Current Status of the HIV Vaccine

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ABSTRACT

As the HIV pandemic continues, our best current treatments (reverse transcriptase inhibitors and protease inhibitors) only manage to slow the progression of the disease and do not represent a cure. Thus, the development of a prophylactic HIV vaccine would be of enormous benefit in controlling the HIV crisis. However, designing an HIV vaccine will require researchers to overcome many obstacles including the ability of the virus to integrate in the host genome and thus avoid immunological attack, it's transmission as a free or cell-associated virus, HIV's rapid and frequent antigenic variation and the limited number of animal models available for testing. Currently, more than 20 candidate vaccines are undergoing phase I/II testing. Three main vaccine types are being developed, HIV subunit vaccines, live-virus vector vaccines and combinations of these vaccines. The combination vaccines, which induce strong and broadly reactive humoral and cell mediated immunity appear to be the best candidate vaccines. Despite the enormous advances in our understanding of the biology and immunology of HIV, it is unlikely that a vaccine will be ready for large scale use within the next 10 years.

Key Words: AIDS, HIV, vaccine.

RÉSUMÉ

La pandémie du VIH poursuit sa course et notre arsenal thérapeutique actuel (inhibiteurs de la transcriptase inverse et inhibiteurs de la protéase) ne réussit qu'à ralentir la progression de cette maladie, et ne constitue malheureusement pas une cure. La mise au point de vaccins anti-VIH serait donc un avantage indéniable dans la lutte contre cette infaction. Le développement d'un tel vaccin demandera aux chercheurs de surmonter de nombreux obstacles dont la capacité qu'a le virus à s'intégrer au génome hôte et ainsi à éviter les défenses immunologiques, son mode de transmission libre ou à médiation cellulaire, sa variation antigénique fréquente et rapide, sans compter le nombre restreint d'animaux disponibles pour l'expérimentation. À l'heure actuelle, plus de 20 vaccins sont à l'essai en phase I/II. Les chercheurs ont mis au point trois principaux types de vaccins: les vaccins à sous-unité VIH, les vaccins à vecteur de virus vivant et les vaccins combinant ces deux derniers types. Les vaccins combinés qui induisent une immunité humorale et cellulaire forte et étendue semblent être les plus prometteurs. Mais malgré les progrès spectaculaires dans notre compréhension de la biologie et de l'immunologie du VIH, il semble peu probable qu'un vaccin pouvant être utilisé à grande échelle puisse voir le jour d'ici les dix prochaines années.

Mots clés : SIDA, vaccin, VIH

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INTRODUCTION

The incidence of HIV infection continues to increase at an alarming rate. The World Health Organization estimates 30-40 million cumulative cases of HIV by the year 2000.[1] The best treatments currently available, reverse transcriptase and protease inhibitors, only manage to slow the progression of the disease, and are ineffective at eliminating the virus.[2] Clearly, the development of a prophylactic HIV vaccine would be of enormous benefit in controlling the HIV pandemic. An effective prophylactic vaccine administered to HIV-seronegative individuals would induce protective immunity against HIV upon exposure. This article will briefly review the different types of prophylactic HIV vaccines currently under investigation, and discuss the recent findings regarding the safety and immunogenicity trials. Therapeutic vaccines, which propose to treat HIV infected persons, will not be discussed.

Vaccine Development and Vaccine Types

Faced with the difficult task of producing a safe and effective vaccine, researchers must also struggle to develop a vaccine which is easy to administer, inexpensive, and stable under field conditions.[3] Due to HIV's significant antigenic variation, this 'ideal' vaccine would have to provide long-lasting protection (through the induction of antibodies and/or activation of cytotoxic T-lymphocytes) against the multiple strains of HIV.[4] It should be mentioned that target concentrations of neutralizing antibodies have not been defined. Development of an HIV vaccine will also require researchers to overcome several obstacles including the ability of the virus to integrate into the host genome and establish latent infection, its transmission as a free or cell-associated virus,

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unknown correlates of immunity (i.e., clinical or lab parameters), and limited animal models.[5]

