



Vaccine Research Center

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Should There be Further Efficacy Testing of T-cell Based Vaccines that do not Induce Broadly Neutralizing Antibodies?

International AIDS Vaccine 2008 Conference
Cape Town
South Africa

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October 15, 2008

What Do We Want from an AIDS Vaccine?

- 1. Prevent infection (acquisition)**
- 2. Prolong survival and/or time to treatment**
- 3. Decrease transmission**

What Do We Want from an AIDS Vaccine?

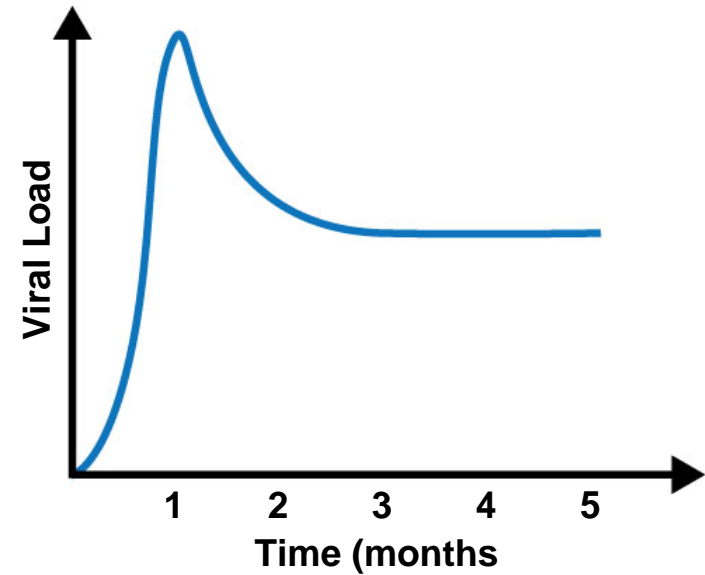
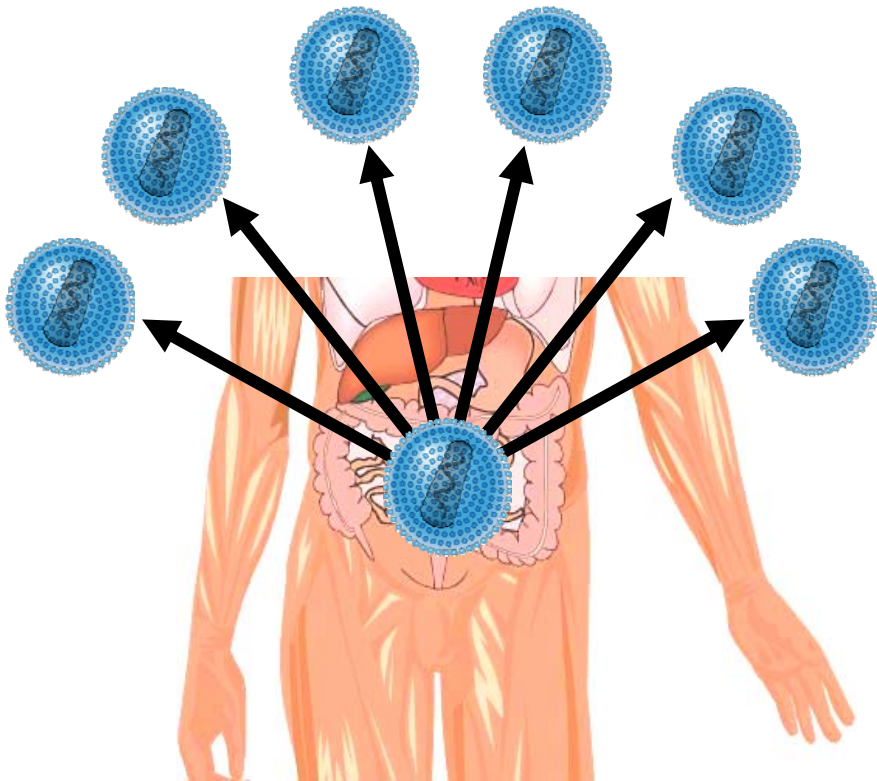
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How Might a Vaccine Prevent Infection?

Hypothesis: Virus infection in a susceptible individual can be prevented through the induction of a neutralizing antibody response or T cell response (direct cytolysis or cytokine secretion) at the site of entry and dissemination.

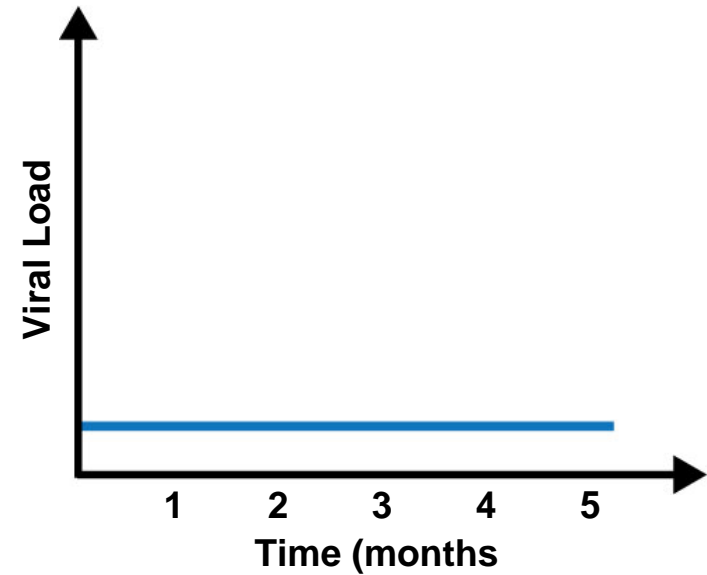
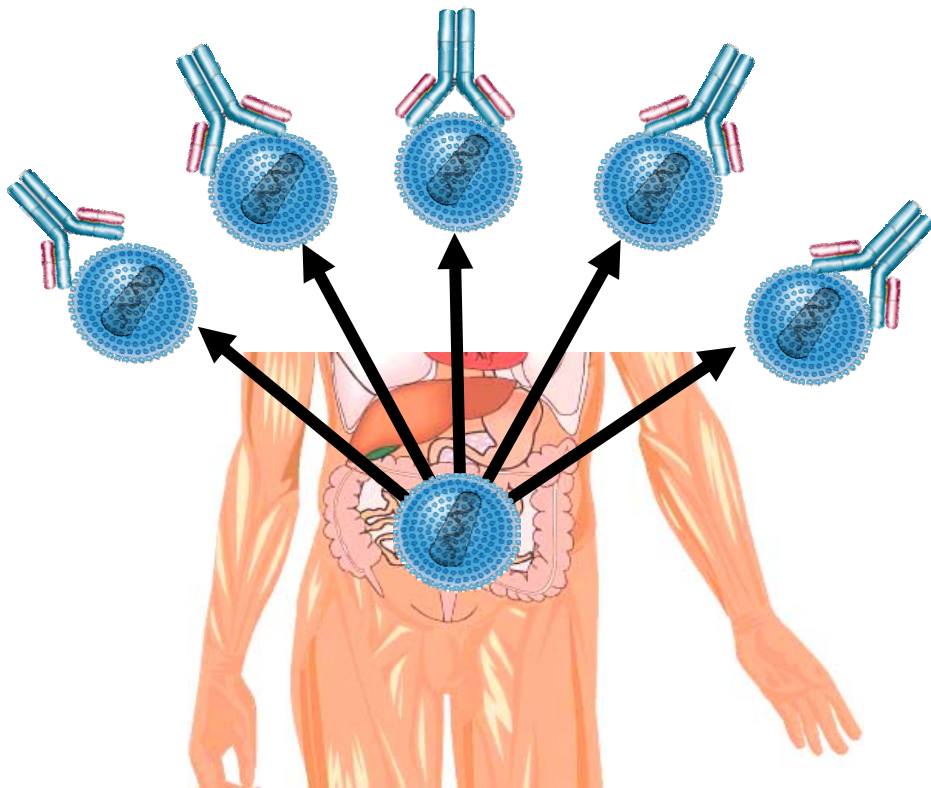
How Might a Vaccine Prevent Infection?

