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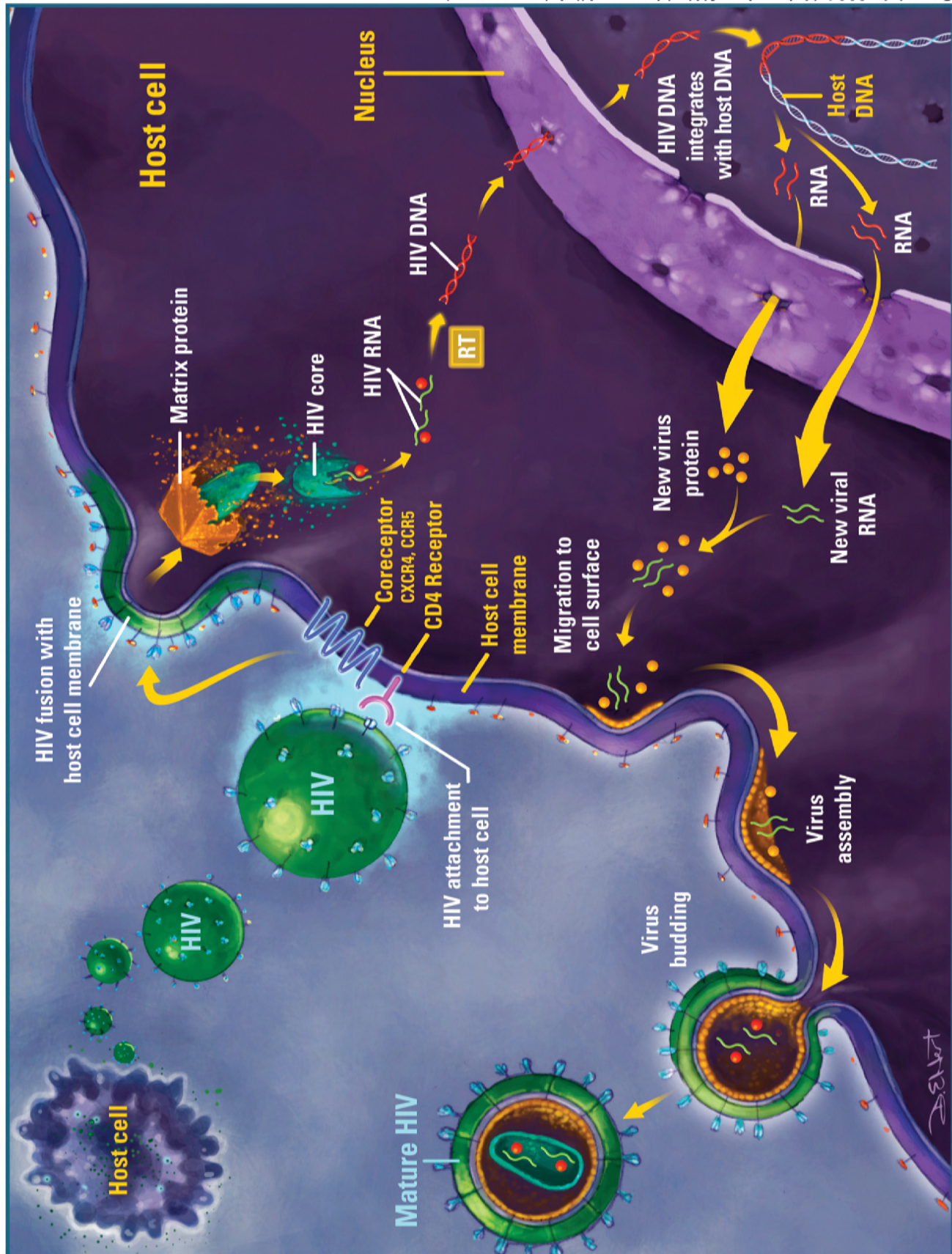
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- Declaration of Helsinki
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Overview of HIV infection



HIV Background

Viruses: Living Or Non-living?

(Before teaching this section review characteristics of living and non-living cells.)

When a virus is outside a living cell it is crystalline in nature. It produces no energy and performs no life functions since it has no nucleus or cytoplasmic organelles. All living substances grow and reproduce but a virus cannot do that until it enters a living host. A virus is many times smaller than a bacterium and can be seen only by an electron microscope. The HIV virus is so small that if it were the size of a softball, the white blood cell would be about the size of a classroom! It may contain either a single or double strand of DNA or single stranded RNA within a protective protein coat called a capsid. The capsid protects the RNA from harsh environmental conditions.

The RNA Molecule

- A. RNA is similar in structure to DNA, but it is single stranded and uses the sugar ribose. The backbone is made up of ribose and phosphoric acid groups, which alternate. A nitrogenous base side chain is attached to each ribose-phosphoric acid group. The four side chains or bases in RNA are adenine, cytosine, guanine and uracil. Uracil is the base which takes the place of thymine in the DNA model. The combination of one phosphate, a 5 carbon sugar and one of the 4 bases is called a nucleotide.
- B. In a normal cell there are 3 major types of RNA:
 - i. mRNA (messenger RNA)
 - 1. mRNA serves as a temporary «messenger» which makes a complementary copy of DNA genes and carries them from the nucleus to the ribosome in the cytoplasm.
 - ii. tRNA (transfer RNA)
 - 1. As the mRNA attaches to the ribosome, the tRNA acts like a «trucker» with two ends. One end «fits» the mRNA code and the other end carries specific amino acids. As the first end «fits» into the mRNA code each amino acid links to the next amino acid forming a long chain which eventually becomes a protein.
 - iii. rRNA(ribosomal RNA)
 - 1. rRNA, found in the ribosome helps the tRNA to work more efficiently.

The HIV Virus

- A. HIV fuses with the lipid-protein cellular membrane of a T-cell (or other target cell) and sneaks through it to invade the host cytoplasm. Once inside, the viral reverse transcriptase copies the single strand of HIV RNA to make a single strand of DNA. The reverse transcriptase then makes a second complementary strand of DNA. This double stranded DNA is now ready to invade the cell's nucleus.

B. HIV is a retrovirus - the flow of genetic information of the virus is reversed from the usual 'central dogma' of DNA->RNA. In a retrovirus, the information is copied backwards from RNA to make DNA, which is then inserted into the cell's DNA. In translation the DNA then forms mRNA. This method of copying happens in no other living system. When HIV inserts itself directly into the cell's DNA this sequence remains integrated in the host genome. This extra step in replication from RNA to DNA to mRNA results in many mutations in replication. (This high mutation rate causes drug developers to have to play «catch up» when they try to develop new drugs to interfere with the HIV in the viral replicating process.).

