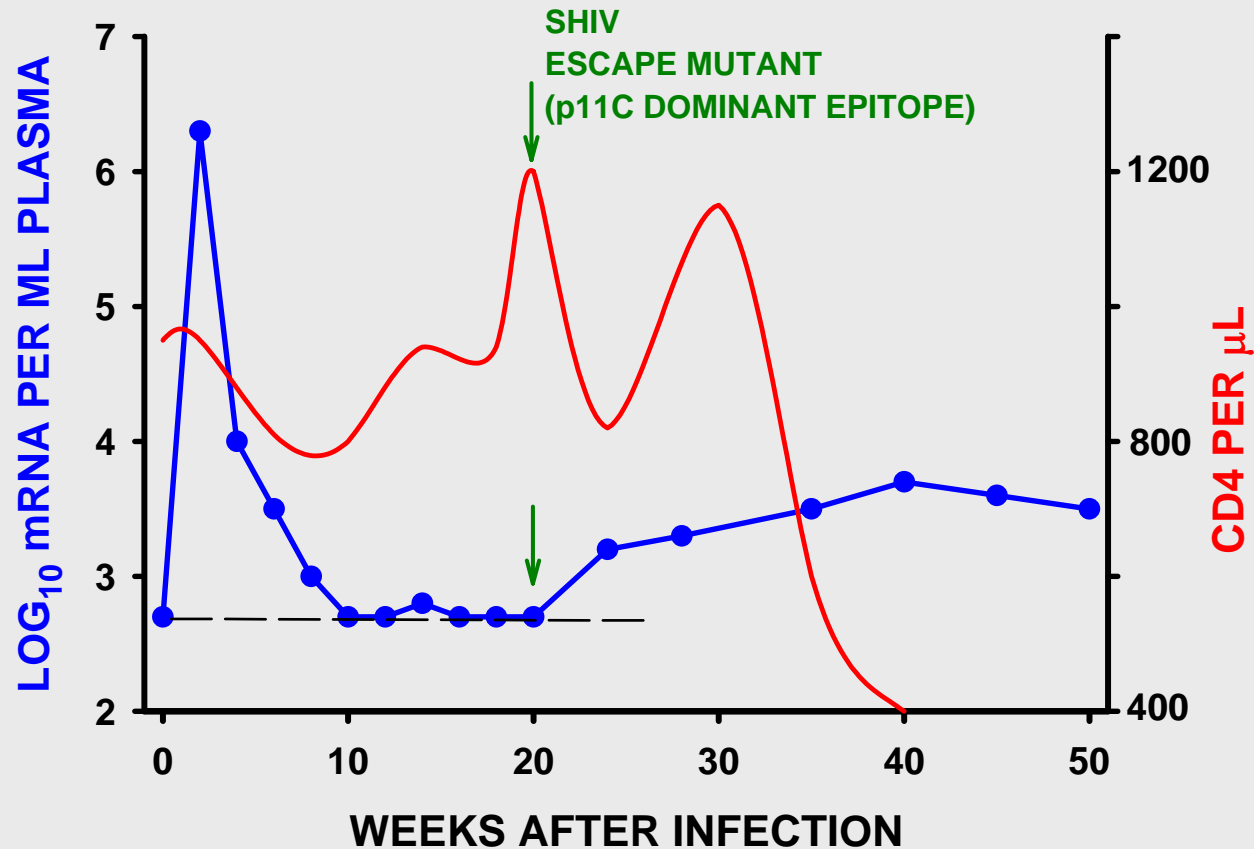
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CD8 CELLULAR IMMUNE RESPONSE GOVERNS VIRUS SETPOINT
Schmitz et al, Science 1999, 238: 857.



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VACCINE FAILURE DUE TO ESCAPE FROM A SINGLE CD8 EPITOPE
recombinant env-gag DNA/IL-2 vaccine; SHIV challenge
Barouche et al, Nature 2002, 415: 335.



