The Science of HIV/AIDS Vaccines

An introduction for community groups

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THE SCIENCE OF HIV/AIDS VACCINES: AN INTRODUCTION FOR COMMUNITY GROUPS

Prepared by the International Council of AIDS Service Organizations (ICASO).

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ICASO works to strengthen the community-based response to HIV/AIDS in all the regions of the world.

Our mission is to:

- mobilize communities and their organizations to participate in the response to HIV/AIDS;
- articulate and advocate the needs and concerns of communities and their organizations;
- ensure that community-based organizations, particularly those with fewer resources and within affected communities, are strengthened in their work to prevent HIV infection, and to provide treatment, care and support for people living with and affected by HIV/AIDS;
- promote the greater involvement of people living with, and affected by HIV/AIDS in all aspects of prevention, treatment, care and support, and research;
- promote human rights in the development and implementation of policies and programs responding to all aspects of HIV/AIDS.

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INTRODUCTION

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"An AIDS Vaccine is possible, overcoming the challenges will take a sustained, focused effort. Developing an AIDS vaccine to save lives and economies will be one of the world's greatest achievements. Not to do so would be one of its greatest failures."
IAVI website, www.iavi.org

In a world where 14, 000 people are infected every day, finding an effective method to prevent HIV/AIDS is the best long-term hope for controlling an escalating epidemic. In rising to the challenge, researchers worldwide have expanded their research efforts, communities have become more involved in understanding clinical research, and great achievements have been made in understanding the Human Immunodeficiency Virus (HIV).

This science primer provides a basic introduction to 'The Science of HIV/AIDS Vaccines,' a field of research on a strategy researchers hope will provide a significant measure of protection against HIV infection and disease.

Although by no means a comprehensive review of the science of HIV/AIDS vaccines, the primer aims to provide the reader with a clearer understanding of the science behind the search for an HIV vaccine, starting with an introduction to the immune system. This is the basis for understanding vaccine science. Vaccines immunize different components of the immune system. Some of these immune cells are also the primary targets of HIV. By learning about the ways that the body usually responds to illness-and the ways that HIV is able to disrupt that response-we can shed light on the challenges involved in finding a vaccine for HIV.

Language used in the primer has been adapted to help non-scientists grasp the ABCs of AIDS vaccines in layman's terms.

This document is part of a series of primers that are being developed by the International Council of AIDS Service Organizations. Community groups who would like more detailed information on HIV/AIDS vaccine development should consult the list of resources at the end of this document.

THE IMMUNE SYSTEM 2

i. How the Immune System Functions

The best way to understand the immune response to an invader-whether it is a virus, a bacteria or another is in terms of a microscopic war that takes place inside the body. In terms of this metaphor, we can characterize the immune system as an army or defense force that defends a country from external threats and invasions. Just as the soldiers of an army defend their country from attack and invasion, the components of the immune system respond to attacks on the human body.

The body's immune system is comprised of a complex system of blood proteins and white blood cells that work together to respond to, and limit, the damage or illness caused by invading organisms. The white blood cells (which are formed in the bone marrow) form three different 'regiments', namely phagocytes (including macrophages), and two types of lymphocytes, T-cells and B-Cells. Phagocytes form part of the non-specific defense mechanism of the body, while T-Cells and B-Cells form part of the specific defense mechanism.

The components of the immune system are divided into two categories, or arms: humoral and cell-mediated immunity. Humoral refers to antibody-producing B-cells (see below for more details.) Cell-mediated immunity refers to T-cells and CD-8 cells. These terms are important in vaccine science, since different vaccines are better or worse at inducing responses from the different arms of the immune system. Humoral responses effectively stop virus particles (or other invaders) that have not yet entered cells. They are an important first line of defense. But once a virus has infected a cell, cell-mediated immune responses become crucial.

While each of these 'regiments' has its own mission and defense strategy, they all have the same objective, which is to identify and destroy all invasive substances or organisms that might be harmful to the body, and to create an immunological "memory" of these substances, so that the forces can mount a swift, effective response if the invader returns. There are different stages in each immune response that the body makes:

