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Human Immunodeficiency Virus (HIV)

Infectious Diseases/Microbiology Sequence Course
David J. Miller, M.D., Ph.D.

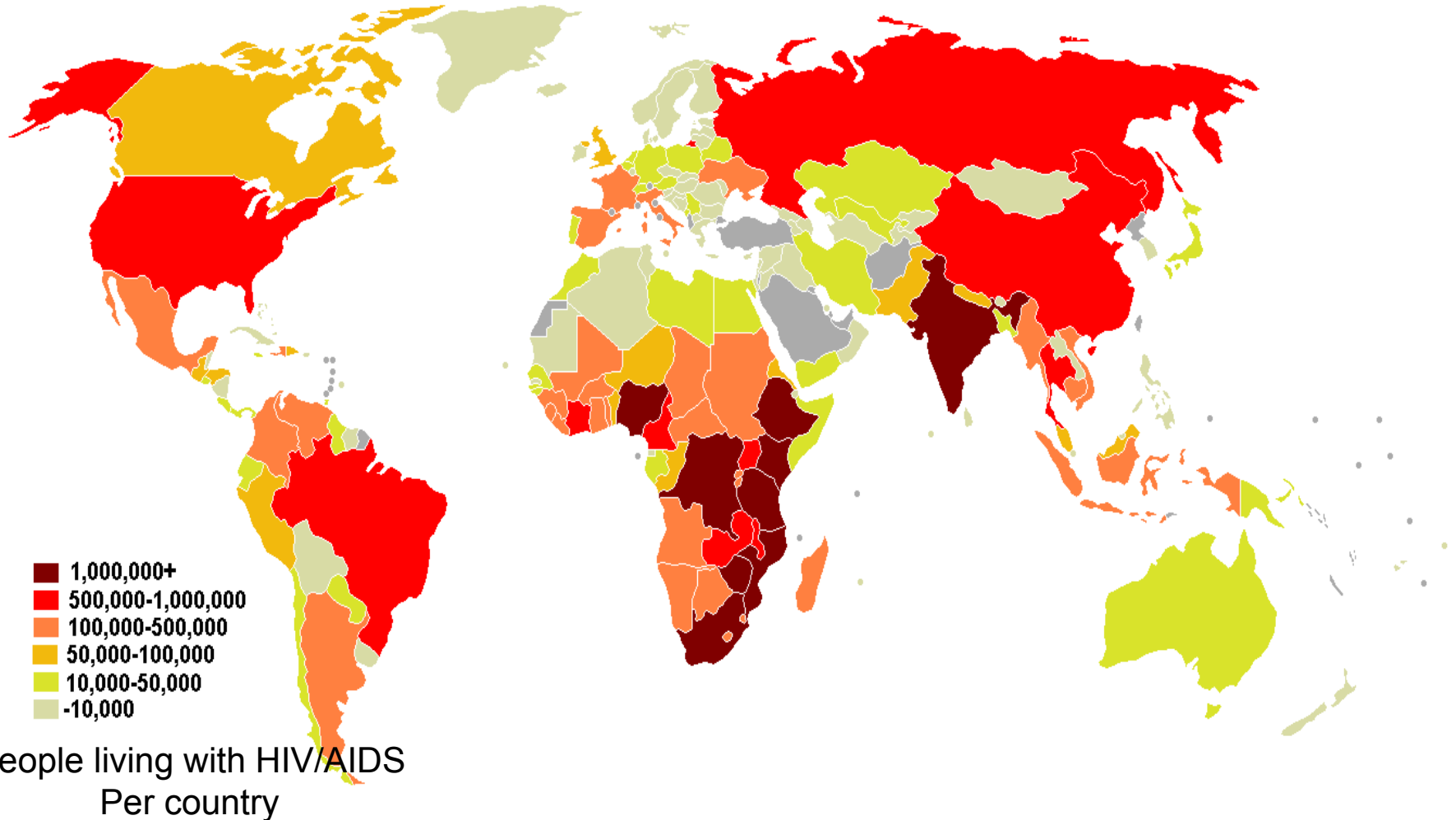
Spring 2010



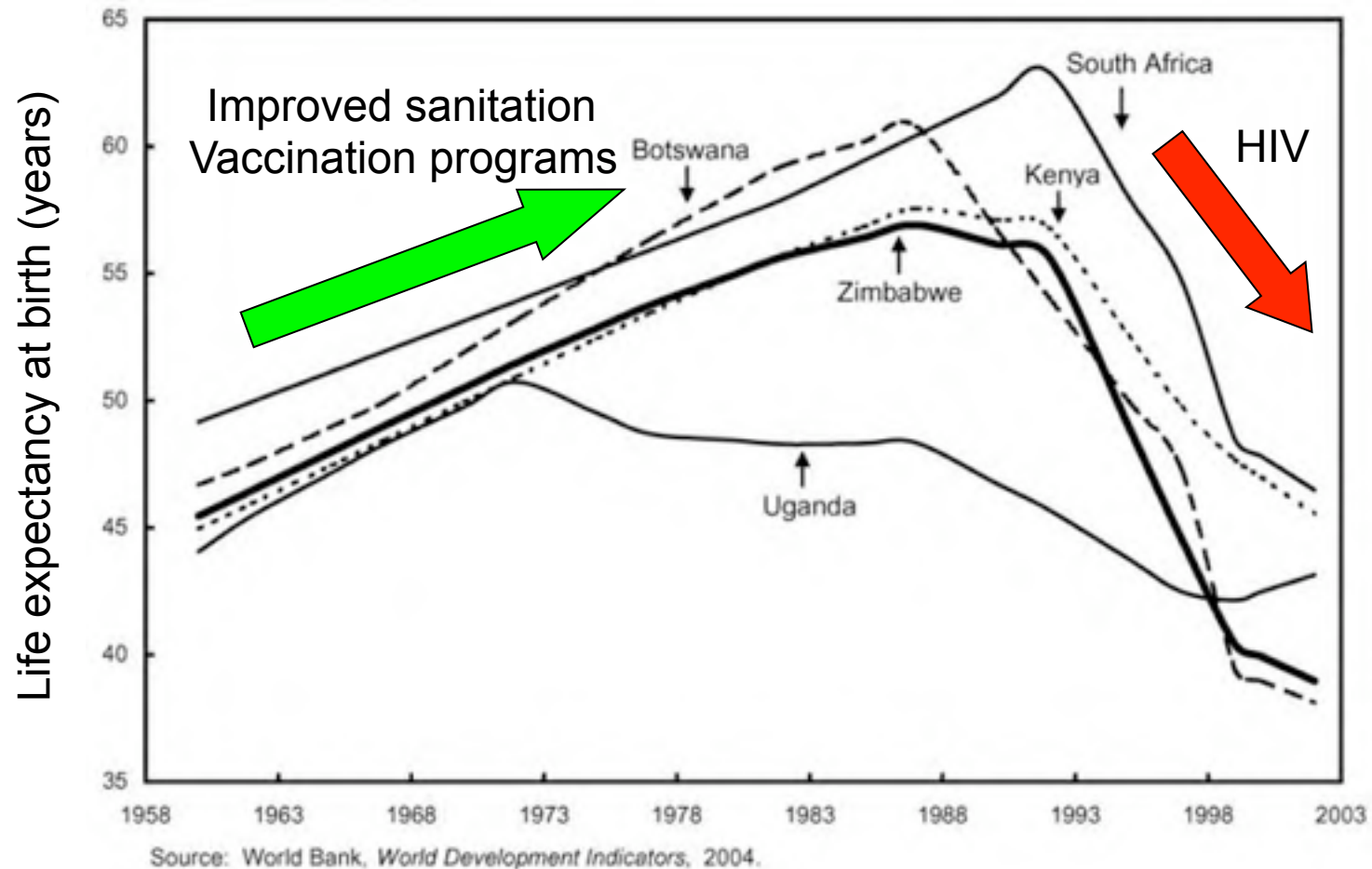
Objectives

- **Appreciate scope of HIV pandemic**
- **Know the viral replication steps targeted by antiretroviral drugs**
- **Understand the mechanism whereby HIV suppresses immunity**
- **Appreciate the underlying difficulty with developing an HIV vaccine**

HIV/AIDS disease world-wide (2006)

