



HIV VACCINE  
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# HIV vaccine development: a scientific challenge and a public health necessity

Ann Duerr, MD, PhD, MPH

HIV Vaccine Trials Network

November, 2007



# Almost 2 decades of HIV vaccine research

- more than 30 products tested
- more than 85 trials conducted
- Thousands of volunteers, investigators & staff from over 25 nations participated in clinical trials
- more than \$3 billion invested





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**So where are we now?**



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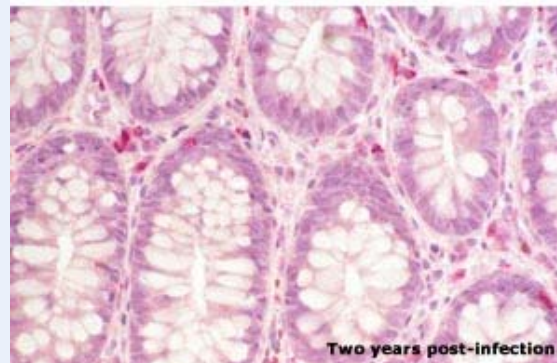
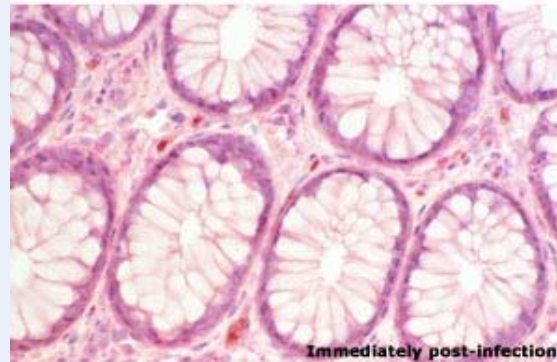
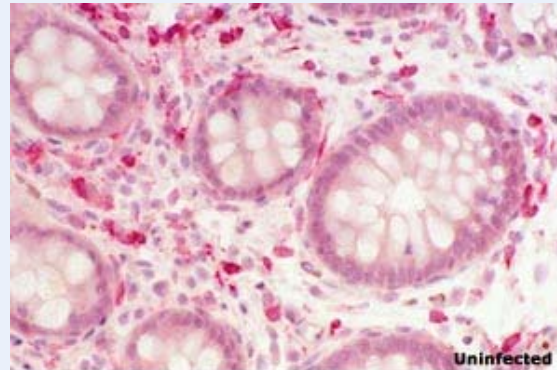
## Overview

1. Why do we need an HIV vaccine?
2. What does an HIV vaccine need to do?
3. How do we measure vaccine efficacy?
4. Update on recent data from efficacy testing of HIV vaccines.



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## HIV strikes fast: CD4 memory cells massively depleted in 1st weeks



(Image courtesy of Rockefeller University)



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## Other efforts fall short...

### Other preventive efforts

- Education, counseling & behavioral interventions
- STDs: early detection & treatment
- Safe blood supply
- Circumcision
- Microbicides – not yet
- Barrier methods – condoms but not diaphragm
- Antiretroviral therapy
  - PEP and PrEP – potentially helpful but unproven and controversial
  - Reduction of HIV transmission: only a small fraction of 36 million infected have access to HAART

**Preventive HIV vaccine is critically needed!**



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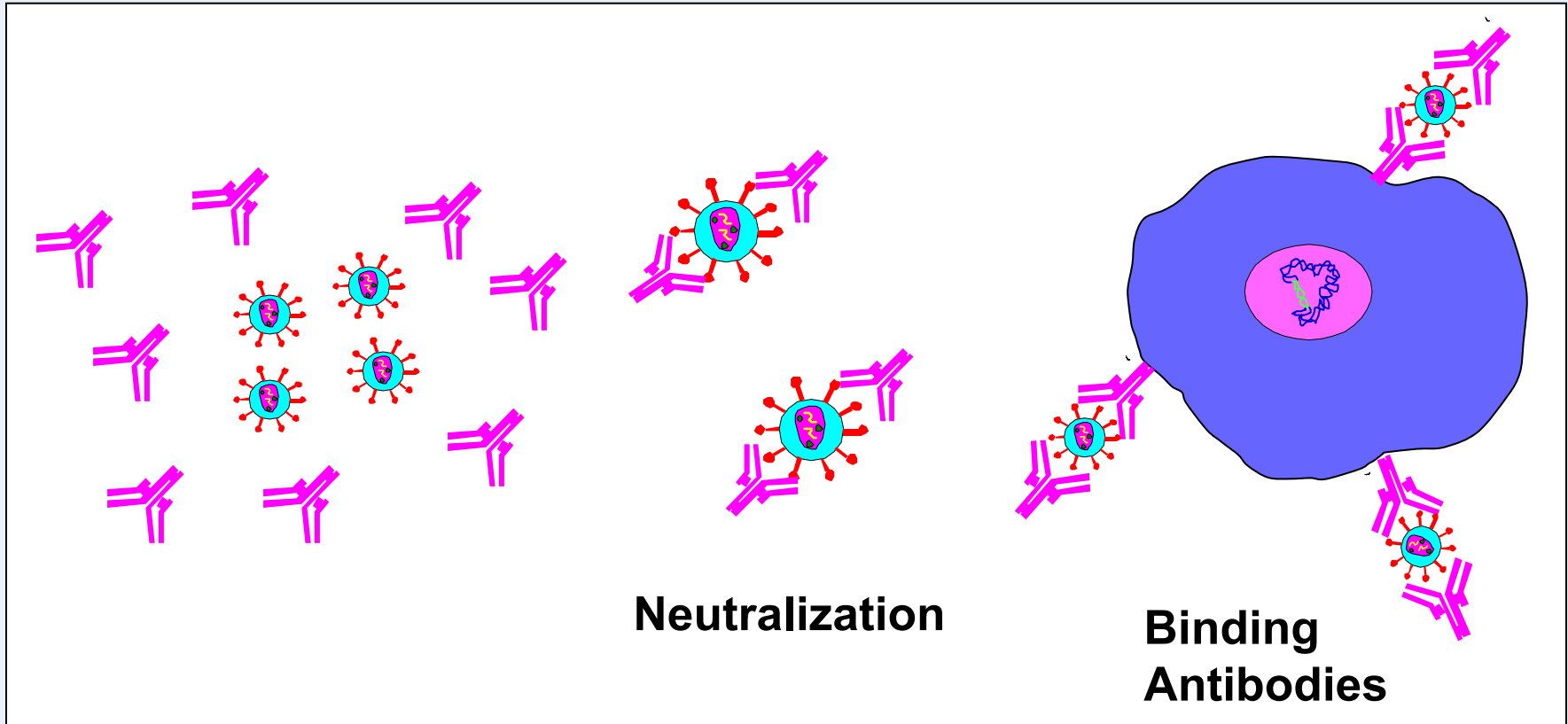
## Goals for an HIV Vaccine

- Prevent infection
- Abort infection early on
- Allow persistent infection with mild or no disease



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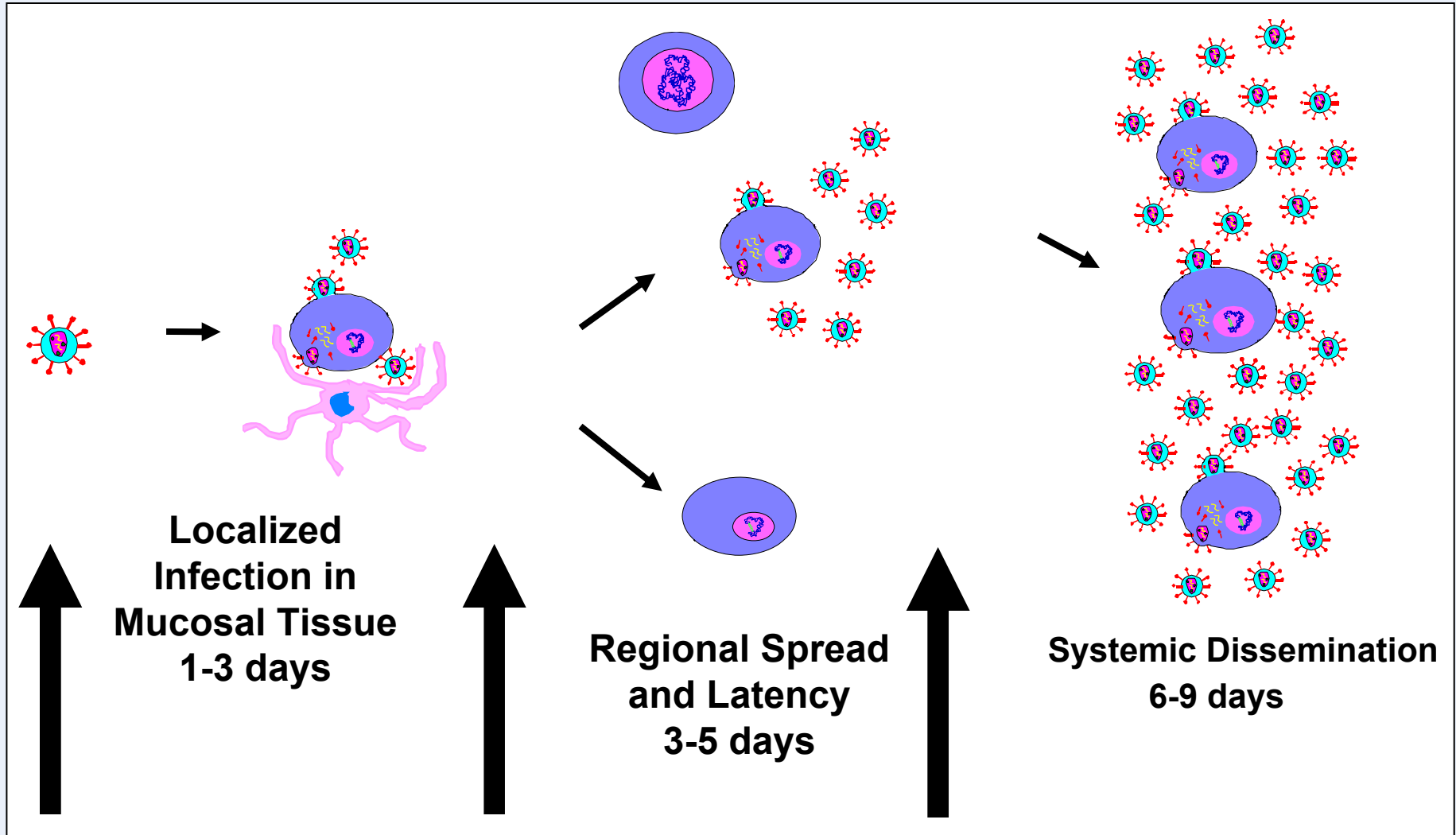
# Vaccines could elicit neutralizing antibodies to bind up free virions





