An HIV vaccine: how and when?

José Esparza[1]

Abstract The best long-term hope for controlling the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) pandemic is a safe, effective and affordable preventive vaccine, but its development has encountered unprecedented scientific challenges. The first phase I trial of an HIV vaccine was conducted in 1987. Subsequently, more than 30 candidate vaccines have been tested in over 60 phase I/II trials, involving approximately 10 000 healthy volunteers. Most of these trials have been conducted in the USA and Europe, but several have also been conducted in developing countries. The first phase III trials began in the USA in 1998 and in Thailand in 1999 to assess the efficacy of the first generation of HIV vaccines (based on the HIV envelope protein, gp120); the results will be available within the next 1–2 years. To accelerate the development of an HIV vaccine, additional candidate vaccines must be evaluated in parallel in both industrialized and developing countries. This will require international collaboration and coordination and critical ethical issues will need to be addressed. To ensure that future HIV vaccines contribute to the overall HIV/AIDS prevention effort, we should begin planning now on how best to use them.

Keywords HIV infections/prevention and control; Acquired immunodeficiency syndrome/prevention and control; AIDS vaccines/immunology; HIV/genetics; Clinical trials; Models, Animal (*source: MeSH*).

Mots clés HIV, Infection/prévention et contrôle; SIDA/prévention et contrôle; Vaccin anti-SIDA/immunologie; HIV/génétique; Essai clinique; Modèle animal (*source: INSERM*).

Palabras clave Infecciones por VIH/prevención y control; Síndrome de inmunodeficiencia adquirida/prevención y control; Vacunas contra SIDA/inmunología; VIH/genética; Ensayos clínicos; Modelos animales (*fuente: BIREME*).

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Voir page 1136 le résumé en français. En la página 1136 figura un resumen en español.

Introduction

Although acquired immunodeficiency syndrome (AIDS) was described only in June 1981, it has subsequently become the most important infectious disease, being the leading cause of death in Africa and the fourth leading cause of death worldwide (*1*). Despite international efforts to control the HIV/AIDS pandemic, through behavioural modification and other interventions, more than 15 000 people become infected with human immunodeficiency virus (HIV) every day, 95% of whom live in developing countries, particularly in sub-Saharan Africa. The best long-term hope for controlling the pandemic would be a preventive vaccine that is safe, highly effective, and affordable (*2, 3*).

In 1983–84, the discovery that HIV was the etiological agent of AIDS raised hopes that a preventive vaccine would soon be developed and, in fact, the first human trial of a candidate HIV vaccine was carried out in 1987 in the USA. At that time, however, the magnitude of the scientific challenge presented by the development of a vaccine was not appreciated. Since then, several candidate vaccines have been tested in human trials and efforts to develop an HIV vaccine are increasing (*2–4*).

Depending on the results from ongoing and planned large-scale phase III trials, the first HIV-preventive vaccine could be available within the next 2–6 years. If these first-generation HIV vaccines work, they may not be highly effective, and we must decide how they could be used in public health programmes. An HIV vaccine with moderate efficacy (ca 50%) could still play a significant role in preventing new infections, especially in populations with high incidences of HIV infection and where other preventive interventions are not readily available. In any case, we should not expect that a future HIV vaccine, especially one with only moderate efficacy, will be a "magic bullet" that replaces other preventive interventions. Instead, vaccines will be part of comprehensive HIV prevention packages that also include health promotion and behavioural interventions (*2*).

The scientific challenges

There are three major scientific challenges for HIV vaccine development, as discussed below (*2–4*).

[1] Coordinator, WHO/UNAIDS HIV Vaccine Initiative, World Health Organization, 1211 Geneva 27, Switzerland (email: esparzaj@who.int).

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The immunological correlates of HIV/AIDS protection are not known

A major stumbling block for the rational development of HIV vaccines has been the lack of information on the immunological correlates of protection against HIV/AIDS. With most vaccine-preventable diseases, naturally occurring (or vaccine-induced) immune responses correlate with protection against infection or disease. In contrast, even though most people infected with HIV develop a broad range of immune responses against the virus, these responses neither eliminate the infection nor prevent progression to AIDS. Ongoing HIV vaccine development strategies are targeted at the two major types of immune responses, humoral and cell-mediated immunity, and include strategies to induce both of them.