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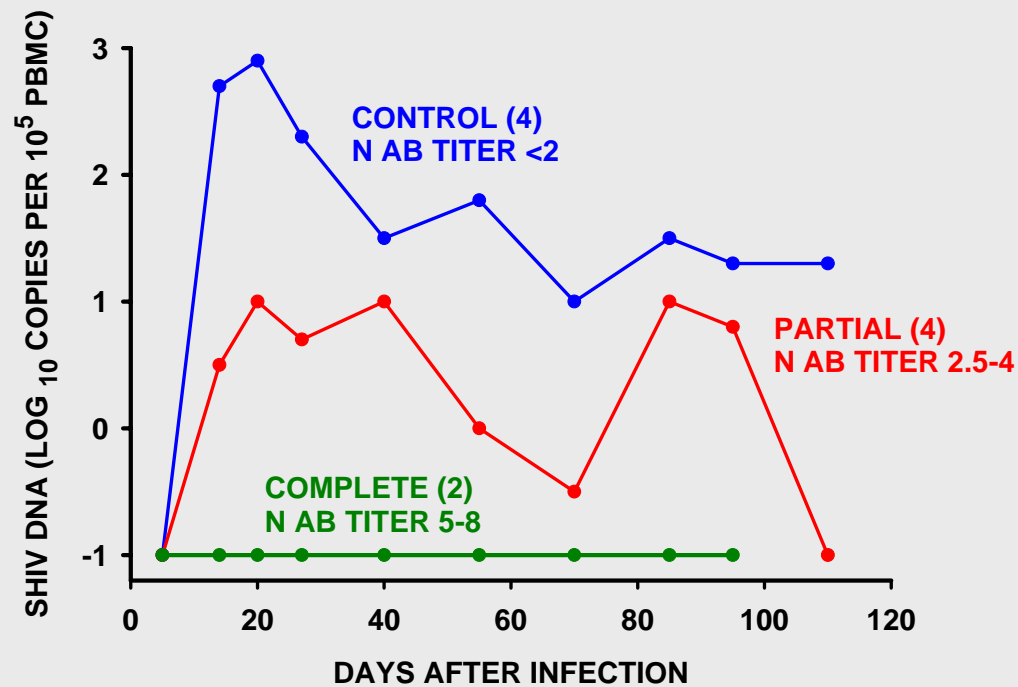
NEUTRALIZING ANTIBODY: A DAUNTING CHALLENGE

TOWARDS AN HIV VACCINE

NEUTRALIZING ANTIBODY INFLUENCES VIRUS SETPOINT

chimp anti-HIV passive antibody; challenge: iv virulent SHIV (matched gp120)

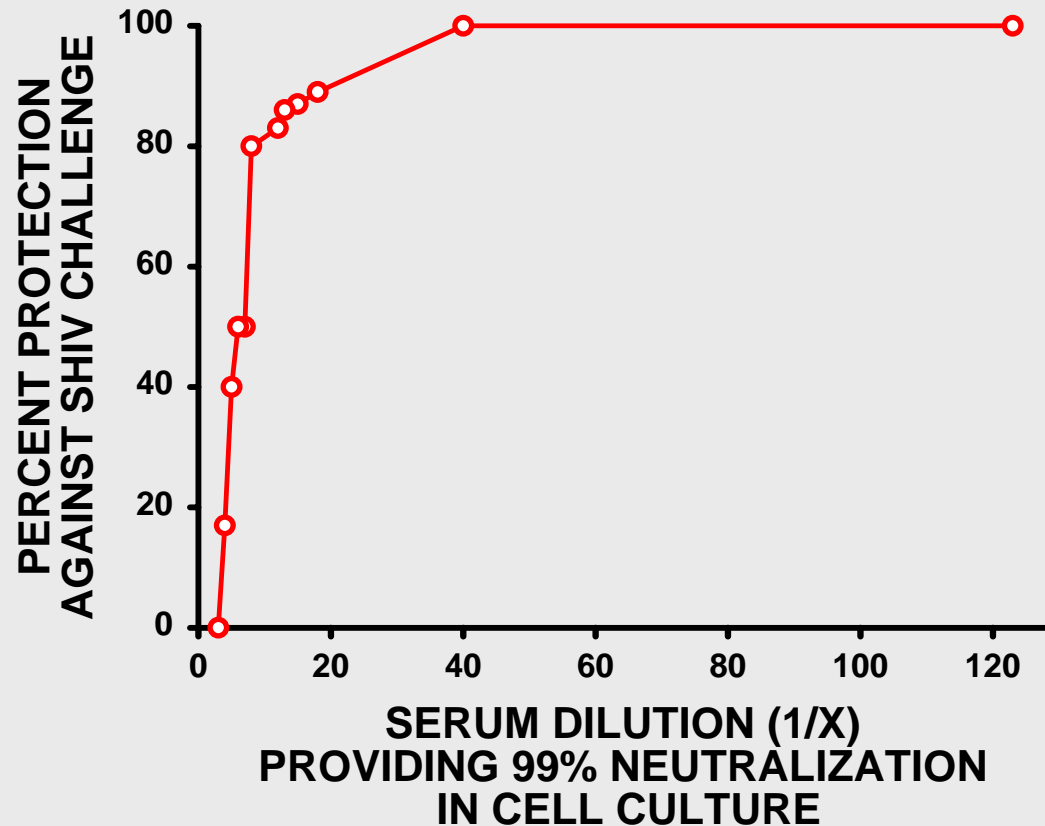
Shibata et al, Nature Medicine, 1999, 5: 204; Nishimura et al, JV, 2002 76: 2123



