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TECHNICAL ISSUE BRIEF

PATHWAYS OF DISCOVERY: HIV VACCINE RESEARCH AND DEVELOPMENT

Introduction

The HIV/AIDS pandemic continues to impose a global burden, especially on developing countries. In the present as in the past, viral infectious diseases are most effectively controlled – some even eradicated – through prevention programs that include a vaccine. No single approach to HIV/AIDS prevention is likely to have a dramatic impact. Integrated approaches to prevention, detection, and management that are tailored to specific populations yield the best results. Reversing the course of the AIDS pandemic will require carefully combined strategies that include behavioral, biomedical, and even surgical methods to prevent HIV, as is the case with male circumcision. An effective HIV vaccine would significantly advance successful prevention strategies to control the AIDS pandemic.

Vaccine Research and Development: A Complex Scientific Endeavor

Although vaccines have proven to be among the most efficient tools to stop epidemics like smallpox, polio, and measles, their development is neither easy nor rapid. Vaccines that are currently administered routinely and are saving countless lives have taken up to 50 years to discover and develop. The first HIV vaccine trial began in 1987; since that time, many challenges have surfaced in the pursuit of a safe and effective vaccine against the virus. If HIV caused disease in animals the way it does in humans, testing vaccines for their potential effects could be done in predictive animal models. Since such a reliable model does not exist for HIV, the only way to confidently prove the efficacy of a candidate vaccine is to conduct clinical trials in people who are at risk for HIV infection.

The goal of all vaccines is to create an immunological response that can either prevent infection or minimize the symptoms and the course of a disease.

Necessarily, these trials are lengthy, complicated, and expensive endeavors. Adding to their complexity is HIV's high rate of genetic variability, which may render a vaccine effective against only some clades, or variants, of the virus. Ideally, a vaccine would provide global protection.

M. McCLUSKEY/USAID

YRG Care, a premiere HIV referral center in Chennai, Tamil Nadu, India, actively educates communities about HIV vaccine research in many venues. These young people are watching a play about adults being encouraged to get tested for HIV as part of participating in a clinical trial for a novel HIV vaccine.

USAID's Approach to HIV Vaccine Research and Development

As an agency committed to international development and a key partner in the expansion of care and treatment to ease the grip of the pandemic, the U.S. Agency for International Development (USAID) brings valuable expertise and resources to the goal of developing a globally relevant HIV vaccine. In addition to five decades of experience in international development and field presence in nearly 100 countries, USAID has in-house expertise in clinical trial design and conduct, immunology, virology, product development, pharmaceutical regulatory affairs, ethics, community engagement and gender issues. Inevitably, more large-scale human trials are needed in developing countries to understand how the human immune system behaves after being stimulated by a preventive HIV vaccine. USAID's broad international partnerships in HIV prevention, care, and treatment, and its perspective, are fundamental to the eventual success of HIV vaccine discovery and distribution.

International AIDS Vaccine Initiative

Since 2001, USAID has funded the International AIDS Vaccine Initiative (IAVI), a nonprofit organization that acts as a virtual pharmaceutical company to accelerate the development and clinical testing of HIV vaccine candidates. This support is an important

part of U.S. Government (USG) efforts to address the pandemic from every conceivable direction.

IAVI facilitates collaboration among universities, governments, and private-sector groups to ensure that the appropriate resources are available for each phase of product development.

IAVI also provides analyses of important issues affecting the HIV vaccine field, such as regulatory and licensing issues, normative laboratory values in African populations, new strategies to engage biopharmaceutical companies in HIV vaccine development, and preparation for the manufacture and distribution of vaccines once they are proven effective. Under a five-year cooperative agreement initiated in 2006, USAID is supporting IAVI to strengthen clinical trial capacity in developing countries, advance the development and testing of novel vaccine candidates, enrich the pipeline of next-generation HIV vaccine candidates, and analyze policy and future access-related issues in the HIV vaccine field.