The genetic variability of HIV

Genetic analysis of HIV strains isolated from different parts of the world has revealed that several HIV genes exhibit extensive sequence heterogeneity, particularly in the gene coding for the viral envelope proteins, gp120 and gp41.[a] This heterogeneity has been used to classify HIV type 1 (HIV-1) strains into groups and subtypes; most HIV infections are caused by viruses belonging to HIV-1 group M (or "major") which, in turn, is divided into at least nine genetic subtypes (A–J).[b] Viruses from different subtypes can also recombine among themselves, generating *unique and* circulating recombinant forms (CRFs).

HIV subtypes and CRFs have unequal geographical distributions. For example, in the Americas most infections are caused by subtype B, whereas subtype E causes the major HIV/AIDS epidemic in Thailand. In Africa, several subtypes cause the epidemic, but most are of subtype C. Although much is known about the genetic variability of HIV, it is unclear how the *genetic* variability relates to *potential* vaccine-induced protection. For example, it is not known whether the genetic subtypes define immunological types, or whether specific vaccines will need to be designed for each subtype. The results of human trials with candidate vaccines that are based on *different* genetic subtypes may provide the answer to this (*5*).

The lack of good animal models

Several experimental HIV vaccines have induced different degrees of protection in primate models, including chimpanzees challenged with HIV or monkeys challenged with the analogous simian immunodeficiency virus. The problem is that different experimental vaccines produce different results in these two animal models. It is also unclear whether the animal results will be predictive of vaccine-induced protection in humans — such information will only result from human trials.

Candidate vaccines

Despite the uncertainties, a number of experimental vaccines have been developed in the laboratory and are being tested in animal models (and some in human volunteers). For safety and ethical reasons, the two classic approaches for developing viral vaccines — using whole inactivated or live-attenuated viruses — have not been seriously considered for HIV. Instead, the effort has concentrated on developing subunit vaccines, which contain only part of the virus obtained using genetic engineering techniques.

The first-generation HIV candidate vaccines were based on the envelope proteins of HIV, especially gp120. These vaccines, which are designed to induce the production of neutralizing antibodies, may have the limitation that the gp120 protein is the most variable component of the virus. Second-generation candidate vaccines are being designed to induce cell-mediated immunity, using either live vectors (such as vaccinia, canarypox, and others) or "naked" DNA that codes for different HIV genes. Third-generation vaccines, based on regulatory nonstructural proteins of HIV, such as Tat (a transactivator of HIV gene expression) and Nef (a multifunctional myristylated protein), are also emerging. Some immunization protocols use a combination of two different vaccines to induce broader and/or stronger anti-HIV immune responses. Many of these experimental vaccines and their combinations are being tested in primate models, with different degrees of success, and it is expected that several will eventually move to clinical trials in humans.

Clinical trials in humans

Once a promising candidate vaccine is identified and tested in the laboratory and in animal models, it can be moved to clinical evaluation in humans (*6*), a long process with several phases. Phase I trials are conducted with a small number of volunteers, usually 20–50, to obtain initial information on the immunogenicity and safety of the candidate vaccine. Phase II trials usually involve several hundred volunteers and are conducted to obtain additional safety and immunogenicity data, as well as information about different populations, vaccine doses, etc. Phase III trials are large-scale field trials to assess the efficacy of the candidate vaccine for preventing infection or disease.

Phase III trials usually involve several thousand healthy volunteers at a relatively high risk of HIV infection. For statistical reasons, the number of volunteers participating in a phase III trial depends largely on the frequency of HIV infections in the

[a] Note: Both these envelope proteins are expressed at a gp160 precursor that is subsequently cleaved into gp120 and gp41.