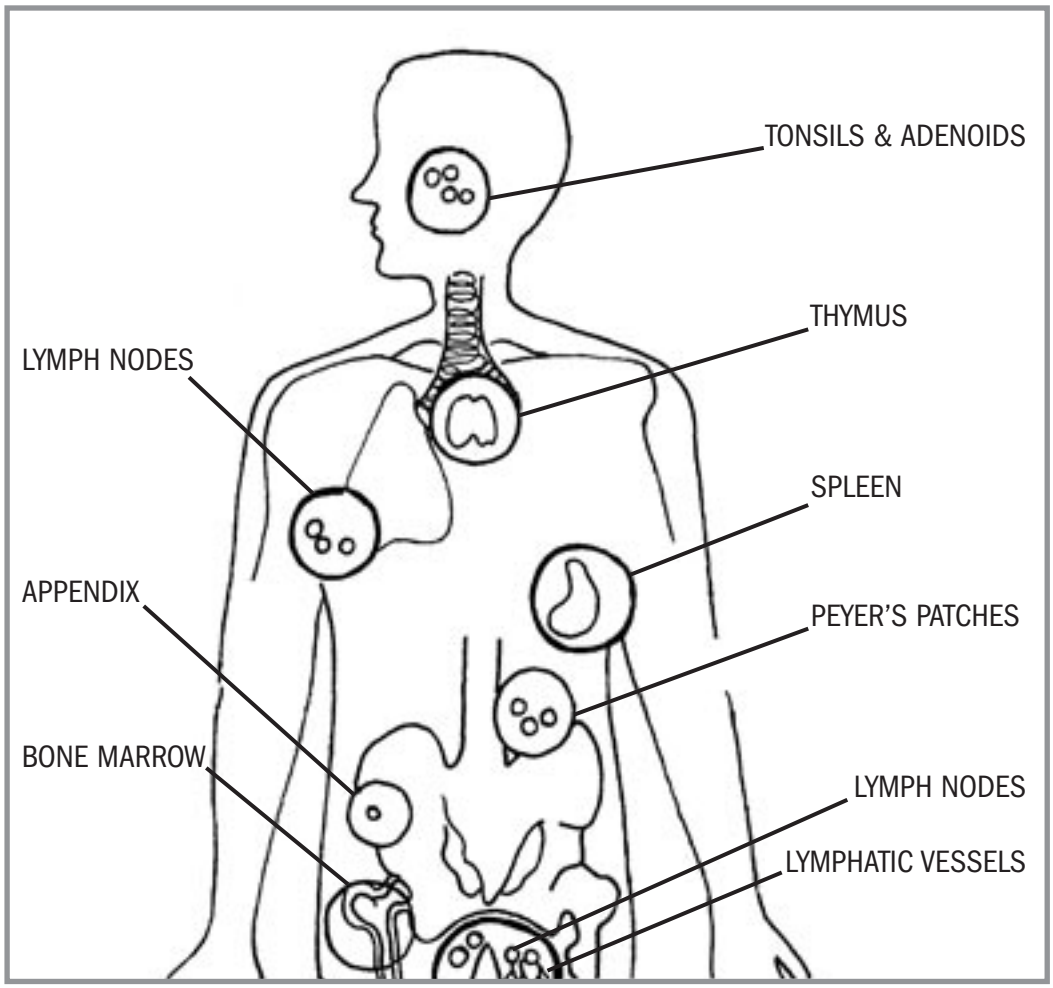
Stage 1: The battle begins

Stage 2: The forces multiply

Stage 3: The attack and victory

Stage 4: The cessation of hostility

ii. Organs of the Immune System



iii. Stages of an Immune Response

Stage 1: The Battle Begins

Phagocytes, which may be called the 'spies' of the immune system, constantly 'patrol' the whole body (the bloodstream, tissue and lymphatic system). Their purpose is to identify any substance, object, or organism that is foreign (and potentially dangerous) to the body. Phagocytes are also called the 'scavengers' of the immune system. When the phagocytes detect an enemy, they immediately try to engulf and destroy it. While phagocytes are usually effective in destroying chemical poisons and environmental pollutants such as dust, smoke, and asbestos particles, they cannot destroy organic invaders such as viruses, bacteria, protozoa, and fungi. Thus, when organic invaders (such as flu virus) invade the

body, the phagocytes put out chemical or molecular signals alerting the macrophages to mobilize, and the macrophages (special types of phagocytes) help them attack the invaders.

An important function of the macrophages is to mobilize the elements of the immune system that are developed to respond to specific viruses; the defense system, which consists of lymphocytes (T and B cells). To do this, the macrophage engulfs the virus and then displays specific pieces of it on its surface, a process called "antigen presentation." The processed bits of virus on the macrophage surface serve as a 'captured banner or red flag', letting the T-cells know that a foreign invader has breached the body's borders, thereby activating the cellular immune system.

T-cells get their name from the thymus, an organ found at the base of the neck.

The thymus generates many, many T-cells, each of which has the ability to recognize a different set of antigens (an antigen is any substance that is recognized and acted upon by a component of the immune system e.g. antibodies and cells). Which antigens a T-cell recognizes is determined by the receptors that are on the T-cell's surface. Every T-cell has many, many receptors on its surface, which is like having many locks, each of which fits a different key. The antigens presented on the surface of macrophages are the keys. There are many millions of antigens, and we have the remarkable ability to generate T-cells that "lock into" many of these antigens, allowing the body to mount a sustained immune response. Depending on which receptors it has on its surface, a T- cell may recognize a type of hepatitis virus, chicken pox, or the flu. T-cells have the ability to recognize these antigens without ever having "seen" them before. T-cells that fall into this category are called naïve T-cells. They are the fresh, untested troops that are called into action when we fall ill with a new disease or infection.

There are even T-cells which can recognize artificial antigens that have been manufactured in laboratories - antigens that the body has never encountered in millions of years of evolution.

The type of T-cell which recognizes the antigen is known as a CD4 cell, after one of the receptors on its surface, CD4 (it is also called a T Helper cell or CD4 lymphocyte). Although they do not actually kill invaders themselves, CD4 cells are the most important cells in the

immune system. This is because they are responsible for sending signals that direct and mobilize troops that battle diseases. Think of T-helper cells as the 'generals' or 'commanders' of the body's defensive army. These CD4 cells combine forces with the macrophages and so the next phase of the war begins.