Scenario 1: No Immune Protection



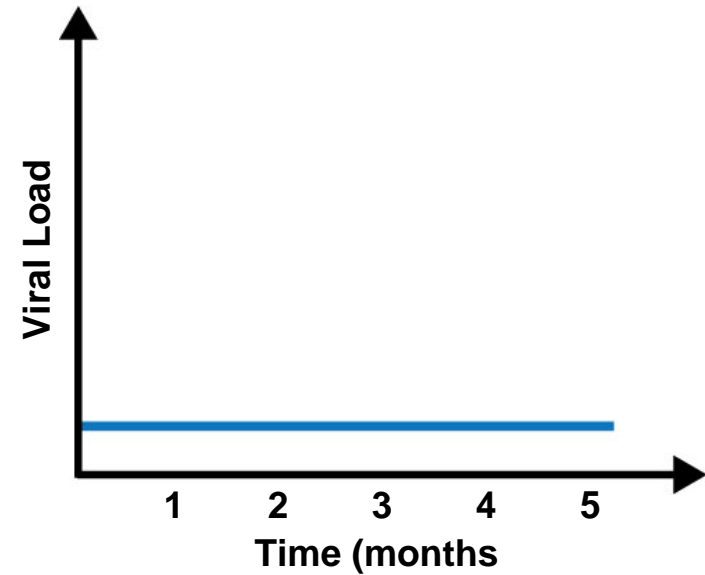
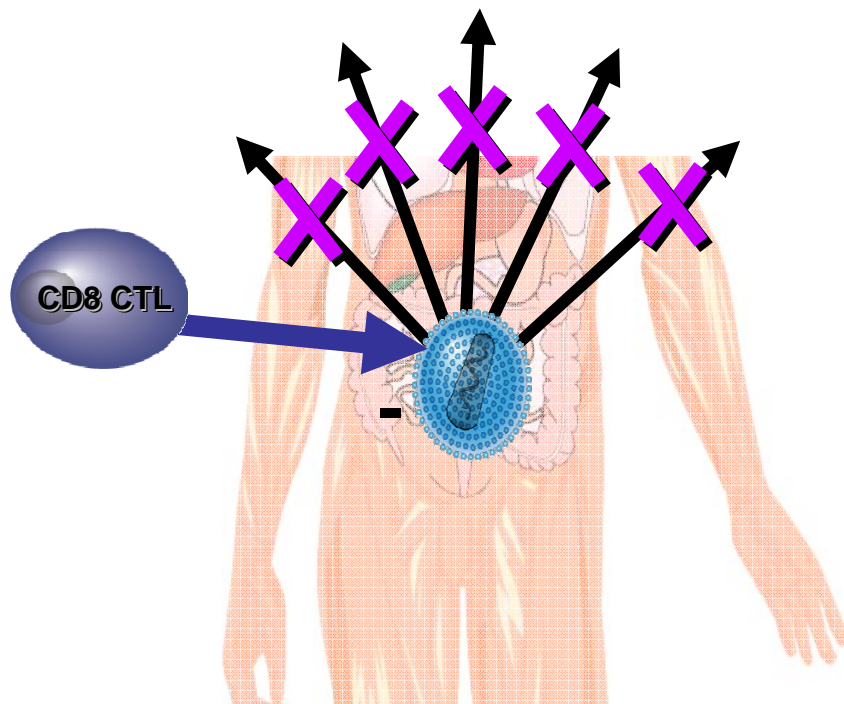
How Might a Vaccine Prevent Infection?

Scenario 2: Broadly Neutralizing Antibodies



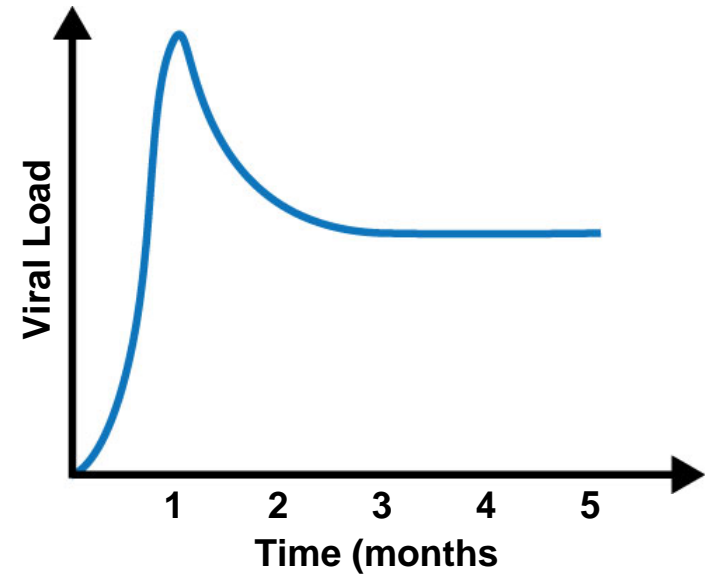
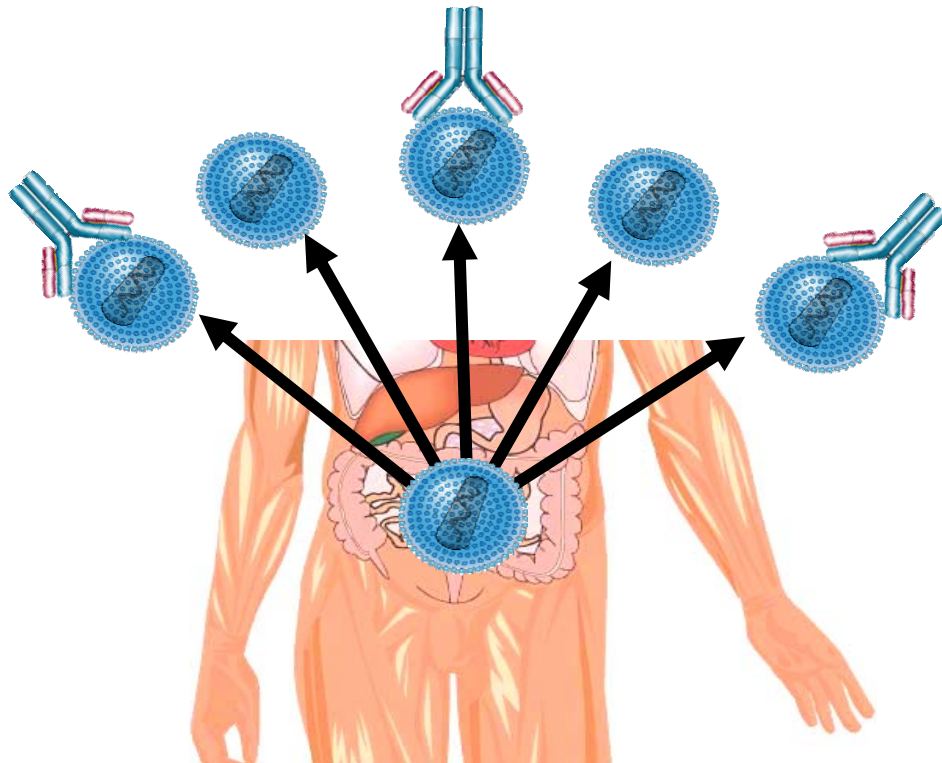
How Might a Vaccine Prevent Infection?