HIV Transmission

- A. Transmission: Have students work in pairs and develop a list of how HIV is transmitted and risk behaviors.
- B. Body fluids –
- i. Semen
 - ii. Vaginal fluid
 - iii. Blood
 - iv. Breast milk
- C. Risk behaviors
- i. Unprotected sex
 - ii. IV drug use with needle sharing
 - iii. Infected mother to child
- D. Heterosexual transmission is the most common cause of disease transmission.
- E. Individuals capable of infecting others may not know they have the disease as the initial symptoms may mimic the flu and then the person will be asymptomatic for a fairly long period of time.

HIV Origins

Research based on genetic similarity of the viral genome and proteins indicates that HIV-1 arose through a transmission of SIV (Simian Immunodeficiency Virus) from Chimpanzees to Humans, and HIV-2 arose through transmission from SIV from Sooty Mangabeys to Humans.

In some communities, it is believed that the US government developed HIV as a tool for the genocide of segments of the population (African-American, for example). Although this is not a hypothesis considered by most scientists, it does impact the willingness of certain groups to participate in HIV research.

Immune System – Background

Natural or Innate

- A. relatively nonspecific – only recognizes a limited number of different pathogen characteristics
- B. when activated is called the inflammatory response
- C. born with capacity fully developed, does not change after birth
- D. includes
 - i. physical & chemical barriers that block pathogen entry into body
 - ii. phagocytic cells, (neutrophils & macrophages), attack & engulf pathogens
 - iii. other cells: mast cells, eosinophils, basophils,
 - iv. blood protein systems: complement, coagulation, acute phase, and kinin systems
 - iv. cytokines secreted by inflammatory cells that influence both the innate and the acquired immune responses

Acquired or Adaptive Immune Response

- A. very specific, responds to specific sites on invading pathogens
- B. response is different for each pathogen, even for different types of a given pathogen
- C. when activated is called the immune response
- D. response to a pathogen only develops after an individual encounters a pathogen, therefore continues to develop over a lifetime
- E. includes only lymphocytes (3 kinds) and the antibodies produced by B cells which are one of the types of lymphocyte
 - i. T cells – are three main types,
 - 1. Helper T cells (CD4+),
 - helper T cells are key to the entire immune response
 - activate cytotoxic T cells, B cells & macrophages
 - 2. Cytotoxic T cells (CD8+)
 - effective against intracellular pathogens
 - kills virally infected cells & tumor cells
 - recognizes specific antigens on cells
 - requires activation
 - 3. Natural killer cells
 - a primitive lymphocyte
 - lacks the specificity of a cytotoxic T cell
 - sometimes considered part of innate immunity
 - kills virally infected cells & tumor cells

ii. B cells

- produce antibodies that are specific to pathogen antigens
- are 5 different types of antibody, each with different functions
- 5 types of antibody are IgM, IgA, IgD, IgG, IgE
- effective against extracellular pathogens
- each type of antibody activates a different set of mechanisms that work to destroy or inactivate pathogens

F. once activated a fraction of either T or B cells will become memory cells

- some immune memory is retained for many years and other types are only retained for a period of months.
- we do not understand why there are differences in the duration of immune memory for various pathogens.

G. immunity can be acquired actively via the processes described above or passively via transfer of antibodies as happens when an infant receives antibodies from the mother via breast milk

- can be active or passive

**Artificially
Acquired
Immunity**

Discuss students' experiences with vaccines first – What vaccines have they had?

- i. Some form of the pathogen is introduced by the vaccine which stimulates the immune response by presenting the antigen

Creating an HIV Vaccine-Background

HIV Life Cycle – Review

- A. Discuss life cycle based on animations shown
- B. Why can't the immune system fight HIV like other viruses?
 - i. attacks cells responsible for mounting immune response
 - ii. high mutation rate
 - iii. many viral regions that immune system could target for response are shielded
 - iv. Inserts itself into the host DNA
 - 1. part of that cell until it dies
 - 2. replicated as part of DNA each time cell divides

Basic Genetic Structure of HIV

- A. Retrovirus
 - i. Composed of single strand of RNA
- B. High Mutation Rate
 - i. Inherent nature of RNA leads to more mistakes than DNA
 - ii. RNA transcriptase has “built-in” mistakes generator
 - iii. 1000s of copies made a day – high chance of variability
 - iv. in 24 hrs 10¹⁰ new virions a day! – averages one mutation per replication
 - v. leads to variations of HIV:
 - 1. within one person
 - 2. can be changes between two people – one who had HIV originally and one who contracted it from them
 - 3. variation throughout the world – different “clades” in different parts of the world (HIV in Africa different from HIV in United States or Thailand). 7-8 major types
- C. Three main genes
 - i. Gag: structural proteins – give rise to main structures such as capsid, general envelope, etc.
 - ii. Pol: enzymes – direct development of reverse transcriptase, protease, and other important enzymes which aid in “hijacking” the host cell and forcing it to make multiple copies of the virus
 - iii. Env: surface proteins - these are the proteins involved in recognition and binding to T cells; they are constructed of a trimer of three ‘ball’ units (gp 120, or glycoprotein 120) attached to three ‘stick’ units (gp 41) that span the viral membrane.

Developing a Vaccine for HIV

A. Desired responses:

- i. Want to create neutralizing antibodies that will be broadly reactive. Neutralizing antibodies bind to the virus and prevent it from infecting cells. Neutralizing antibodies ideally need to attach to, or label, viruses from many different clades of HIV (not just one type)
- ii. Neutralizing antibodies need to target specific protein regions, which are more conserved (not mutated) in HIV. However, these conserved regions are not in readily accessible regions of the protein
- iii. Increase cytotoxic T cell (CTL) response-A vaccine also needs to enable T cells to respond to many variations of HIV env proteins. The CTL response is necessary to keep the HIV infection from overwhelming an individual's immune response, but cannot prevent infection from occurring in the first place.
- iv. The desired immune response needs to somehow allow for, or change with, the many virus variations and escape mutations that occur or vaccine will not be effective for any length of time

B. Focus on Env protein

- i. Exposed regions are largely covered by glycoproteins, which shield regions that might invoke a neutralizing antibody response. Glycoproteins themselves do not elicit a strong antibody response.
- ii. Conserved regions of the Env protein are only exposed when binding with receptor (CD4 on T cells) and co-receptor (CXCR4 or CCR5, depending on the cell). The exposed regions are more prone to changes, and much more common (found on other cells, etc.) and thus a vaccine to exposed regions of the protein is not likely to be effective.