The role of CD4 cells in the body's immune response

CD4 plays a crucial role in the body's immune response. CD4 cells protect the body from invasion by certain bacteria, viruses, fungi and parasites; they destroy some cancer cells. They do many things, including orchestrating the secretion of a variety of substances, including chemical messengers (such as interferon and interleukins) that are necessary for the body's defense, and they influence the development and function of macrophages and monocytes. Opportunistic infections can only overwhelm the body once the number of CD4 cells has become radically depleted.

Stage II: The Forces Multiply

Once the CD4 cells have received "intelligence" on the identity of the new invader from the macrophages, they start to divide and to send signals that activate additional components of the defense system in order to mobilize its full capacity. These additional forces include B-Cells (named after the bone marrow, where they are derived) and CD8 "killer" T-Cells, named after a receptor on their surface. Both B-cells and CD8 cells are involved in direct attacks on foreign invaders.

The B-Cells (or third regiment) are located in the lymph nodes. They are part of the humoral immune system. Like T-cells, different B-cells respond to different antigens. When an invader that is recognized by a B-cell enters, it begins to divide, increasing the size of the battalion that is prepared to fight the enemy. As the B-cells mature, some become plasma B-cells, which are factories for antibodies-substances that can surround and immobilize virus or bacteria that is "free" in the blood, and has not yet invaded a cell. When the virus has disappeared from the blood, these cells will die off, leaving the battlefield clear for the future. But a second population of B-cells, called

memory B-cells will not die, and will, instead, remain in the blood stream, ready to mount an even more rapid response to the invader, should it reappear. The plasma B- cells manufacture antibodies which render invading organisms harmless by neutralizing them or by clinging to their surfaces (thus preventing them from performing their function). Memory cells remember the specific invader and remain in the blood and lymphatic system.

Stage III: The Attack and Victory

One of the ways that bacteria and viruses use our bodies for their own needs is by invading cells in the body and hijacking them, so that they become factories for the bacteria or virus. Responding to orders by T-helper cells, killer T-cells destroy these infected cells by chemically piercing their membranes so that the contents spill out. This 'spilling out' interrupts the replication cycle of the virus. Once the contents of an infected cell have spilled out, antibodies neutralize the viruses by attaching themselves to the viruses' surface, thereby preventing them from attacking other cells. This slows the progress of the invading organisms and makes them easy victims for the phagocytes or the macrophages, which then come to 'digest them' (clean up). Antibodies also produce chemical reactions, which can kill infected cells. When all the invaders have been destroyed, the war is won and all that remains is to 'call the troops home'.

Stage IV: The Cessation of Hostility

Once the attackers have been vanquished, a third member the T-cell family takes control: the "suppressor T" or peacemaker. Suppressor T-cells release a substance that stops B-cells from doing their work (namely the production of antibodies). They also 'order' the killer T-cells to stop attacking and the CD4 cells to stop their work. Like B- cells, most mobilized T-cells will die off once the battle is over, but a few 'memory' troops will remain in the blood and lymphatic system - ready to act defensively should the same virus once again invade the body. At this point, the 'war' has been won and the person will be immune in the future to this particular invader.

It usually takes anywhere from a week to a few months to develop effective immunity against invading agents. While a person may therefore become very ill when he or she is first exposed to a disease to which he/she has not yet developed immunity, subsequent exposure to the same invading agent could quickly be countered before any damage can be done.