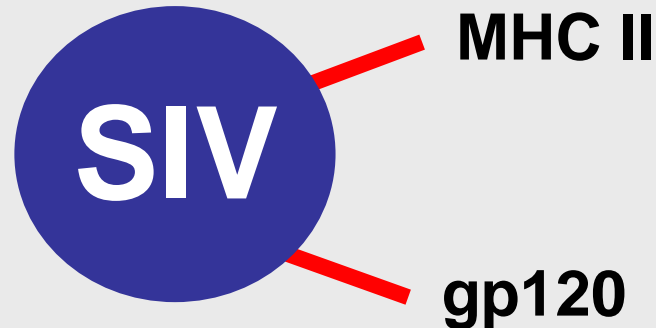
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PASSIVE ANTIBODY PROTECTS MONKEYS AGAINST SUBSEQUENT CHALLENGE WITH VIRULENT SHIV

Nishimura, 2002



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THE NEUTRALIZING ANTIBODY ENIGMA

- Using gp120, it is difficult to raise neutralizing antibody
- Using MHC Class II, anti-SIV neutralizing antibody can be readily induced

INFERENCE?

- the problem lies with gp120 and not in any intrinsic ability of SIV to resist neutralization
- Query: is SIV gp120 a poor target for neutralization? Do gp120 neutralization escape mutants play a role?

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HIV INFECTION INDUCES AUTOLOGOUS NEUTRALIZING ANTIBODY THAT SELECTS FOR ESCAPE VARIANTS