Historically, effective vaccines have been developed only against viral infections in which natural immunity plays a major role in the pathogenesis of and recovery from infection. Small pox, measles, mumps, rubella, and Hepatitis B are examples.[3] It should be noted the HIV exhibits three important properties not possessed by viruses for which effective vaccines have been created: 1) HIV is not neutralized by the host's natural immune system, 2) HIV integrates into the host's genome and establishes latent infection, 3) HIV destroys the immune system.[3]

Vaccines traditionally have been based on live-attenuated virus (a less virulent but equally immunogenic form of the original) or whole inactivated (killed) virus. Research into HIV vaccines has established in three main vaccine concepts: HIV subunit vaccines, live-virus vector vaccines (based on non-HIV viruses genetically altered to express HIV envelope proteins), and a combination of these vaccines. However, due to safety concerns, researchers developing HIV vaccines have focused on utilizing subunits of HIV. Currently, more than 20 candidate vaccines are under-going phase I/II testing (Table I). The first HIV subunit vaccines to enter into human studies (young healthy subjects) were based on recombinant HIV envelope proteins (proteins on the outside of the virus) formulated with various adjuvants.[6] Adjuvants such as alum/deoxycholate and muramyl/tripeptide covalently linked with dipalmitoyl phosphatidyl ethanolamine (MTP-PE) serve to stimulate the immune response. These vaccines were able to elicit antibody responses, as well as lymphoproliferative responses characteristic of general immune system stimulation. Unfortunately, the concentrations of neutralizing antibodies induced in this young healthy seronegative population were found to be 3-10 times lower than those found in seropositive individuals.[4,7,8] Some cross-reactivity with other strains of HIV has been achieved,[8] but to date, no vaccine has been able to induce antibodies capable of neutralizing HIV isolated from infected patients.[9]

Less attention has been given to the duration of the immune response induced by the recombinant envelope protein vaccines. However, studies involving the rgp120 vaccine have reported the presence of binding antibodies after 6-12 months, and lymphoproliferative responses lasting several years.[4] Immunization schedules of 0,1,6, and 12 months with or without an 18 month booster are normally used. Accelerated dosing schedules, usually of 0,1,2, and 5 months of 0,1,2,3, and 4 months have been tested, yielding results similar to the conventional regimens, although it has been found that a delay of at least three months between the initial priming dose and the subsequent boosts tends to produce higher antibody concentrations.[10,11] Studies are underway using new adjuvant preparations, and differing vaccine doses and dosing schedules in an effort to improve immunogenicity.[10]

Compared to the vaccines based on soluble recombinant envelope proteins, live-virus vector vaccines have had better success eliciting HIV-specific cytotoxic T-lymphocytes, but appear to be less successful at inducing antibodies.[5,11,12] Researchers suspect that both antibody and cytotoxic T-lymphocyte responses will be necessary to eliminate both free virus and cell-associated virus. Thus, strategies involving the administration of a live-virus vector vaccine (inducing a T-cell response) followed by soluble recombinant envelope vaccine boosting (inducing an antibody response) are being examined. This combination vaccine regimen appears to have potential, with at

Table I. Prophylactic HIV Vaccines under Investigation

Candidate Vaccine	HIV Strain	Testing Status	Developer
Envelope proteins			
rgp160	LAI	Phase II	MicroGeneSys
rgp160	LAI,MN	Phase I	Immuno AG
rgp120	LAI,MN	Phase II	Genentech
rgp120	SF2	Phase II	Biocine
Live-virus vectors			
vaccinia-gp160	LAI	Phase II	Bristol-Myers Squibb/Oncogen
canarypox-gp160	MN	PhaseI/II	Pasteur-Merieux-Connaught Virogenetics
Peptides			
V3-MAPS	MN	PhaseI/II	United Biomedical, Inc.
V3 peptide(s) conjugated to PPD	MN, multiple	Phase I/II	Swiss Serum and Vaccine Institute
Virus-like particles			
Ty.p24.VLP	LAI	Phase I/II	British Biotechnology, Ltd.
Ty.V3.VLP	LAI	Phase I/II	British Biotechnology, Ltd.
Combination vaccines			
vaccinia-gp160 plus rgp160	LAI/LAI	Phase I/II	Bristol-Myers Squibb/Oncogen
or rgp120	LAI/SF2		
canarypox-gp160 plus rgp160	MN/MN-LAI	Phase I/II	Pasteur-Merieux-Connaught Virogenetics