Scenario 3: Highly Effective T Cell Vaccine



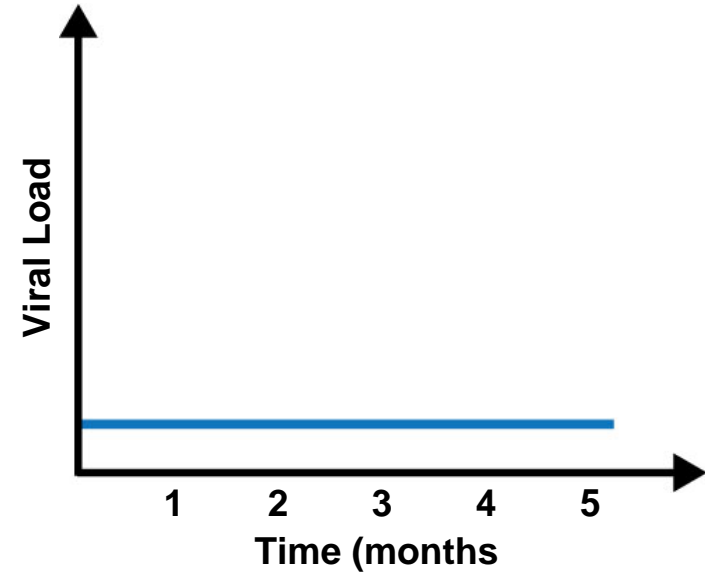
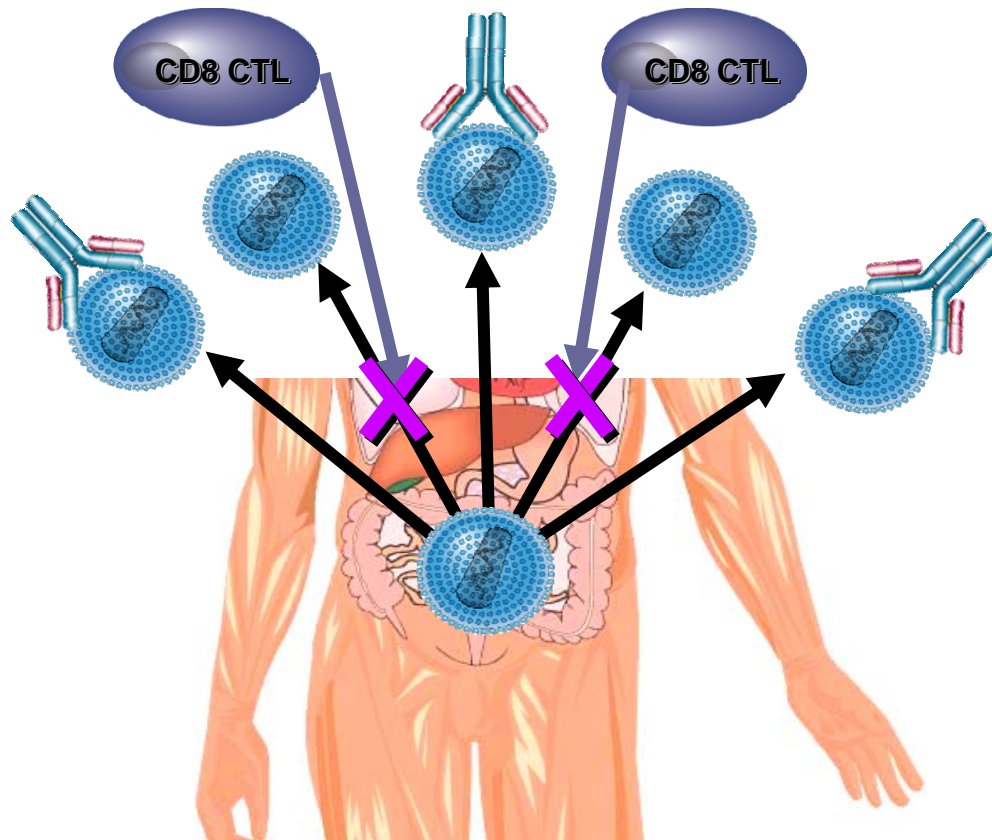
How Might a Vaccine Prevent Infection?

Scenario 4: Partially Effective nAb Response



How Might a Vaccine Prevent Infection?

Scenario 5: Partially Effective nAb and T Cells



Can T Cells Prevent HIV Infection ?

- 1. Previous studies of T cell vaccines in nonhuman primates have provided proof of concept for T cell immune protection but have not modeled natural HIV infection.**
- 2. There is emerging evidence in relevant nonhuman primate vaccine models that T cells can prevent or strongly contain viral infection.**

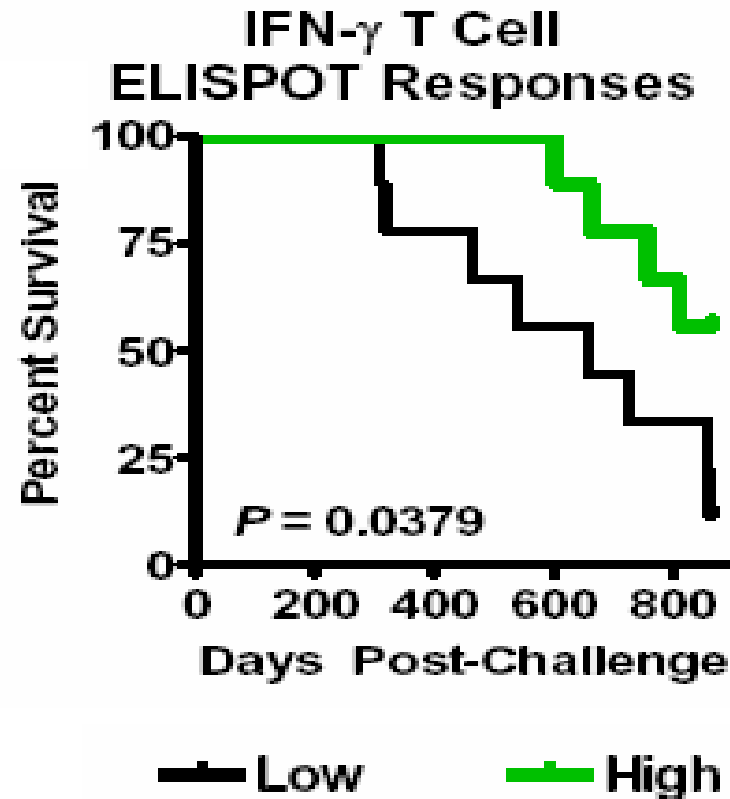
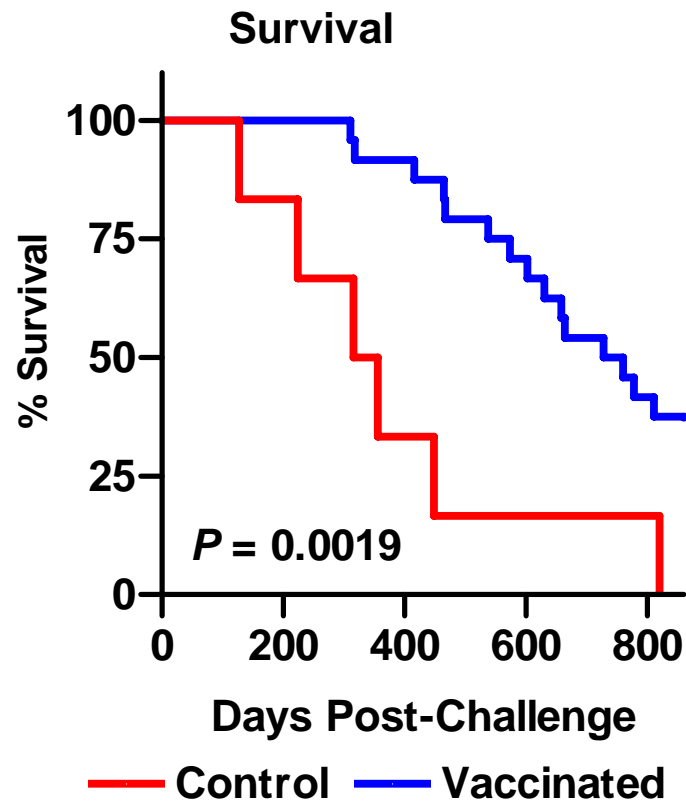
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Cohort of Exposed, Uninfected Rhesus Monkeys