C. Vaccines which have been developed:

- i. AIDSVAX vaccine
 1. being tested by VaxGen and NIAID (National Institutes of Allergy and Infectious Disease)
 2. uses a protein subunit of the virus to stimulate the immune response of a vaccinated individual
 - a. disappointing results – This vaccine was highly immunogenic (people's immune systems really responded well and produced lots of antibodies). However, these antibodies were not effective at neutralizing HIV.

3. contains multiple viral protein sequences to ensure a response to a broad range of HIV strains
4. also being researched in conjunction with another vaccine to boost cytotoxic T cells. Inducing a 'dual response' (both neutralizing antibody and CTL) may prove effective.

ii. HIV-1ΔkURNe vaccine

1. strain of HIV genetically altered in the laboratory to produce a weakened form of the virus
2. large portions of HIV genetic code have been snipped out – cannot produce lethal effect
3. tested in monkeys
 - a. initial trials encouraging – monkeys developed immunity to the virus
 - b. over time the weakened virus mutated back into a deadly form
 - c. vaccinated monkeys developed SIV from the vaccinations!

iii. Many other vaccines in “production”

1. expected that by the end of 2004 more than 30 clinical trials will be underway globally.
2. can show chart of research at this point, or save for later lesson
 - a. Developing an AIDS vaccine, THE LANCET, Infectious Diseases Vol 4 July 2004 – page 408-409

If a Vaccine is Developed...How is it Tested?

- A. Many research models are used before a vaccine can be tested in humans
- B. Scientific Methods Used in Biomedical Research (see table 2.3 from For the Greater Good Curriculum, available from Northwest Association for Biomedical Research, www.nwabr.org)
- C. Primate Models and HIV Research
 - i. Contributions to understanding of HIV
 1. Most Primates DO NOT contract HIV, but they DO contract a similar infection from Simian Immunodeficiency Virus (SIV).

2. Chimpanzees can contract HIV-1 but:
 - a. Disease is very rare
 - b. Takes more than 10 years from contraction to death
 - c. Now on endangered species list
3. Macaques, a species of monkey including pig-tailed macaques
 - a. Contract SIV
 - b. Show a range of pathogenicity – different strains and species (like HIV in humans)
 - c. Death in 6 months – 2 years after infection
 - d. Disease similar to AIDS in people
 - i. CD4+ T-cell decline
 - ii. Wasting
 - iii. Envelope uses the same coreceptors as HIV, but differs in amino acid sequence
 - e. SHIV
 - i. Hybrid of HIV-1 and SIV
 - ii. Contains HIV-1 env in SIV backbone
 - iii. Animal-passaged virus is more pathogenic (Animal-passaged virus is grown/cultivated in an animal and then transferred to another animal, as opposed to being grown in cell culture)
- ii. Vaccine research
 1. can use primates as models
 - a. produce similar vaccine which targets SIV instead of HIV and test in primates
 2. SHIV
 - a. Causes disease in monkeys, like SIV
 - b. Vaccine can contain HIV env gene or protein
 - i. Components of a successful vaccine could move directly into formulations for humans
 3. Can give HIV vaccine to test toxicity, etc. in primate model, but cannot challenge (infect with HIV) so gives incomplete information
- iii. Challenges:
 1. cannot test complete HIV vaccine in primate model

Vaccine Challenges

Overview

There are many challenges to finding a vaccine against HIV, yet finding an effective vaccine against HIV may be the only realistic approach to controlling the ever-expanding global HIV epidemic. Worldwide efforts are focused on designing an effective vaccine to prevent infection with HIV, to limit illness if infected or to reduce the amount of virus found in the bloodstream of a person already infected with HIV.

Characteristics of an Ideal HIV Vaccine

An ideal HIV vaccine would have all the characteristics mentioned below. Finding such a vaccine, however, becomes a formidable challenge as we try to balance the effectiveness of the vaccine and the practicality of the vaccine.

An ideal HIV vaccine would:

1. Be effective in preventing transmission through sexual contact, mother-to-child contact, and through tainted IV drug use.
2. Be very safe, with minimal risk of adverse reactions even in unscreened “real world” populations.
3. Be given in a single dose.
4. Offer long-lived protection many years after vaccination
5. Be low cost, allowing widespread vaccination in developing countries
6. Be easy to transport and administer, even in countries with minimal infrastructure.
7. Work well against different variations of the virus.

This ideal vaccine may not be practical or realistic in the face of today’s AIDS epidemic, however. Given the scope of the disease, even an imperfect AIDS vaccine that limits HIV growth in an infected person but does not necessarily prevent infection will result in a significant impact on the spread of the disease. If we could find a vaccine that would slow the progression of HIV in already-infected individuals, this could delay the onset of AIDS, reduce the risk of HIV transmission from those individuals to their sexual partners and from infected mothers to their children. An effective HIV vaccine would therefore slow the spread of HIV in human populations and provide hope of its eventual eradication. However, despite extraordinary advances in knowledge there are still many challenges to developing an HIV vaccine.

Challenges in HIV Vaccine Development

Challenges to HIV vaccine development can be broadly classified into the following categories:

1. **HIV Sequence variation:** HIV continually evolves because of genetic mutation introduced when the viral RNA polymerase makes more copies of HIV genome and recombination between the two strands of the viral RNA genome. Initially, a person is infected with only one or a limited number of HIV variants. Once HIV infection becomes established, however, the virus continually undergoes genetic changes, and many variants may arise within an infected person. Whenever a drug or immune response destroys one variant, a distinct but related resistant variant can emerge. In addition, certain variants may thrive in specific tissues or become dominant in an individual because they replicate faster than others. Any of these changes may yield a virus that can escape identification and attack by (i) neutralizing antibodies (NAbs) that bind the viral variants and prevent the virus from binding and infecting its target cell and (ii) cytotoxic T lymphocytes (CTL) that perform immune surveillance and kill the virus infected cells.

There are two types of HIV, HIV-1 and HIV-2. HIV-1 is primarily responsible for the global pandemic. Using HIV-1 **isolates** obtained from patients around the world, the genes encoding their envelope and core proteins have been analyzed and compared. On this basis, scientists have grouped HIV-1 isolates worldwide into three groups, M, N, and O. The M (Major) group can be further divided into nine **subtypes**, or **clades**. Each subtype within a group is about 30 percent different from any of the others. If an individual is infected with two different subtypes, a new (recombinant) form of virus can develop that contains gene fragments from both parental viruses. Hence, since there are a vast number of HIV variants circulating worldwide, a successful vaccine will need to induce an immune response that protects against a large portion of these variants. In contrast, successful vaccines for other viruses have only had to protect against one or, like polio, a limited number of virus subtypes. Thus, HIV researchers will need to account for strain variation within individuals and among populations when developing HIV vaccines.