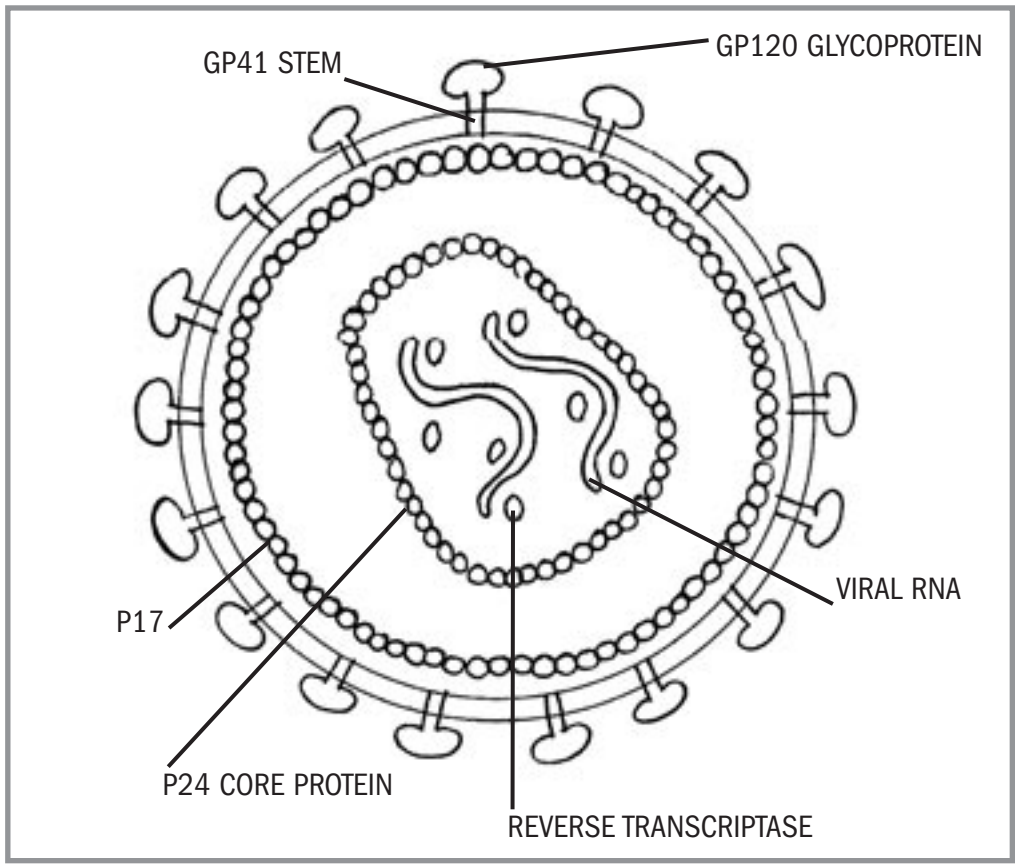
NOTES

THE EFFECT OF HIV ON THE IMMUNE SYSTEM 3

AIDS is caused by HIV (human immunodeficiency virus); [see figure below]. HIV has a circular shape and it consists of an inner matrix of protein called the core, in which the genetic material (viral RNA) is housed. The core is surrounded by an outer layer of protein with numerous small glycoprotein projections on its surface.

Like other viruses, HIV can only reproduce itself inside a living cell. It needs human cells to live and multiply. But since all viruses possess these very same characteristics, what then makes HIV so dangerous? The answer is that HIV does something that no other virus known to humankind has ever done: it directly attacks and hijacks the most important defensive cells of the human immune system, the CD4 or the T Helper cells.

i. Structure of HIV



As it does this, it slowly diminishes the total number of healthy CD4 cells in the body - thereby undermining the ability of the human immune system to defend itself against attack from exterior pathogens.

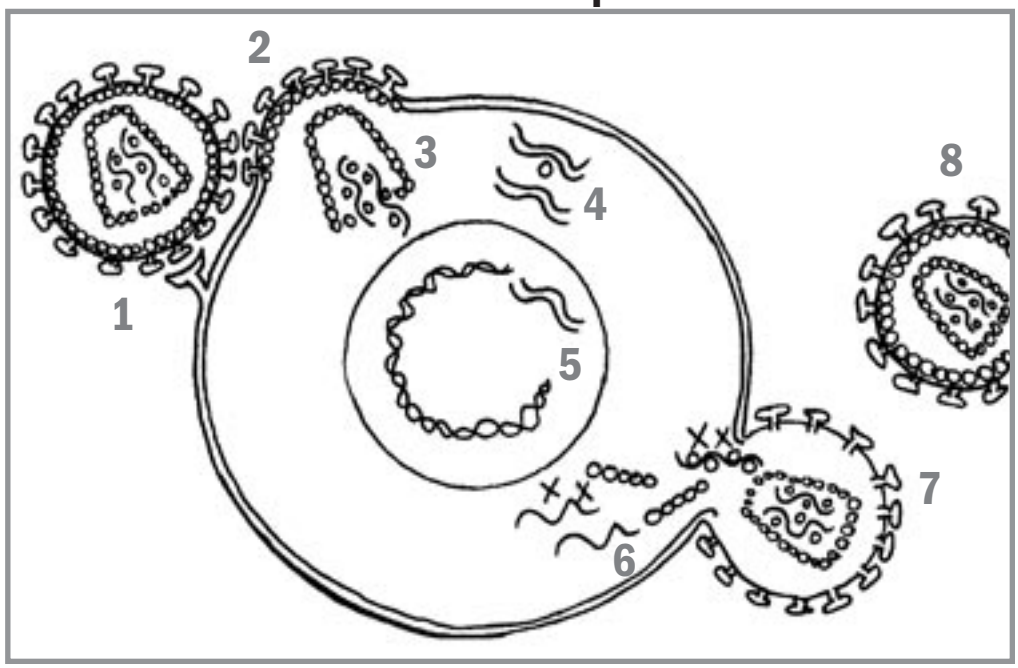
When HIV invades the body, the macrophages attempt to do their usual job by engulfing HIV and displaying the antigen. But when CD4 cells respond to the scene of the crime, they become infected by HIV, thus starting the attack on the immune system that makes HIV so dangerous to human beings. The figure on the following page shows the life cycle of HIV and shows how HIV enters and 'hijacks' CD4 cells and 'forces' it to channel its activities into manufacturing more viruses.

The glycoprotein projections on the virus' outer layer attach themselves firmly to the outer layer of the CD4 cell (onto a CD4 receptor on the host cell wall - Step 1). The CD4 cell and the virus now join membranes (Step 2). The virus then sheds its outer layer and enters the CD4 cell with its own genetic material (Step 3).

In order to use the cell to manufacture more viruses, the HIV's viral RNA must be changed (or reverse transcribed) to DNA. The HIV itself carries with it an enzyme called reverse transcriptase which (Step 3) it then uses to transform its viral RNA into double-strand viral DNA (Step 4).

