Author(s): David Miller, M.D., Ph.D., 2009

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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

Reading assignment: Schaechter’s, 4th edition, chapter 38

People living with HIV/AIDS
Per country

UNAIDS 2006 global report, wikimedia commons
Impact of HIV on life expectancy in Africa

Improved sanitation
Vaccination programs

HIV

Life expectancy at birth (years)

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

Source Undetermined
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

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• Essential
  - pol
  - tat
  - rev
  - nef

• Universal
  - gag
  - vpr
  - vpu

Source Undetermined
HIV attachment and entry

- Binding inhibitors
- Entry inhibitors (maraviroc)
- Fusion inhibitors (enfuvirtide)

Sources Undetermined
HIV reverse transcription/integration

First strand DNA synthesis
RNA strand degradation

Complementary DNA strand synthesis

RT, integrase
Capsid

(+) strand RNA

Cytosol

RT inhibitors (zidovudine, nevirapine)

Nucleus (integration)

Integrase inhibitors (reltegravir)

Source Undetermined
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

Direct viral killing
Immune-mediated killing
"Bystander" killing

Various cytokines
IFN-γ
TNF

Antibody response
Macrophage activation → Phagocytosis and bacterial killing
Inflammation

Sources Undetermined
HIV-mediated disruption of CD4$^+$ T cell mediated immune responses
Clinical course of HIV infection

Time (years)

Plasma HIV RNA

CD4

Opportunistic infections

AIDS
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
HBV life cycle

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

Neutralizing antibodies (HBsAg-specific)

HBV polymerase inhibitors (Lamivudine, Adefovir, Entecavir, Telbivudine, Tenofovir)
HIV life cycle

Attachment/entry

Neutralizing antibodies

Binding-entry inhibitors

Chemokine coreceptor

Integrase inhibitors

Integration

Maturation

Release

Protease inhibitors

Fusion inhibitors

Reverse transcription

RT inhibitors

Gag/GagPol

Envelope

Source Undetermined
HIV envelope as vaccine target

?Neutralizing antibodies?

CCR5/CXCR4
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

Legend

- HIV particle
- host cell
- viral RNA/intergrated provirus

Inspired by: AIDS 2002. 16: S3-S16.
HIV envelope protein

Prime target for neutralizing antibodies
Cytotoxic T cell-mediated killing

- Virus-infected target cell
- MHC-I with bound peptide
- Perforin
- Granzyme
- Activation of caspase enzymes for apoptosis
- cytotoxic T-lymphocyte (CTL)
- TCR
- CD8

Sources Undetermined
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.

Nature 449, 390 (27 September 2007) | doi:10.1038/449390c; Published online 26 September 2007
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.

Published in New York Times, July 18, 2008
ALVAC-HIV vaccine (Sanofi Pasteur)

+ AIDSVAX® B/E

HIV gp120

Canarypox vector

Sources Undetermined
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:
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