Despite HIV changing so much due to genetic mutation and recombination, HIV still needs to preserve certain regions on its viral proteins for efficient function. For example: HIV is coated with viral envelope that helps in the viral binding and entry leading to infection of target cells. The viral envelope glycoprotein changes its outside such that it escapes from powerful neutralizing antibodies (NAbs), but retains the structural integrity of the core that it exposes just before binding to target cells. This core is highly conserved amongst diverse isolates from different clades. In fact, NAbs that recognize the conserved core of the HIV envelope glycoprotein

(broad NAbs) tend to recognize and prevent infection of HIV virus isolates from different clades suggesting that targeting these conserved regions will result in a vaccine that can recognize the wide variety of circulating HIV vaccine. Though these broad NAbs have been shown to prevent infection in animal models of HIV infection, it has been very difficult to develop these exact responses through vaccine approaches in animal models and in infected patients. Notwithstanding, efforts should still focus towards developing an HIV vaccine that incorporates parts that elicit immune responses against the conserved regions of HIV genes.

2. Protective immunity in natural infection not clearly established: Despite advances in our knowledge regarding immune responses against HIV in infection, we are not yet clear on which immune responses are important for the protection against HIV infection. One way to understand this is to study (i) a subset of people who appear to resist HIV infection despite multiple exposures to HIV called “exposed seronegatives” (ii) HIV infected patients who control HIV replication to such low levels that they do not progress to disease for decades and are called “long-term nonprogressors” (iii) monkeys that carry ancestral viruses to HIV that are resistant to disease despite extremely high viral loads.

Studies of “exposed seronegatives” showed that they are not completely virus negative as they carry 100 to million fold lower virus than patients with typical disease progression. But why these people carry such low-levels of virus despite multiple exposures to HIV is unknown. Earlier research studies in this cohort of people indicated that they might have had abortive infection as a result of (i) exposure to lower virus levels from their sexual partner resulting in quick immune control or (ii) increased resistance to infection due to their genetic predisposition. Studies also indicated that these HIV exposed individuals mount strong cytotoxic T lymphocyte responses and antibody responses at the mucosal sites showing that infection may be prevented if immune responses at the mucosal (genital, oral) areas are developed and persist. Such mucosal responses should be a part of future vaccine efforts.

Studies of “long-term nonprogressors” indicated that these HIV infected patients mount very strong (higher quantity and quality), durable and broad immune responses, both cytotoxic T lymphocytes and neutralizing antibodies. CTLs from these patients have been shown to produce more than what is typically produced in an HIV infected patients of a killer protein called “granzyme” that punches holes in the virus infected cells. NAbs that arise in these long-term nonprogressors also tend to be stronger and more potent at preventing HIV virus from infecting cells. In fact, the only “broad NAbs” mentioned in the earlier section were found in

a long-term nonprogressor. To date, no vaccine strategy has predictably induced broadly neutralizing protective antibodies in humans.

Monkeys naturally infected in the wild with viruses closely related and yet distinct from HIV called Simian immunodeficiency virus (SIV) have been shown to support high levels of virus replication without any suffering from disease in contrast to humans. How can these monkeys be seemingly resistant to disease? Again research studies in these macaques show that these monkeys turn a blind eye to the virus replicating in them. An analogy to this phenomenon would be why certain people are allergic to peanuts and pollen, whereas others are not. It is due to the hyperactivation of the immune cells in the allergic individual that results in the allergic reaction. Immune cells in non-allergic individuals turn a blind eye to the same peanuts and pollen allergens resulting in no tissue damage or allergic reactions. Similarly, monkeys naturally infected with SIV do not mount any anti-viral immune responses and inflammatory responses to the virus. Disease in HIV infected humans occurs as a result of widespread damage to tissues and immune cells that traffic to the site of infection from the anti-viral immune responses in the patient attacking infecting cells and cause a cascade of inflammatory events. This tissue damage is lacking in these naturally infected macaques and is thought to be the consequence of millions of years of co-evolution of SIV in these monkeys such that these monkeys have learned to adapt to infection. Since we cannot wait for millions of years for us to co-evolve with HIV, vaccine efforts should target prevention of HIV's direct and indirect damage to tissues and immune cells.

3. HIV Latency: HIV like other retroviruses in its class integrates into the host genome upon entry into the target cell and makes a double stranded DNA copy from its RNA genome. So, once HIV enters and infects the target cell, the cell is permanently infected and can be eradicated only by cytotoxic T lymphocytes. In infected cells, HIV can remain latent from years to decades by not expressing any of the viral proteins on the cell surface thus escaping immune surveillance by CTLs and natural killer cells (NK cells). HIV not only infects CD4+ T helper cells (immune cells that stimulate CTLs

to kill infected cells), but also cells of the innate immune system called macrophages that attack and engulf pathogens. Macrophages present pathogens to T cells comprising of CD4+ T helper cells and CTLs, and B cells that produce antibodies and stimulate the latter into action. It has been shown even after prolonged virus suppression by antiretroviral therapy that upon cessation of treatment, latently infected macrophages can be reactivated leading to productive infection. It is not entirely clear whether virus multiplication and exit occurs differently within macrophages, but it has been recently shown that HIV that is released from macrophages are inherently more resistant to the body's NABs than viruses emerging out of CD4+ T cells. Not only are the viruses from macrophages resistant to NABs, but the macrophages themselves are found to be resistant to killing by virus-specific CTLs, showing that macrophages are specialized compartments for HIV infection. Vaccine efforts should therefore target latent reservoirs of HIV infection such as in macrophages.

4. HIV Transmission is complex: Sexual transmission accounts for nearly 90% of all HIV transmission from one person to another. Sexual transmission and mother-to-child transmission occurs in the mucosal areas (genital, oral mucosa). Our current knowledge of the events that occur during mucosal infection and the immune responses important for defense against mucosal infection is quite limited. Unlike other viruses, HIV can be transmitted and can exist in the body not only as free virus but also within infected cells. While free viruses are found to be resistant to NABs, cell-associated viruses have been found to be resistant to virus-specific CTLs. Viruses found in these mucosal areas have been found to be different from the viruses floating in the blood and thus vaccine strategies should target not just virus infection in the blood but also HIV infection in the genital and oral mucosa, which offer the frontline of defense against HIV and other infectious organisms. Recent data from studies using mucosal vaccines and microbicides (small drug inhibitors that prevent HIV from binding to receptor on target cells) have shown sterilizing immunity in monkey models showing promise of this approach to control HIV transmission in the mucosa.