Neutralizing Antibody Consortium

USAID provides funds for the IAVI-sponsored Neutralizing Antibody Consortium (NAC), which was established in 2002 on the belief that the induction of broadly neutralizing antibodies capable of preventing viral entry, and thus infection, is critical to the eventual success of an HIV vaccine. Most vaccines work by neutralizing the infectious agent with antibodies and then eliminating the agent and/or infected cells. Because of HIV's many ways of immune evasion, the infection does not usually result in the body's creation of broadly neutralizing antibodies. Since nature has not been capable of aborting HIV infection altogether, or been clear on how it rarely controls HIV, we must be able to improve upon these responses.

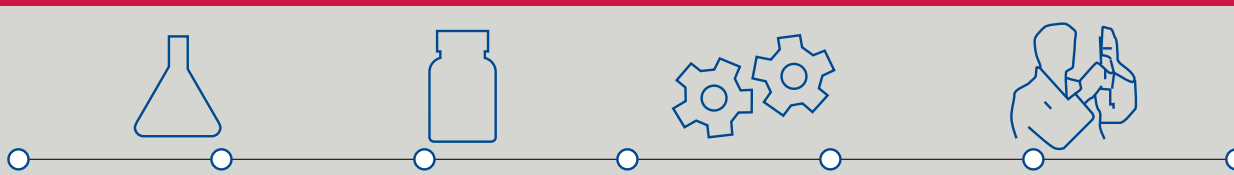
Currently, it remains unclear how to generate broadly neutralizing antibodies against HIV. IAVI established the NAC to delve into novel strategies of structure-based designs by a consortium of scientists with wide-ranging skills, supported by a generous supply of core resources and a quasi-industrial approach to problem-solving and management practices. Because relatively few broadly neutralizing antibodies to HIV are known and characterized, IAVI initiated a major undertaking in 2006 to generate more of them. "Protocol G" was initiated at clinical sites worldwide to seek out the rare HIV-infected individuals who seem to be making antibodies that can react with a broad array of HIV viruses and who use their lymphocytes to generate broadly neutralizing monoclonal antibodies (mAbs)/h.

How USAID Ensures Scientific Review and Due Diligence

As an agency responsible for development assistance, USAID is composed of experts who are accountable for the stewardship of U.S. resources used to introduce and manage evidence-based programs and practices through highly skilled implementing partners. In addition to the internal, rigorous procedures that USAID relies upon to approve funding for these cooperating agencies, the Agency also looks to its partners and their processes for vetting their respective scientific portfolios.

IAVI is a good example of an organization that systematically scrutinizes its scientific agenda of research and development in search of an HIV vaccine. IAVI's Scientific Advisory Committee (SAC) is a formally constituted committee reporting to IAVI's Board of Directors and, as such, advises the Board on scientific issues and is represented on the Board by the SAC Chair. USAID has access to SAC meeting reports, which provide the recommendations of the SAC and how IAVI has approached each recommendation. This group of internationally acclaimed immunologists, vaccinologists, and

The Process of HIV Vaccine Research and Development



Basic Research
Scientists study the basics of HIV/AIDS and the immune system.

Applied Research
Basic research is translated into the design of potential vaccine candidates.

Preclinical Development
Vaccine candidates are screened in animals to determine if they are safe, elicit immune responses, and show protection in these animals.

Process Engineering
The process for manufacturing a vaccine must be reliable and practical. Ideally, it will also be inexpensive.

Small-scale Human Clinical Trials
Phase I and II safety and immunogenicity trials test if the vaccine candidate elicits immune responses.