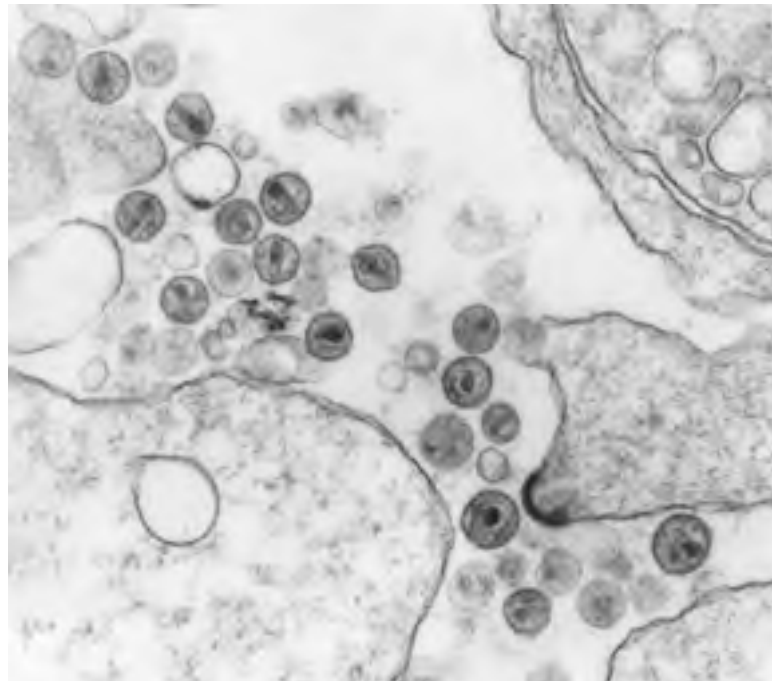


Impact of HIV on life expectancy in Africa



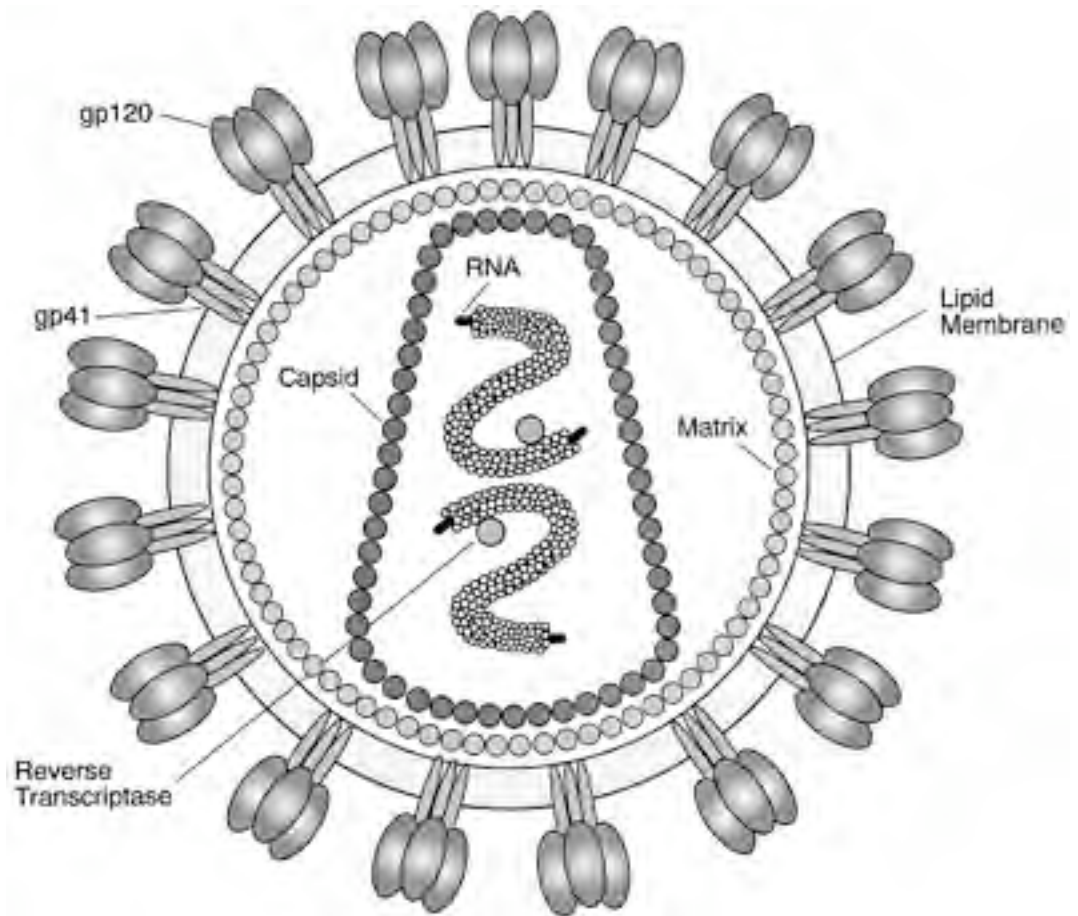
Human immunodeficiency virus (HIV)

- **Family: *Retroviridae***
 - Other members: human T-cell leukemia virus 1 and 2 (HTLV-1, 2)
- **Enveloped**
- **Positive (+) strand RNA genome**
 - *Significant differences* with other (+) RNA viruses

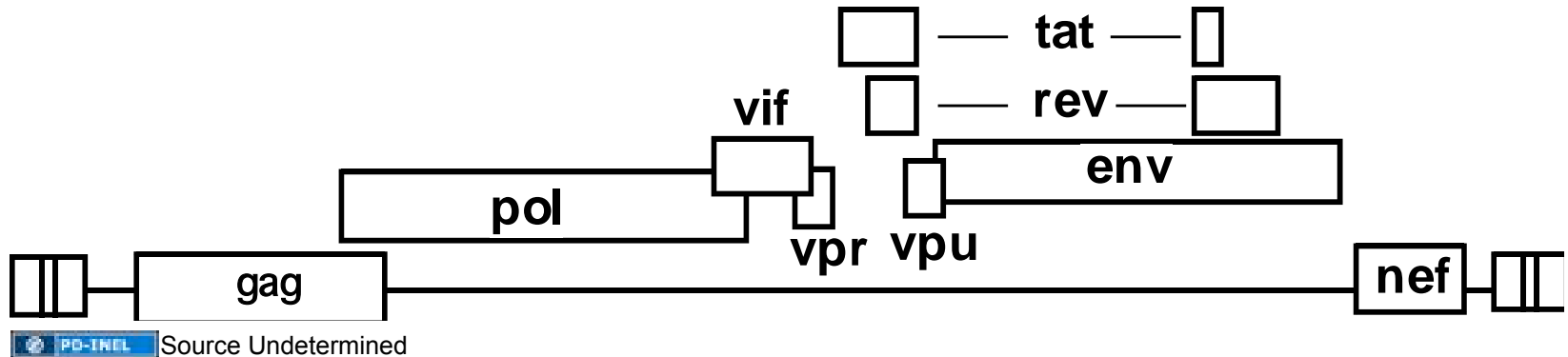


HIV Structure

- **Surface glycoproteins (Env)**
 - gp120, gp41
 - receptor binding
- **Structural proteins (Gag)**
 - capsid and matrix
- **Replicase proteins (Pol)**
 - reverse transcriptase
 - integrase
 - protease
- **Genomic RNA**
 - *TWO* copies per virion



HIV Genome



- **Universal**

- *Present in all retroviruses*
- Gag - structural
- Pol - replication
- Env - structural

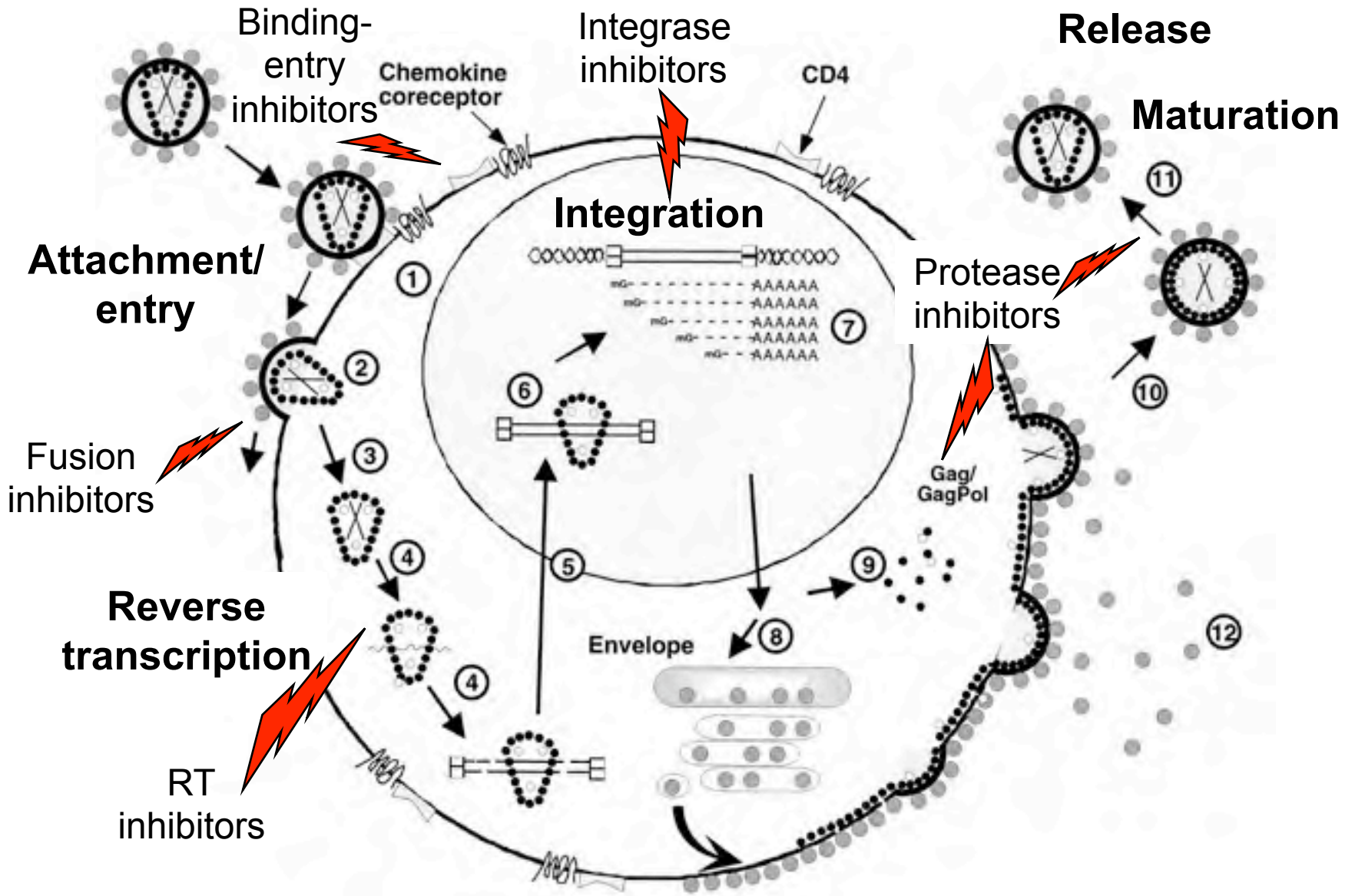
- **Essential**

- *Required for HIV replication*
- Tat - transcription
- Rev - RNA transport
- Vif - genome fidelity