The Role of Non-Human Primates

Overview

Most of the progress in studying HIV disease pathogenesis and immunity has been possible through studies of Simian immunodeficiency virus (SIV) and related chimeric viruses called Simian/human immunodeficiency virus (SHIV) in non-human primates. The following section will discuss the importance of non-human primates to HIV/AIDS research.

Characteristics of an Ideal Animal Model

Animal models are tools for understanding elements of infection and disease pathogenesis and in the development, and evaluation of potential drug/vaccine strategies before their testing in the human populations. The characteristics of an ideal animal model for HIV would be:

1. Infection/ disease in the animal model is similar to infection in humans
2. The immune system in the animal model is similar to the immune system in humans so that the immunity that develops against the infectious organism can be compared to (though not exactly applicable) what happens in humans.
3. Easy to test potential drug therapies and vaccine strategies, that might be considered unethical in humans.
4. Smaller experimental time-frame of disease
5. Ease of sample collection from the animals, low-cost, easy maintenance

Despite concerted efforts by scientists to develop low-cost, easy to maintain animal models using mice, it has not been possible to obtain a murine model for HIV as mice are resistant to HIV. Cats can only be infected with distantly related Feline immunodeficiency virus (FIV). HIV fails to replicate and cause disease except in humans and chimpanzees, thereby limiting the ability to evaluate drug therapies or vaccines prior to human testing. However, non-human primates (macaques) can be infected with related viruses and have been valuable as adjunct testing systems to prioritize future drug/vaccine strategies.

Viruses and Non-Human Primate Models

One of the first models to be developed to study HIV disease was the experimental infection of chimpanzees (*Pan troglodytes*) with HIV-1. This model was useful in recapitulating the infection process, route of infection, and antiviral immunity that developed after infection. Though disease pathogenesis was similar to that observed in humans, the disease occurrence too was similar to that in humans with occurrence only after 10 yrs of study. In addition, chimpanzees, our closest primate relative, are an endangered species and are extremely expensive and difficult to maintain. Thus for these reasons, the chimpanzee model has been excluded as a suitable animal model for HIV.

In the early 1980s, primate centers in the New England area reported disease in a group of Indian rhesus macaques (*Macaca mulatta*), whose disease profile was similar to AIDS in humans. It was discovered that these macaques were accidentally exposed to SIV from other naturally infected macaques resulting in what is now called as simian (or monkey) AIDS. Since then, these macaque models that simulate HIV pathogenesis in humans have helped in gaining valuable insight into HIV-1 transmission and pathogenesis. The primate lentivirus family includes HIV-1, HIV-2 and SIV, and these viruses infect a variety of non-human primates, endemic in certain species while leading to pathogenesis in others. It has now been documented based on phylogenetic relatedness (similarity in the viral genome and proteins) that HIV-1 arose from zoonotic transmission events of SIV from chimpanzees (SIVcpz) while HIV-2 arose through separate zoonotic transmissions of related SIV from Sooty Mangabeys (SIVsm). These ancestral viruses do not cause disease in the naturally infected macaques in the wild, however, they cause disease (simian AIDS) when transferred to other macaque species. Thus a non-human primate model using macaques was developed to study HIV disease pathogenesis. To further study immune responses directed against HIV envelope, chimeric viruses have been developed where the SIV envelope has been swapped with HIV envelope within the backbone of the SIV genome. The HIV portion of the genome enables studying immune responses to HIV envelope while the SIV portion helps to infect macaques. These viruses are called simian-human immunodeficiency viruses (SHIV) and also cause disease similar to SIV in macaques and HIV in humans. However, disease occurs much faster within 1-3 yrs making it much easier to follow infected macaques, perform experiments and evaluate therapies within a short time-frame.

Importance of Non-human Primate Models

The importance of non-human primate models to our current understanding of HIV disease cannot be stressed enough. SIV or SHIV infection of non-human primates has been instrumental in:

1. Understanding HIV disease in humans in the following ways:
 - a. Helped study the role of individual genes involved in SIV/HIV disease pathogenesis
 - b. Proved that virulence of the virus during SIV infection in macaques (and HIV infection in humans) was dependent on the virus and upon the host, suggesting patients' genetic factors play an important role in controlling infection and disease
 - c. Showed the importance of CD8⁺ T-cells in controlling early acute infection and the importance of B-cells and neutralizing antibodies (NAbs) in controlling disease outcome
 - d. Correlated the human finding that the plasma viral load predicts time to disease, thereby validating the non-human primate model for studying HIV pathogenesis.
2. Evaluating drug/immuno therapies:
 - a. Helped in the study of timing of post-exposure prophylaxis of the anti-HIV drug called D4T. The macaque study showed that short course treatment at very high doses followed by stopping the treatment was effective in controlling virus load and preventing CD4⁺ T cell loss for more than a year after withdrawal of treatment. These studies are important to study if adverse outcomes will arise when an HIV infected patient stops treatment.
 - b. Determined the role of NAbs as pre-exposure or post-exposure therapies. Macaques passively infused with broad NAbs were found to be completely protected against infection (sterilizing immunity) or have delayed disease in infected macaques even against the most pathogenic of SHIVs. This led to further studies on the timing of NAbs treatment, the different combinations of NAb to use, which injection route to use, and dosing of NAbs without risking human lives. These advances have led to the testing of NAbs as therapy for preventing mother-to-child transmission in humans wherein HIV infected mothers or newborn babies will be exposed to these broad NAbs capable of preventing infection in macaques. Stay tuned for results on these clinical trials.

3. Evaluating vaccine strategies:

- a. Have been useful in determining the relative efficacy of different types of vaccines (subunits, live recombinant viral vectors, prime boost and live-attenuated)
- b. Showed that live-attenuated vaccine that is effective in preventing infection in adult macaques actually causes disease in newborn macaques thereby halting the testing of live-attenuated vaccine in humans.
- c. The advantages of using individual and multiple components in the vaccine (eg. One HIV protein or multiple proteins, and which combinations are better)
- d. Advantages of including adjuvants in the vaccine cocktail. Adjuvants help in stimulating the immune system and help in making better immune responses to the vaccine and subsequent to virus infection.
- e. Effects of infection through different routes. Injection through intravenous route simulates injection-drug use exposure and results in infection directly in the blood. Infection in the mucosal areas such as genital, and mouth simulate sexual and mother-to-child transmission and recapitulates the most common mode of transmission.