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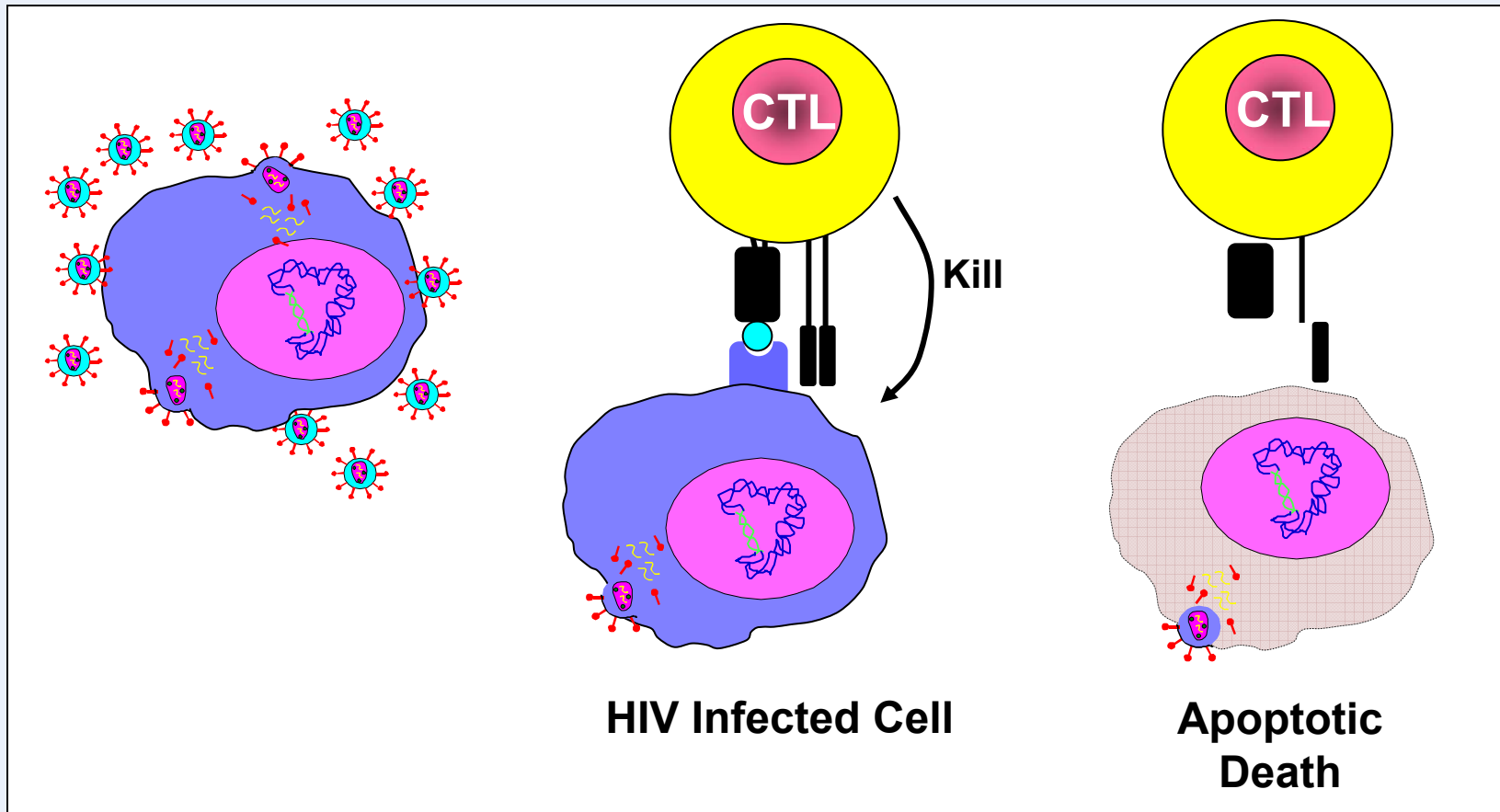
# These immune responses act early and could block infection





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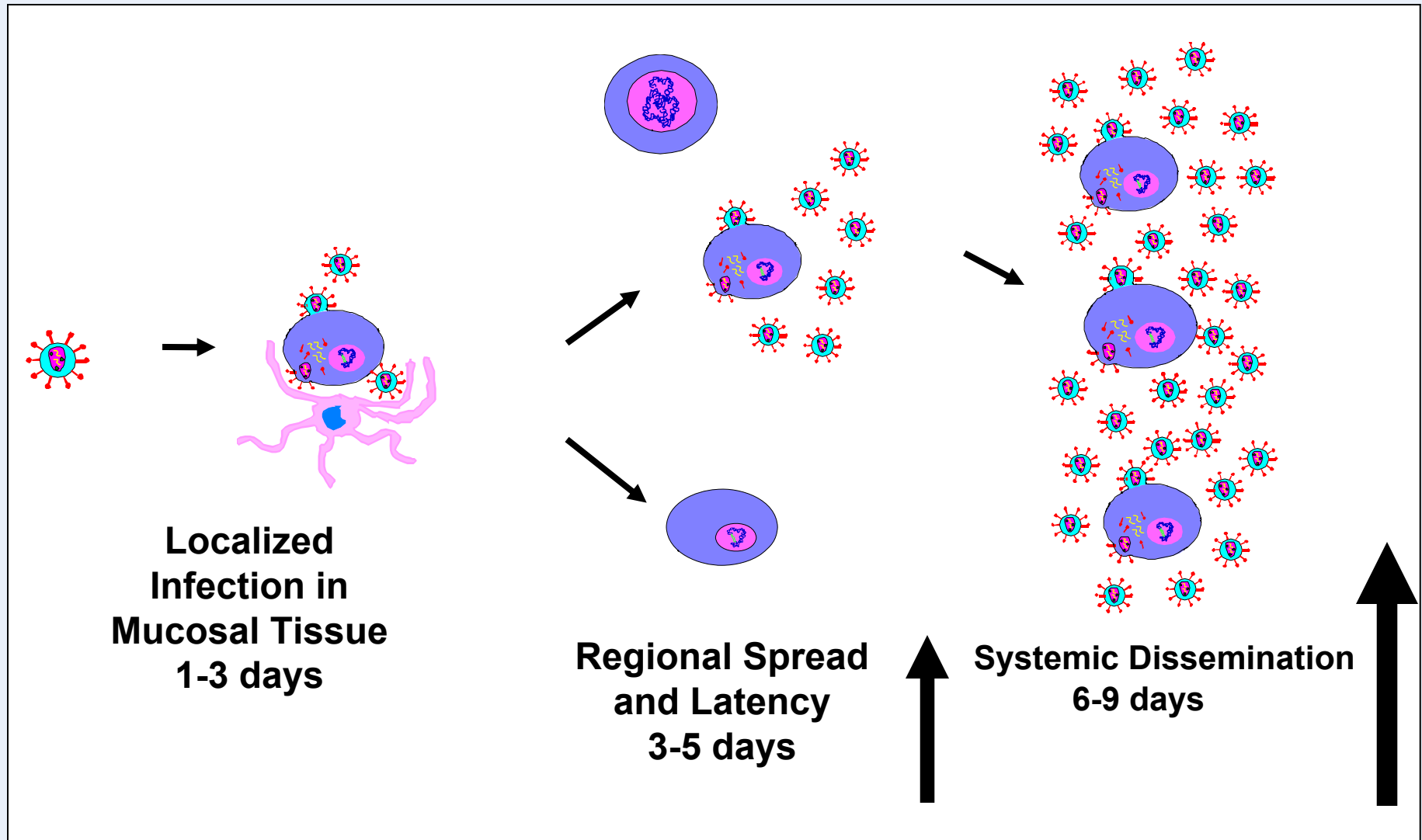
# Vaccines could produce T-cell memory to eliminate HIV-infected cells





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# These immune responses act later and may not block infection





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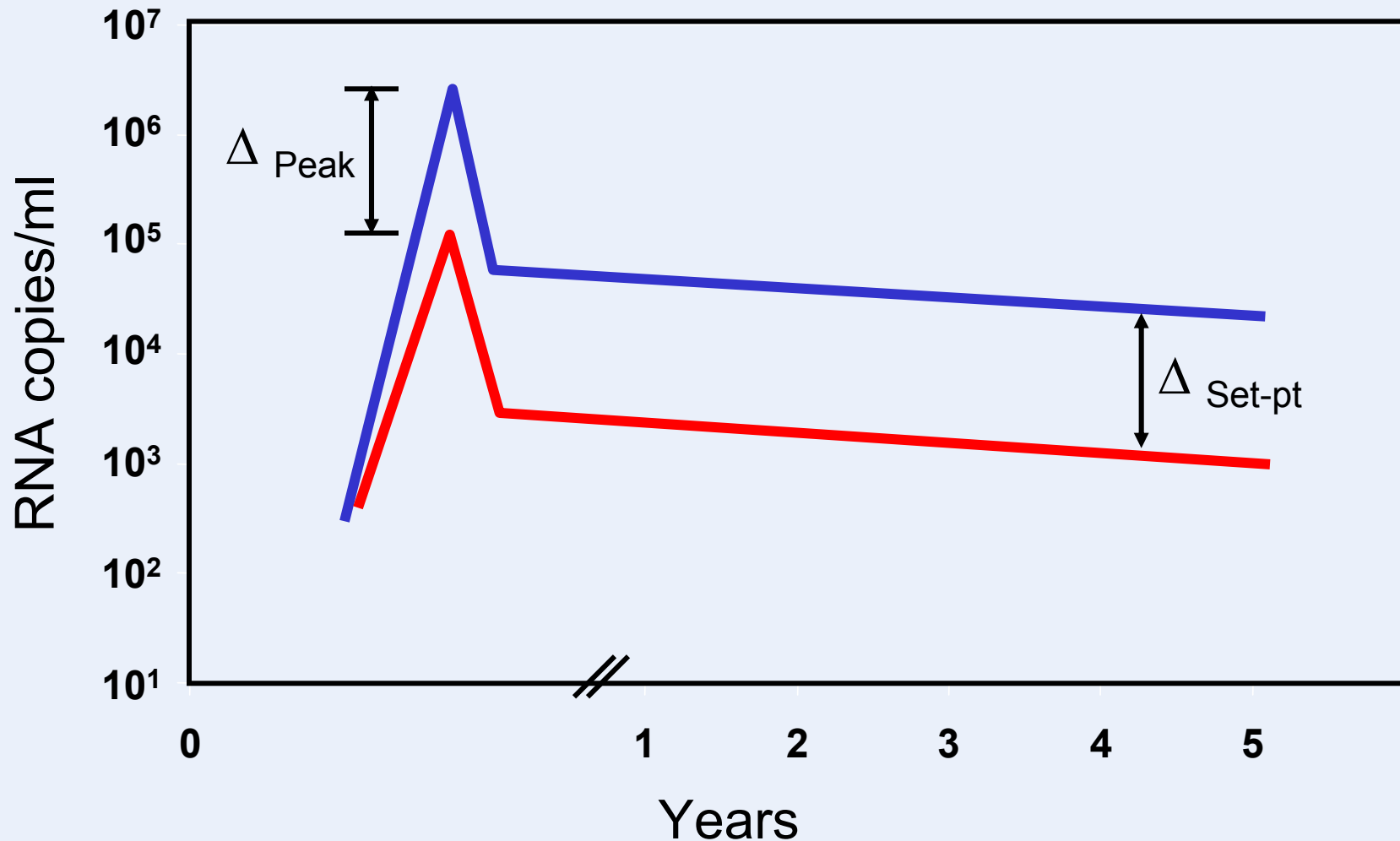
## Vaccine Efficacy: Susceptibility, progression & infectiousness

- $VE_S$ : Vaccine efficacy susceptibility
  - In uninfected individuals, reduction in risk of acquiring HIV
- $VE_P$ : Vaccine efficacy disease progression
  - In individuals who become HIV infected, reduction in the cumulative risk of progressing to AIDS or death
- $VE_I$ : Vaccine efficacy infectiousness
  - In individuals who become HIV infected, reduction in the risk of transmitting HIV to others