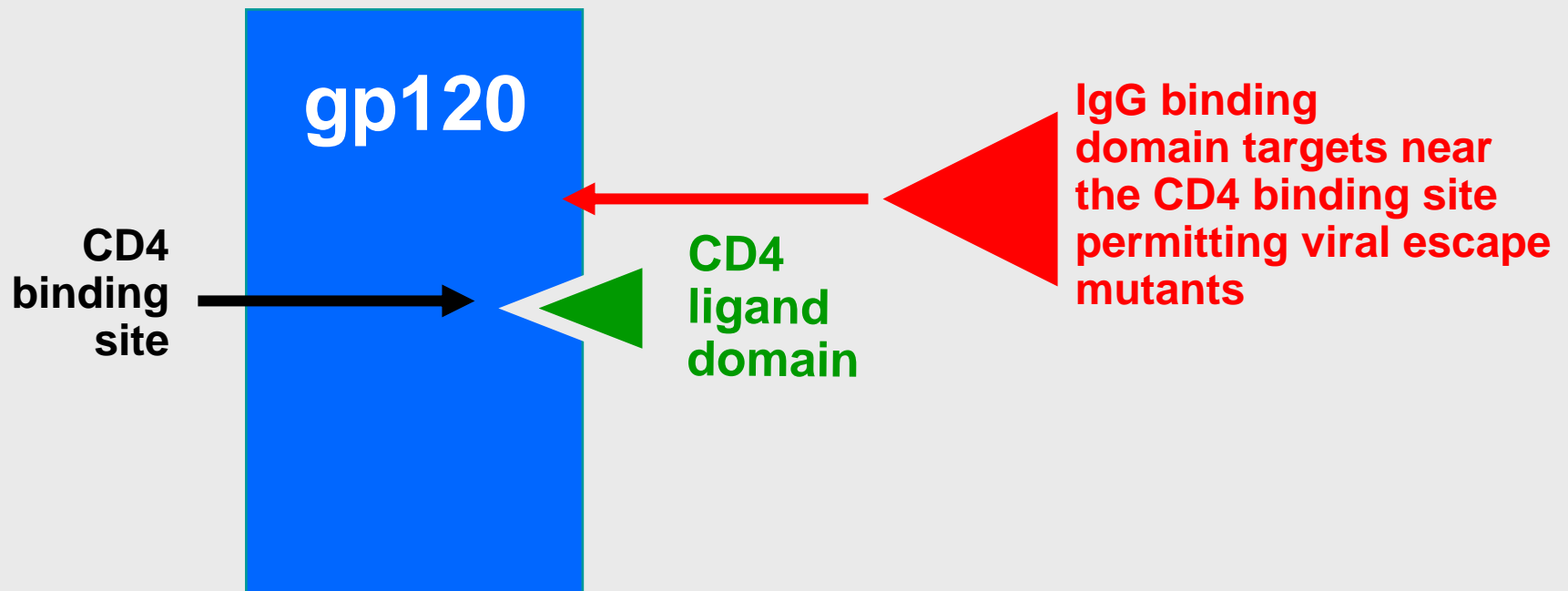
Richman et al, PNAS 2003, 100: 4144

PLASMA NEUTRALIZING TITER MONTHS AFTER INFECTION

		0	6	12	18
VIRUS MONTHS	0	<100	675	2670	2190
	6	<100	<100	1769	2247
	12	<100	<100	<100	556
	18	<100	<100	117	122

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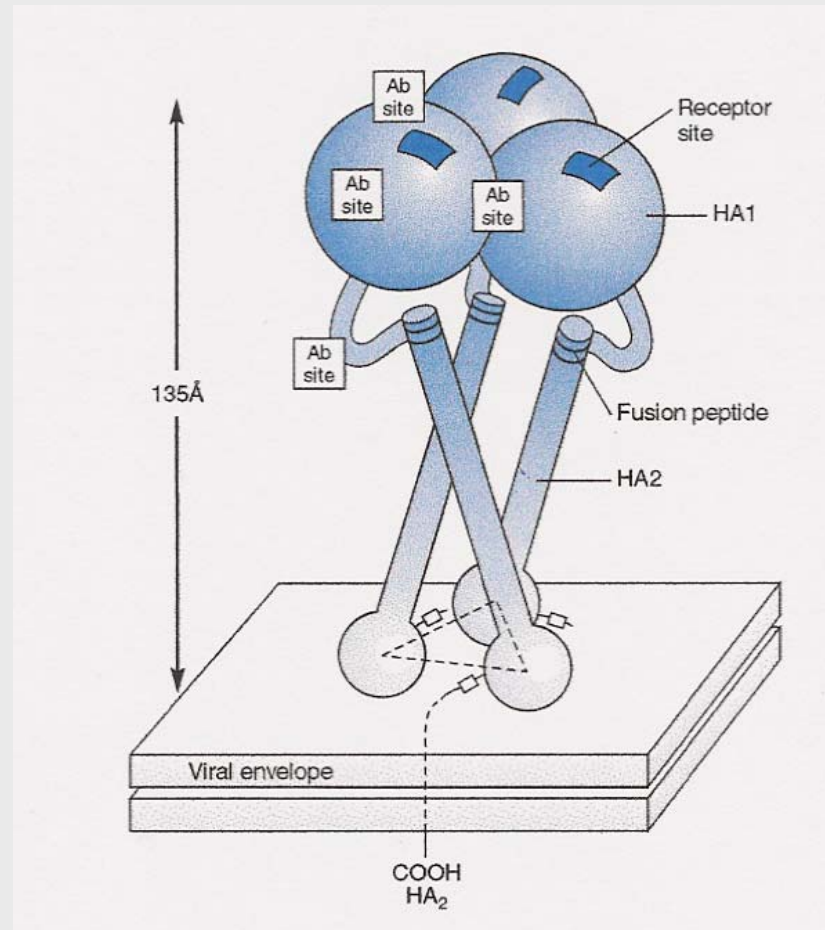
THE NEUTRALIZING ANTIBODY ENIGMA



if CD4 can dock why can't IgG block attachment?

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Influenza virus has a receptor site on each trimer head and can be neutralized by antibodies that bind to any of four different sites that are near the receptor binding site. Viral escape mutants can be selected for each of these neutralizing antibody sites