**Limitations of
Non-human
Primate Model**

Genes of HIV and SIV differ and therefore drug therapies that target certain HIV regulatory proteins may not be fully effective against SIV infection. The rate of disease (1-3 yrs) is faster than in humans (5-20yrs) and it is not entirely clear if such a rapid disease course is representative of HIV-1. No single animal model is likely to be perfect, each with its own advantages and disadvantages. Non-human primate models should be used as adjunct testing grounds of potential antiviral strategies to weed out the not so effective drug/vaccine strategies prior to testing in humans. Any vaccine/drug strategy that is deemed protective in the non-human primate model may then be trial tested in humans. Scientists should bear in mind that while non-human primate models help in the understanding of HIV disease pathogenesis, there is no substitute for information that can be gleaned directly from HIV infected humans.

Audience

9-12, but may be modified for 7-8

Time required

2 x 50 minutes minimum

Materials

Background information on HIV, Overheads/Butcher paper, markers, and other presentation materials

Objective

Students will demonstrate their understanding of process of HIV infection by suggesting potential interventions.

WA State EALRs addressed

1. The student understands and uses scientific concepts and principles.
- 1.2 Recognize the components, structure, and organization of systems and the interconnections within and among them
2. The students knows and applies the skills and processes of science and technology.
- 2.2 Apply science knowledge and skills to solve problems or meet challenges

Outline

1. Divide students into 6 groups, roughly corresponding to steps in HIV infection/replication:
 - Binding/Entry
 - Reverse Transcription
 - Integration and Transcription
 - Translation and Cleaving of Viral Proteins
 - Assembly and Budding
 - Immune System Response
2. Provide a brief overview of steps to the entire class, then provide each group with a written summary of the events that occur during their assigned step.
3. Have students brainstorm possible interventions for their step. Students should focus on the creativity of their solutions.
4. If time permits, have students research their assigned step in more detail and to refine their ideas. The enclosed list of web resources may be helpful. In researching, students may come across strategies that are currently being pursued. Encourage them to explore these also.
5. Allow students to share their ideas with the class, and to discuss as a group the feasibility of their proposals.
6. As a follow-up, comment on some of the recent research strategies.

Assessment

Students synthesize their understanding of the overall infection/replication process and the immune response into a written/graphic summary.

Additional Lesson Plan Ideas:

Secondary School

<http://www.nsta.org/pubs/nstapress/online.htm> — The Science of HIV (also 12 pg update in pdf)

<http://www.pbs.org/newshour/extra/teachers/lessonplans/health/aids/>

http://www.uen.org/utahlink/lp_res/HIVAIDS001.html (HIV testing)

Elementary:

http://www.uen.org/utahlink/lp_res/HIVAIDS001.html

Selected possible interventions

Binding/Entry

siRNA, antisense RNA, ribozymes

antibodies to gp120

soluble CD4 receptors

fusion proteins consisting of part of CD4 and Fc of immunoglobulin

fusion proteins consisting of part of CD4 and toxin

block action of gp41

Reverse Transcription

Reverse Transcriptase Inhibitors

AZT (Zidovudine) and other nucleoside analogues

Nevaripine

siRNA, antisense RNA, ribozymes

Integration and Transcription

siRNA, antisense RNA, ribozymes

RNA decoys

Translation and Cleaving of Viral Proteins

Protease Inhibitors -viral protease, HIV aspartyl protease, cleaves products from pol and gag genes into functional proteins, including structural units and enzymes

Intracellular antibodies and transdominant proteins

Assembly and Budding

Targeting the ‘viral assembly line’

Immune System Response

Vaccine strategies- Stimulate neutralizing antibodies and cytotoxic lymphocytes via vaccine (subunit, vector, peptide, DNA vaccines)

Stimulate natural immune system (interferons, interleukins, actions of adjuvants)

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles For All Medical Research

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort

it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles For Medical Research Combined With Medical Care

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

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5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Footnote: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Page back to paragraph 29.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

<http://www.wma.net/e/policy/b3.htm>

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Reprinted from Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182.. Washington, D.C.: U.S. Government Printing Office, 1949.

<http://ohsr.od.nih.gov/guidelines/nuremberg.html>



HIV VACCINE
TRIALS NETWORK

Resources for HIV Vaccine Information

www.hvtn.org/resources

Agence Nationale de Recherches Sur la Sida (ANRS)

www.anrs.fr/index.php/article/home/16 (en français)

The ANRS, funded by the French government, is one of the principal international actors in the search for a preventive HIV vaccine.

AIDSinfo www.aidsinfo.nih.gov, www.aids.gov

Both are a service of the U.S. Department of Health and Human Services.

AIDS Vaccine Advocacy Coalition (AVAC) www.avac.org

www.aidsvaccineclearinghouse.org/

AVAC is an advocacy group in the U.S. that publishes an annual review of progress in HIV vaccine development.

American Foundation for AIDS Research www.amfar.org

Supports AIDS research, AIDS prevention, treatment education, and the advocacy of sound AIDS-related public policy.

Capitol Area Vaccine Effort www.aidsvaccine.org

Washington D.C. volunteers organized around trial participation.

Centers of Disease Control and Prevention www.cdc.gov/hiv/vaccine.htm

The U.S. government's disease control and prevention agency.

Global Alliance to Immunize Against AIDS (GAIA) www.gaiavaccine.org

GAIA is a non-profit foundation for a global AIDS vaccine.

HIV and Hepatitis.com www.hivandhepatitis.com/hiv_vacc.html

A resource for HIV vaccine news articles.

International AIDS Economics Network (IAEN) www.iaen.org

IAEN focuses on the economics of HIV/AIDS prevention and treatment.

International AIDS Vaccine Initiative (IAVI) www.iavi.org

IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV/AIDS, focusing on developing countries.

International Council of AIDS Service Organizations www.icaso.org

ICASO promotes and supports the work of community AIDS organizations around the world.

National AIDS Trust (NAT) www.nat.org.uk

NAT, a U.K. based organization, aims to promote a wider understanding of HIV and AIDS.

National Institute of Allergy and Infectious Diseases (NIAID) / NIH

www.niaid.nih.gov/daids/vaccine/default.htm

NIAID is the primary agency of the U.S. government devoted to research on HIV/AIDS

South African AIDS Vaccine Initiative (SAAVI) www.saaui.org.za

SAAVI was established to coordinate the research, development and testing of HIV/AIDS vaccine in South Africa.

UNAIDS www.unaids.org

The Joint United Nations Programme on HIV/AIDS.