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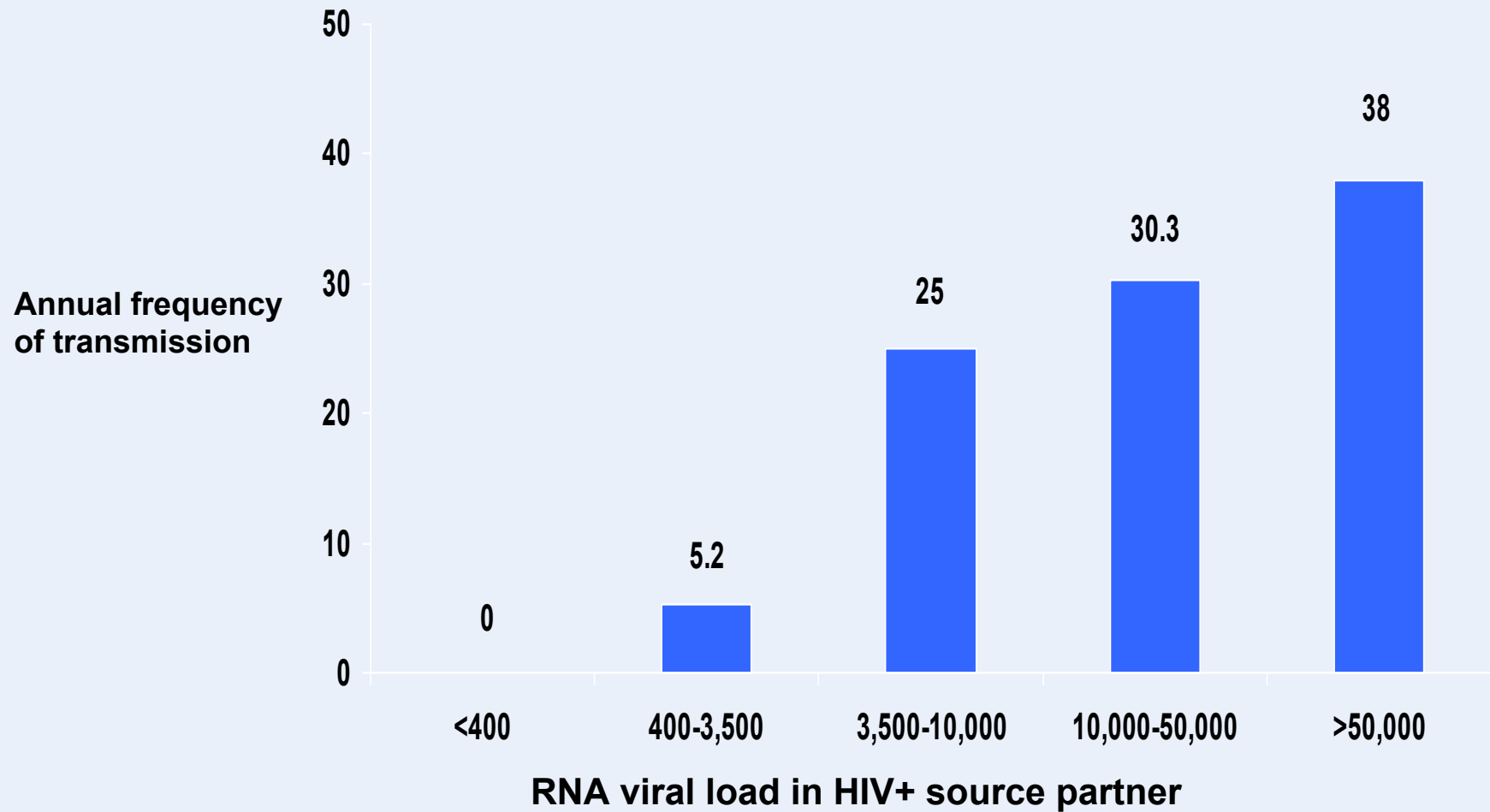
## VEp: reduction in VL set-point may ameliorate disease





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## VEi: lowered viral load may reduce transmission



Quinn et al, NEJM 342:921-9, 2000

# Overview of Experimental HIV Vaccine Designs

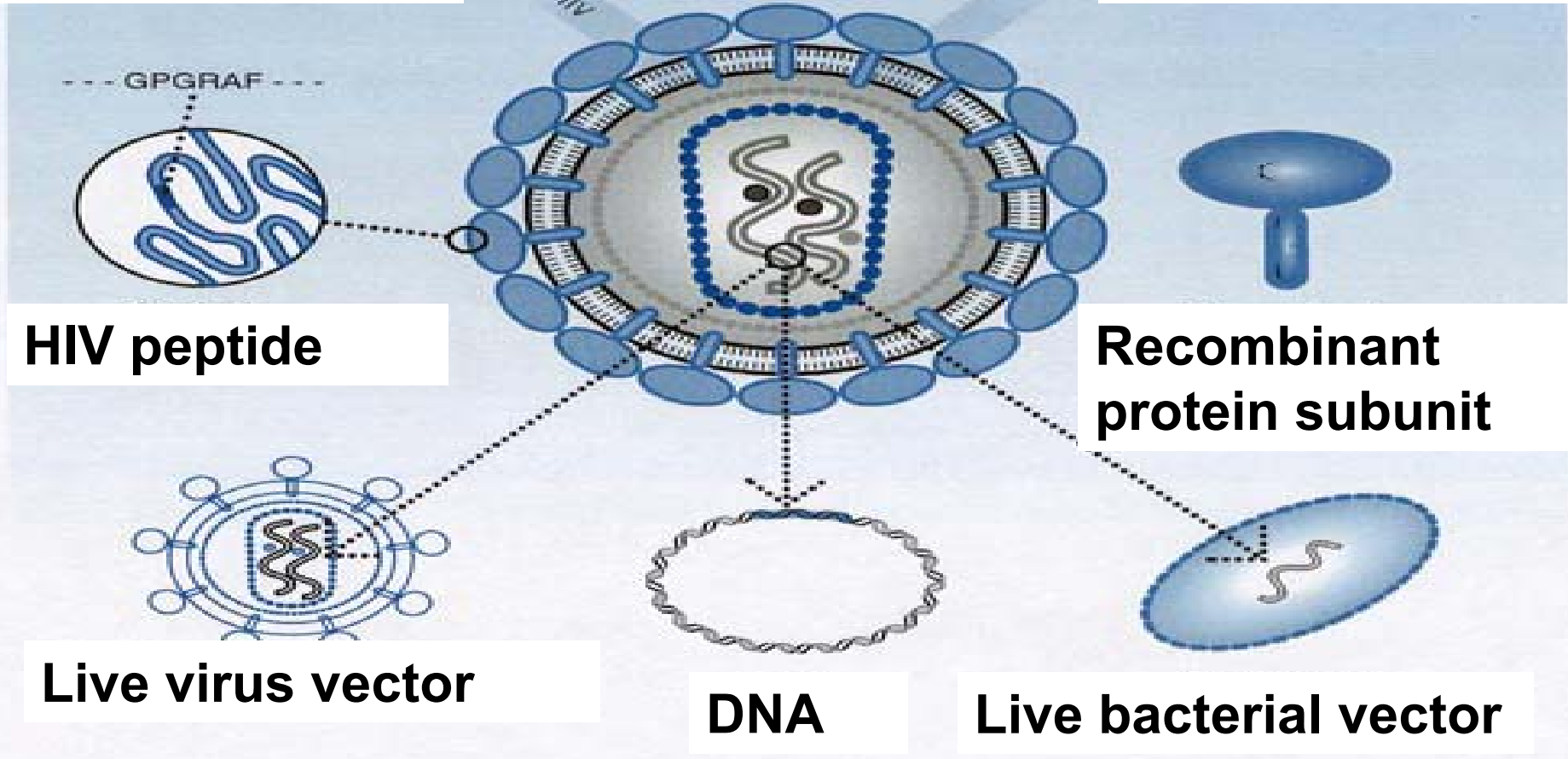


## Other Designs

- Combination Vaccines
- "Jennerian" Vaccines
- Virus-like Particles
- Complex Vaccines

**Whole inactivated**

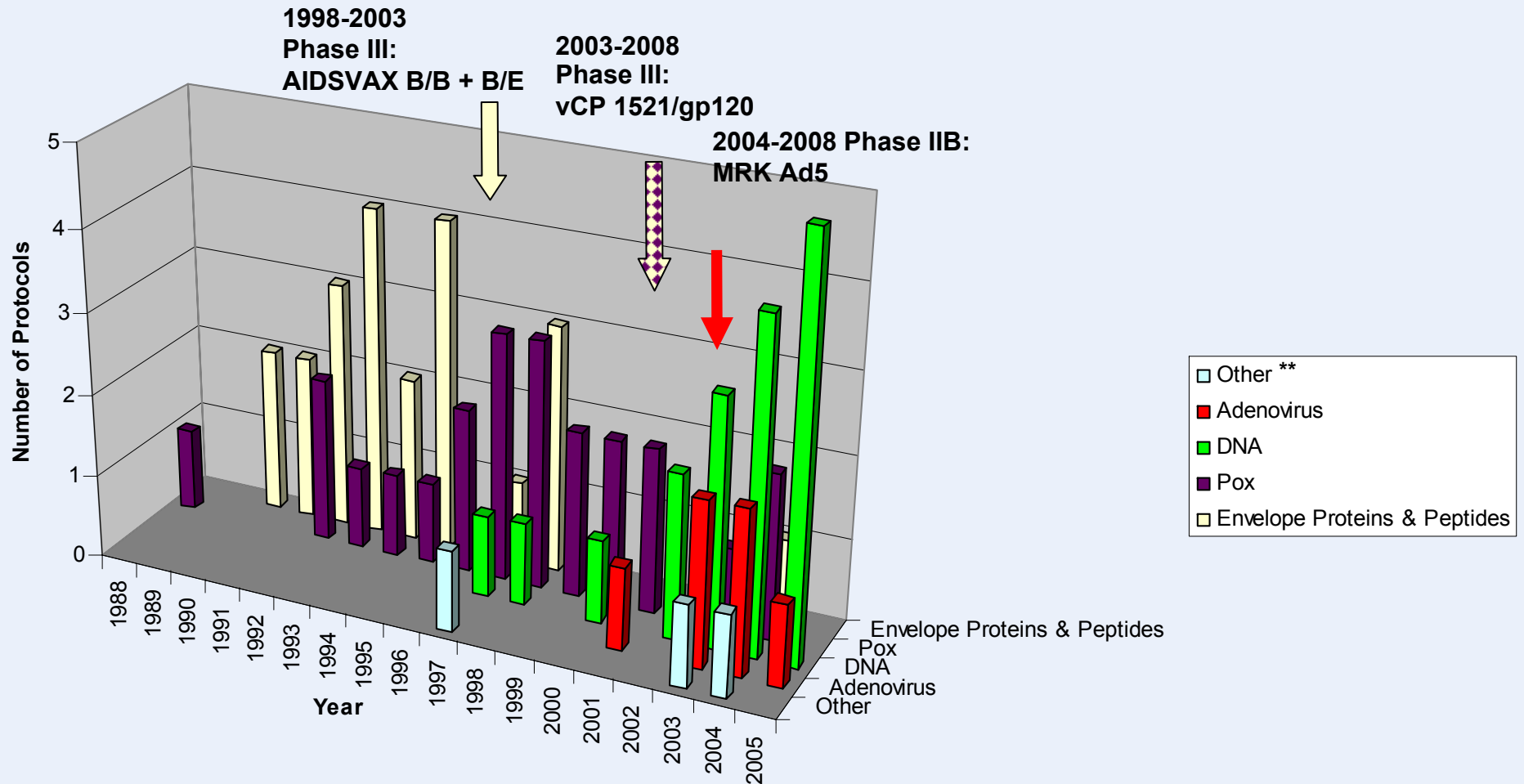
**Live Attenuated**





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# Clinical Trials of HIV Vaccines, 1988-2005\*



\*includes AVEG, HIVNET, HVTN, Merck, VRC, & selected USMHRP trials

\*\* Other includes Alphavirus and Salmonella vectors



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# The Washington Post

MONDAY, FEBRUARY 24, 2003

## 1st AIDS Vaccine in Large Test Found to Be Mostly Ineffective

By DAVID BROWN  
*Washington Post Staff Writer*

The first AIDS vaccine tested in a large population of people at high risk for the disease has proven to be largely ineffective, according to data released early today by the vaccine's manufacturer.

AIDSVAX reduced the rate of infection 3.8 percent in people receiving the vaccine, compared with those who received placebo injections, said VaxGen, based in Brisbane, Calif. Vaccines generally need to be at least 70 percent effective in reducing infection from human immunodeficiency virus (HIV) to gain approval for widespread use. VaxGen officials had said that a real-world efficacy of 30 percent for AIDSVAX might be enough to make the product useful in some populations.

The vaccine appeared to be effective, however, in a subgroup of recipients, notably African Americans. Among them, 2 percent who received the vaccine became infected with HIV, compared with 8.1 percent who were given the placebo—a statistically significant difference. When Asians and mixed-race volunteers were added to the group of blacks—totaling, in all, about 500 of the 5,000 volunteers—the protective effect was nearly as strong.