- **Repeated mucosal exposure**
 - SIVsmE660
 - doses of virus: 1:10 (6×10^7 copies), 1:100 (6×10^6), 1:1000 (6×10^5)
 - 3 monkeys/dose
 - 6 weekly intrarectal exposures
- **Monitored: plasma SIV RNA**

Survival advantage in vaccinated monkeys was associated with T cell response to vaccine



Can T Cells Prevent HIV Infection ?

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 - David Watkins (this session-DNA/rAd)
 - Louis Picker (today-Parallel Symposium 03 17:00- rhesus CMV)

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Gene insert - SIV Challenge Study

Immunogens:

Plasmid DNA prime/rAd5 boost

SIVmac239 *gag/pol*, SIVmac239 *env*

Groups: 13 rhesus monkeys/group, *all Mamu-A*01 negative*

1) SIV *gag/pol*

2) SIV *env*

3) SIV *gag/pol* + SIV *env*

4) Control: sham DNA/empty Ad5

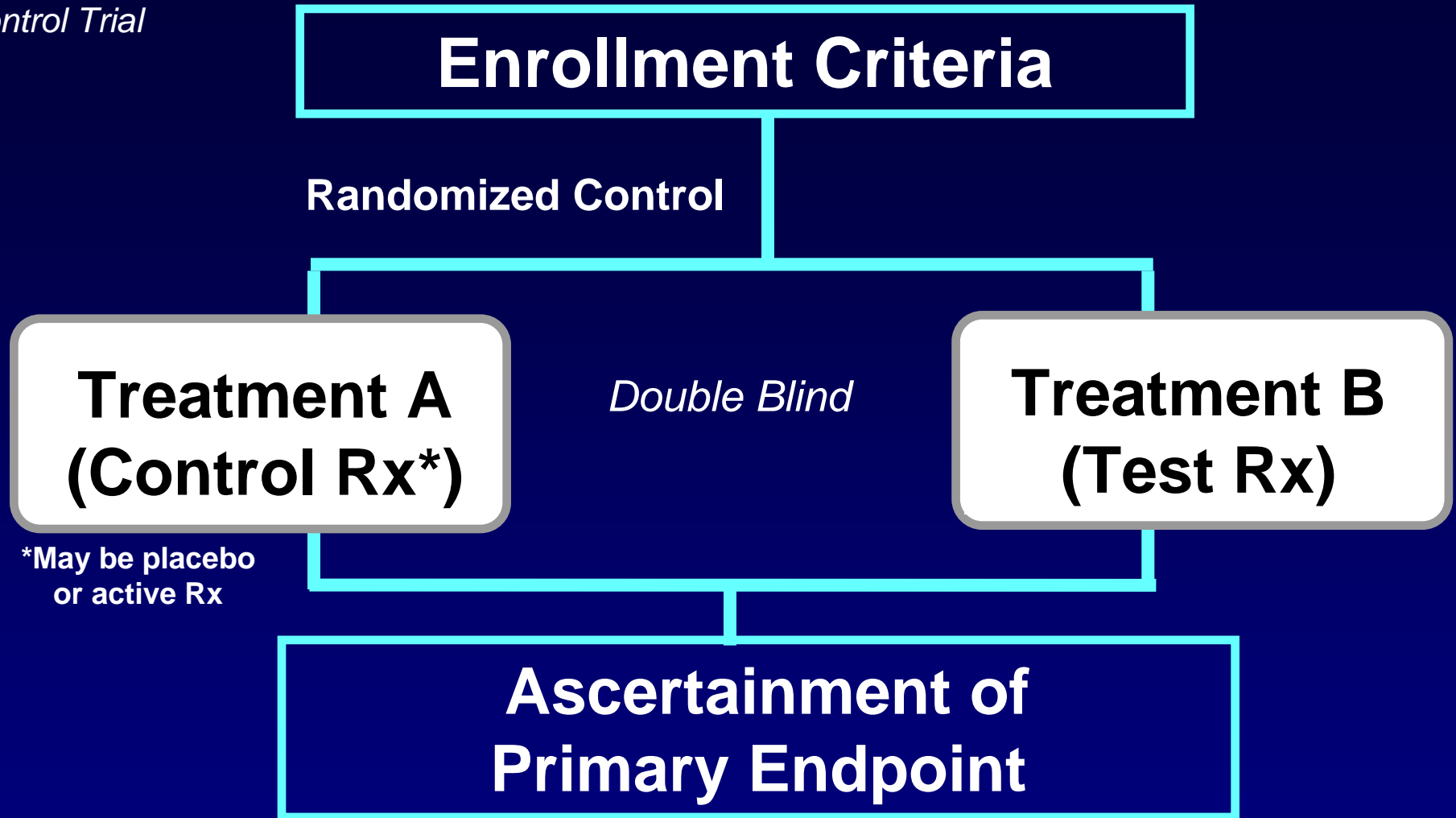
Challenge: 20 wks following last vaccine inoculation