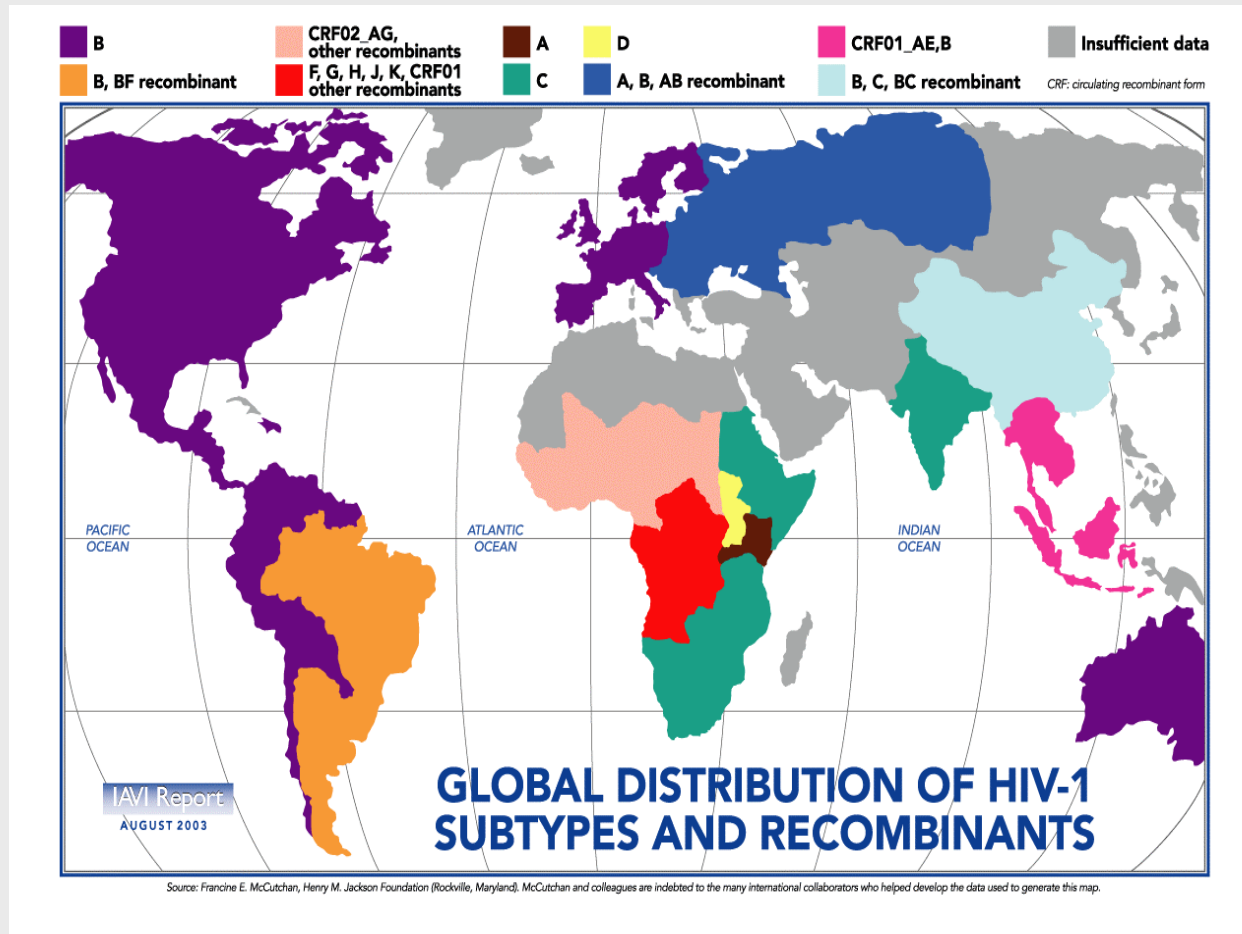


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**CROSS CLADE
IMMUNITY?**

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THERE ARE ABOUT 10 DISTINCT CLADES (GENOTYPES) OF HIV-1



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ARE THE ~10 CLADES DISTINCT IMMUNOTYPES?

- **Will neutralizing antibody cross clades?**
- **Will cellular immunity cross clades?**
- **Relevance of conserved vs variable epitopes?**
- **Are multivalent HIV-1 vaccines needed?**

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MULTICLADE VACCINE IS EQUAL TO MONOCLADE VACCINE

Rhesus monkeys immunized with env DNA @ 0, 4, 8 wks; rAdV env DNA @ 26 wks

Tested 1 week post vaccine

Letvin et al, 2003

env IMMUNOGEN BY CLADE mg DNA				env RESPONSES BY CLADE IFN ELISPOT/10⁶ PBL		
A	B	C		A	B	C
-	4.5	-		1200	2900	1300
-	-	4.5		1500	1200	2700
1.5	1.5	1.5		2500	2200	2600

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CURRENT STATUS OF AIDS VACCINES