"It appears that blacks, Asians and the other non-white volunteers were able to induce a higher level of antibody than others. There appears to be a correlation between that and protection. We need to continue to do more analysis," VaxGen spokesman James Key said of that finding.

Company officials were not available to comment on what their next step will be. They scheduled two telephone conferences with reporters and investors today.

The vaccine was tested in 5,417 volunteers at high risk for HIV infection in the United States, Canada, Puerto Rico and the Netherlands. The company is testing a similar vaccine in Thailand, but the results of that study will not be known until later this year.

More than a dozen vaccines have been tested in small numbers of people for their ability to stimulate immunity or, in some cases, slow the progression of HIV infection. The AIDSVAX trial, however, was the first one to test a vaccine's ability to protect against infection in a large and diverse population of volunteers.

The vaccine consists of a protein, called gp120, that is on the outer surface of the AIDS virus and is one of many viral structures that stimulate production by the immune system of disease-fighting antibodies. In this case, the gp120 was made by recombinant DNA technology, not by extraction from the virus itself.

About twice as many people were randomly assigned to be given the vaccine as to receive a placebo, or inactive, immunization. The vaccination schedule consisted of three initial shots spaced three months apart, and then booster shots every six months. Although slightly more than 5,400 people were enrolled in the study, only 5,009 received at least three shots. The results announced today were limited to them.

Over three years, 5.7 percent of the people receiving AIDSVAX became infected with HIV, compared with 5.8 percent of people receiving the placebo shots.

It is unclear what significance the finding of variable efficacy among different racial groups might mean in terms of the vaccine's possible usefulness. Although some racial and ethnic groups are at higher risk for certain infections—and therefore are more urgent targets for a vaccine's use—licensing vaccines for specific racial groups is without precedent.

The volunteers in this trial consisted of 5,108 gay or bisexual men, and 309 women at high risk of HIV infection because they are the sexual partners of those men, or of intravenous drug users. All of the volunteers were given frequent counseling to practice safer sex, and not to count on protection from the vaccine.



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# rgp120 Vaccine: No Effect on HIV-1 Acquisition

## MAJOR ARTICLE

### **Placebo-Controlled Phase 3 Trial of a Recombinant Glycoprotein 120 Vaccine to Prevent HIV Infection**

The rgp120 HIV Vaccine Study Group

654 • JID 2005:191 (1 March) • rgp120 HIV Vaccine Study Group



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## rgp120 Vaccine: No Effect on HIV-1 Disease Progression

### MAJOR ARTICLE

# **HIV-1 Virologic and Immunologic Progression and Initiation of Antiretroviral Therapy among HIV-1–Infected Subjects in a Trial of the Efficacy of Recombinant Glycoprotein 120 Vaccine**

Peter B. Gilbert, Marta L. Ackers, Phillip W. Berman, Donald P. Francis, Vladimir Popovic, Dale J. Hu, William L. Heyward, Faruk Sinangil, Bryan E. Shepherd, and Marc Gurwith

974 • JID 2005:192 (15 September) • Gilbert et al



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# Trials of Vaccines Designed to Elicit T Cell Immunity



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## The ALVAC + gp120 Thai trial

- A large (n = 16,000), simple trial with the sole goal of determining efficacy, cost ~\$120m.
- Primary end-point: protection from infection
- Secondary endpoint: protection from disease
- Initial assumption was ~5% infection rate, observed rate may be much less



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## The ALVAC + gp120 Thai trial

**Science**

**POLICY FORUM**

PUBLIC HEALTH

### A Sound Rationale Needed for Phase III HIV-1 Vaccine Trials

Dennis R. Burton,<sup>1</sup> Ronald C. Desrosiers,<sup>2</sup> Robert W. Doms,<sup>3</sup> Mark B. Feinberg,<sup>4</sup>  
Robert C. Gallo,<sup>5</sup> Beatrice Hahn,<sup>6</sup> James A. Hoxie,<sup>3</sup> Eric Hunter,<sup>6</sup> Bette Korber,<sup>7</sup>  
Alan Landay,<sup>8</sup> Michael M. Lederman,<sup>9</sup> Judy Lieberman,<sup>2</sup> Joseph M. McCune,<sup>10</sup>  
John P. Moore,<sup>11</sup> Neal Nathanson,<sup>3</sup> Louis Picker,<sup>12</sup> Douglas Richman,<sup>13</sup> Charles Rinaldo,<sup>14</sup>  
Mario Stevenson,<sup>15</sup> David I. Watkins,<sup>16</sup> Steven M. Wolinsky,<sup>17</sup> Jerome A. Zack<sup>18</sup>

Science 303, 316 (16 January 2004)

**Science**

**POLICY FORUM**

POLICY REBUTTAL

### HIV Vaccine Trial Justified

John G. McNeil,<sup>1\*</sup> Margaret I. Johnston,<sup>1</sup> Deborah L. Birx,<sup>2</sup> Edmund C. Tramont<sup>1</sup>

Science 303, 961 (13 February 2004)

A difference of opinion exists over the merits of this trial.  
It is fully enrolled and results are expected in 2009.



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**Yesterday's News  
November 8, 2007**

## **The New York Times**

**“In tests, AIDS vaccine seemed to increase risk”**

## **The Wall Street Journal**

**“Merck HIV vaccine may have made some more susceptible to the virus”**

## **The Seattle Times**

**“Failure of AIDS vaccine punctures soaring hopes”**



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# The story behind the headlines

## Efficacy testing of Ad5 vector vaccine

### 2 Test-Of-Concept Studies

- Guide later development
- May use surrogate endpoint or prototype product
- Study population may be limited and focused
- Smaller, cheaper, faster

### STEP: Testing MRK Ad5 trivalent clade B HIV vaccine

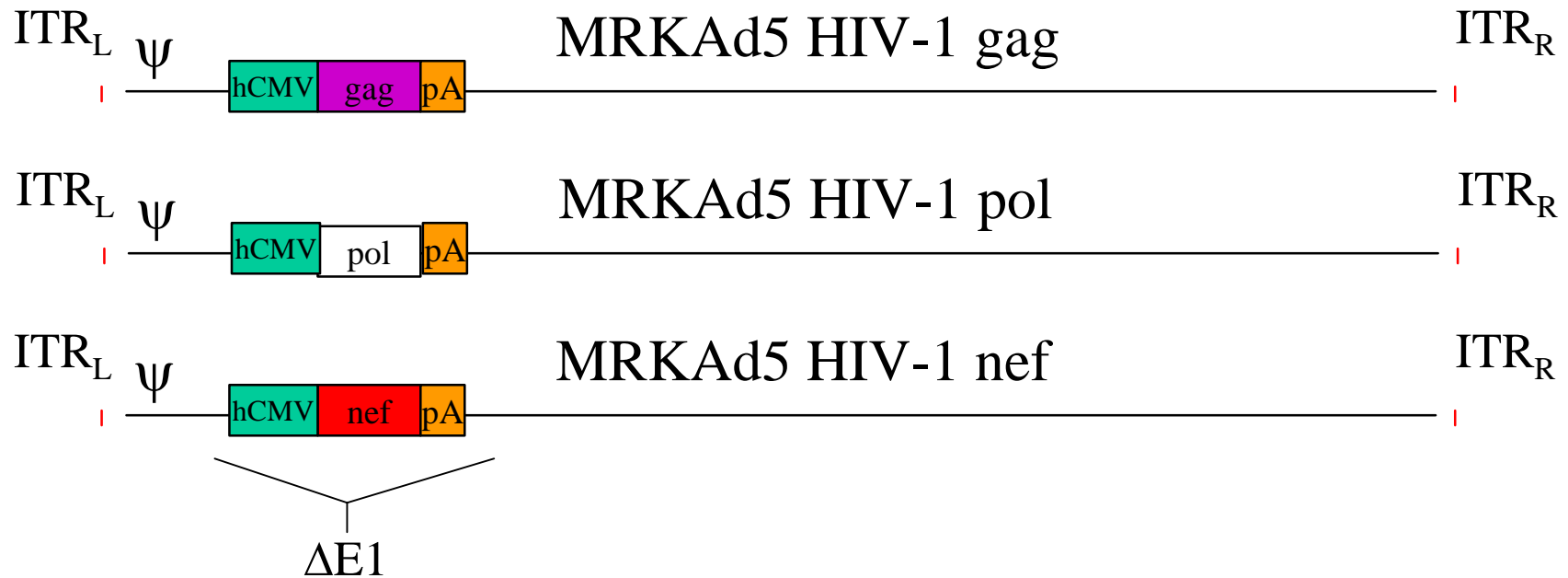
- Decrease HIV acquisition and/or
- Reduce viral load set-point
- Initiated in population thought to be most likely to benefit
  - Participants in clade B regions
  - Low prior immunity to Ad5

Phambili: planned for 3000 in South Africa (clade C region)



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## MRKAd5 trivalent clade B HIV vaccine

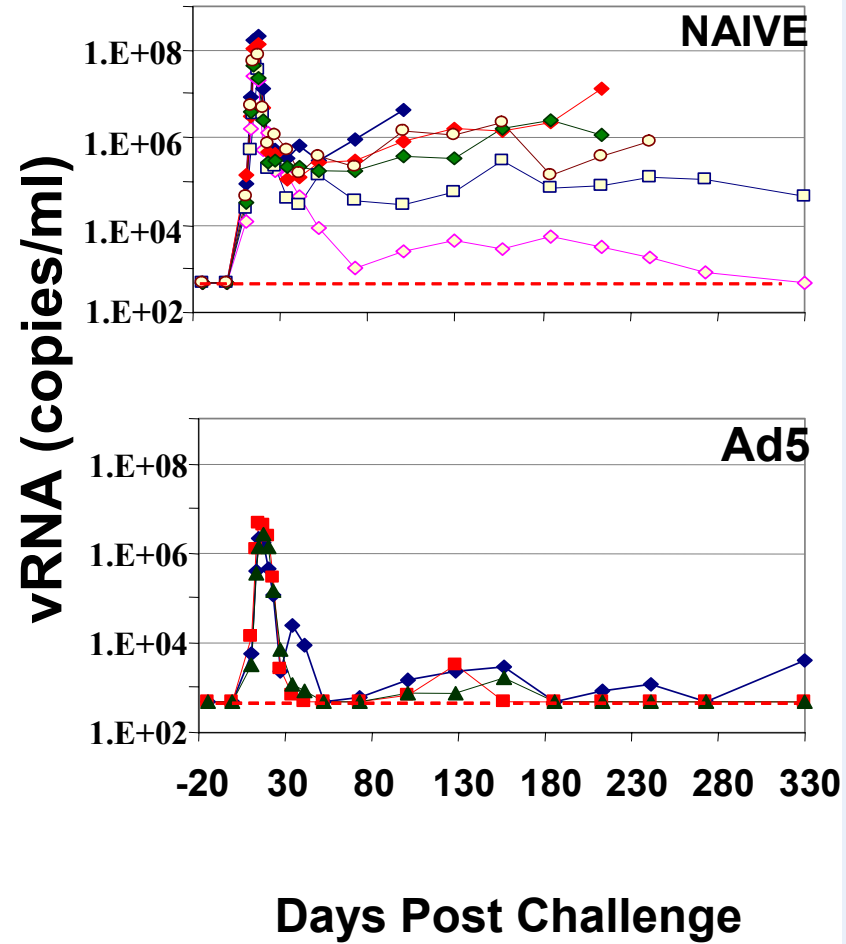
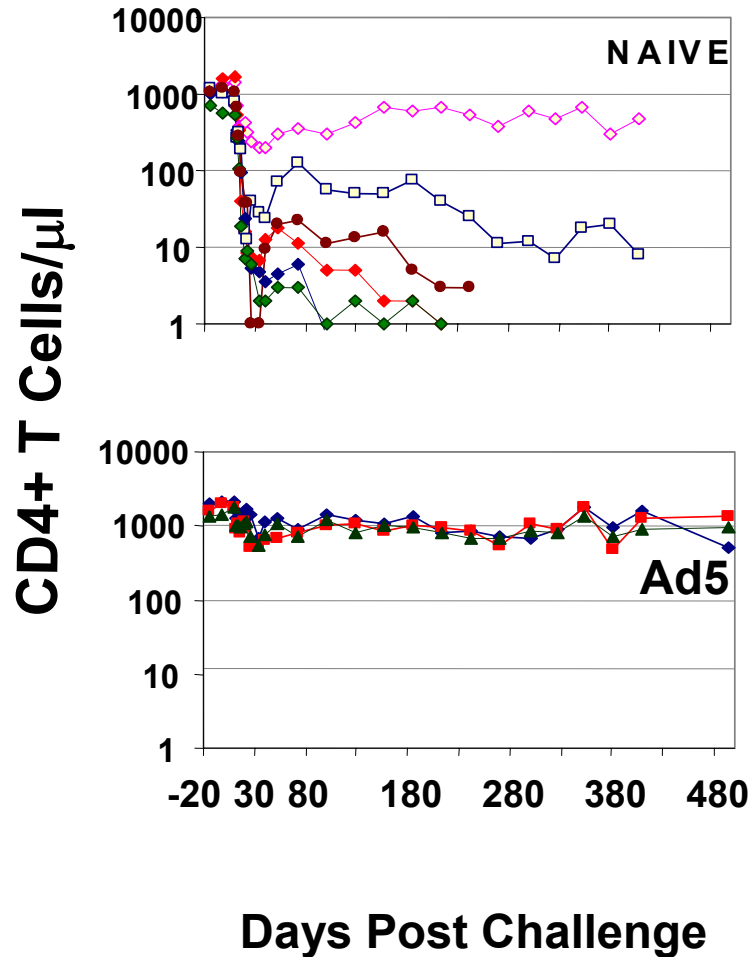