The viral DNA then fuses with the host cell's own DNA or genetic material in the nucleus of the cell (Step 5), and makes numerous copies or replicas of viral RNA and viral proteins (Step 6). The protease enzymes enable this new viral RNA and the viral proteins to merge and bud from the cell membrane as fully functional HIV viruses - perfect replicas of the original HIV that entered the cell in the first place (Step 7). As new HIV bud from the cell, they kill the hijacked cell in the process. This doesn't happen right away. Each cell can serve as a factory for replicating copies of virus before it finally dies. They then move out into the bloodstream or surrounding tissue to infect more cells - and repeat the whole process again.

ii. How HIV virus invades and replicates



1 • *protrusions or glycoproteins (gp120 and gp41) on the virus' outer shell attach to a CD4 receptor on the host cell wall*

2 • *the virus and host cell now join membranes*

3 • *p24 nucleoid enters host cell and infects it with its own genetic material (viral RNA)*

4 • *new HIV DNA then moves into host cell nucleus*

5 • *with the help of the enzyme integrase HIV DNA joins with host cell's DNA*

6 • *once fusion occurs, host cell begins process of making numerous copies or replicas of HIV virus*

7 • *new viruses break out through the host cell's outer membrane*

8 • *new viruses infiltrate the body*

Although all viruses live and multiply solely in cells, HIV hijacks a critical immune player, the CD4 cell, and turns it into an efficient virus factory to manufacture replicas of itself. When this happens, the CD4 cells are unable to do what they would normally do when confronted by an intruder.

Although several antibodies are formed during this process, they are ineffective at neutralizing against HIV for several reasons. One is that the virus itself has an elaborate outer coating which shields its 'weapons' - the elements (composed of glycoproteins already mentioned above) that it uses to break and enter into the cells-from the antibodies. Instead, antibodies attach to other shielded parts of the virus which do not stop it from invading cells.

Another reason is that HIV is capable of changing its structure to evade immune defenses. There is evidence that the body does mount an antibody response which helps control HIV early on, but that over time, the virus evolves away from these antibodies-changing its armor and shifting its shield so that the antibodies are rendered powerless.

In a further complication, the CD8 cells which would ordinarily kill the virus are unable to complete their job. As with antibodies, cellular immune responses to HIV do exist in HIV-infected people-and there is evidence that they help control the virus, at least for a time. But, in most people, eventually the virus outwits both arms of the immune system. The exact reason for this immune dysfunction is not known. Some explanations include simple exhaustion of the troops, and the fact that some regiments-including CD8 T-cells, are left without orders from their generals-they cannot mobilize or attack because the T-cells are infected, and their ability to issue coherent orders is reduced.

Does HIV infect only CD4 cells?

It is not only the CD4 cells that HIV infects. The glycoprotein projections on the virus' outer layer attach themselves to CD4 receptors, which are present on various types of cells such as monocytes (a large phagocytic white blood cell), macrophages, tissue cells in mucous membranes (mucous membranes are found for example in the genital tract and anal-rectal areas), and certain brain cells. Scientists were initially astonished by the presence of the virus in the brain because the blood-brain barrier usually prevents all foreign substances such as viruses from entering the brain. Because macrophages are among the few cells that move through the blood-brain barrier, researchers quickly deduced that HIV enters the brain by hiding in these very cells (Levy, 1990).

What do we mean when we say that HIV mutates very rapidly?

HIV has yet another extraordinary property which allows it to evade the immune system, even when the entire set of regiments has been mobilized against it. HIV is able to mutate or change very rapidly. When it copies itself inside a cell, it is literally making copies of its genetic code, a series of proteins

which can be represented by a string of letters. Every time HIV makes a "typo" in this copy, a virus with a slightly different genetic make-up is born. Many of these viruses will have no advantage over the most common 'wild type' strain of the virus, but some of them will-especially if the "typos" cause changes in the viruses appearance that help it to evade the immune system. The body's immune system relies heavily on its ability to recognize micro-organisms from their outer protein layer. The body does its best to control the virus-and it does, to some extent-which is one reason that people with HIV do not get sick right away. But, over time, the virus outstrips the immune system, both by killing off T-cells and by constantly changing its appearance to evade fresh forces. (We may compare the virus to a thief who leaves different fingerprints every time he or she commits a crime). This feature of HIV (the fact that it rapidly changes its identity) is one of the reasons why it is so difficult to develop an HIV vaccine.

NOTES

WHAT IS A HIV VACCINE? 4

i. Introduction

The scientific consensus is that an HIV/AIDS vaccine is an achievable goal. This consensus is based on more than a decade of careful scientific research. Monkeys have been protected by experimental vaccines, and a number of candidate vaccines have been shown to be safe and trigger immune responses in small numbered human Phase I trials. However, it is also important to remember that vaccine development is a long and complicated process and while there are exciting advances and more vaccine candidates moving into human trials, there are also setbacks and failures. There is no guarantee that one of the vaccines currently being tested will prove to be effective.

An effective HIV vaccine, given before exposure to HIV, could help the body completely block infection (sterilizing immunity), or help the body control HIV enough to prevent progression to AIDS and/or transmission to others. The development of a preventive HIV vaccine is believed to be possible based on the successful protection of chimpanzees and monkeys against infection with simian (primate) versions of HIV by similar vaccines; evidence that the human immune system can prevent or delay HIV infection and disease; and the immune responses seen in humans from current experimental HIV vaccines. An ideal preventive HIV vaccine would protect people against infection of all subtypes of HIV and against all routes of possible transmission. An ideal HIV vaccine would also be inexpensive, easy to transport and administer to people, and would require few booster shots.

ii. Vaccine Approaches

Although there are different designs that might lead to a useful HIV/AIDS vaccine, most of them share in common the use of specific parts of HIV (genes or proteins) to activate the body's immune defenses. Once the immune system has learned to recognize these viral components, the hope is that it can mount a vigorous defense when it encounters the real virus.