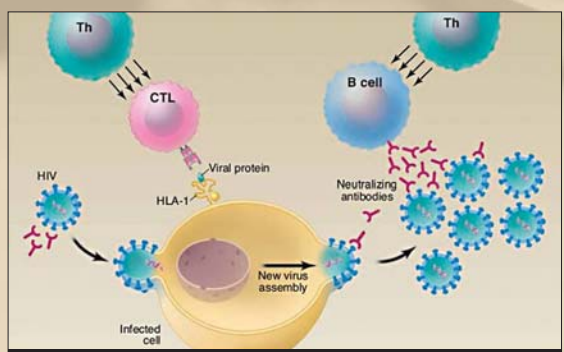
Large-scale Clinical Trials
Phase IIb and III efficacy trials test if the vaccine candidate is protective.

Licensure and Delivery

Source: International AIDS Vaccine Inititiative.

The Science Behind HIV Vaccine Research and Development

Using History to Inform the Future



COURTESY OF DR. BRUCE WALKER

Antibodies that are created by B-cells can:

- attach to free virus and prevent viral entry into T-cells
- neutralize newly released virus particles
- bind to infected cells and trigger their elimination

Cytotoxic T-cells are coordinated by helper T-cells and can act by recognizing viral proteins (HLA-1) attached to the surface of infected cells and effectively destroy the cells. The viral proteins are attached to the cell surface by HLA molecules, which are part of a person's genetic signature.

It is possible that the first generation of HIV vaccines will be unable to prevent acquisition of the virus, but will be able to preserve the immune system by limiting the damage of the initial infection by containing viral replication and by delaying the progression to AIDS – both of which also may lead to less transmission of HIV.

The search for an HIV vaccine is particularly challenged by the complex properties of the virus, specifically its uncanny ability to mutate and recombine, its ability to integrate into the genome of host cells and create latent infection, and its ability to avoid and escape immune responses by concealing the part of its outer coat that induces protective antibodies.

Despite these difficulties, scientists are making advances in defining early events in HIV transmission. These critical findings may lead to understanding what enables protection from HIV acquisition and replication in, for example, those who are highly exposed yet uninfected, and those known as "elite controllers": individuals who control HIV replication for several years in the absence of highly active antiretroviral therapy, known as HAART. Their immune systems provide convincing evidence that an effective vaccine against HIV is possible, despite the scientific challenges being faced.

Much work is being done to understand the potential effect of vaccines designed to produce protective cytotoxic and memory T-cells that might hold HIV "at bay" by limiting viral replication, thereby preserving the immune system of the infected person. There is serious emphasis on which vectors might enhance HIV-specific immune responses by introducing the vaccine antigens into the body to create functional and long-term defenses in the human immune system.

Several groups are striving to elicit effective antibody responses that can neutralize HIV before it can enter the host T-cell. Others are characterizing how the genetic makeup of each person plays a role in seemingly being less susceptible to HIV and being able to delay the onset of AIDS. These studies may hold the promise of providing scientific insights into defining the correlates of protection from HIV and, as such, defining what will be required of a vaccine to create a similar immunity against HIV. USAID provides substantive support to many of the scientific responses to these extraordinary challenges through its strategic partnership with IAVI and allegiances with related organizations interested in discovering an effective HIV vaccine.

- Since 2001, USAID has contributed $134 million to help discover an HIV vaccine. Currently, USAID is committing annual funding of $28 million through 2011 for HIV vaccine R&D.
- USAID provides support for all phases of HIV vaccine applied R&D, infrastructure, and capacity building for clinical trial conduct, public communications, and policy analysis through a partnership with the International AIDS Vaccine Initiative. USAID does not support basic research.
- USAID plans involvement with the Global HIV/AIDS Vaccine Enterprise.
- USAID facilitates coordination between HIV vaccine clinical trial activities and HIV/AIDS prevention, care, and treatment programs in developing countries.

virologists convenes twice a year to review the R&D portfolio under consideration by the organization. USAID receives its proceedings and is confident in this method of intense examination of scientific research while exercising its authority to call upon additional independent external advisors as needed. All scientific proposals reaching the level of IAVI's SAC are pre-evaluated using standardized selection criteria by a group of internal experts in vaccine discovery and product development. A detailed scientific and business due diligence is conducted for the proposals of interest, the intensity of which depends upon the stage of the technology platform and to what degree IAVI's support is expected. The Chair of IAVI's SAC and its R&D management committee review each proposal and offer their final recommendations to the senior management team. Approval from IAVI's Board of Directors is also sought when projects require substantive organizational resources and funding. The SAC subcommittees – Project Management Committee and Clinical Trials Committee – provide ongoing oversight of approved projects and their respective progress against milestones on a quarterly and biannual basis.