- Vaccine: 1:1:1 admixture of 3 Ad5 vectors
  - Encoded transgenes: codon-optimized, near-consensus clade B HIV-1 sequences
- Placebo: vaccine dilution buffer without Ad5



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# Improved course after SHIV challenge in Ad5-SIV gag immunized rhesus monkeys

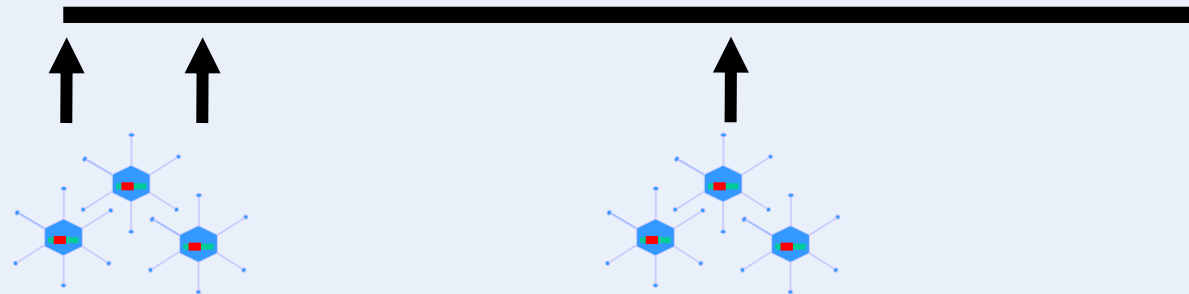




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# STEP Study Design

Months 0 1 2 3 6 9 12



## 3 Adeno vectors:

clade B gag

clade B pol

clade B nef



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## STEP Study: primary hypotheses

### Efficacy

- Subjects who receive the vaccine will have a lower likelihood of acquiring HIV-1 infection than those who receive placebo,
  - AND/OR
- Among subjects who become HIV-1 infected, those who receive the vaccine will have a smaller average viral load set-point than those who receive placebo.

### Safety



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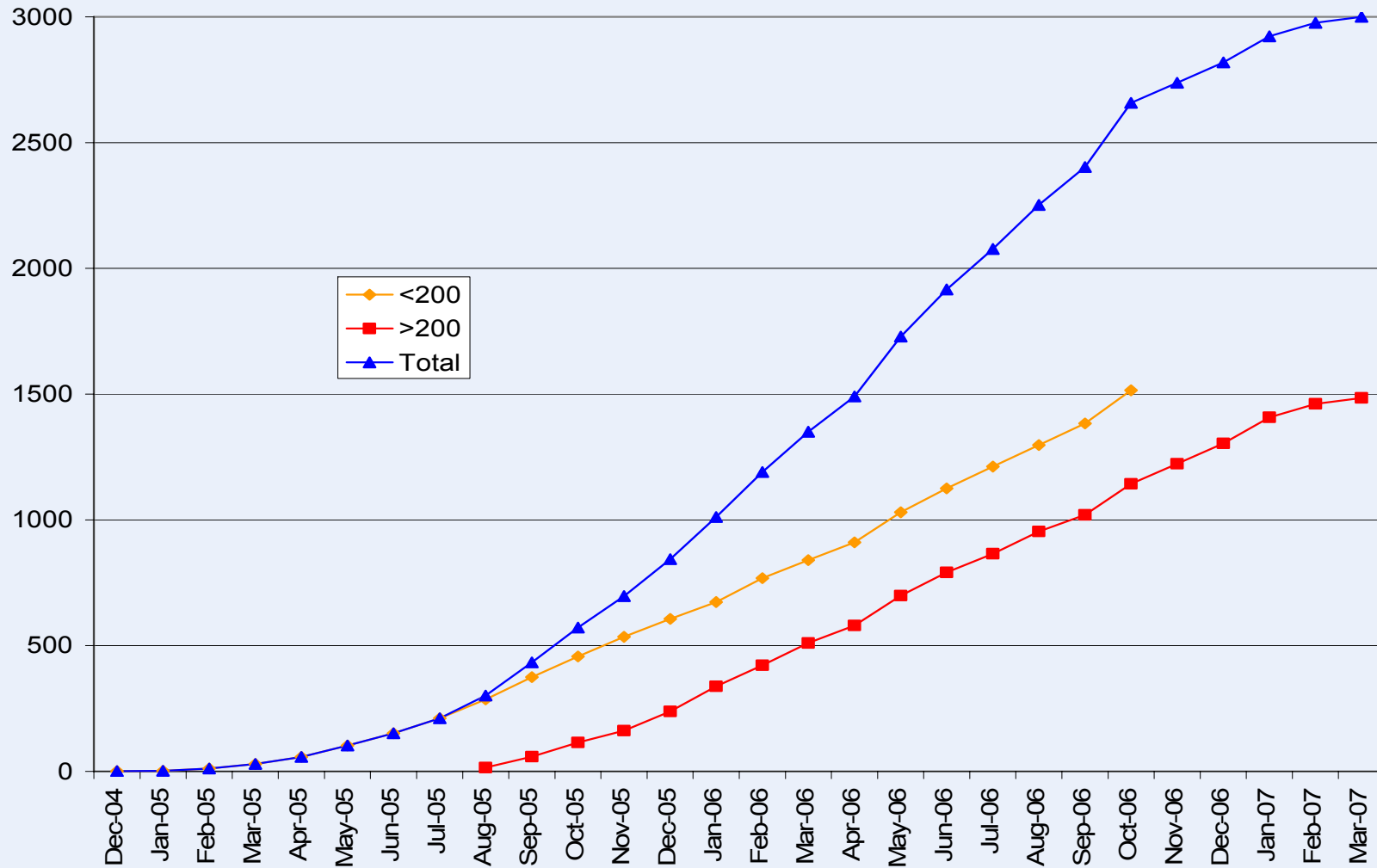
## STEP Study design: Ad5 stratification

- Initial trial design: 1500 HIV-negatives with low ( $\leq 200$ ) Ad5 titers
- July 2005: add 1500 HIV-'s with high ( $> 200$ ) Ad5 titers
- Maintained original study hypotheses in low Ad5 group as primary:
- Secondary hypotheses same but for entire study population ( $\leq 200$  and  $> 200$ )
- Enrollment stratified by Ad5 titer
  - $< 18$ ,
  - 18-200,
  - 201-1000,
  - $> 1000$



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# Enrollment in high Ad5 stratum lagged behind low Ad5 stratum





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## The STEP Study inclusion criteria

- Between 18 and 45 years old
- IDU not excluded but must have sexual risk factors.
- MSM
  - Unprotected anal intercourse with another man
  - Anal intercourse with  $\geq 2$  male sexual partners
- Women
  - Unprotected vaginal or anal intercourse with a man known to be HIV-1 infected
  - Unprotected vaginal or anal intercourse with a man who uses injection drugs
  - Exchanged sex for money, drugs, services, or gifts
  - Used crack cocaine at least 3 times



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## STEP Study sites





# STEP Study Data and Safety Monitoring Board (DSMB)

## Members & their institutions not directly involved in STEP

- Vaccine specialist / physicians
- Statisticians
- Ethicist

## Meets 3 times per year

- Reviews unblinded data on safety
- Reviews study operations

## Two planned interim analyses for efficacy and futility

- 30 infections in the Ad5 titer  $\leq$  200 group (primary analysis)
- 30 infections in the Ad5 titer  $>$  200 group and at least 30 in the Ad5  $\leq$  200 group
- Futility assessment: p-value  $>$  0.50 (1-tailed) for **EACH** endpoint



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# Participant characteristics

## Well-balanced in vaccine vs. placebo

Characteristic	Vaccine Group N = 1494	Placebo Group N = 1506	Total Population N = 3000
	<i>value</i>	<i>value</i>	<i>value</i>
Female sex	38%	38%	38%
Median age	29 years	29 years	29 years
Residence			
- Caribbean	21%	21%	21%
- North America & Australia	56%	57%	56%
- South America	23%	22%	23%
Race			
- Black	30%	30%	30%
- Hispanic	15%	15%	15%
- Multiracial	21%	20%	20%
- White	32%	33%	33%
- Other	2%	2%	2%



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## Racially diverse population; Over 1/3 women

Characteristic	Men N = 1850	Women N = 1150
	<i>value</i>	<i>value</i>
Median Age	30 years	28 years
Residence		
- Caribbean	5%	46%
- North America & Australia	64%	45%
- South America	31%	9%
Race		
- Black	10%	62%
- Hispanic	10%	24%
- Multiracial	25%	7%
- White	50%	5%
- Other	6%	3%
Ad 5 Titer > 200	43%	61%



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## Important differences between men with high vs. low Ad 5 titer

Baseline Characteristics	≤200 Group N = 1066	>200 Group N = 784
Location: United States	73%	44%*
Race: White	61%	34%*
Age: ≤30 yrs old	48%	59%*
Any Drug Use	47%	39%*
Unprotected Anal Receptive Sex	51%	49%
Unprotected Anal Insertive Sex	61%	58%
History of STD	14%	14%
Circumcision status:		
Yes	65%	40%*
No	31%	58%*
No Data	3%	2%

\* P < .05



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## Case split for infection endpoint at 1<sup>st</sup> interim analysis (Ad5 ≤ 200)

	Vaccine	Placebo
Total MITT cases	<b>24</b>	<b>21</b>
Cases <u>included</u> in PP efficacy analysis	<b>19</b>	<b>11</b>