[b] Note: The original subtype I was subsequently found to be a recombinant.

study population: the higher the HIV incidence, the lower the number of volunteers required in the trial. In a typical phase III trial, a total of approximately 5000 volunteers would be required if the incidence of HIV infection in the population is 1.5% per year. Half of the volunteers would receive the experimental vaccine and the other half, a control injection (a placebo or an unrelated vaccine). For ethical reasons, all trial participants should receive counselling and other risk-reduction interventions. Hopefully, these actions will decrease the baseline incidence of HIV infections in the study population, an effect that should be considered when estimating the trial sample size. To avoid experimental bias, neither the volunteers nor the investigators should know who is receiving the candidate vaccine and who is receiving the control injection (i.e. it should be a "double-blind, placebo-controlled" trial). The study population is usually followed for three years, after which the code is broken and the number of HIV infections in the control group is compared with that in volunteers receiving the vaccine, from which the vaccine efficacy can be estimated. For example, if the number of infections in the vaccine group is ten times less than in the control population, vaccine efficacy would be 90%. Phase III trials are long and complex and in the most optimistic scenario it takes 6–9 years between phase I trials and the results of a phase III efficacy trial.

The first phase I trial of an HIV candidate vaccine was conducted in the USA in 1987, using a gp160 candidate vaccine. Subsequently, more than 30 HIV candidate vaccines have been tested in 60 phase I or phase II trials, involving more than 10 000 healthy volunteers. Most of the trials have been conducted in the USA and Europe, although some have also been conducted (or are being conducted) in developing countries, including Brazil, China, Cuba, Haiti, Kenya, Thailand, Trinidad and Tobago, and Uganda. Trials in developing countries are important for several reasons. First, most infections occur in such countries, where an effective vaccine would eventually be used and be most beneficial. Second, to produce valid and timely results, phase III efficacy trials need to be conducted in populations with high incidences of HIV infections. Third, the genetic and antigenic variability of HIV may necessitate testing candidate vaccines in different areas of the world. Finally, it may be necessary to evaluate how different routes and/or cofactors for HIV transmission influence vaccine protection (*7*).

Human trials of HIV candidate vaccines have provided important information that has permitted new generations of improved candidate vaccines to be designed. Phase I/II trials have shown that candidate vaccines are safe, with the only significant side-effect being pain at the site of the injection. Candidate vaccines based on gp120 induce antibodies in essentially 100% of volunteers, although the antibodies are basically directed against homologous laboratory-adapted strains of the virus. Novel HIV envelope constructs are being designed, with the ultimate purpose of inducing broadly neutralizing antibodies against clinical isolates of the virus. The leading HIV candidate vaccine designed to induce cell-mediated immunity uses a canarypox vector to express several HIV genes, but has induced cytotoxic T-lymphocytes in only a fraction of the vaccinees and stronger immunogens may have to be designed.

Phase I/II trials do not provide information on the protective efficacy of the candidate vaccine; for this, phase III trials are required. The first phase III trial of an HIV candidate vaccine began in June 1998 in the USA (with "sites" in Canada and the Netherlands), using a bivalent BB (i.e based on two different subtype B strains) gp120 candidate vaccine (VaxGen, Brisbane, CA, USA). This candidate vaccine is being tested in 5400 human volunteers, the majority of whom are homosexually active men. The second phase III trial, started in March 1999 in Thailand, is designed to assess a bivalent BE gp120 candidate vaccine (also from VaxGen) in 2500 volunteers recruited among recovering injecting-drug users in Bangkok. Results from these trials will be available within the next 1–2 years and offer the first opportunity of having an HIV vaccine. A phase III trial is being planned by the US National Institutes of Health, to be initiated in several countries in the Americas early in 2003. This will assess the efficacy of a prime-boost regime, combining a canarypox–HIV vector (Aventis Pasteur, Lyon, France) and gp120 (VaxGen, Brisbane, CA, USA). Both vaccines are based on HIV subtype B, the most prevalent in the region. A similar prime-boost phase III trial using candidate vaccines based on the subtype E of the virus is also being planned in Thailand. Efficacy results from these trials will be available around 2006 at the earliest, and would represent a second chance of identifying an effective vaccine.

Conclusions

During the United Nations General Assembly Special Session on HIV/AIDS, held in New York on 27 June 2001, it was recommended to "increase investment in and accelerate research on the development of HIV vaccines" (*8*). Numerous institutions are contributing to this global effort, especially the US National Institutes of Health, the US Military HIV Research Programme, the US Centers for Disease Control and Prevention, the French National Agency for Research on AIDS, the European Community, the International AIDS Vaccine Initiative, WHO, UNAIDS and others, including the vaccine industry. In addition, several developing countries are establishing their own national AIDS vaccine plans and initiatives. The participation of multiple partners is a welcome development, but will require international coordination and collaboration.