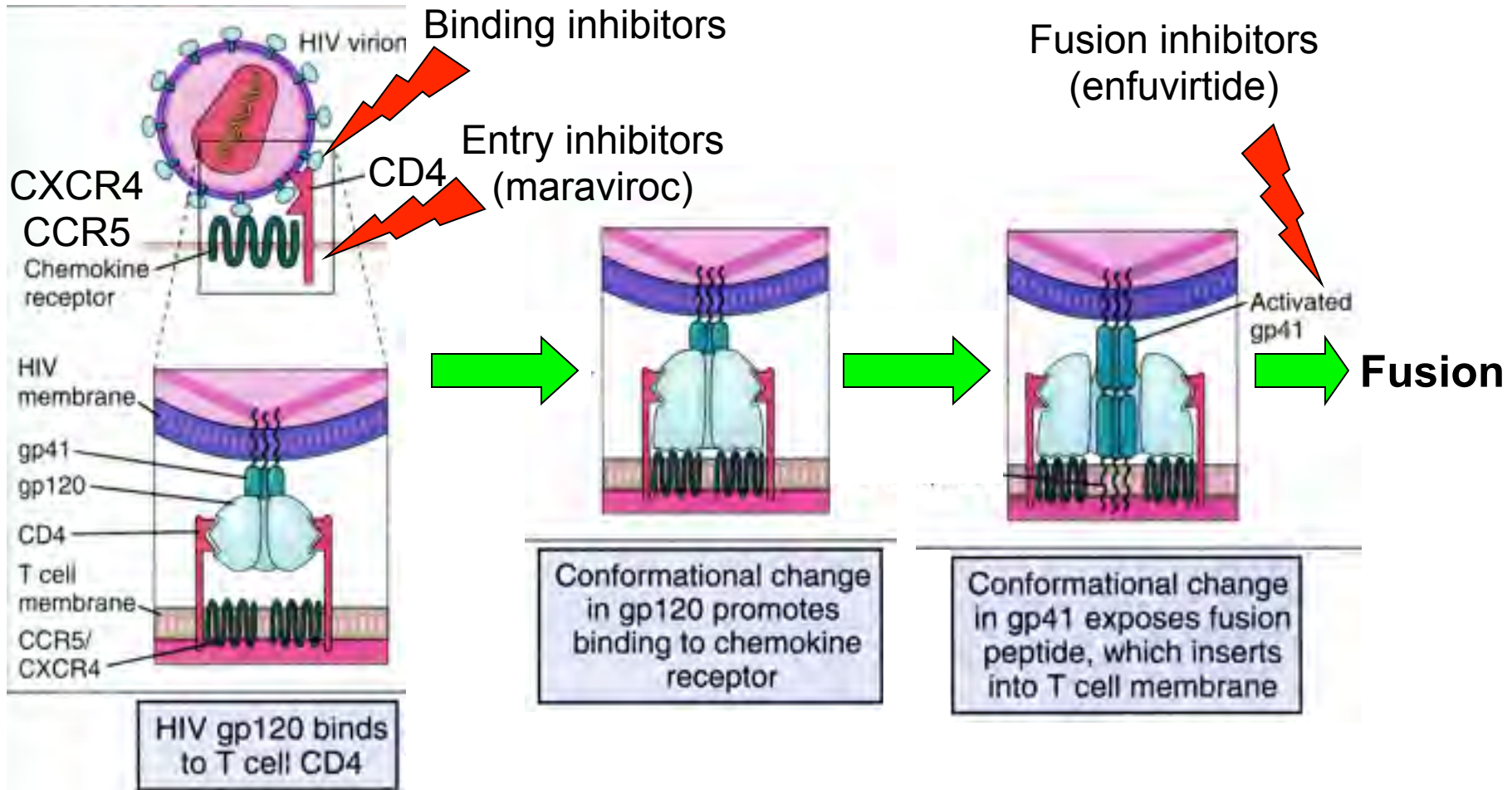
- **Accessory**

- *Enhance HIV production*
- Nef
- Vpr
- Vpu

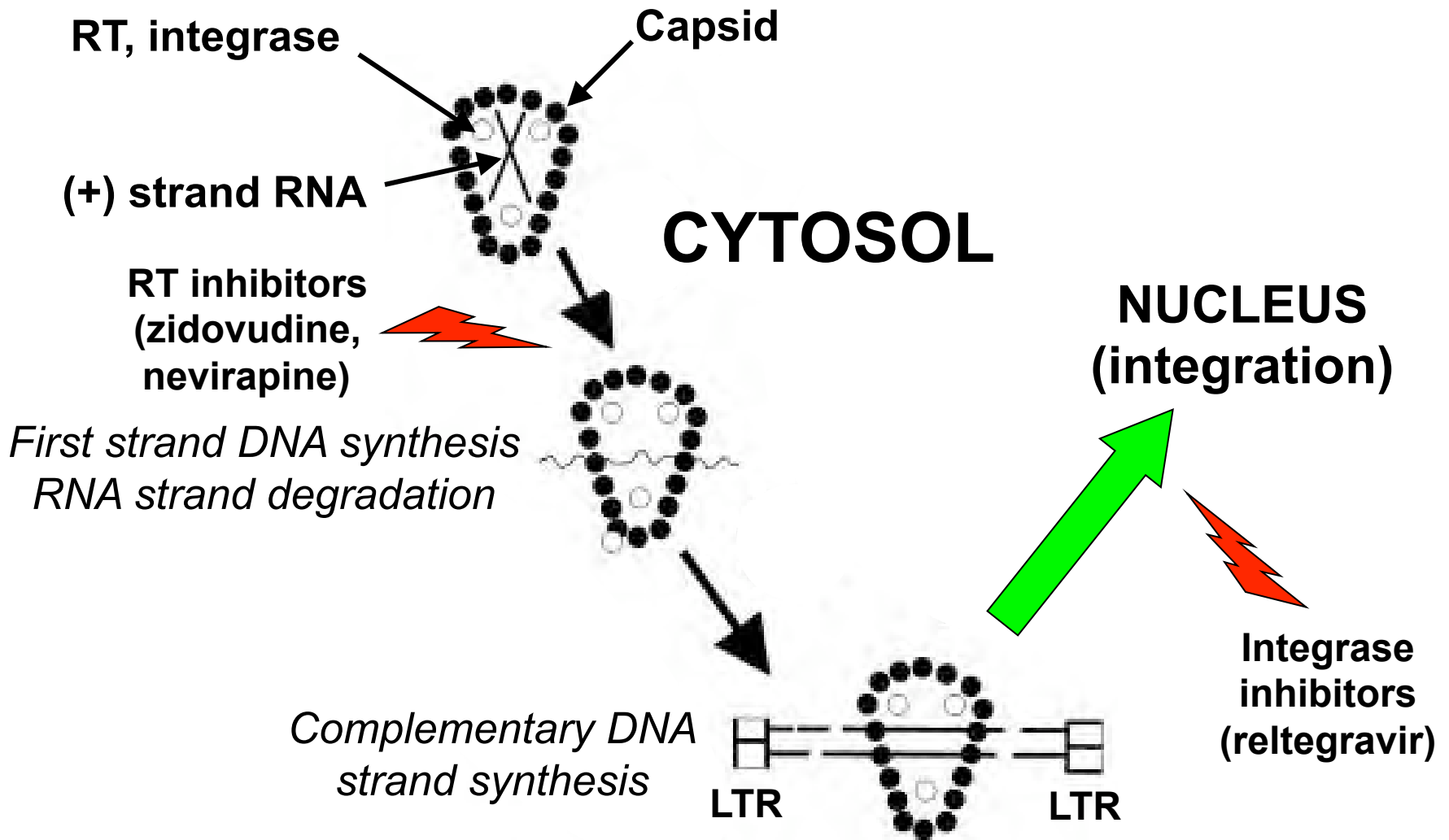
HIV life cycle



HIV attachment and entry



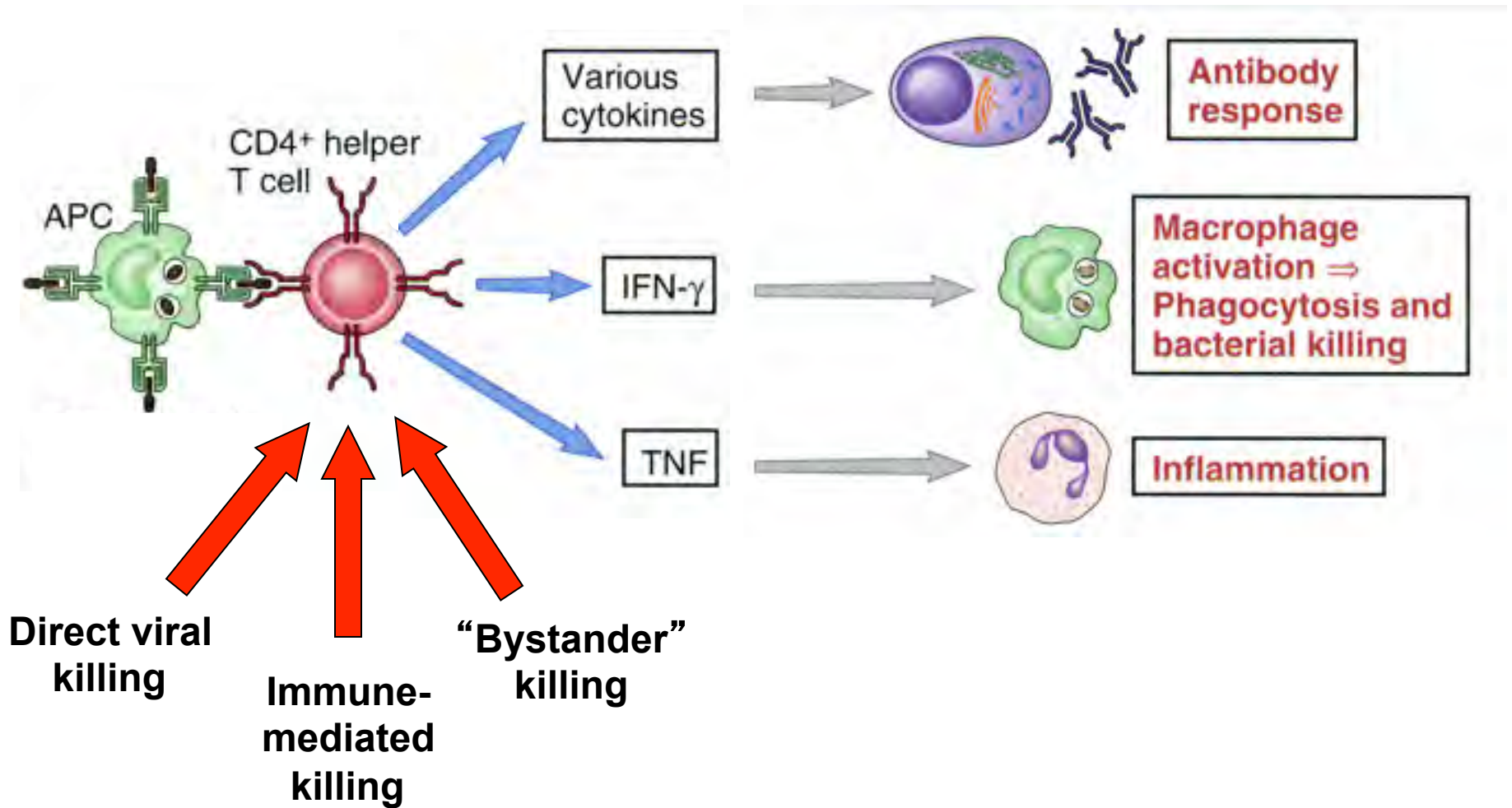
HIV reverse transcription/integration



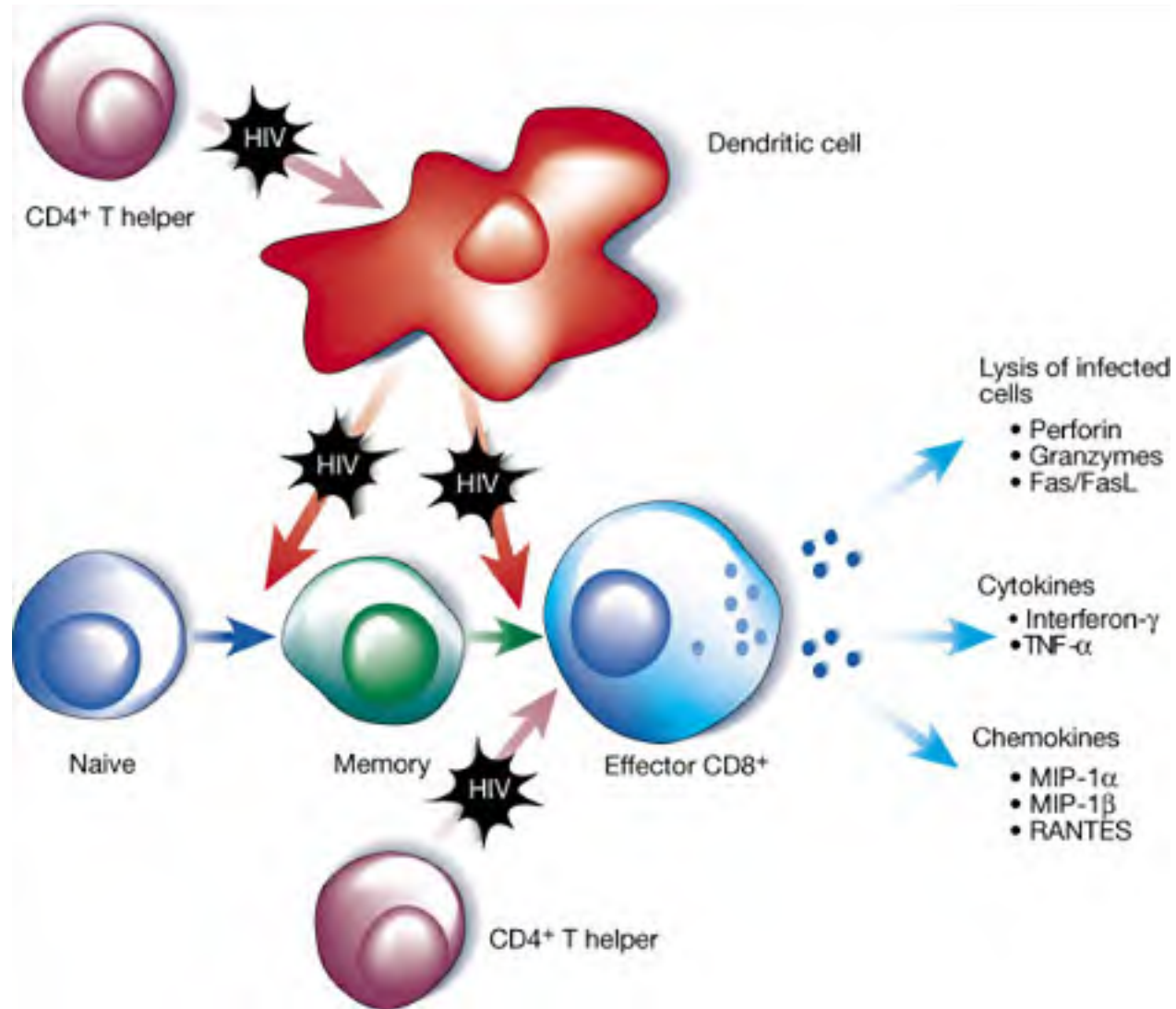
HIV Pathogenesis

- **Direct infection of essential immune effector cells**