To date over 30 different preventive HIV/AIDS vaccines have been tested in several thousand volunteers. Most of this research has consisted of safety studies (Phase I trials). Only one vaccine candidate, however, has progressed to Phase III trials (over 10,000

volunteers) and only two other concepts have reached the stage of Phase II trials (hundreds of volunteers). (For a full listing of current trials in progress please refer to the websites mentioned under the section "Informative Websites".)

The following list summarizes the main vaccine approaches:

i) Recombinant subunit vaccines
ii) Recombinant vector vaccines
iii) DNA vaccines
iv) Combination vaccines
v) Live-attenuated vaccines
vi) Whole-inactivated vaccines

i) Recombinant subunit vaccines

This is a vaccine approach founded on the principle that it is possible to elicit a powerful immune response by exposing the immune system to a portion of a disease-causing micro-organism. This approach stimulates cells to produce synthetic versions of different viral proteins-components that the B-cell arm of the immune system, which produces antibodies, will see and remember. When a virus arrives which has some of these components, the anti-bodies will respond immediately and effectively.

ii) Recombinant vector vaccines

This vaccine approach uses a virus or bacteria (not HIV) as a carrier (or vector) for genetic material from HIV. Usually, these vectors are "live," meaning that they make copies of themselves. As they copy themselves, they also copy the HIV genes that have been selected and inserted into the vector. The immune system sees the proteins produced by these genes and, with any vaccine, mounts a mock response that sets the stage for the real battle. Since viruses or bacteria infect cells, this type of vaccine can elicit helper and killer cytotoxic T-cell responses in animals and humans.

Recombinant vector vaccines currently being explored:

Live bacterial vectors currently in clinical trial:
Salmonella

Bacterial vectors currently under development:
Shigella, listeria, BCG

Live viral vectors currently in clinical trial:
Canarypox

Viral vectors currently under development:
Pox viruses, rabies, adenovirus, semliki forest viruses, etc.

iii) DNA vaccines

This vaccine approach uses the body's own cells to produce relevant pieces of the virus. It does this by introducing pure genetic material directly into the body. This 'naked DNA' contains the genetic instructions for making a few proteins in a language that the cell understands (remember that HIV carries its own genetic material as RNA, which is not usually present in human cells at rest). Once the naked DNA is introduced into the skin or muscle, it is incorporated into the body's cells. HIV proteins are then produced that will stimulate the immune system.

iv) Combination vaccines

As inferred by its name, this vaccine group uses a 'combination' of approaches to elicit a larger variety of immune responses. Some research groups have been exploring the use of two or more vaccine approaches that generate different types of immune responses together. By doing this they hope to generate a vaccine that is safe and provides more protection. (Examples include DNA and MVA, canary pox and GP120.)

v) Live attenuated vaccines

Many of the world's most common vaccines, including yellow fever and polio, use this approach. Live-attenuated viruses are organisms that have been "disarmed"-they are no longer able to cause disease, and they are still able to copy themselves. This approach is effective because it closely mimics the conditions of actual infection, allowing the immune system to learn to respond to the weakened virus, setting the stage for a full-strength response to the disease causing form. HIV vaccines do not use this approach because of fears that a live attenuated virus could mutate into a virulent, disease causing form.

vi) Whole-inactivated vaccines

This is another wide-spread approach. There are whole inactivated (or whole killed) Hepatitis A, cholera, polio and influenza vaccines. In these vaccines, the disease-causing agent is killed using chemicals or heat. In this case, the immune system is able to view the entire viral particle without any virus infection or replication taking place. The history of vaccines includes an episode, called the Cutter incident, in which an early batch of whole killed polio

vaccine was not properly treated, leaving some of the organism alive and resulting in some polio infections. Even though this incident took place in the 1950s, and technologies have improved significantly since then, there are still fears that a similar event could occur with an HIV vaccine. While a few researchers are investigating whole killed HIV vaccines, it remains a little-explored area of the field.

NOTES

CONCLUSION 5

i. Key Challenges in Developing an HIV Vaccine

Finding out what makes the immune system respond most effectively against HIV

The world's two most successful vaccine approaches - live attenuated and whole-killed vaccines - are unlikely to be used in making a vaccine against HIV. This means that scientists face the relatively new challenge of identifying key pieces of the virus that will induce strong, lasting immune responses against HIV. This is even more difficult since HIV is capable of so much genetic change. An effective vaccine will induce responses against a portion of the virus that does not change very often, allowing protection even when the virus has mutated.

Finding out why HIV still manages to survive and replicate in HIV-positive people with strong immune responses

This primer contains an explanation of the relationship between HIV and the immune system as it is understood today. There are still many facets of this interaction that are poorly understood. Until there is a better sense of when and how the virus disrupts immune function, it will be difficult to say with certainty what the components of a strong, protective immune response might be.