50 AID SIVmac251, i.v.

Clinical Trials

Endpoints and Study Design

*Randomized
Control Trial*

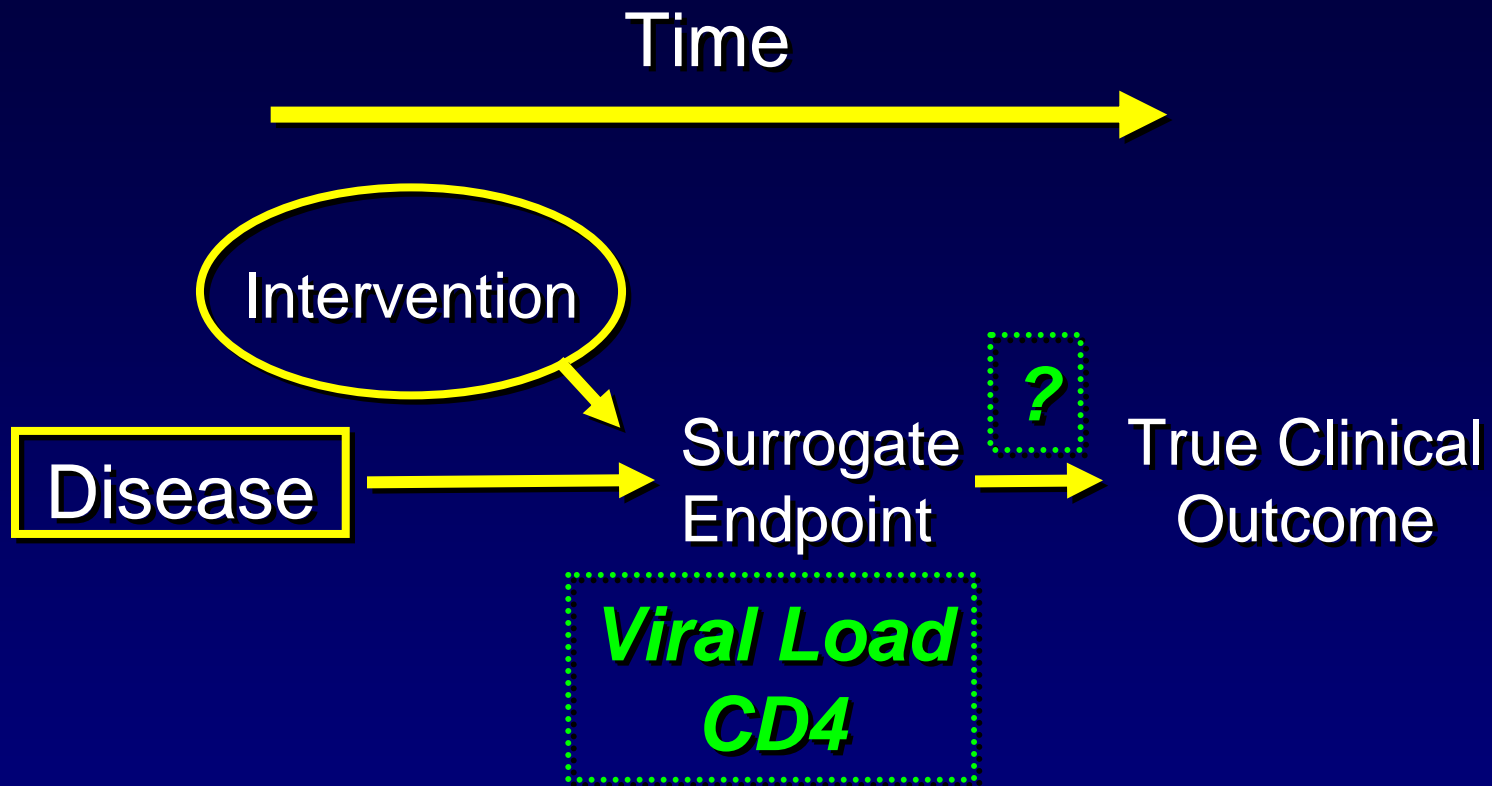


*May be placebo
or active Rx

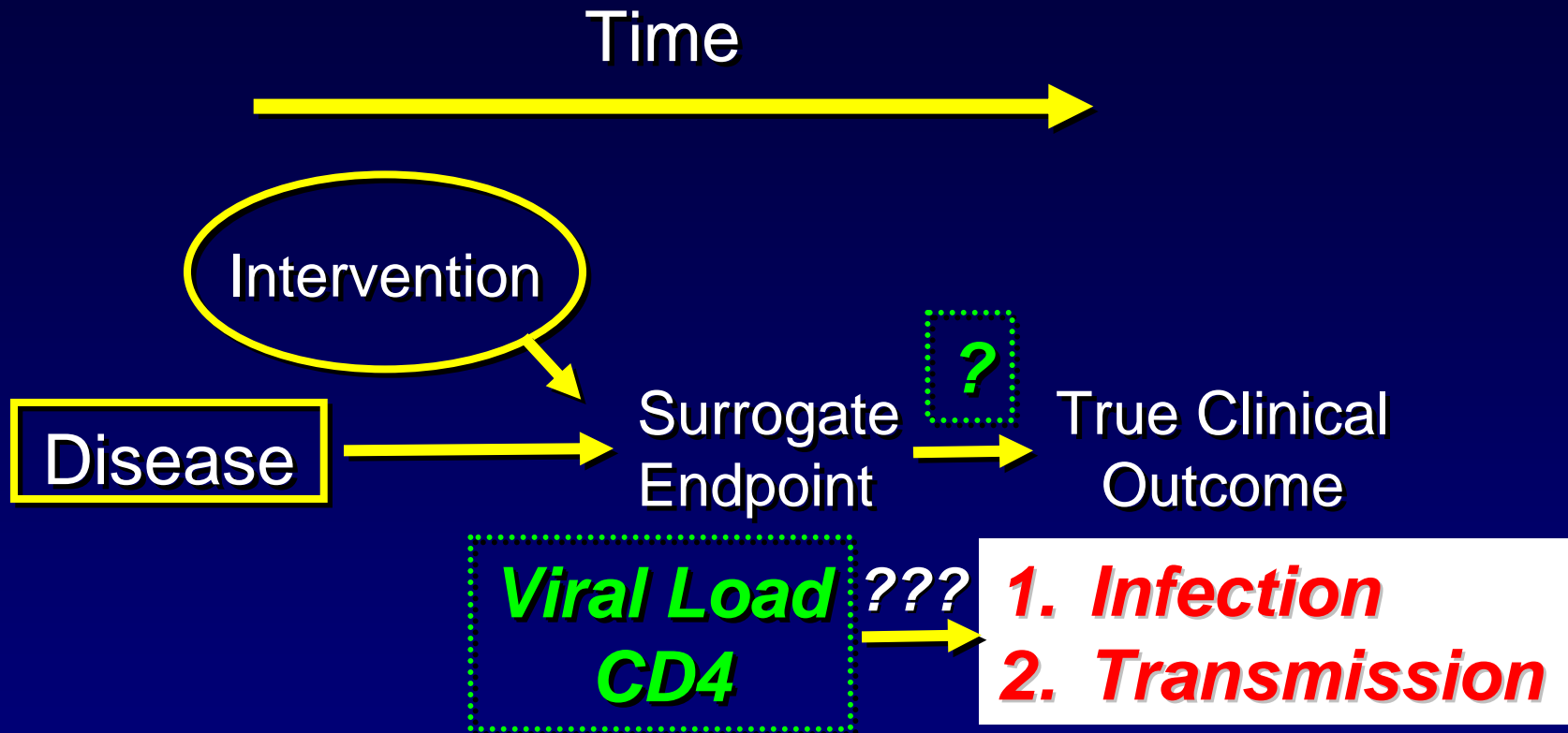
“An RCT is at the top of a pyramid of research”
Gina Kolata Science Times NYT Sept 30 , 2008