 - CD4⁺ T cells
 - Patients infected with HIV don't die from HIV infection
- **Ability to establish “latency”**
 - Clinical vs. virological latency
 - Antiviral drugs target replicating virus
- **Genetic variation impedes effective immune response**
 - Vaccine development

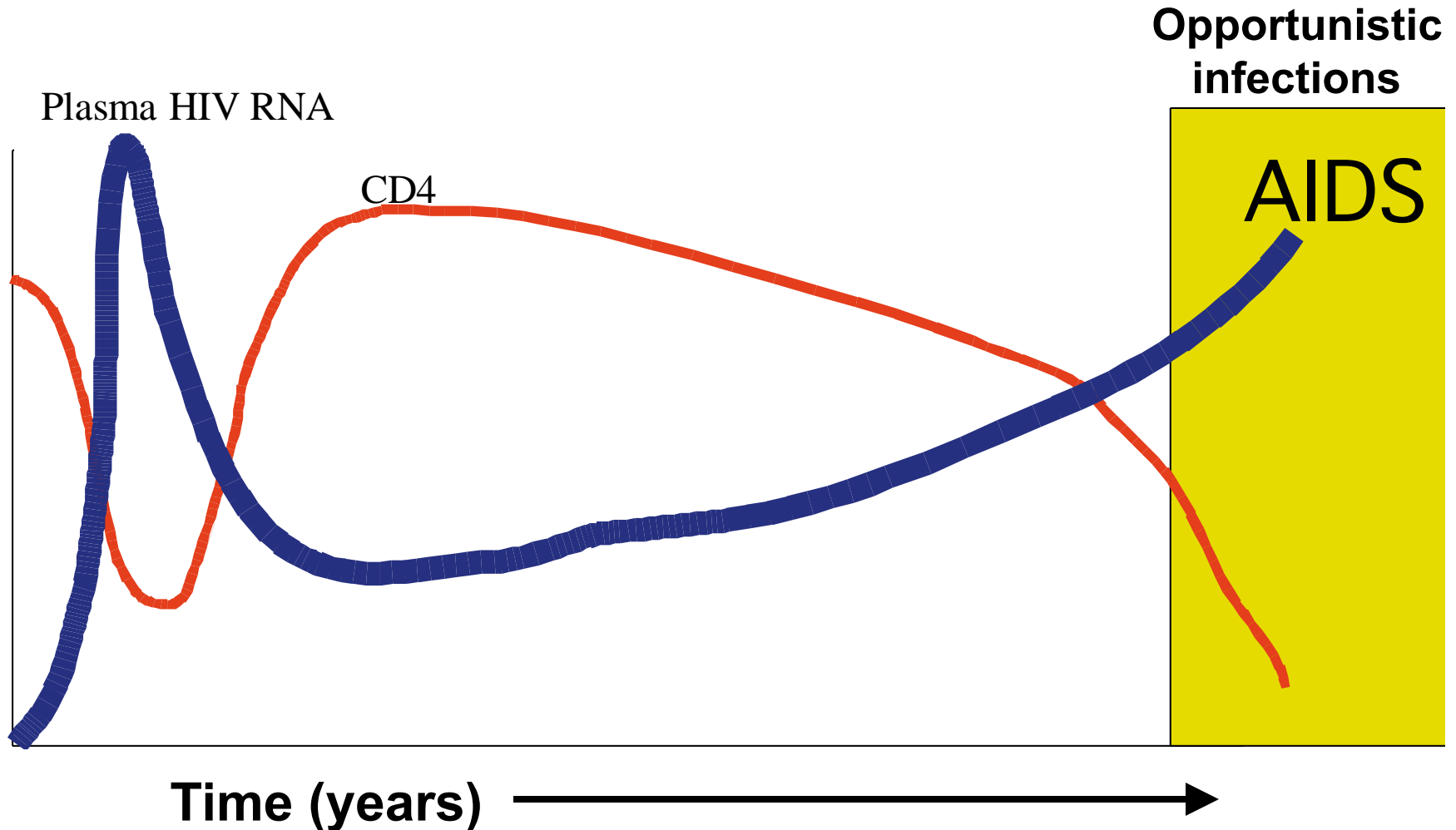
Central role of CD4+ T cell in immune response