Future Directions

Through its key partnership with IAVI and interactions with other organizations, USAID engages in HIV vaccine R&D and related activities. As the Global HIV/AIDS Vaccine Enterprise evolves into a growing global initiative to coordinate resources, share technology and data, and foster greater collaboration, USAID looks forward to contributing its developing-country expertise to this valuable endeavor. USAID also facilitates linkages between HIV vaccine clinical trial activities in Africa and Asia and HIV/AIDS treatment, care, and prevention services under the U.S. President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

As promising vaccine candidates are identified, USAID will provide support through IAVI to assess how the availability of an HIV vaccine might contribute to changing risk behavior, and how these effects can be countered. USAID is planning for the introduction of HIV vaccines in developing-country settings. These activities will eventually include engaging host-country governments to register the new products, managing supply chain and logistics of vaccine delivery, developing protocols and training health care workers through partnerships that pre-exist in current USAID networks.

Although there is little doubt about the potential for an effective HIV vaccine to curb the pandemic, the road to one is long and arduous. Given the challenges, it is likely that no single candidate will provide a definitive solution to the pandemic. The likely scenario is one of discovering and mobilizing a variety of new tools to stop HIV, each with its own limitations. When used in combination with other approaches, such as consistent condom use and partner reduction where possible, we may be able to turn the tide against the growing epidemic.

USAID is an established technical assistance and development agency with a reputable history of supporting programs to improve public health. Vast improvements in public health are not accomplished in a hurry. Indeed, it will take time to discover and develop a safe and effective HIV vaccine. USAID has the foresight to support HIV vaccine research while preparing for the introduction of this invaluable tool in tandem with governments, nongovernmental organizations, and the private sector, which are also faithfully pursuing the promise of a vaccine to control AIDS.

"We must never lose sight of what a vaccine against HIV could accomplish. So many have suffered for so long; the least we can do is patiently focus our hopes and hard works on the science that can lead us to a promising vaccine capable of diminishing this epidemic."

Margaret M. McCluskey, RN, MPH,
Senior Technical Advisor for HIV Vaccines,
USAID Office of HIV/AIDS

The U.S. Agency for International Development works in partnership with the U.S. President's Emergency Plan for AIDS Relief.

GLOSSARY OF KEY HIV VACCINE TERMS

Adaptive immune response – a "learned" response in which the immune system responds specifically to an invader, such as a virus, and retains the ability to respond more quickly in the future (called immune memory). Vaccines can induce immune memory.

Antibody – (also called immunoglobulin) an infection-fighting protein, made and secreted by B-lymphocytes, in blood or secretory fluids that recognizes, neutralizes, and helps destroy pathogenic microorganisms (e.g., bacteria, viruses) or toxins. Antibodies are made in response to stimulation by antigens. Generally, each antibody binds only to the specific antigen that stimulated its production.

Antibody-mediated immunity – (also known as "humoral immunity") protection provided by antibodies as opposed to cellular immunity.

Antigen – any foreign substance that enters the body and is recognized by a component of the immune system (i.e., antibodies, cells), causing an immune response. Antigens are often agents such as invading bacteria or viruses (see immunogenicity).

B-cells or B Lymphocytes – white blood cells of the immune system derived from bone marrow and spleen. B-cells develop into plasma cells, which produce antibodies (see memory cells).

Cell-mediated immunity – (also called cellular immunity) the branch of the immune system that targets host cells infected with microorganisms, such as viruses, fungi, and certain bacteria. It is coordinated by helper T-cells and Cytotoxic T-cells (as opposed to humoral immunity, which is driven by antibody responses).