The most rational way to accelerate HIV vaccine development is to proceed with multiple clinical trials simultaneously, thereby permitting assessment of the protective efficacy of different candidate vaccines against different HIV subtypes in different countries and populations. More basic research is also needed to improve understanding of the human immune response to HIV and vaccination, and to design better immunogens for future clinical trials (*9*). A major effort must be made to develop and evaluate candidate vaccines in Africa, the most affected continent. WHO and UNAIDS are promoting an "African AIDS Vaccine Programme" — a network of African scientists working to promote HIV vaccine research and evaluation in Africa through capacity-building and regional and international collaboration.

Critical ethical issues will need to be tackled during these trials, including the level of care and treatment that should be offered to volunteers who become infected during the course of the trial, and how to make vaccines available to the population once their efficacy has been demonstrated (*10, 11*). To ensure that the policies contribute to the overall HIV/AIDS prevention effort, we should begin planning now on how to introduce and use future HIV vaccines (*12*). ■

Conflicts of interest: none declared.

Résumé

Un vaccin contre le VIH : quand et comment ?

Le meilleur espoir à long terme pour la lutte contre la pandémie de virus de l'immunodéficience humaine/syndrome d'immunodéficience acquise (VIH/SIDA) serait de disposer d'un vaccin préventif sans danger, efficace et abordable, mais le développement d'un tel vaccin s'est heurté à des difficultés techniques sans précédent. Le premier essai de phase I d'un vaccin anti-VIH a été réalisé en 1987. Par la suite, plus de 30 vaccins candidats ont été testés au cours de plus de 60 essais de phase I/II sur environ 10 000 volontaires sains. La plupart des essais ont été réalisés aux Etats-Unis d'Amérique et en Europe, mais plusieurs ont également eu lieu dans des pays en développement. Les premiers essais de phase III ont débuté aux Etats-Unis d'Amérique en 1998 et en Thaïlande en 1999 afin d'évaluer l'efficacité de la première génération de vaccins anti-VIH (dirigés contre la protéine d'enveloppe gp120) ; les résultats seront connus d'ici un à deux ans. Pour accélérer la mise au point d'un vaccin contre le VIH, d'autres vaccins candidats devront être évalués en parallèle dans les pays industrialisés et dans les pays en développement, ce qui nécessitera une collaboration et une coordination internationales ainsi que l'examen de questions éthiques fondamentales. Pour assurer que les futurs vaccins anti-VIH contribueront à l'effort global de prévention du VIH/SIDA, nous devons dès maintenant commencer à réfléchir à la manière dont ils seront le mieux utilisés.

Resumen

Una vacuna contra el VIH: ¿cómo y cuándo?

Aunque la mejor esperanza a largo plazo para controlar la pandemia de VIH/SIDA es una vacuna preventiva que sea segura, efectiva y accesible, su desarrollo ha obligado a afrontar varios retos científicos sin precedentes. La primera prueba clínica de fase I de una vacuna contra el VIH se llevó a cabo en 1987. Desde entonces se han probado más de 30 vacunas experimentales en más de 60 pruebas de fase I/II, con la participación de unos 10 000 voluntarios sanos. La mayoría de esas pruebas clínicas se han hecho en los Estados Unidos y Europa, pero también se han hecho varias en países en desarrollo. Las primeras pruebas de fase III, diseñadas para determinar la eficacia de la primera generación de vacunas contra el VIH (dirigidas contra la proteína gp120 de la cubierta del virus) comenzaron en 1998 en los Estados Unidos y en 1999 en Tailandia. Dentro de 1-2 años tendremos los resultados de esas pruebas. Para acelerar el desarrollo de vacunas contra el VIH, deberán emprenderse simultáneamente pruebas clínicas adicionales tanto en países industrializados como en países en desarrollo. Ello exigirá colaboración y coordinación a nivel internacional, y obligará a resolver varios aspectos éticos de crucial importancia. También es esencial comenzar a planificar la manera de usar las futuras vacunas contra el VIH, para asegurar que contribuyan al esfuerzo integral de prevención del VIH/SIDA.

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