HIV-mediated disruption of CD4⁺ T cell mediated immune responses



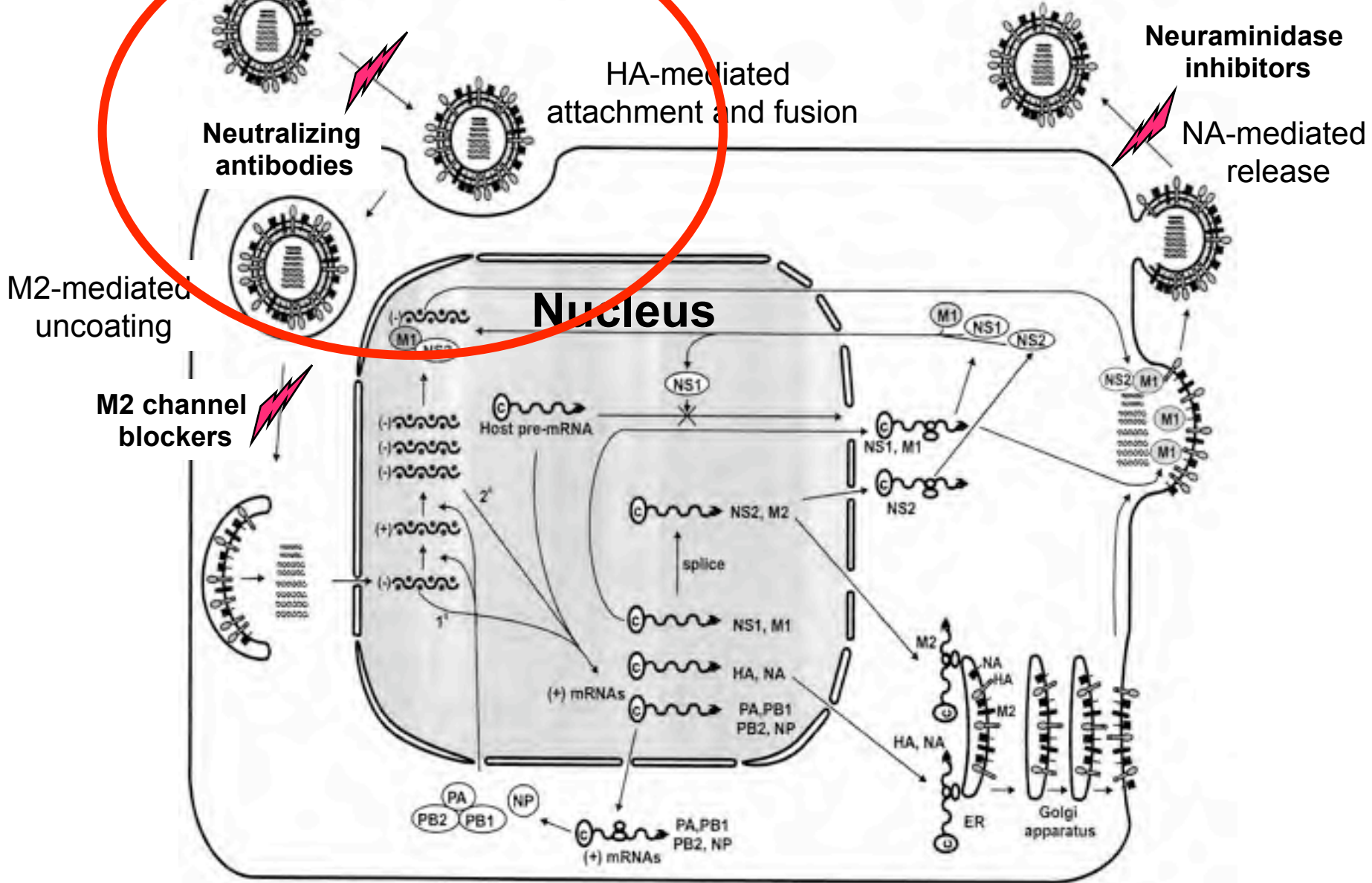
Clinical course of HIV infection



HIV vaccine

- **Traditional approaches**
 - Live attenuated (eg. VZV, MMR, influenza)
 - Inactivated (eg. influenza, HAV)
 - *Subunit (eg. HBV, HPV)*
- **Development of “protective” immunity**
 - Humoral immunity (antibody-mediated)
 - Prevent infection
 - Cellular immunity (T cell-mediated)
 - Clear infection

Influenza virus life cycle

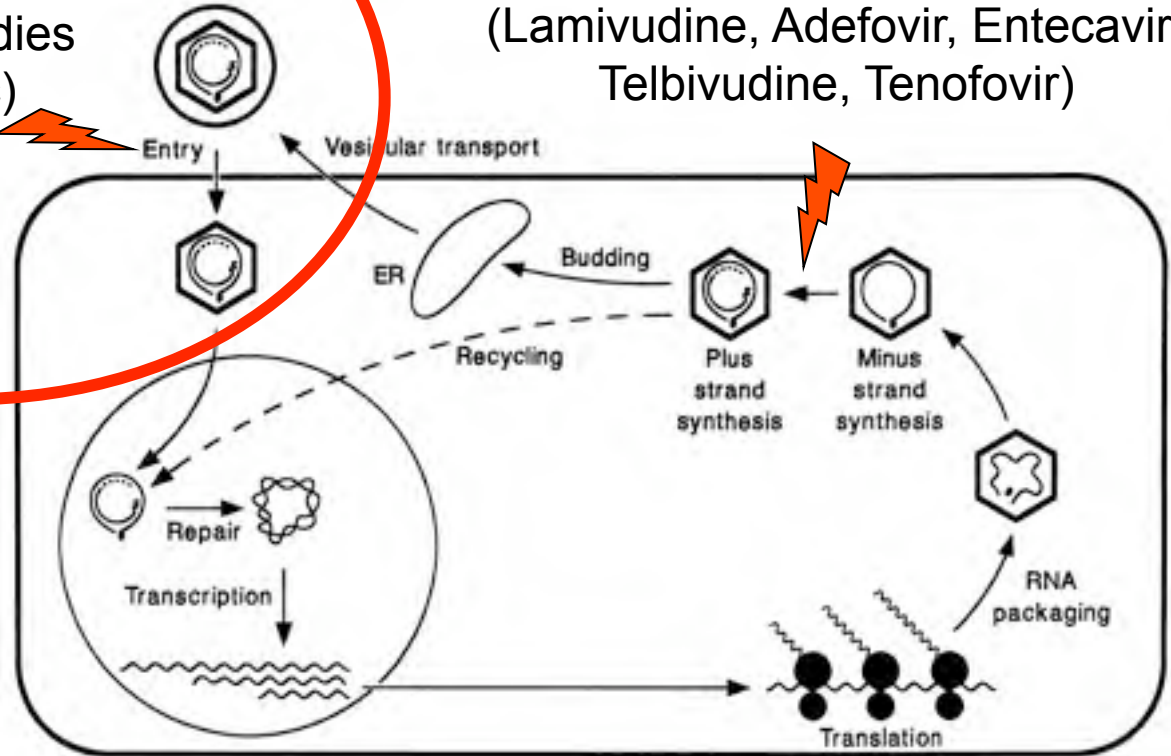


HBV life cycle

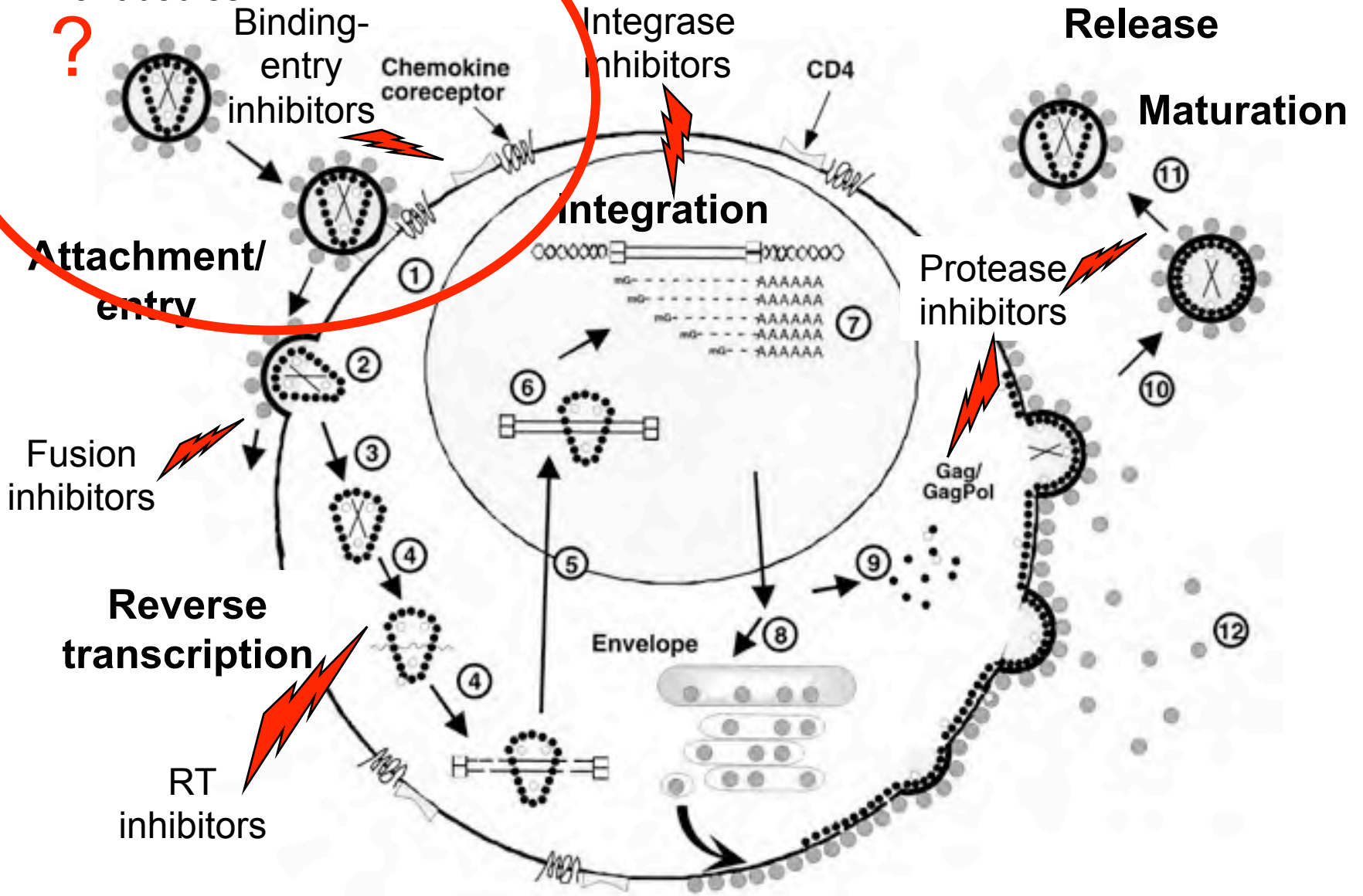
Neutralizing antibodies
(HBsAg-specific)