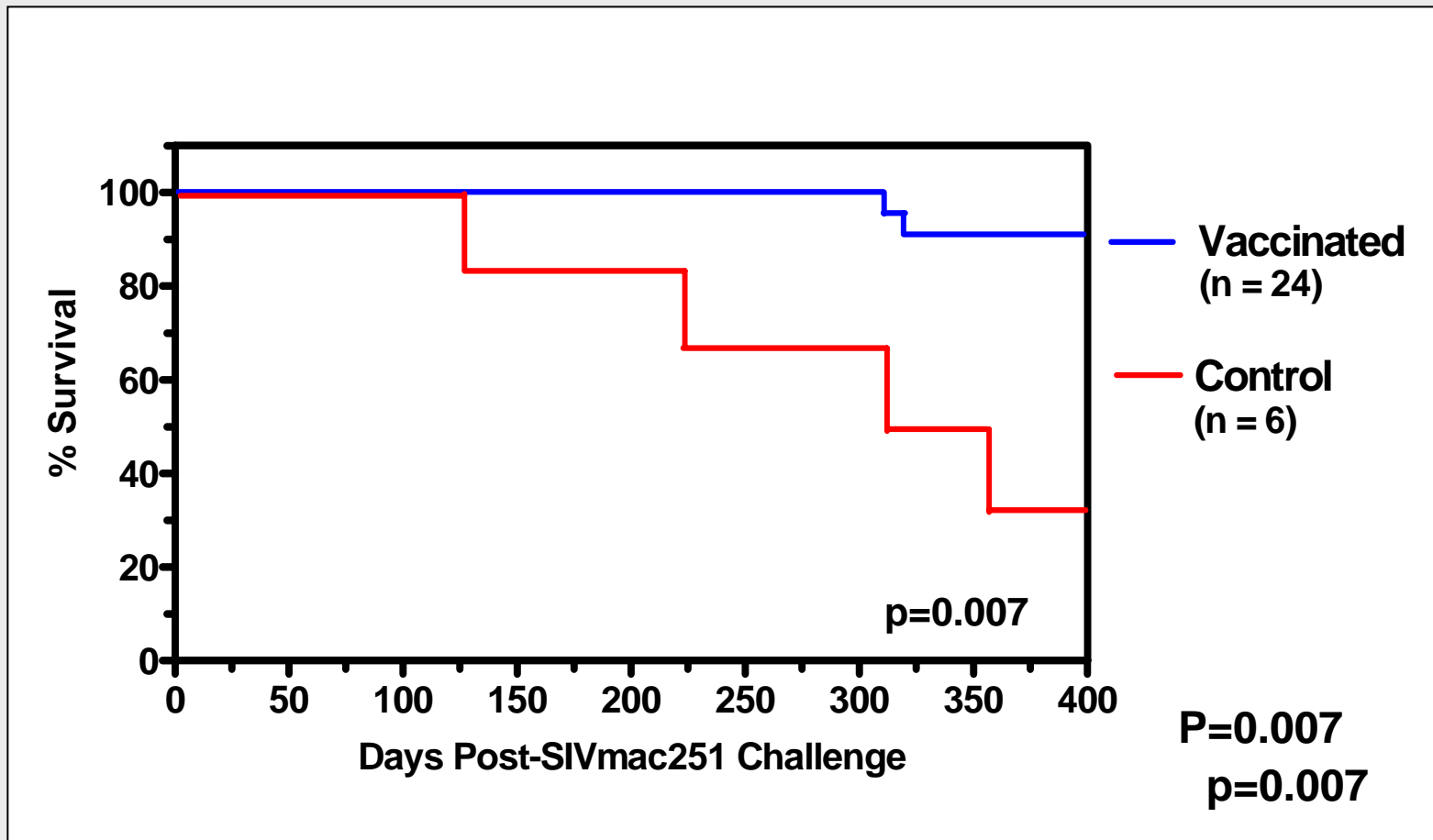
TOWARDS AN HIV VACCINE

vaccine provides partial protection in SIV model

rDNA plus rAdv (SIV239 gag, pol, env) immunization

iv SIV 251 (heterologous) challenge

Letvin et al, unpublished, 2005



TOWARDS AN HIV VACCINE

lessons from poliovirus vaccine

“In 1945, Professor Burnet of Melbourne wrote ‘While I was in America recently I had good opportunity to meet with most of the men actively engaged on research in poliomyelitis...The part played by acquired immunity to poliomyelitis is still completely uncertain, and the practical problem of preventing infantile paralysis has not been solved. It is even doubtful whether it ever will be solved.’

...most of us doing research on poliomyelitis in 1945 were mainly motivated by curiosity, rather than by the hope of a practical solution in our lifetime.”

David Bodian, 1976

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