University of California at San Francisco (UCSF) <http://hivinsite.ucsf.edu>

UCSF's HIVinsite web page contains extensive information (información en español también)

Vaccine Research Center (VRC) www.vrc.nih.gov/VRC/

The Dale and Betty Bumpers Vaccine Research Center at NIH.

WHO-UNAIDS HIV Vaccine Initiative

www.who.int/vaccine_research/diseases/hiv/en/

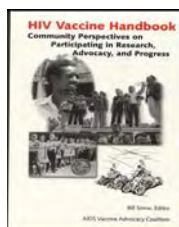
A joint activity of the World Health Organization and the United Nations Programme on HIV/AIDS.

Advocates for Youth

www.advocatesforyouth.org/hivvaccine.htm

HIV vaccines from a youth perspective.

Booklets



HIV Vaccine Handbook Community Perspectives on Participating in Research, Advocacy and Progress.

Edited by Bill Snow

AIDS Vaccine Advocacy Coalition

www.avac.org/primer.htm

For your free copy, please call NPIN 1-800-458-5231

Inventory item D305



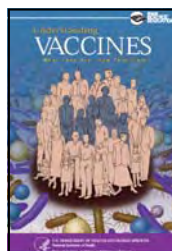
Glossary of HIV/AIDS-Related Terms

Produced by AIDSinfo

For a free copy, contact AIDSinfo

1-800-448-0440

ContactUs@aidinfo.nih.gov



Understanding Vaccines

Produced by NIH/NIAID

[http:// www.niaid.nih.gov/publications/ vaccine/pdf/undvacc.pdf](http://www.niaid.nih.gov/publications/vaccine/pdf/undvacc.pdf)

For a free copy, contact the NIAID

Office of Communications

(301) 496-5717



Getting the Global House in Order

AIDS Vaccine Advocacy Coalition
May 2004

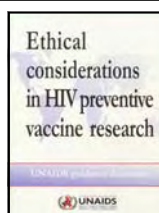
www.avac.org/pdf/reports/2004AVACReport_High.pdf



Developing Vaccines for HIV and AIDS: An Introduction for Community Groups , 2nd Edition.

Produced by the International Council of AIDS Service Organizations (ICASO)

Available in French, English, Spanish at: www.icaso.org/icaso/vaccines.htm



Ethical considerations in HIV preventive vaccine research

UNAIDS Guidance Document

[www.unaids.org/publications/ documents/vaccines/index.html](http://www.unaids.org/publications/documents/vaccines/index.html)

Bulletins



VAX Bulletin

Community-focused monthly

Produced by the International AIDS Vaccine Initiative (IAVI)

www.iavi.org

Available in French, Spanish, English, German, and Portuguese.



WHAT IS AN HIV VACCINE?

A preventive HIV vaccine is a substance that teaches the body's immune system to recognize and protect itself against HIV, the virus that causes AIDS. HIV vaccines currently being tested in humans are made from man-made materials that **CANNOT** cause HIV infection.

Scientists believe that an effective HIV vaccine, given before exposure to HIV, could have a number of possible outcomes. These include:

- Preventing infection in most people
- Preventing infection in some people
- Preparing a person's immune system to block continued infection and eliminate the virus (vaccines against measles, mumps and polio work this way)
- Delaying or preventing the onset of illness or AIDS

The long-term goal is to develop a vaccine that is 100 percent effective and protects everyone from infection. However, even if a vaccine only protects some people, it could still have a major impact on controlling the epidemic. A partially effective vaccine could decrease the number of people who get infected with HIV; those people, in turn, would not pass the virus on to others. Even when an HIV vaccine is developed, education and other prevention efforts will be needed so that people continue to practice safe behaviors.

HISTORY OF VACCINES

The value of vaccines was recognized approximately 200 years ago, beginning with a vaccine against smallpox. The smallpox vaccine saved millions of lives, and its success helped people understand that introducing a vaccine into the body can actually trigger a protective immune response, and prevent disease.

Today, there are numerous safe and effective vaccines. Vaccines have been used successfully against many life threatening diseases, including measles, and polio in most of the world.

COMMUNITY PARTICIPATION IN VACCINE RESEARCH

By raising awareness and encouraging study participation, individuals and communities can contribute to the successful development of HIV vaccines. Although tens of thousands of people have already volunteered to take part in HIV vaccine studies, many more will be needed. A large HIV vaccine trial will require thousands more participants of all race/ethnicities, genders and socioeconomic backgrounds to ensure that the vaccine works in all populations.

Therefore, community support is essential in efforts to break down stigma and myths about HIV vaccine research. Developing an effective HIV vaccine depends upon individuals and communities informing, educating and supporting others.

HOW TO HELP

- Let others know you support HIV vaccine research
- Educate others about the need for an HIV vaccine
- Support vaccine trial volunteers and/or volunteer yourself

The National Institute of Allergy and Infectious Diseases (NIAID), at the National Institutes of Health (NIH), supports a comprehensive program of HIV vaccine research.

For more information about HIV vaccines, please visit:
www.niaid.nih.gov/data/vaccine
www.hiv.nih.gov
www.addinfo.nih.gov
 or call 1-800-448-0440.

Para información en español sobre las vacunas contra el VIH, llame al:
 1-800-448-0440.



February 2004

NIH Publication No. 04-5279

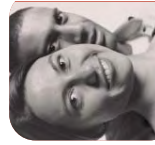


HIV VACCINES EXPLAINED

MAKING HIV
VACCINES
A REALITY



HIV VACCINE RESEARCH
Our best minds. Our best science. Our best hope.



THE NEED FOR AN HIV VACCINE

Despite the availability and success of HIV treatment drugs in the United States, the best long-term hope for controlling the AIDS epidemic worldwide is the development of safe, effective and affordable preventive HIV vaccines. Consider these facts:

- ### HIV/AIDS IN THE UNITED STATES
- Nearly half a million Americans have died of AIDS since the epidemic began.
 - The Centers for Disease Control and Prevention (CDC) estimate that as many as 950,000 Americans are living with HIV, and more than one-third of them do not know it.
 - Each year, over 40,000 people become infected with HIV, a rate that has remained virtually unchanged in recent years. Seventy percent are men and 30 percent are women. Of these, half are younger than 25 years of age.
 - Minority communities are disproportionately affected by the epidemic. More than half of all new HIV infections occur in African Americans, who make up 12 percent of the U.S. population. AIDS is the fifth leading cause of death of Americans aged 25-44, and is the number one cause of death in African American men of all ages. Nineteen percent of new HIV infections occur in Latinos, who make up 13 percent of the population.
- ### HIV/AIDS AROUND THE WORLD
- To date, nearly 25 million men, women and children have died from AIDS worldwide.
 - Currently, 40 million people are estimated to be living with HIV/AIDS and 14,000 new infections occur each day.
 - Today, more than 13 million children under the age of 15 have lost one or both of their parents to AIDS, most in sub-Saharan Africa.