Primary dataset reviewed by DSMB

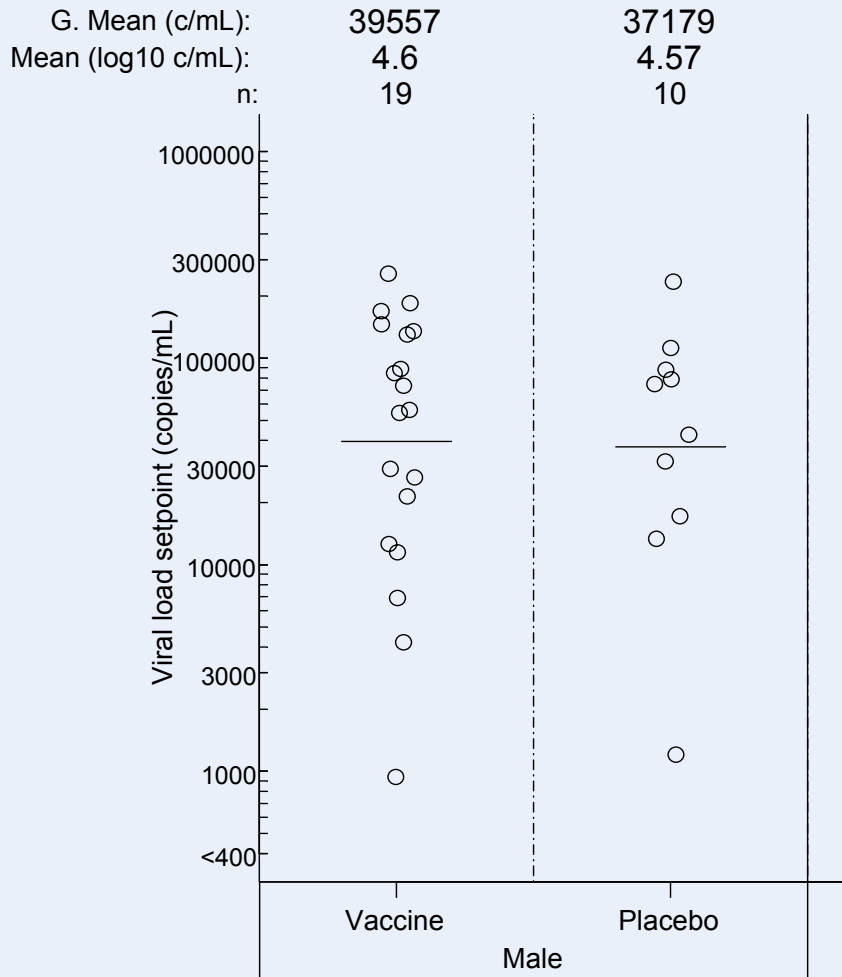


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# VL set-points not different: Ad5 $\leq$ 200

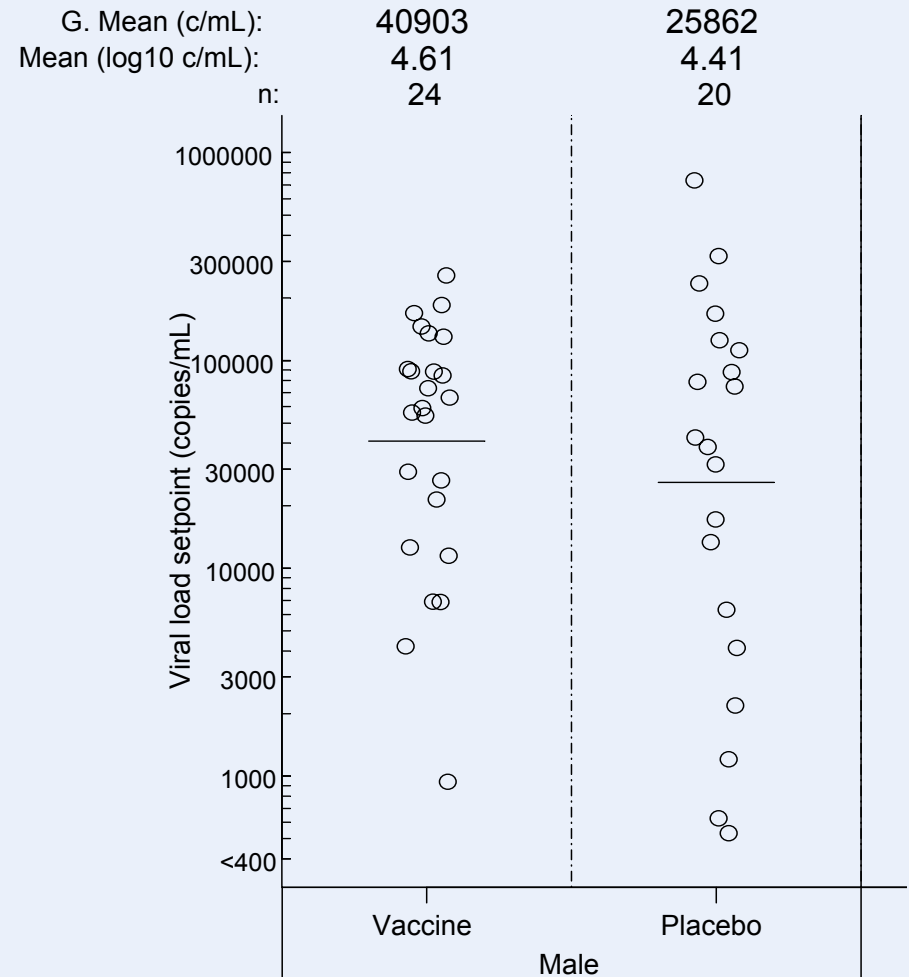
Per-protocol

MITT



— G. Mean (copies/mL)

1-tailed p-value = 0.528 (for  $VE_{VL} > 0$ )



— G. Mean (copies/mL)

1-tailed p-value = 0.656 (for  $VE_{VL} > 0$ )

There was 1 female infection: VLS = 20,207 c/mL (4.31 log<sub>10</sub> c/mL)



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## Futility cutoffs met at first interim analysis

p-value  $> 0.50$  (1-tailed) for **EACH** endpoint

- Trend favored placebo for each endpoint
- Strongly suggests the vaccine neither prevents HIV infection nor reduces the amount of virus

Based on results, DSMB recommended

- No further injections; enrollment in other trials stopped (Phambili)
- Encourage volunteers to return for all visits: is there an increased risk of infection in vaccinees over time
- Trial Oversight Committee determine steps and timing of release of trial results to volunteers, investigators, the public



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## Post hoc analyses focus on men only; MITT population

Since futility declared by DSMB, the team felt it was justifiable to proceed (**cautiously**) with post-hoc analyses

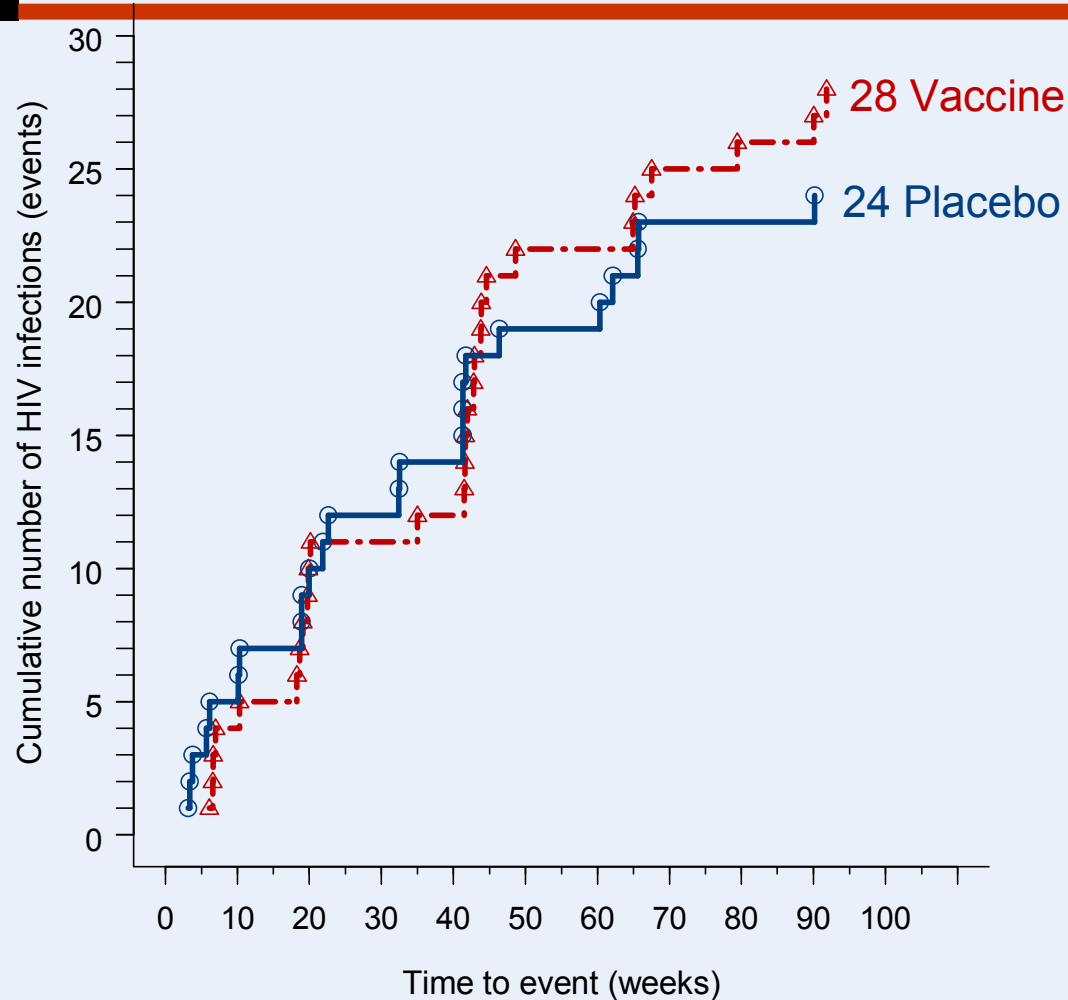
- Only 1 female case, all subsequent analyses in males only
- Additional analyses focus on MITT population: most conservative approach
- Analyses in other Ad5 strata
- Analyses of infection endpoint which include additional cases accrued since first interim analysis
- Focus on reasons for lack of efficacy and the implications

**All analyses which follow are post-hoc**



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# Cumulative Number of HIV Infections: MITT population (males), Ad5 $\leq$ 200



1-tailed p-value = 0.322 (for  $VE_{INF} \neq 0$ )

2-tailed p-value = 0.581 (for  $VE_{INF} \neq 0$ )

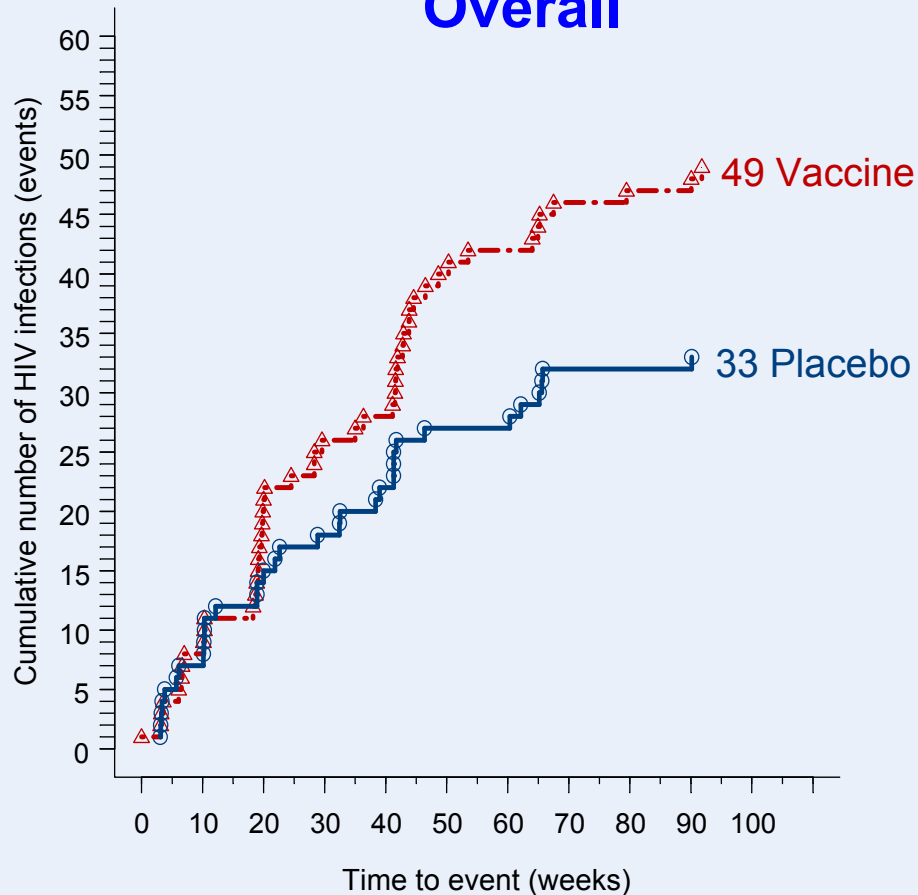
Cases accrued as of Oct 17, 2007



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# Cumulative Number of HIV Infections: MITT population (males)