Isolating specific parts of the immune system that are effective in protecting against HIV

The fact that many people with HIV can live for years, even without treatment, means that there are elements of the immune system which do respond effectively during the early and middle stages of infection. More evidence for natural protection comes from people who are at high risk for HIV but do not become infected, in spite of repeated exposures. We still don't understand what the components of this protection are. We are also limited by what our current laboratory tests can measure - (e.g. there may be an aspect of immune strength that has yet to be identified, or that doesn't get picked up by current tests, that is key in immune protection). Further research is needed to understand which elements of immune protection are critical - and to link this to vaccine development targeted at these elements.

5

Fully understanding how HIV infection operates in humans and developing a more complete understanding of animal models

HIV vaccines aren't tested in people until they have been tested in animals. This allows us to determine whether or not they are safe and whether or not they protect against infection. Unlike in human trials, which never deliberately expose people to HIV, animal studies do "challenge" animals with HIV-like viruses. This gives a sense of whether or not the vaccine works and what type of protection it provides. But there are key differences between human and animal immune responses, and there are limits to what the data from an animal experiment can tell us about how a vaccine will work in humans. Even as vaccine trials in humans move forward, we must advocate for continued research on the relevance and limitations of animal models.

NOTES

ADDITIONAL RESOURCES 6

i. Glossary

A **adjuvant**: a substance sometimes included in a vaccine formulation to enhance or modify its immune-stimulating properties.

antibody: (also called immunoglobulin) an infection-fighting protein in the blood or secretory fluids that recognises, neutralises and helps destroy pathogenic microorganisms (e.g. bacteria, viruses or toxins).

antigen: any substance that is recognised and acted upon by a component of the immune system (e.g antibodies and cells). Antigens are often agents such as invading bacteria or viruses.

attenuated: weakened. Attenuated viruses are often used as vaccines as they no longer function as a disease-causing agent, but can still produce a profound immune response.

B **B-lymphocyte (B-cell)**: white blood cells of the immune system originating in the bone marrow and spleen that generally target free-floating viruses in the blood. B-cells develop into plasma cells that produce antibodies.

booster: a second or subsequent vaccine dose given after the primary dose to increase immune responses.

breakthrough infection: an infection that the vaccine should prevent, but that nevertheless occurs (e.g. in a volunteer during a clinical trial).

C **canarypox**: a virus that infects birds and is being used to carry HIV genes into human cells in some of the current vaccine trials.

CD4 T-lymphocyte: (also called T helper cell) immune cell that carries a CD4 marker on its surface. CD4 cells are the primary targets of HIV. CD4 cells are at the heart of the body's defensive immune response.

CD8 T-lymphocyte: immune cell that carries the 'cluster differentiation of 8' marker. CD8 T-cells may be cytotoxic (killer) T-cells or suppressor T-cells.

cell-mediated immunity: that part of the immune system that targets host cells infected by viruses, fungi and bacteria.

clade; or subtype. A group of related HIV viruses classified by their degrees of genetic similarity.

core: the protein capsule surrounding a viruses' DNA or RNA.

correlates of immunity: the specific immune responses that correlate or match up with protection from a certain infection.

cytotoxic T-lymphocyte: also known as killer T-cells. Immune cells that destroy host cells infected with viruses, fungi or certain bacteria.

cytokine: a group of soluble, hormone-like proteins produced by white blood cells that act as messengers between cells. Cytokines can stimulate or inhibit the activity of immune cells.

D **dendritic cell:** an immune cell with thread-like tentacles that capture antigen and present it to T-cells for destruction.

DNA vaccine: an experimental vaccine technology in which one or more genes coding for specific antigens are directly injected into the body, where they hopefully produce antigens in the recipient.

E **enhancing antibody:** a type of antibody that may increase the ability of a pathogen to

infect cells and produce disease. It is currently unknown whether or not enhancing antibodies has any effect on the course of HIV infection.

enzyme: proteins that accelerate the rate of a specific chemical reaction without themselves being altered. Enzymes are generally named by adding the suffix "-ase" to the name of the substance on which the enzyme acts (e.g. protease is an enzyme that acts on proteins).

env: a gene of HIV that codes for gp160, the precursor molecule that gets split into the envelope proteins gp120 and gp41.

envelope: outer surface of a virus, also called the coat.

epitope: a specific site on an immunogen that stimulates specific immune responses such as the production of antibodies or activation of immune cells.

G

gag: an HIV gene that codes for p55. p55 is the precursor of HIV proteins p17, p24, p7 and p6 that form HIV's core, the inner protein shell surrounding the viral RNA.

genome: the complete DNA present in an individual cell or virus.

gp (glycoprotein): a protein molecule with one or branches of sugar molecules attached to it. Many cellular and viral proteins are glycoproteins, including the outer coat proteins of HIV. A number after the gp, is the molecular weight of the glycoprotein.

gp41 (glycoprotein 41): a protein embedded in the outer envelope of HIV that anchors gp120. gp41 plays a key role in HIV's entry into CD4+ T-cells by facilitating the fusion of the viral and cell membranes.

gp120: the glycoprotein on the outer surface of the HIV envelope.gp120 binds to the CD+ molecule on the helper T-cells during infection. It has been studied as an experimental HIV vaccine because the outer envelope is the first part of the virus 'seen' by neutralising antibodies.

H

helper T-cells: T-lymphocyte bearing the CD4+ cell surface marker. Helper T-cells are the chief regulatory cells of the immune system, controlling activities such as turning antibody production on and off. They are the main targets of HIV infection.