PREVENTIVE VERSUS THERAPEUTIC HIV VACCINES

Preventive HIV vaccines currently under development are given to HIV negative people and are designed to prevent infection and control the spread of HIV, not to cure AIDS.

Multiple HIV vaccines may be necessary to prevent infection or disease in the same way multiple drugs are needed to treat people already infected with HIV.

Researchers are also evaluating therapeutic vaccines to treat people with HIV infection or AIDS. While the same vaccine may be tested for both preventive and therapeutic effects, what works to prevent HIV infection may not necessarily work to treat people who are already infected with HIV.

IS AN HIV VACCINE AVAILABLE NOW?

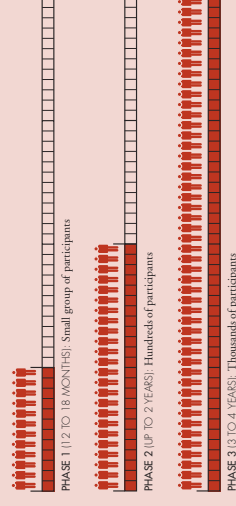
No! Scientists have been studying HIV for over two decades — and continue to make progress. Even when a promising vaccine is discovered, it will take time to test and evaluate its safety and effectiveness.

TESTING HIV VACCINES

Vaccine development requires several years of research in laboratories and animals before testing in humans can begin. A potential vaccine goes through three phases of testing in humans before the Food and Drug Administration (FDA) can consider licensing it for public use. The three phases of preventive HIV vaccine clinical trials are:

- **Phase I** — involves a small number of healthy volunteers (HIV-negative) to test the safety and immune responses of the vaccine; usually lasts 12 to 18 months
- **Phase II** — involves hundreds of volunteers (HIV-negative) to test the safety and immune responses of the vaccine; can last up to 2 years
- **Phase III** — involves thousands of volunteers (HIV-negative) to test the safety and effectiveness of the vaccine; can last 3 to 4 years

Throughout all phases of human testing, independent reviewers regularly monitor the study to ensure the safety of the volunteers.



PROTECTING RESEARCH PARTICIPANTS

HIV vaccine clinical trials are voluntary. Researchers are required to obtain the informed consent of all participants to make sure they fully understand the purpose of the study, how the HIV vaccine will be tested, the number of clinical visits required and the possible risks and benefits associated with receiving the vaccine.

So far, few side effects have been associated with experimental HIV vaccines. Those that have occurred generally have been mild to moderate and similar to those of approved vaccines. The most common side effects are soreness at the site of the injection, a low-grade fever, and body aches, which readily disappear on their own. Throughout the study, volunteers are carefully examined to determine if there are any serious side effects associated with the vaccine.

After a volunteer receives an HIV vaccine, it is possible to test positive for HIV antibodies on a standard HIV test (i.e., ELISA) because the vaccine triggers the body to produce antibodies against HIV.

The HIV vaccines being tested in humans do not contain HIV; therefore, they cannot cause HIV infection. Other tests are available at the study sites to determine whether a volunteer is actually infected with HIV. If volunteers engage in behaviors that expose them to HIV, they may still become infected with HIV.

It is rare for volunteers to encounter problems as a result of testing positive for HIV antibodies. Testing antibody positive does not mean the person is infected. However, volunteers could potentially experience problems donating blood, getting insurance, traveling to other countries or getting employment.

All volunteers are offered an identification card to show they are part of the study, and research staff are available to help address any issues that may arise.

HIV Preventive Vaccine

What is a Vaccine?

A vaccine is a substance that stimulates the body's immune response; the goal of vaccination is to prevent or control an infection. There are several different types of vaccines. The types of vaccines that are being studied to prevent HIV/AIDS are subunit vaccines, recombinant vector vaccines, and DNA vaccines. These vaccines contain only some of the many substances that HIV needs to make more copies of itself; the vaccines themselves cannot cause HIV or AIDS.

A given HIV vaccine may be used either alone or in combination with another HIV vaccine. One approach to HIV vaccination is called the prime-boost strategy, which combines two different types of HIV vaccines.

Subunit Vaccines

Subunit vaccines, also known as "component" vaccines, contain only individual proteins or peptides from HIV, rather than the whole virus. Instead of collecting protein or peptide components from the virus itself, they are made in the laboratory using genetic engineering techniques. Most HIV subunit vaccines are based on laboratory-made forms of the HIV envelope proteins that coat the outside of the virus. These envelope proteins can prompt the body to produce an anti-HIV immune response.

Another type of subunit vaccine is called a virus-like particle vaccine (also known as a VLP or pseudovirion vaccine). Virus-like particles are non-infectious HIV look-alikes that contain one or more, but not all, HIV proteins.

Recombinant Vector Vaccines

Recombinant vector vaccines are based on microorganisms such as viruses or bacteria that do not cause disease in humans or have been weakened so as not to cause disease. The viruses or bacteria are used

as vectors, or carriers, to deliver harmless HIV genes into the cells of the body. The body produces proteins from the HIV genes and these proteins stimulate an anti-HIV immune response.

Some of the viral vectors being studied for HIV vaccines include ALVAC (a canarypox virus), MVA (a cowpox variant), and ADV5 (adenovirus 5). A modified version of the bacterium *Salmonella typhi* is also being studied as a vector for HIV vaccines. Most of the recombinant vector vaccines for HIV deliver several HIV genes.

DNA Vaccines

DNA vaccines introduce pieces of laboratory-made HIV DNA into the body. Unlike recombinant vector vaccines, DNA vaccines do not rely on a viral or bacterial vector. Instead, "naked" DNA containing HIV genes is injected directly into the body. Cells take up this DNA and use it to produce HIV proteins. The proteins trigger the body to produce an anti-HIV immune response.

Prime Boost Strategies

A prime-boost strategy is one approach to HIV vaccination. In this approach, administration of one type of HIV vaccine (such as a recombinant vector vaccine) is followed by a second type of HIV vaccine (such as a subunit vaccine). The goal of this approach is to stimulate different kinds of immune responses and enhance the body's overall immune response to HIV.

For more information:

<http://www.niaid.nih.gov/daids/vaccine/>

<http://www.vrc.nih.gov/VRC/>