Elliot Antman, Harvard Medical School

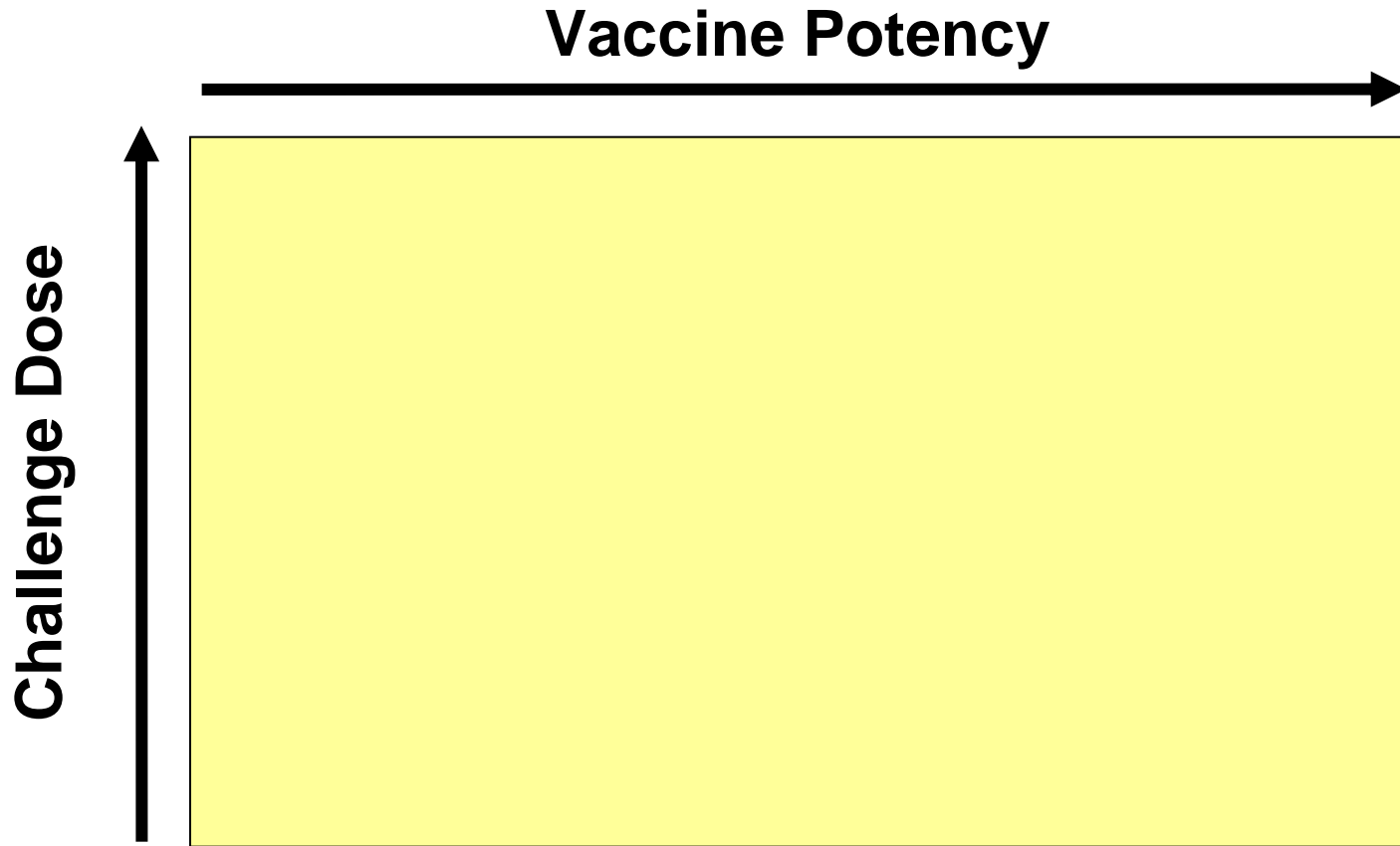
Surrogate Endpoints



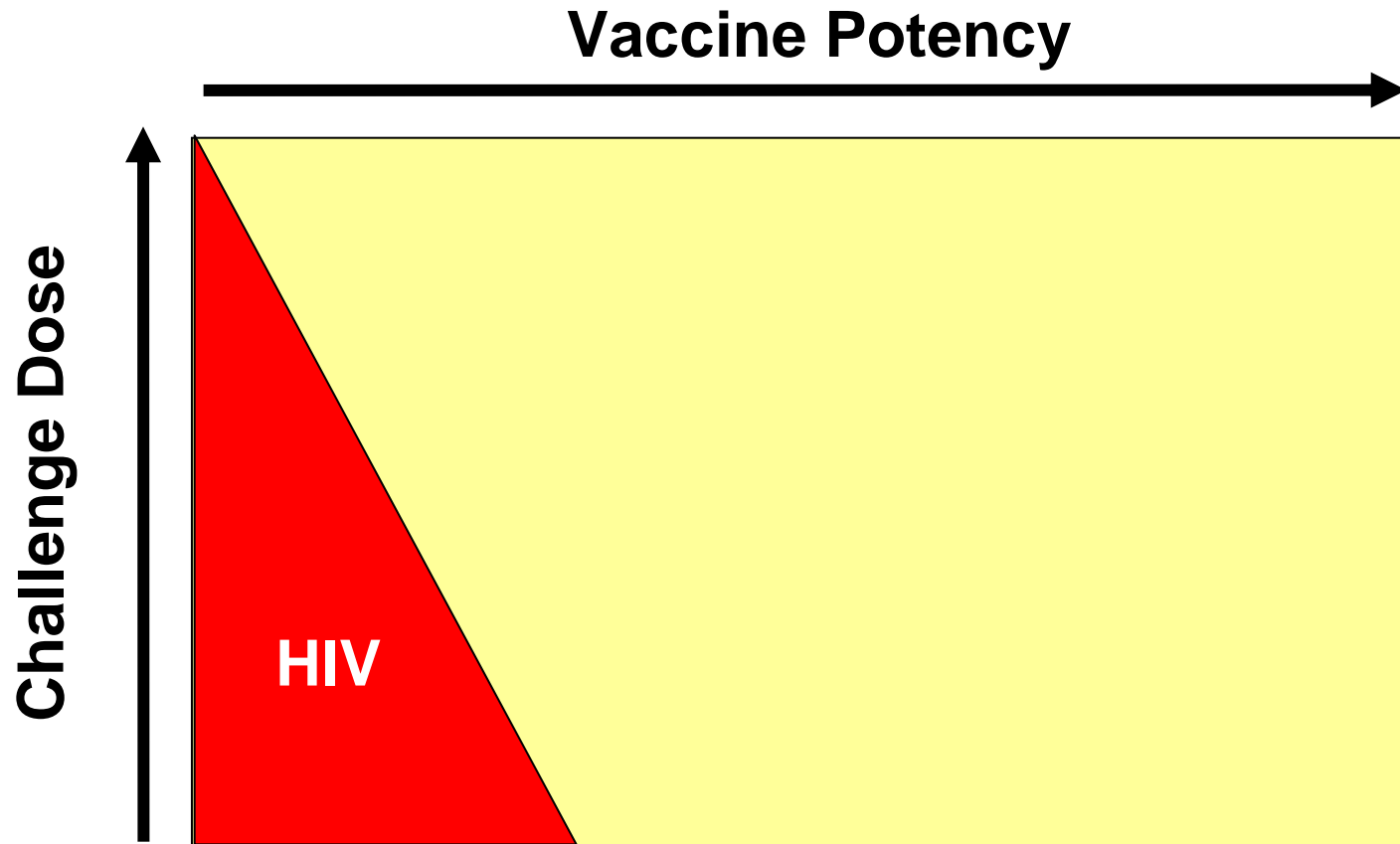
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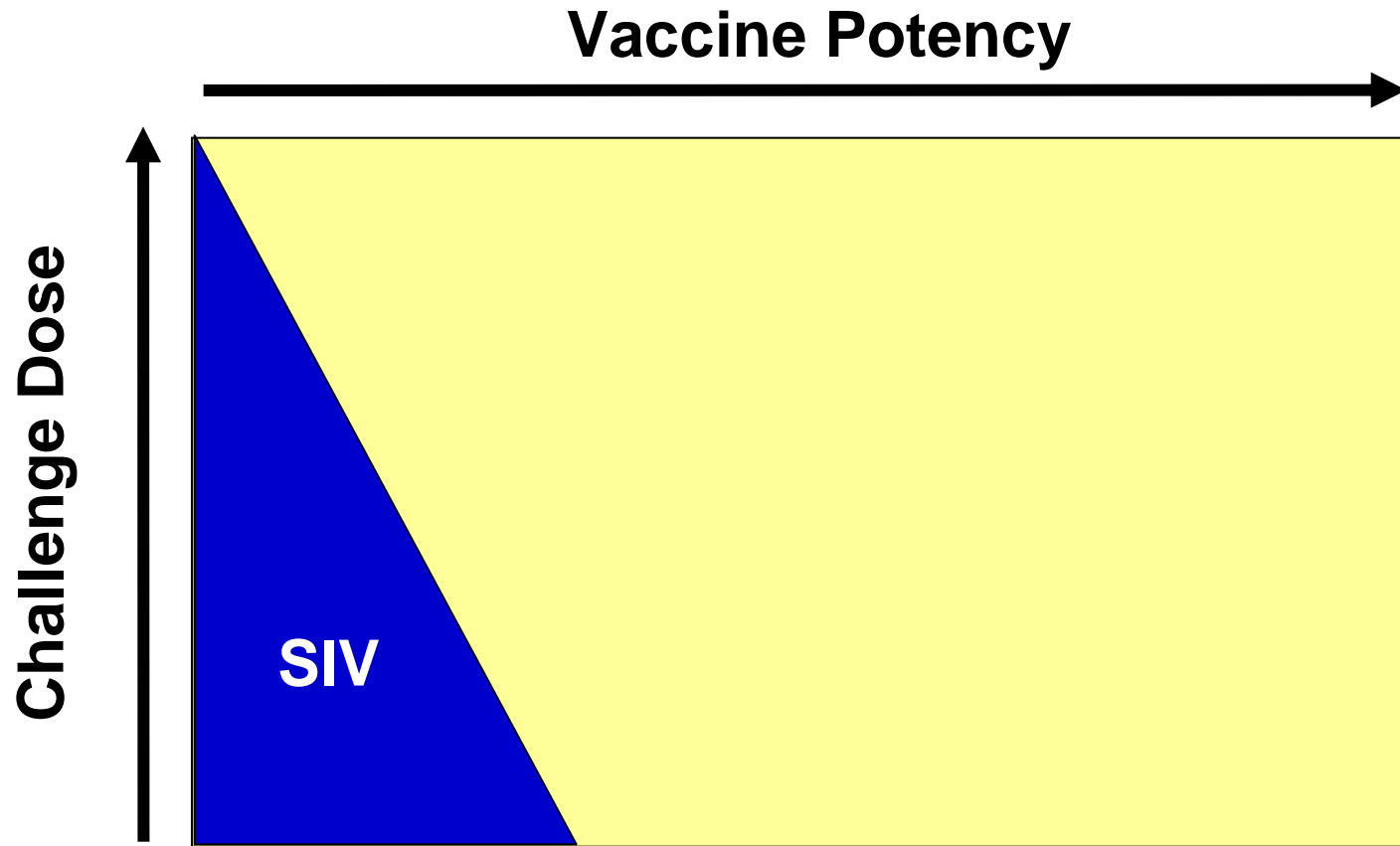
Vaccine Efficacy Against Naturally Transmitted Virus