HBV polymerase inhibitors
(Lamivudine, Adefovir, Entecavir,
Telbivudine, Tenofovir)

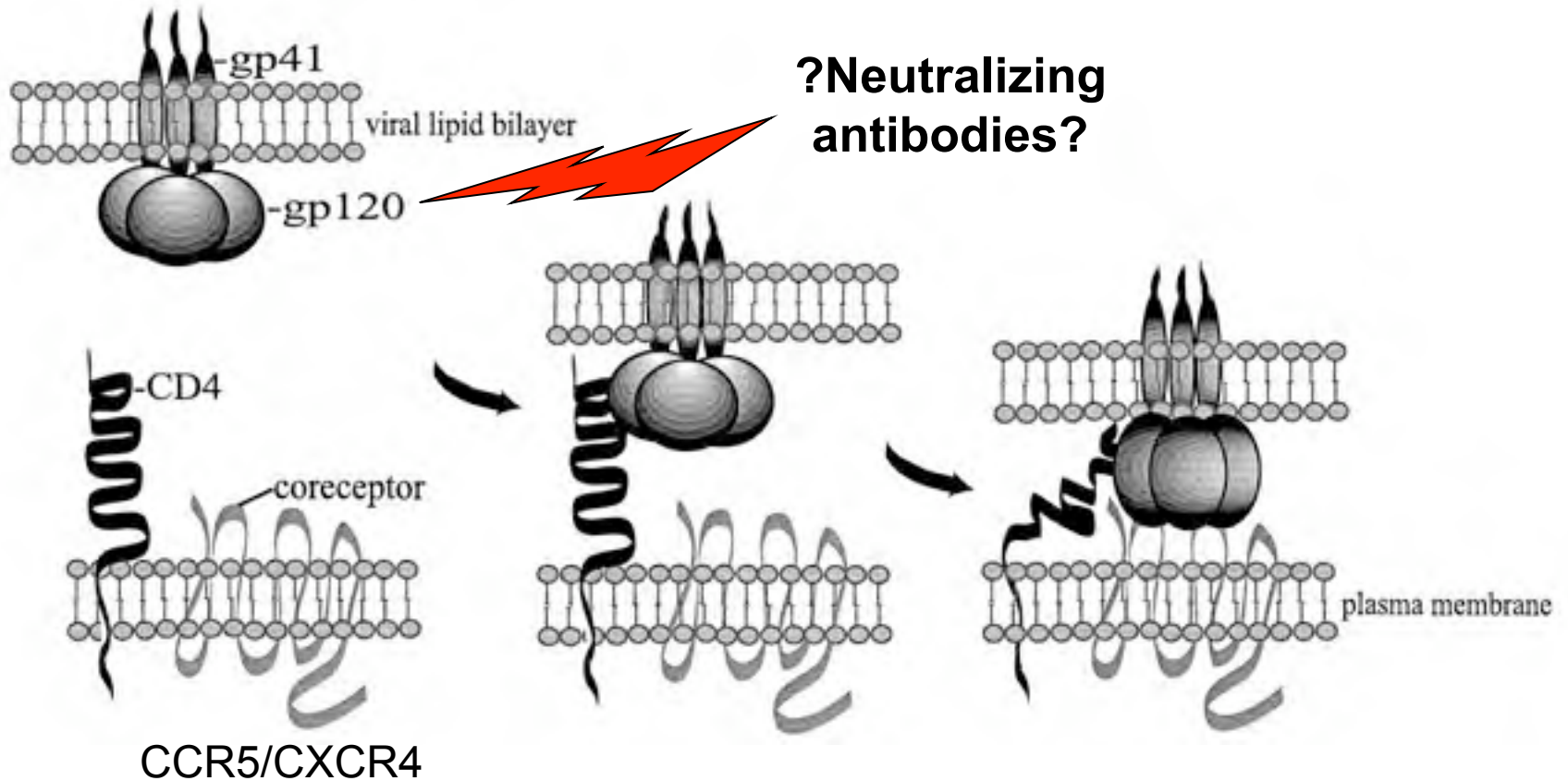
- Hepatocyte-specific receptor
- Nuclear steps require liver-specific elements
- Reverse transcription
 - Essential for virion formation
 - Integration *NOT* essential (contrast to retroviruses)



HIV life cycle



HIV envelope as vaccine target



Vaccine has no impact

AIDSVAX's failure a blow to treatment

[David R. Baker, Chronicle Staff Writer](#)

Thursday, November 13, 2003

VaxGen's experimental AIDS vaccine couldn't block HIV infection among volunteers in Thailand, the Brisbane company said Wednesday, in another blow for the closely scrutinized drug.

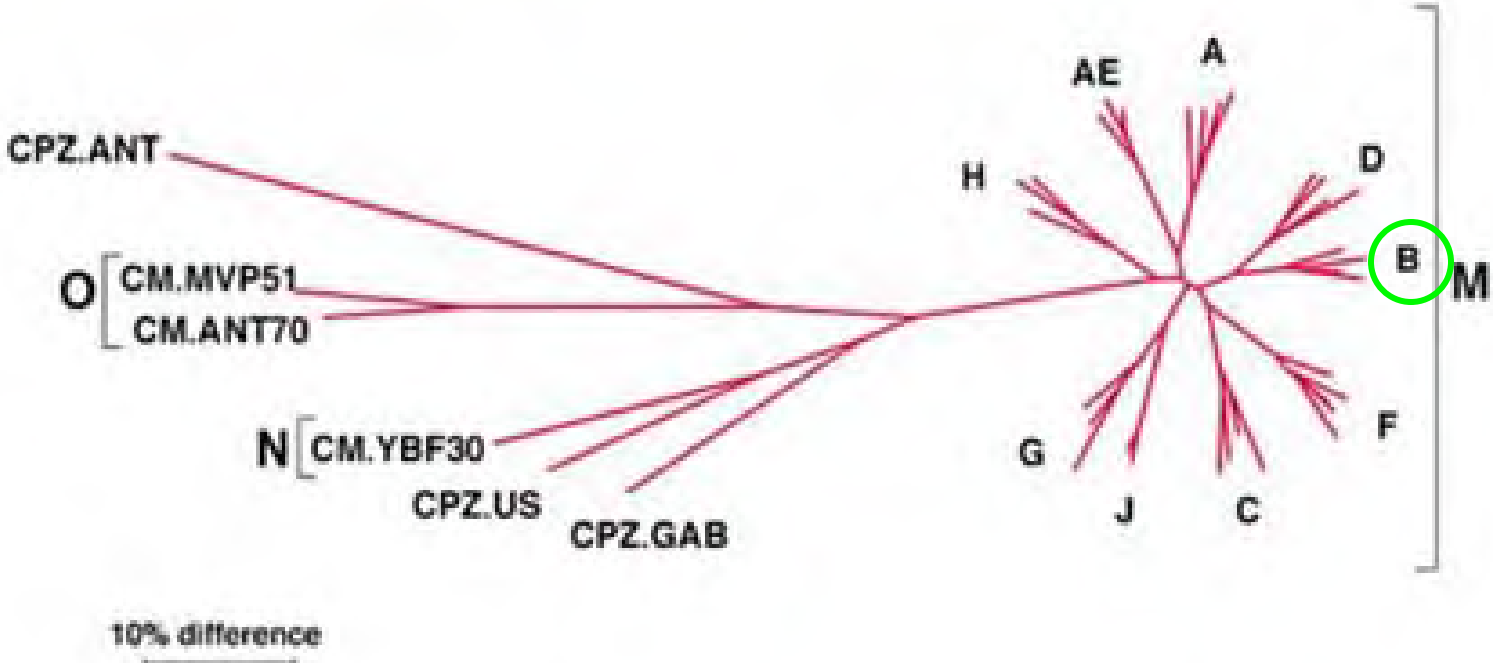
The vaccine, dubbed AIDSVAX, had no noticeable effect on infection rates among the 2,546 intravenous drug users in Bangkok who volunteered for the study. Nor did it slow the disease's progress among volunteers who took the vaccine and later contracted HIV.