## Overall

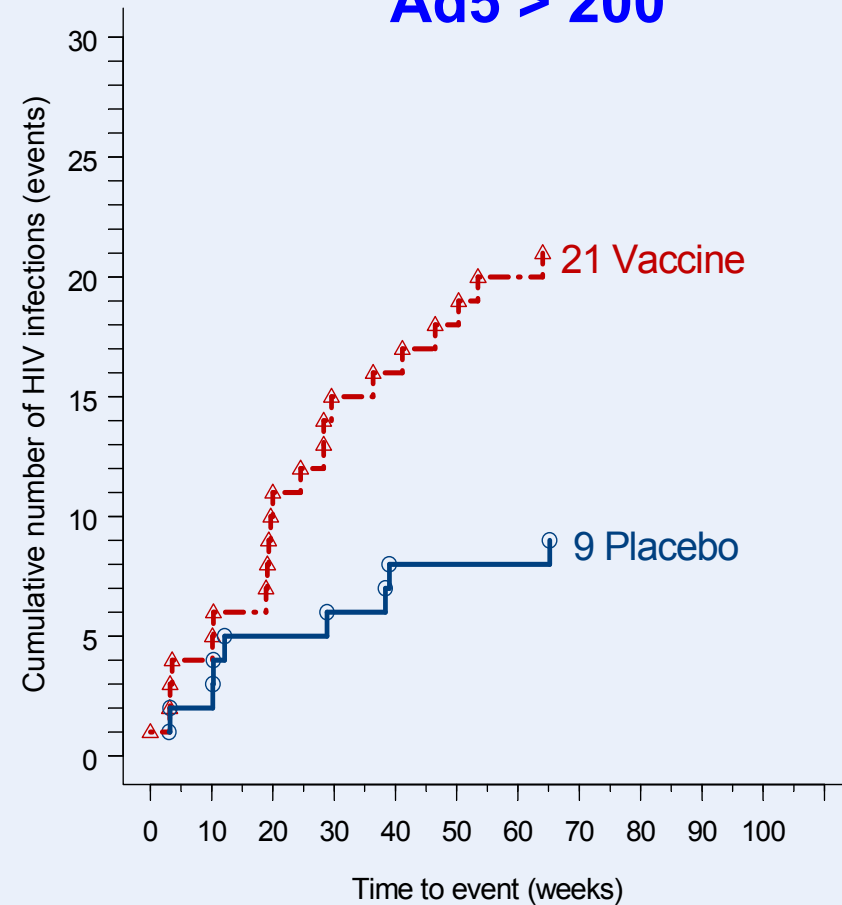


1-tailed p-value = 0.044 (for  $VE_{INF} \neq 0$ )

2-tailed p-value = 0.077 (for  $VE_{INF} \neq 0$ )

Cases accrued as of Oct 17, 2007

## Ad5 > 200



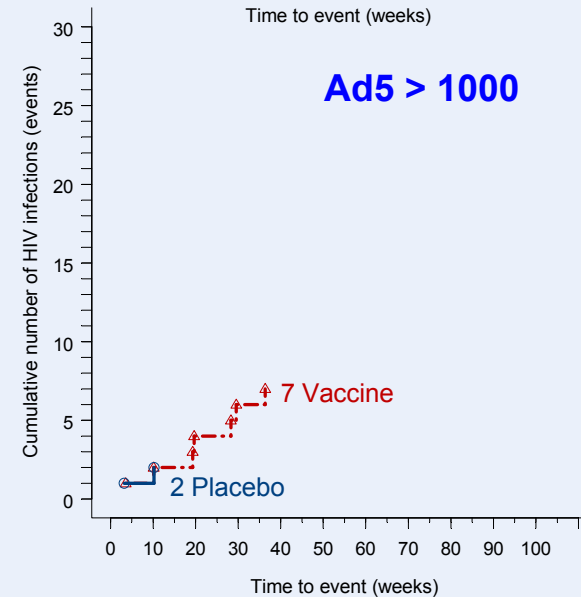
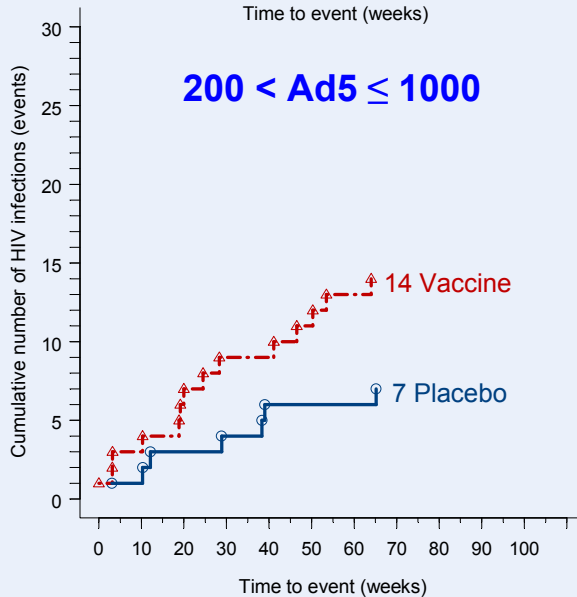
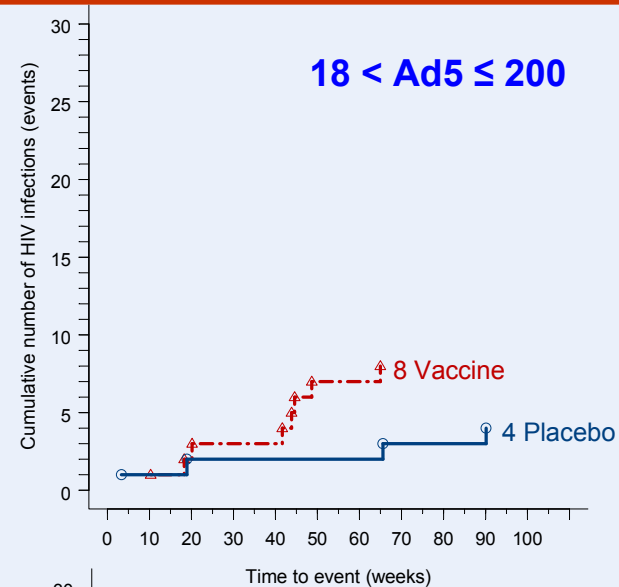
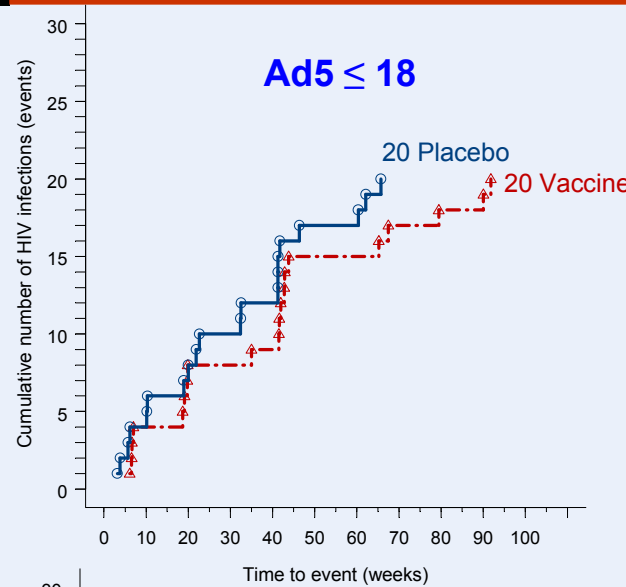
1-tailed p-value = 0.020 (for  $VE_{INF} \neq 0$ )

2-tailed p-value = 0.029 (for  $VE_{INF} \neq 0$ )



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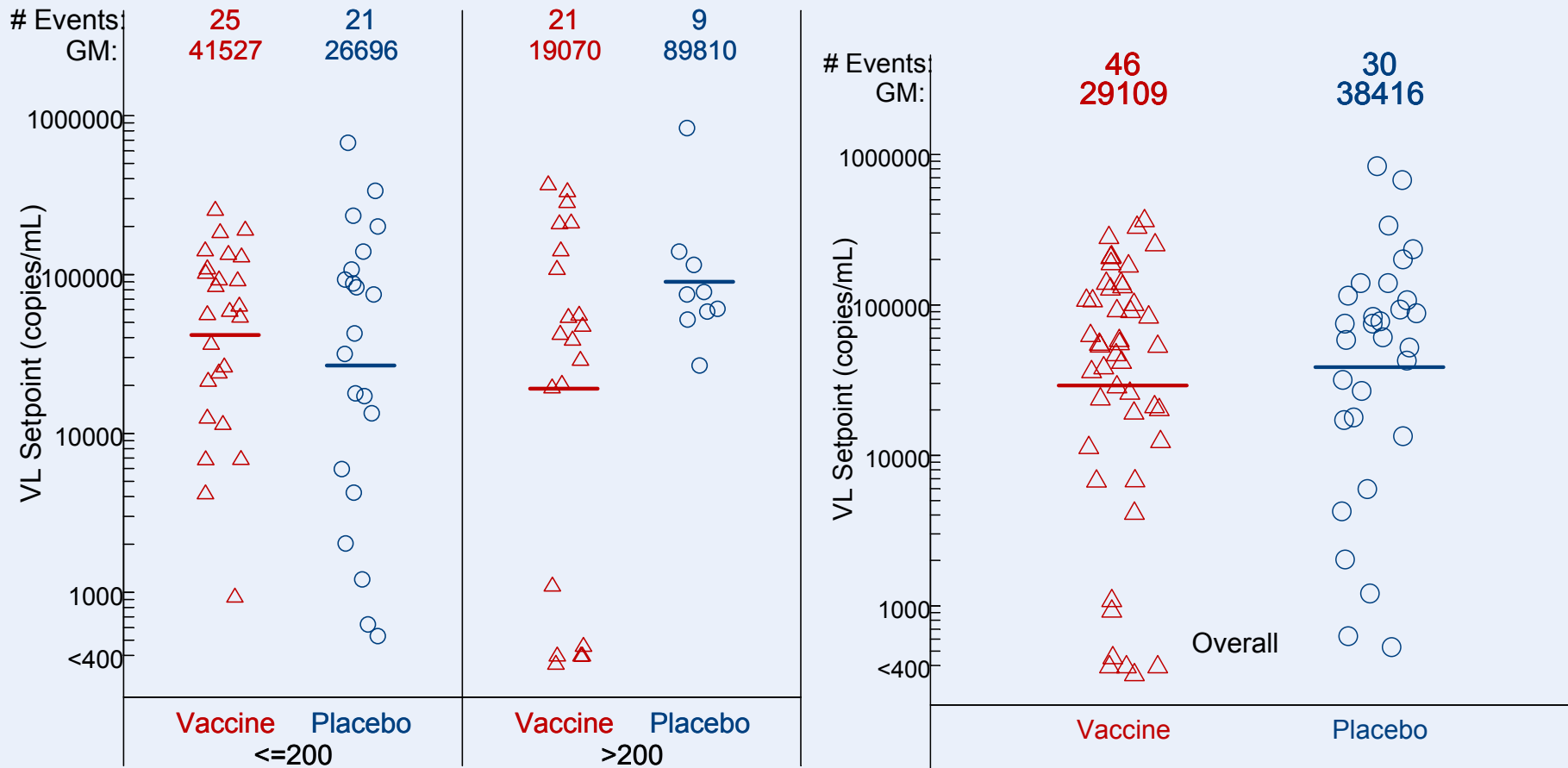
# Cumulative Number of HIV Infections: MITT population (males)





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# No difference in VL Setpoint: MITT population (males)



For subjects with viral load setpoint data available as of Oct 17, 2007.