HIV (human immunodeficiency virus): the virus that causes AIDS.

humoral immunity: immunity to infection caused by antibodies.

I

immunity: natural or vaccine-induced resistance to a specific disease. Immunity may be partial or complete, specific or non-specific, long lasting or temporary.

immunization: the process of inducing immunity by administering a vaccine, thereby teaching the immune system to recognise certain antigens and thus prevent infection or illness when it subsequently encounters the infectious agent.

immunogen: a substance capable of provoking an immune response.
immunogenicity: the extent to which an immunogen or vaccine stimulates immune responses.

in vitro: a laboratory environment outside living organisms (e.g. test tube or culture plate, used to study diseases and biological processes.

in vivo: testing within a living organism (e.g. human or animal studies).

isolate: a particular strain of HIV-1 from a person or cultured cell line.

live-vector vaccine: a vaccine using a non-disease-causing organism to transport HIV or other foreign genes into the body. This type of vaccine often generates cytotoxic T-lymphocyte (CTL) responses.

leukocytes: white blood cells.

lymphatic vessels: vessels of the lymphatic system - one of the routes HIV uses to spread through the body.

lymphocyte: the diverse set of white blood cells that are responsible for immune responses.

macrophage: a type of large immune cell that devours invading pathogens and other intruders. Macrophages can also harbour large quantities of HIV without being killed and may therefore act as viral reservoirs.

memory cell: memory cells are long-lived subsets of T-cells and B-cells that have been exposed to specific antigens and can remember them even if infection occurs years later.

molecule: a very small mass of matter.

mucosal immunity: resistance to infection across the body's mucous membranes, generally believed to be the most frequent routes of HIV infection.

nef: a gene present in SIV and HIV that is not required for but regulates viral production. Vaccines made of live SIV-lacking nef (nef-deleted) have been studied in monkeys.

neutralising antibody: antibody that prevents virus from infecting a cell, usually by blocking viral entry points on the virus.

pathogen: any disease-causing microorganism.

p24: a protein in HIV's inner core.

Peptide: a molecule made of two or more linked amino acids. Proteins are made or peptides.

phagocyte: any cell capable of ingesting particulate matter.

priming: also called prime-boost. Giving one vaccine dose to induce certain immune responses, to be followed by or together with a second type of vaccine (booster). A prime-boost combination may induce different types of immune responses and/or enhance overall responses beyond those seen with only one type of vaccine.

receptor: a molecule on the cell surface that serves as a recognition or binding site for a specific antigen, antibody, enzyme or other molecule.

retrovirus: HIV and other viruses that carry their genetic material in the form of RNA rather than DNA. These viruses also contain the enzyme, reverse transcriptase, which transcribes RNA into DNA. That process is the opposite of what normally occurs in animals and plants, where DNA is made into RNA.

reverse transcriptase: RNA-directed DNA polymerase.

RNA (ribonucleic acid): a single-stranded molecule composed of chemical building blocks similar to those of DNA. RNA is the sole genetic material of retroviruses and an intermediary in making proteins in all living things.

seroconversion: the development of antibodies to a particular antigen. When people develop antibodies to HIV or an experimental HIV vaccine, they seroconvert from antibody-negative to antibody-positive.

SHIV: a genetically-engineered hybrid virus with HIV envelope and SIV core. SHIV is widely used for testing vaccines in monkeys.

SIV (simian immunodeficiency virus): an HIV-like virus that infects monkeys and causes an AIDS-like disease in some species.

strain: one type of HIV.

sub-type: also called clade. For HIV, a classification scheme based on genetic differences among isolates.

sub-unit vaccine: a vaccine consisting of only one protein from the virus or other pathogen. HIV sub-unit vaccines produced by genetic engineering are called recombinant sub-unit vaccines.

T-cell: one of the two main types of white blood cells critical to the immune system. They include CD4+ and CD8+ T-cells.

vaccinia: a cowpox virus, formerly used in human smallpox vaccines and now as a vector in some experimental HIV vaccines.

vector: a bacterium or virus that does not cause disease in humans and is used in genetically engineered vaccines to transport antigen-encoding genes into the body to induce an immune response.

virus: a microorganism composed of a piece of genetic material (RNA or DNA) surrounded by a protein coat. To replicate, a virus must infect a cell and direct its cellular machinery to produce new viruses.

ii. Informative Websites

www.iavi.org
www.avac.org
www.hvtn.org
www.icaso.org
www.niaid.nih.gov
www.who.int/HIV-vaccines
www.aidslaw.ca
www.thebody.com

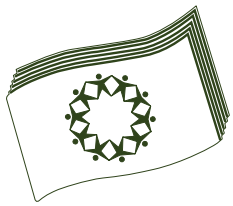
iii. Reference Materials Used

HIV/AIDS Care and Counseling - A multidisciplinary approach; Dr Alta Van Dyk

NIH “Understanding Vaccines”

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

HIV Vaccine Trials Network (HVTN) website - www.hvtn.org



I C A S O

ICASO, the International Council of AIDS Service Organizations, works to strengthen the community-based response to HIV/AIDS, by connecting and representing NGOs throughout the world. Founded in 1991, ICASO operates from regional secretariats based on all five continents, guided by a central secretariat in Canada.

www.icaso.org