Adapted from: Hoff, McNamara, Fowler, et al (1994); Holh, Bolognesi, Corey, et al (1994); Graham (1994).
Abbreviations: rgp- recombinant glycoprotein; PPD- purified protein derivative; MAPS- multiple autogenic peptides presented on an oligolysine backbone; LAI, SF2, MN- strains of HIV predominantly found in the United States and Europe.

least one study showing improved immune responses compared to either vaccine alone.[13]

Two other vaccine types, peptide vaccines and virus-like particles are under study. Peptide vaccines are based on a highly immunogenic and variable region of the HIV envelope protein gp120 called the V3 loop. This 35 amino acid structure has been discovered to be an important target of neutralizing antibodies and cytotoxic T-lymphocytes.[3,14] An early human study administered a vaccine based on the V3 peptide and produced encouraging results, with the induction of neutralizing antibodies in the majority of subjects, and cytotoxic T-lymphocytes in a few subjects.[15]

The virus-like particle vaccine involves the use of a yeast transposon, a large gene capable of expressing several HIV genes, which self-assembles into virus like particles. The advantage of this system is that one can present "virus like" particles to the immune system and likely receive a strong immunological response. Human immunodeficiency virus p24 core protein and V3 loop particles have been produced by modifying the genes encoding for the protein. Tests performed in animals using vaccines based on virus-like particles have reported them to be highly immunogenic, and able to elicit both antibody and cytotoxic T-lymphocyte responses.[16]

Novel delivery systems and different techniques of inducing immune responses continue to be examined. Antigen-encoding plasmid DNA (a plasmid that expresses an HIV antigen to the immune system),[17] transgenic plants (genetically engineered plants that produce large quantities of HIV antigens) which express and accumulate antigens,[18] vaccine containing poly (lacticoglycolic) acid microspheres (a polymer designed to release antigen in a "sustained release" fashion),[19] and orally administered vaccines[20] are some of the new methods being tested. In addition, studies are underway to determine the role of mucosal immunity (production of antibodies such as sIgA in fluids and secretions such as vaginal fluid or semen) in preventing infection.

Safety

Subjects enrolled in the vaccine trials have generally been healthy adults between the ages of 18 and 65, who are at low risk for HIV infection.[21] Concerns about acquiring HIV through the use of current vaccines are unfounded, since the current vaccine types are all based on subunits of HIV, making it impossible to become infected by their use. The candidate vaccines tested to date appear to be safe, with no reports of any serious adverse effects. Itching, tenderness, mild to severe pain, erythema and/or induration at the site of injection were the most commonly reported local effects. Systemic effects usually consisted of fever, headache, nausea, malaise, and myalgia. Both local and systemic effects subsided after 24-72 hours, and were generally attributed to the adjuvant formulation.[8,11,21]

Social, Ethical, Economic Considerations

Aside from the scientific issues, many social, ethical and economic questions remain. In which population will the first efficacy trial take place? What degree of efficacy will be acceptable? If a vaccine is developed, who will receive it and at what cost? Will developing countries, often the most in need of a vaccine, be able to afford it? Before these issues can be dealt with, more progress in vaccine development is required.

The next logical step in the vaccine development process will be the initiation of phase III efficacy trials. Because of the complex and costly nature of these studies, the National Institute of Allergy and Infectious Diseases has decided to delay expanded trials until more studies are completed, to allow for a better comparison of the candidate vaccines available, and to ensure that there is enough evidence to warrant a phase III trial.[5] Consequently, it may take at least several more years before any large scale efficacy trials will be started.

In conclusion, the HIV pandemic is a worldwide problem that will continue to grow in the future. Despite the enormous advances which have been made since the discovery of the virus, there remain many serious obstacles to vaccine development, and it appears unlikely that a vaccine will be ready for large scale use within the next 10 years. An effective vaccine will probably have to induce strong and broadly reactive humoral and cell-mediated immune responses. Among the candidate vaccines currently available, the ones employing a combination strategy appear to have the best chance of succeeding. The continued commitment of the scientific and business community, along with essential government support, will be required to achieve the ultimate goal of producing a prophylactic HIV vaccine.

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