HIV genetic variation

- **Initial starting diversity**
- **Recombination**
 - Duplicate genome enclosed within virion
- **Error prone replication**

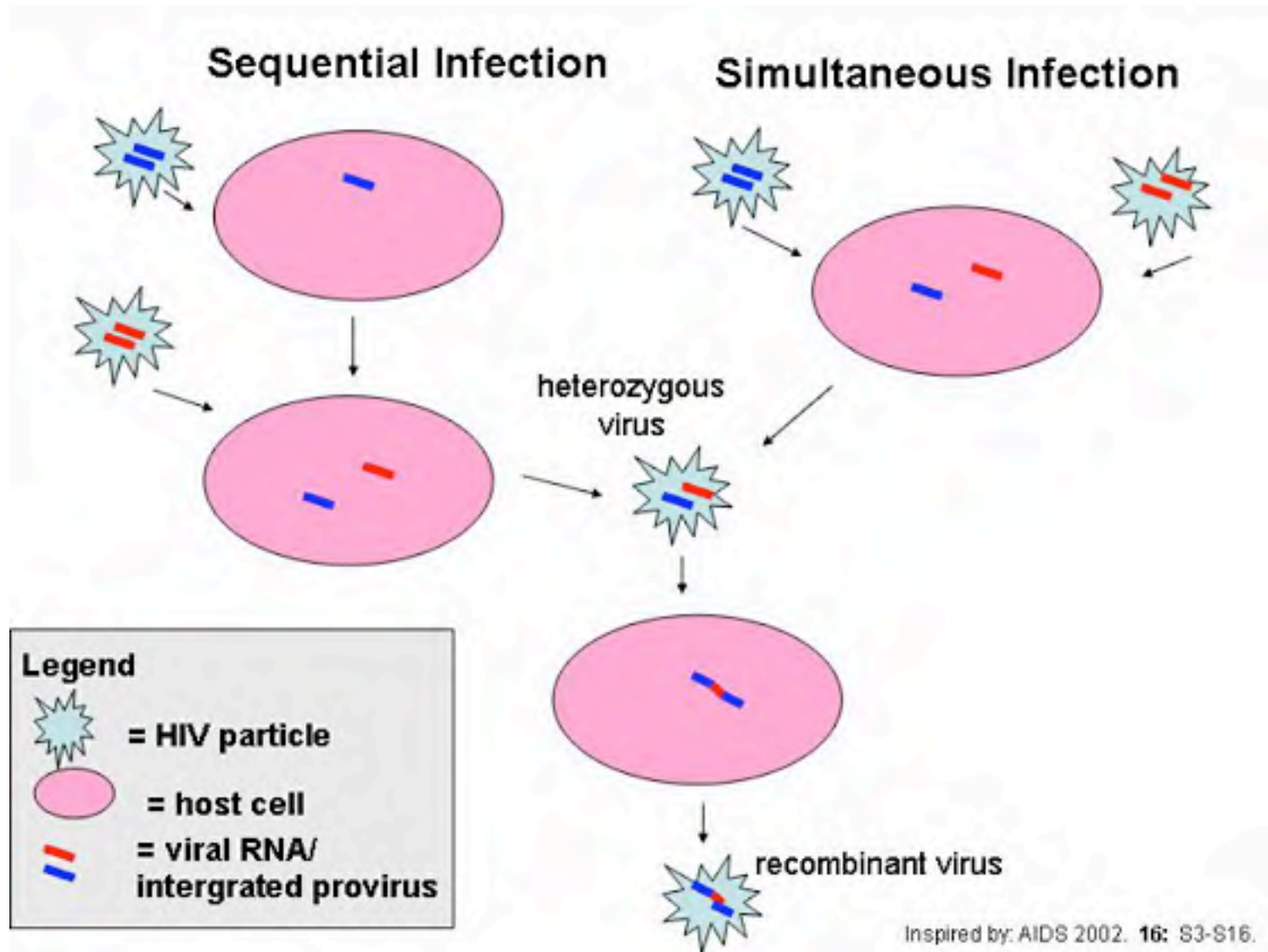
HIV genetic diversity

Genetic Subtypes of HIV-1

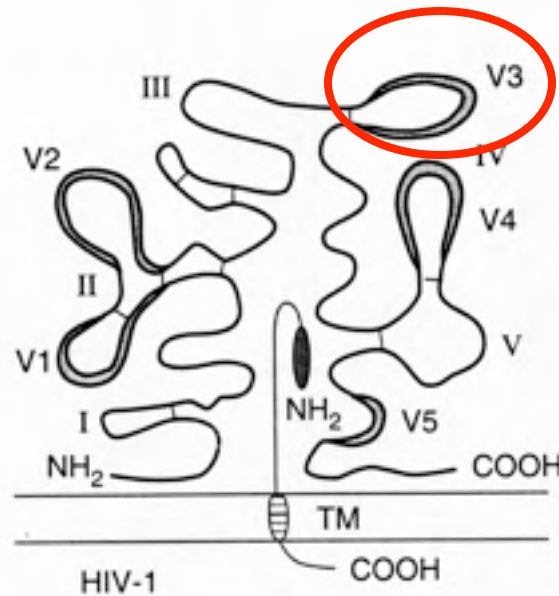
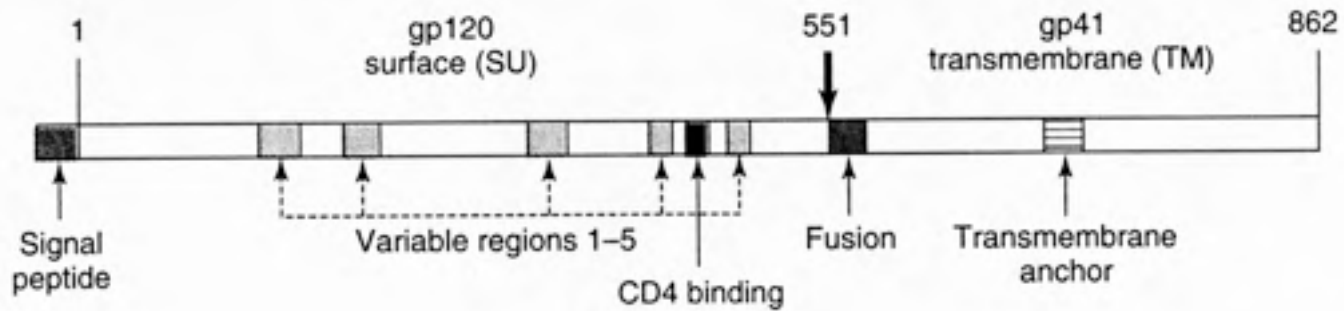


Source: Korber, B et al. Los Alamos National Laboratory

HIV recombination

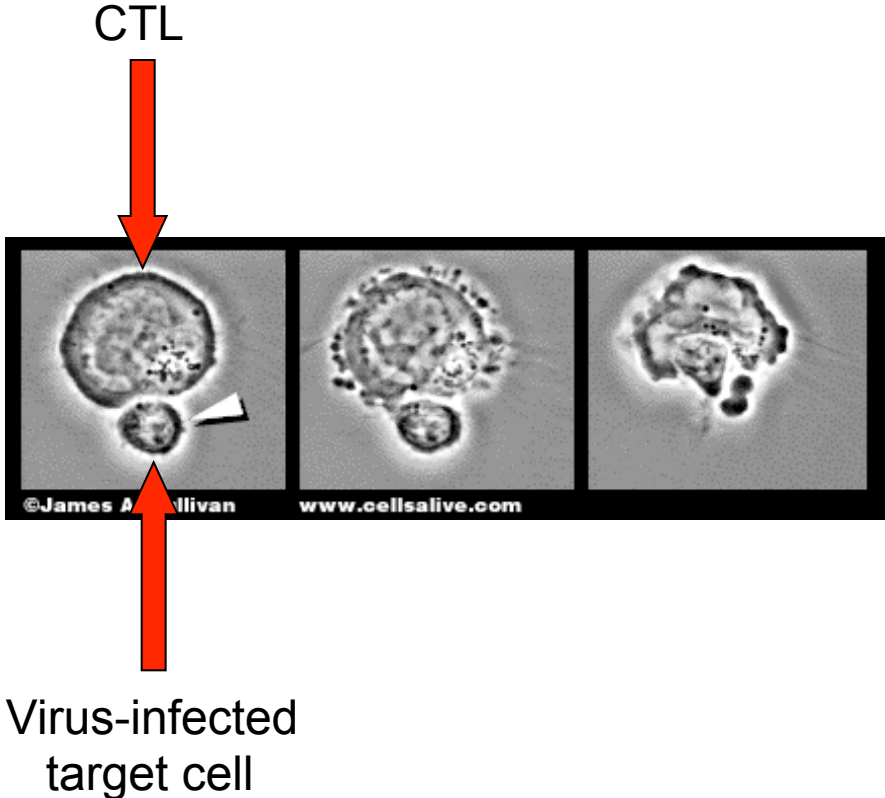
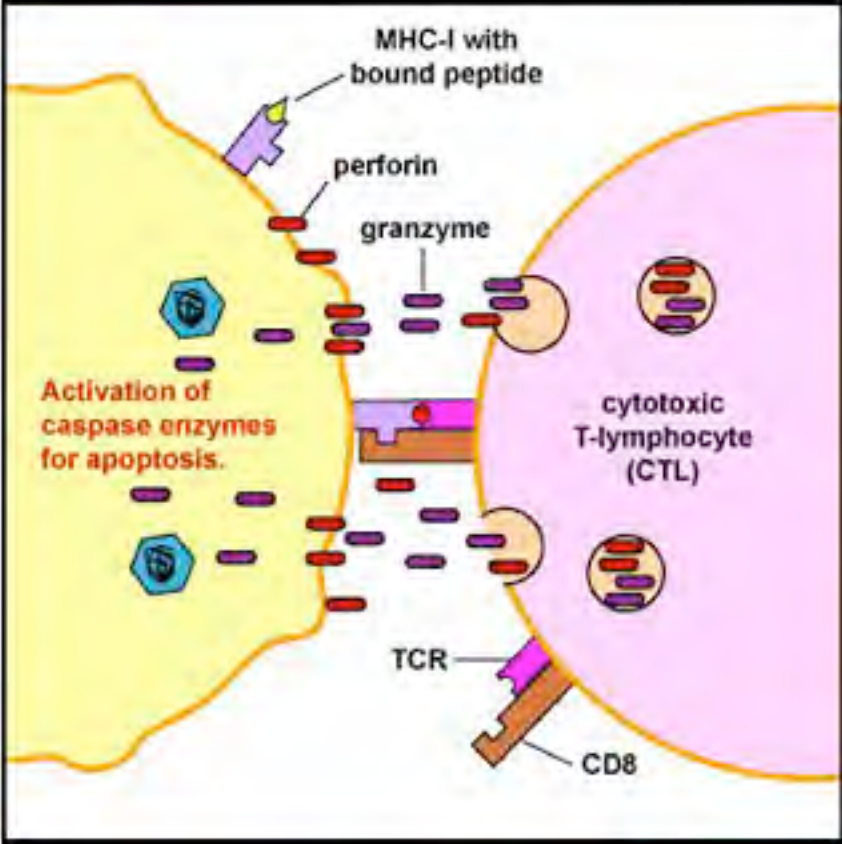