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## Lack of efficacy not explained by poor immune response

		% Responders		GM ELISPOT	
		Cases	Non-cases	Cases	Non-cases
Vaccine	N	19	143	19	143
	gag	74%	76%	354	260
	pol	63%	73%	627	463
	nef	74%	70%	327	237
Placebo	N	11	171	11	171
	gag	0%	1%	52	28
	pol	0%	2%	109	71
	nef	0%	1%	57	31

Week 8 ELISPOT Responses: Ad5  $\leq$  200

ELISPOT responder:  $\geq$  55 SFC/ $10^6$  PBMC and  $\geq$  4-fold over negative control (mock)

GM ELISPOT is for all subjects

Summaries based on 25% random subset of all subjects and all PP cases



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## Why could vaccinees have higher # of HIV infections in high Ad5 group?

- The differences between vaccine and placebo could be unrelated to the vaccine
  1. Differences at baseline between the groups:
    - Vaccine and placebo groups well matched at baseline
  2. Differences in risk over time
  3. Chance (small number of infections)
- The differences could be due to vaccine
  - Is there an immune response that correlates with this risk?
  - Is this response concentrated in high Ad5 group?
- Does this effect persist?



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## Why would change in risk be different in vaccine and placebo groups?

Double-blinded, so for differences to occur, need:

1. Some participants must correctly “guess” at whether they got vaccine or placebo
  - Based on symptoms from injections or
  - Tested outside of study
2. Participants who believe they received vaccine must behave differently than participants who believe they got placebo



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## No obvious difference in perception of treatment assignment, high Ad5 group

### “Do you think you got vaccine or placebo?”

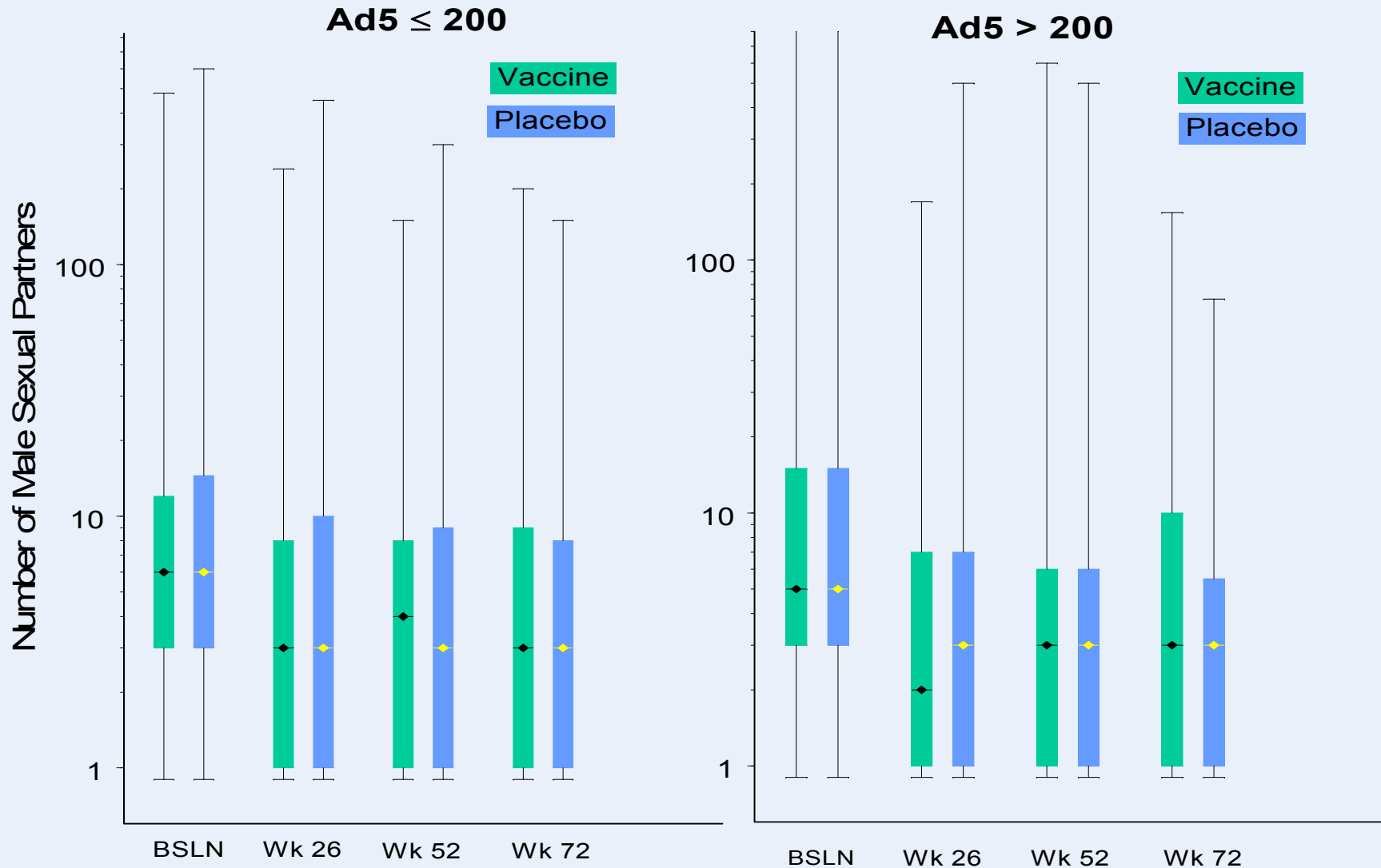
Perception of Treatment Received ↓	Actual Treatment Received			
	Ad5 ≤ 200		Ad5 > 200	
	Vaccine (N = 224)	Placebo (N = 203)	Vaccine (N = 221)	Placebo (N = 219)
“Not Sure”	111 49.6%	116 57.1%	130 58.8%	133 60.7%
“Placebo”	44 19.6%	50 24.6%	36 16.3%	40 18.3%
“Vaccine”	69 30.8%	37 18.2%	55 24.9%	46 21.0%
TOTAL	224 100%	203 100%	221 100%	219 100%

N = number of subjects with data for analysis, recent addition to questionnaire



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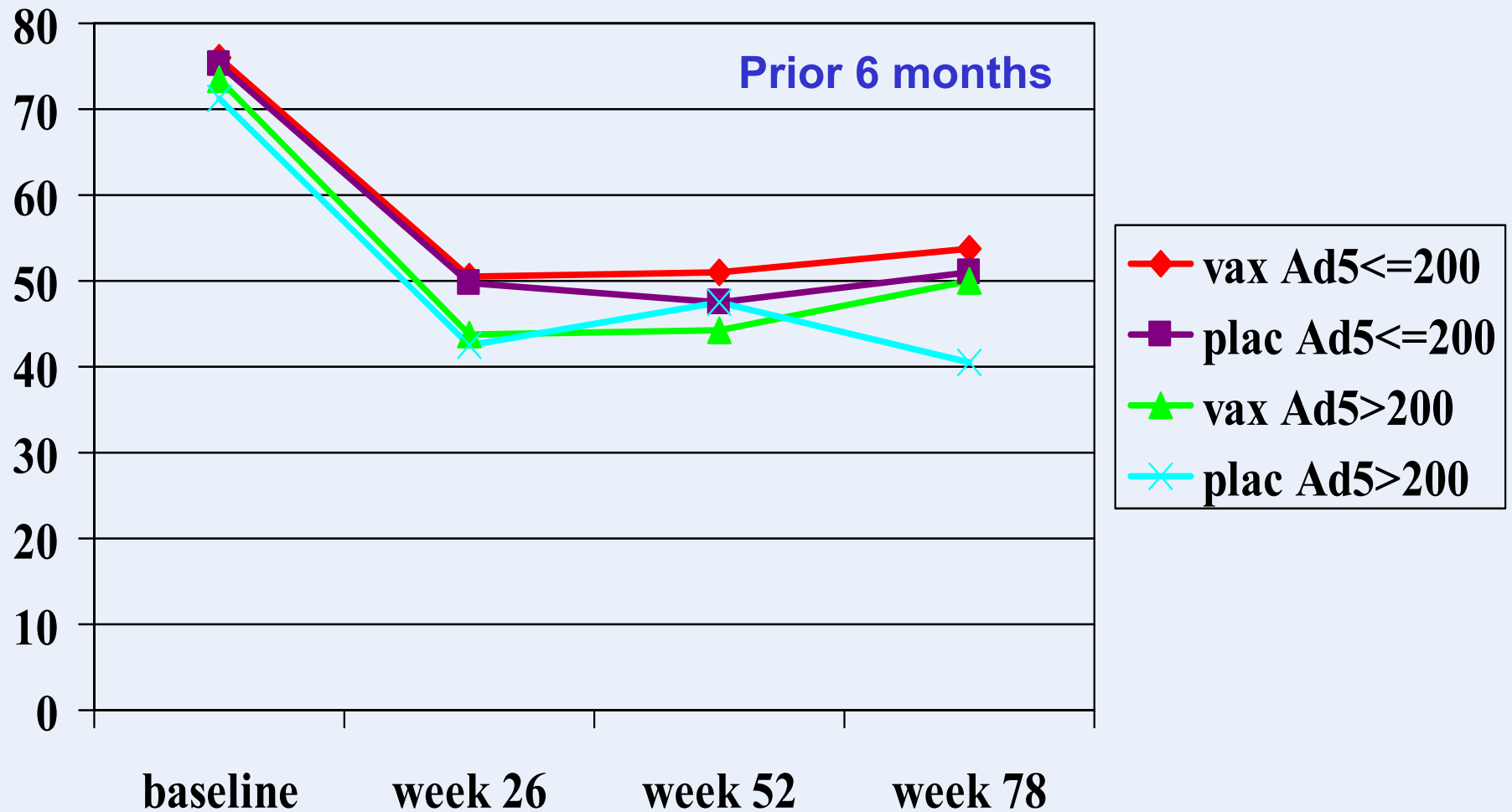
# Number of male sex partners in all groups decreases over time





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## % males reporting unprotected anal sex similar in vaccine & placebo





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## Difference in behavioral risk does not explain differences seen

- Risk declines over time for most behaviors
  - Encouraging, given risk reduction counseling
- On some measures, more risk in low Ad5 than high Ad5 group
  - Another indication that the low and high Ad5 populations may have differences unrelated to the vaccine
- No evidence of differences in knowledge of treatment assignment or risk in high Ad5 vaccine vs. placebo
- P values don't reach threshold after corrections for multiplicity but interpretation tempered by possible harm



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## STEP study results: bottom line

**Well designed trial,  
timely assessment of  
lack of efficacy**

**In Ad5-naïve men, same  
number of infections in  
vaccine and placebo**

**Men with prior Ad5  
immunity: higher # of  
infections in vaccinees**

**Explanation unclear,  
immunologic  
assessments ongoing**





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## What now?

- Continued Phase I testing
  - Alternative Adenovirus vectors (Ad35, Ad26, Ad6)
  - DNA / MVA
  - DNA / NYVAC
  - DNA plus electroporation
  - Alphavirus vectors
- Phase IIB Test-of-concept trial of multiclade, multigene DNA prime with Ad5 boost
- New approaches to eliciting neutralizing antibody



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## A reminder of our need for resolve

“Never give in — never, never, never, never, in nothing great or small, large or petty, never give in except to convictions of honour and good sense. Never yield to force; never yield to the apparently overwhelming might of the enemy.”

Winston Churchill



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## A more recent reminder

“Today, let us commit ourselves to developing an AIDS vaccine..... There are no guarantees. It will take energy and focus and demand great effort from our greatest minds. But.... it is no longer a question of whether we can develop an AIDS vaccine, it is simply a question of when.”

Bill Clinton

May, 1997



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# An AIDS Vaccine



**Our Best Minds.  
Our Best Science.  
Our Best Hope.**