Clade – a subtype or strain of HIV. Different HIV clades exist in various regions of the world as groups of related viruses. Clades are defined by the degree of genetic similarity of the viruses that make them up.

Correlates of immunity – (also called correlates of protection) the specific immune responses that provide protection from a certain infection. The precise correlates of immunity for HIV are as yet unknown.

Cytotoxic T-cells (CTL) – a lymphocyte able to kill foreign cells or cells of one's own body that have a new antigen on their surface; CTLs can destroy cancer cells, cells infected with viruses, fungi, or certain bacteria. CTLs can destroy infected cells, whereas antibodies generally target free-floating viruses in the blood. One type of CTL carries the CD8 marker. CD8 T-cells may be CTL or may also release substances that inhibit the growth of viruses. Also known as killer T-cells.

Genome – the complete DNA present in an individual cell or virus.

Helper T-cells (CD4s) – a group of T-cells that produce antibodies and activate killer T-cells. These immune cells, which carry the CD4 cell surface marker, are the primary targets of HIV. Helper T-cells are the chief regulatory cells of the immune system, controlling activities such as turning antibody production on and off.

Humoral immunity – protection provided by antibodies (as opposed to cell-mediated immunity). Also known as "antibody-mediated immunity."

Immune system – the body system, made up of many organs and cells, that protects against infection, disease and foreign substances or antigens. This response may neutralize or eliminate the antigens and provide immunity.

GLOSSARY OF KEY HIV VACCINE TERMS

Immunogenicity – when attributed to a test vaccine, defines the product's ability to cause the body to produce antibodies or T-cells that may protect against an infection, disease, or foreign substance.

Innate Immunity – a relatively nonspecific response that protects against a whole class or type of invaders but does not generate immune memory (see adaptive immune response).

Killer T-cells – a group of T-cells that is activated by helper T-cells and has the ability to destroy cells infected by foreign invaders (such as viruses). Also known as cytotoxic T-cells, they may belong to the CD8 group.

Lymphocytes – the diverse set of white blood cells (each with different functions) that are responsible for immune responses. There are two main types: B-cells (responsible for producing antibodies) and T-cells (which orchestrate various aspects of the immune response and carry out specialized functions such as destroying cells infected with pathogens). These cells are produced in the bone marrow and thymus, respectively.

Memory cells – T-cells or B-cells that have been exposed to a specific invading organism and remembers the organism. Memory cells help the immune system respond faster when they encounter invading organisms for the second time. Memory cells are long-lived subsets of T-cells and B-cells that have been exposed to specific antigens and can "recall" them (and then quickly mobilize an immune response), even if infection occurs many years later.

Mutation – a change in the genetic material (DNA) inside a cell that results in a new characteristic. HIV is a virus that mutates frequently as it replicates (reproduces itself), often resulting in a stronger and/or drug-resistant virus.

Neutralizing antibody – an antibody that prevents a virus from infecting a cell, usually by blocking viral entry points (receptors) on the virus.

Preclinical – testing of a vaccine or drug in cells or animals before testing in humans.

T-cells – one of two main types of white blood cells critical to the immune system. They include CD4+ and CD8+ T-cells. The "T" stands for the thymus, where T-lymphocytes mature.

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 the cellular machinery to produce new viruses.

Vector – a bacterium or virus that does not cause disease in humans and is used in genetically engineered vaccines to transport encoding genes into the body to induce an immune response. Examples include adenoviruses, vaccinia, and canarypox.

The above definitions are a combination of glossaries compiled by the U.S. National Institute of Allergy and Infectious Diseases and by IAVI, edited by USAID. For more definitions and answers to FAQs, see the following:

http://www.hvtn.org/resources/glossary.html

http://www.iavi.org/viewpage.cfm?aid=34

http://www.vrc.nih.gov/clintrials/clin_faq.htm