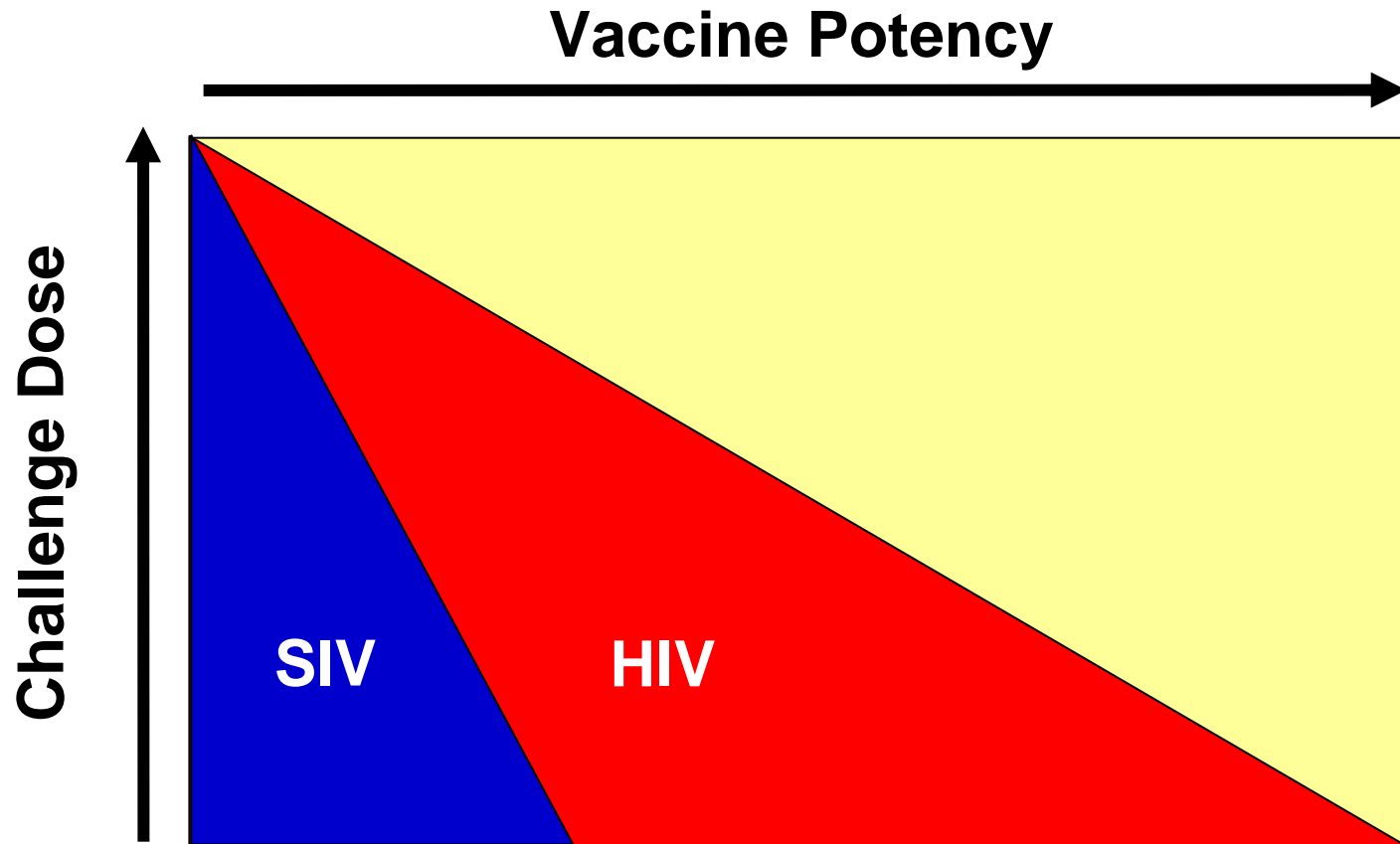
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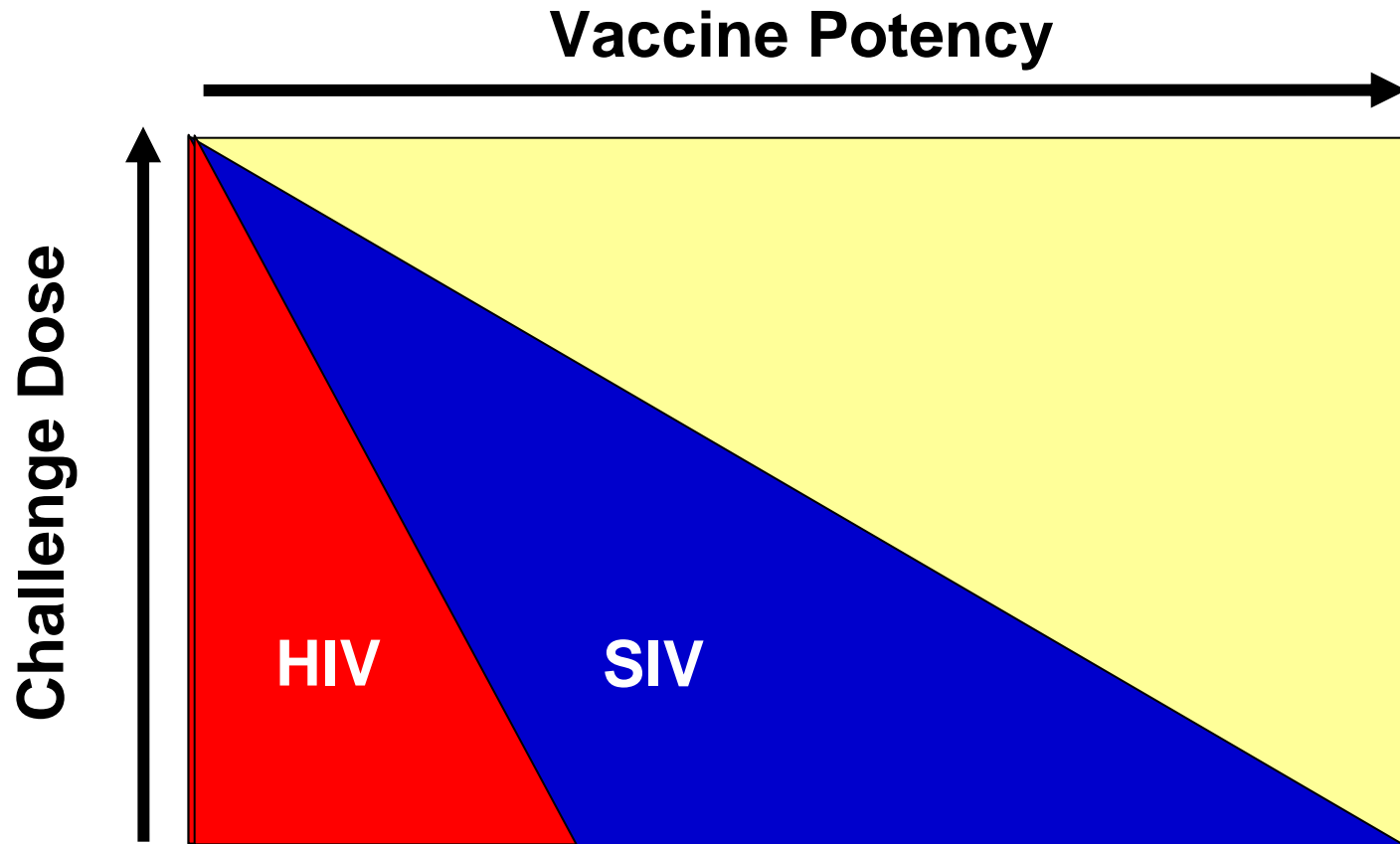
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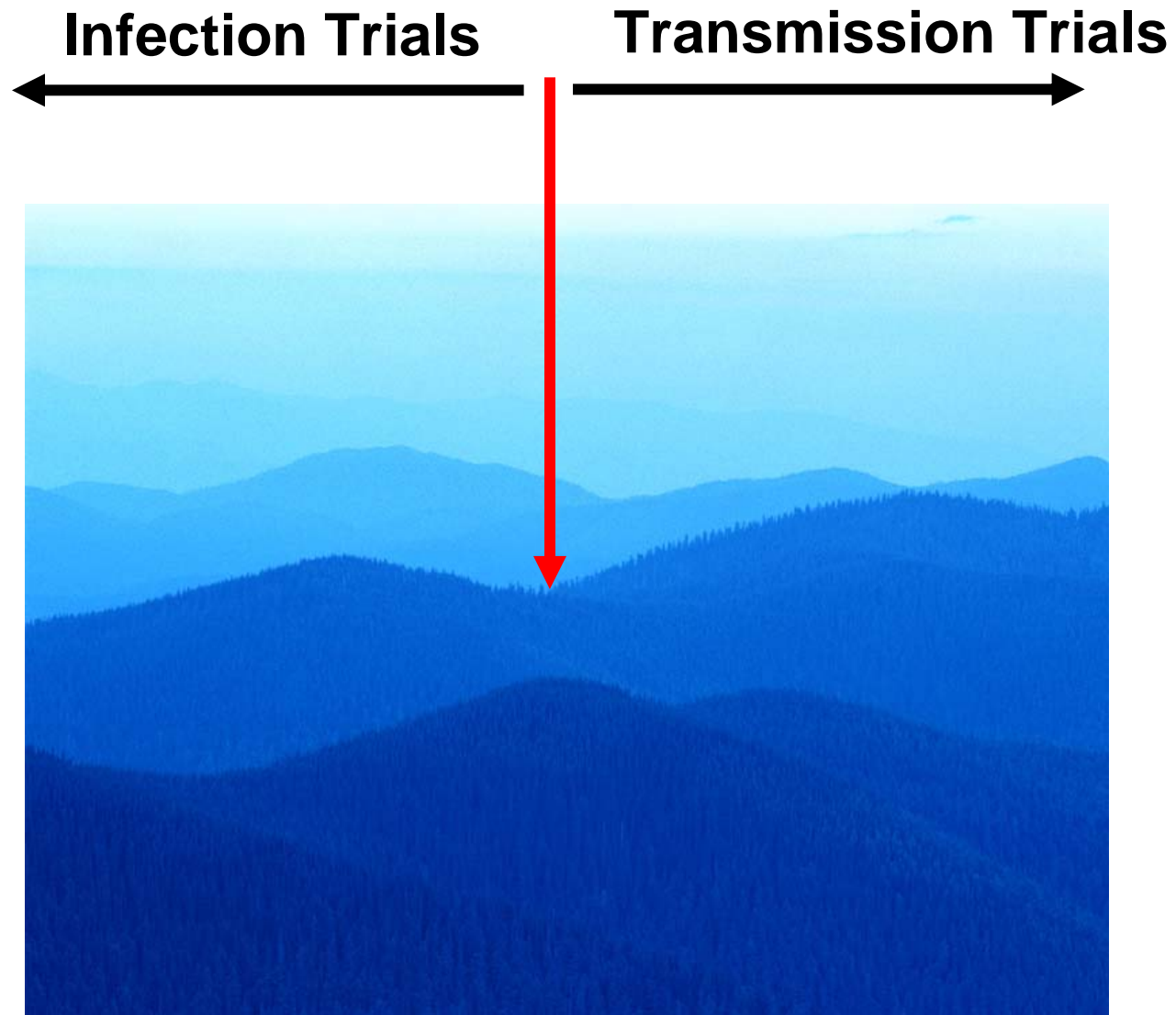
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The Great Divide-Infection vs. Transmission



Conclusions

- 1. Testing of T cell vaccines in human efficacy trials should continue. There is increasing evidence of their efficacy in relevant non-human primate challenge models.**
- 2. Trials should be sufficiently large to test specific vaccine concepts and address the scientific questions related to immune correlates, viral load, and prevention of infection.**
- 3. Priority should be placed on candidates as follows:**
 - a. Prevention of infection based on the T cell response.**
 - b. Prevention of infection in synergy with the nAb response**
 - c. Functional sterilizing immunity with either of the above.**
- 4. If a vaccine only lowers viral load in relevant NHP models, it should be considered for evaluation in a progression/transmission study. This strategy poses significant theoretical and practical challenges and should be prioritized accordingly.**

Acknowledgements

George Shaw and Beatrice Hahn (UAB)

Brandon Kyle

CHAVI (Bart Haynes)

Norm Letvin, John Mascola, Sriniv Rao

Rick Koup, John Mascola, Barney Graham and VRC PI's