HIV envelope protein

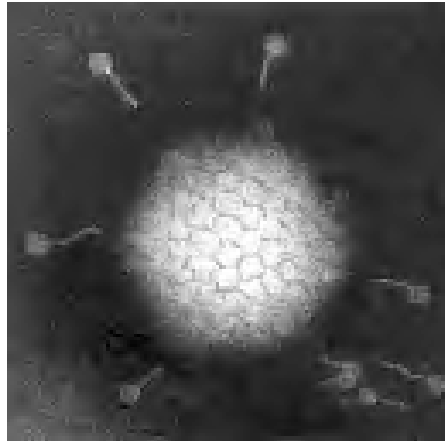
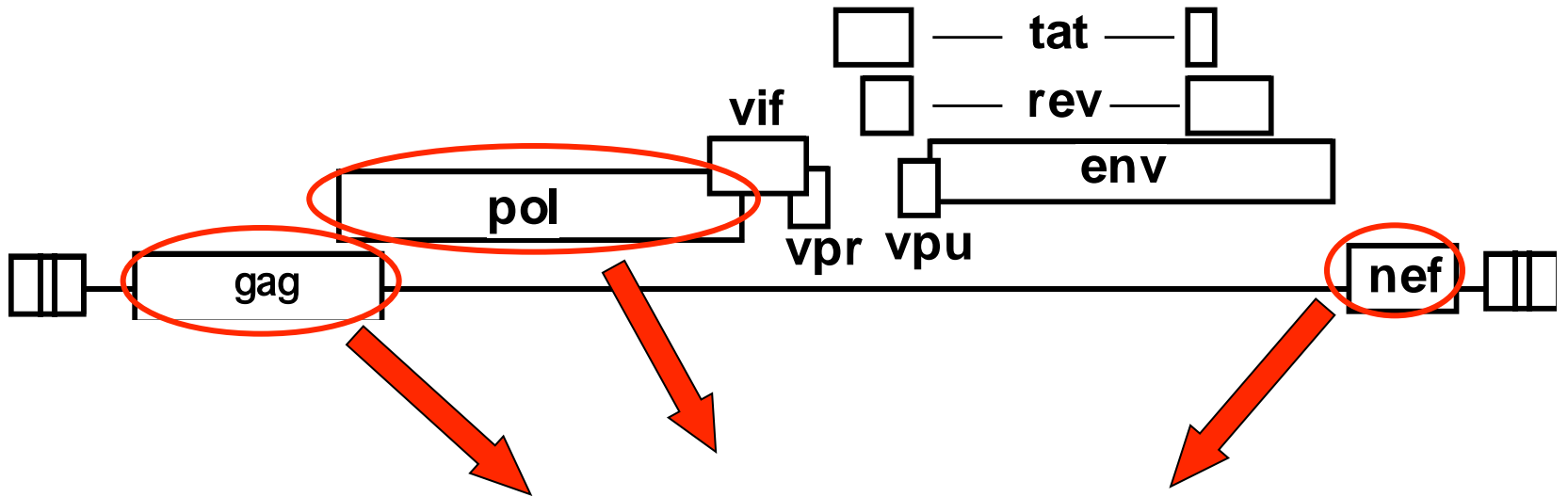


Prime target for neutralizing antibodies

Cytotoxic T cell-mediated killing



V520 vaccine (Merck)



Adenoviral vector

HIV vaccine failure prompts Merck to halt trial

An HIV vaccine being developed by Merck has apparently failed, causing the company to halt a large and once-promising clinical trial last week.

Merck's STEP vaccine used a mixture of components from three weakened adenoviruses to carry three synthetically produced HIV genes. The hope was that each gene would stimulate an immune response against the virus, as earlier trials had suggested.

The latest trial began in 2004 and enrolled 3,000 people considered to be at high risk of infection. But a group of 741 volunteers who received the vaccine saw 24 HIV infections, compared with the control group of 762 people who saw 21 infections. Furthermore, the vaccine did not reduce the amount of HIV in the bloodstream of those infected.

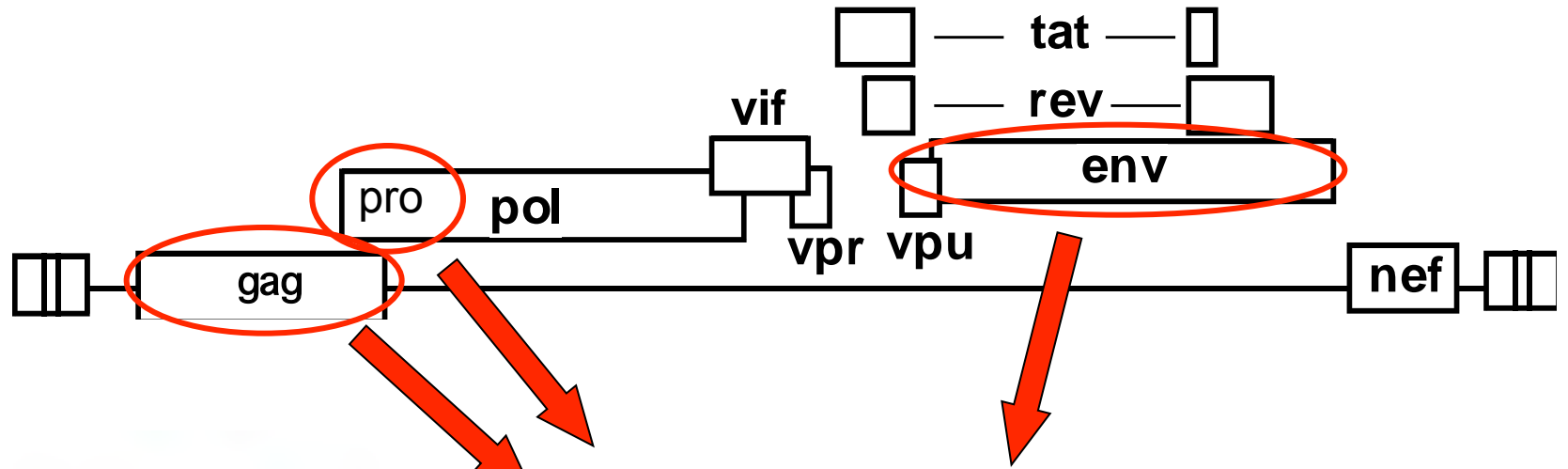
Trial for Vaccine Against HIV Is Canceled

Plans for a large human trial of a promising government-developed HIV vaccine [PAVE trial] in the United States were canceled Thursday because a top federal official said scientists realized that they did not know enough about how HIV vaccines and the immune system interact.

A number of other HIV vaccines are in various stages of testing around the world. But there had been high hopes for the government's trial because the potential vaccine was among a new class that sought to stimulate the immune system in a different way.

The official who canceled the government trial, Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, said it was becoming clearer that more fundamental research and animal testing would be needed before an HIV vaccine was ever marketed.

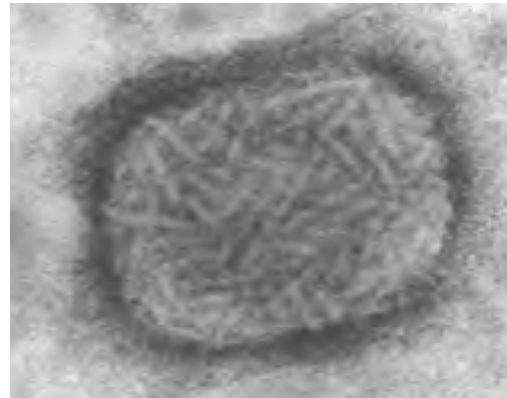
ALVAC-HIV vaccine (Sanofi Pasteur)



+ AIDS VAX[®] B/E



HIV gp120



Canarypox vector

For First Time, AIDS Vaccine Shows Some Success

Scientists said Thursday that a new [AIDS](#) vaccine, the first ever declared to protect a significant minority of humans against the disease, would be studied to answer two fundamental questions: why it worked in some people but not in others, and why those infected despite vaccination got no benefit at all.

The vaccine — known as RV 144, a combination of two genetically engineered vaccines, neither of which had worked before in humans — was declared a qualified success after a six-year clinical trial on more than 16,000 volunteers in Thailand. Those who were vaccinated became infected at a rate nearly one-third lower than the others, the sponsors said Thursday morning. [30% effective]

“I don’t want to use a word like ‘breakthrough,’ but I don’t think there’s any doubt that this is a very important result,” said Dr. [Anthony S. Fauci](#), the director of the National Institute of Allergy and Infectious Diseases, which is one of the trial’s backers. “For more than 20 years now, vaccine trials have essentially been failures,” Dr. Fauci said. “Now it’s like we were groping down an unlit path, and a door has been opened. We can start asking some very important questions.”

Published in New York Times, September 24, 2009
NEJM **361**:2209, 2009

Washington post article titled
“FDA approves prostate cancer 'vaccine' from Dendreon called Provenge“ removed.

Article can be found here:

<http://www.washingtonpost.com/wp-dyn/content/article/2010/04/29/AR2010042902684.html>

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Slide 5: UNAIDS 2006 global report, Wikimedia Commons, http://commons.wikimedia.org/wiki/File:People_living_with_HIV_AIDS_world_map.PNG,
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Slide 6: World Bank, World Development Indicators, 2004

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Slide 24: Korber, Bet al, Los Alamos National Laboratory

Slide 25: Inspired by: AIDS 2002. 16: S3-S16.

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