AIDS Vaccine Trials: Ethical Ramifications and Policy Implications For Developing Countries

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Introduction

The acquired immunodeficiency syndrome (AIDS) epidemic currently affects a large range of the world's population, including homosexuals and heterosexuals, intravenous drug users and commercial sex worker communities. Current statistics from the United Nations estimate that more than 15,000 individuals are newly infected with human immunodeficiency virus (HIV) each day; totalling more than 5.5 million new infections per year. Ninety-five percent of these infections occur in developing countries, where almost all infected people ultimately succumb to the disease or opportunistic infections[1]. Women and children are now among the fastest growing group becoming infected by the HIV today.

In spite of extensive prevention programs, the HIV epidemic is still spreading worldwide. While stabilizing in North America and in Europe, the rate of new infections is rapidly increasing in Latin America, Africa and Asia. Antiretroviral therapy while efficacious cannot eradicate the virus, and is complicated by side effects, problems of compliance, and the emergence of drug-resistant viruses[2]. Furthermore, its prohibitive cost severely limits its use in developing countries. Thus the need for a vaccine against AIDS is great, and a major public health priority.

The nature of HIV, however, means that traditional approaches to vaccine development are inadequate for AIDS. The creation of an effective vaccine for smallpox was relatively simple on account of its short incubation period and singular serotype. In contrast, the complexity of HIV and the changing nature of infection make a safe and effective AIDS vaccine more difficult to construct. The variability of HIV and the long incubation period between infection and the development of AIDS pose interesting problems that did not apply to development of vaccines for diseases such as smallpox and measles.

Therefore, scientific efforts towards developing a preventive HIV vaccine have been intensifying. For maximum efficiency, clinical trials of the vaccine are targeted toward developing countries, rather than in the regions where the vaccines are being manufactured, namely North America and Europe. While the need for an AIDS vaccine is great, this vaccine needs to be relevant to the changing nature of the epidemic, appropriate for the population on which it is being used, and adequately effective.

Characteristics of HIV

As a human retrovirus, HIV has many characteristics that pose obstacles to the development of a safe and effective vaccine. The virus is highly variable; it has two different strains, HIV-1 and HIV-2, and nine different subtypes. HIV has many target cells and infects the central nervous system early: transmission can occur through various routes, including body fluids and infected cells. The virus is also prone to destruction or alteration of immunoregulatory cell function, thereby preventing the effect of a neutralizing antibody[3]. Hence, an effective vaccine needs to stimulate both humoral and cell-mediated immunity. The HIV genome becomes integrated into the host DNA but the infection has a long incubation period that includes subclinical cases, a carrier state, and a non-specific acute clinical disease stage. For many patients, the first recognizable clinical manifestation of the virus may not occur until years after initial infection, being manifest as an opportunistic infection or tumour, such as Kaposi's sarcoma, both secondary to immunodeficiency. Another impediment to the development of an effective vaccine is that the virus does not equally affect animals and humans. Chimpanzees do not develop the disease when infected with the virus and while the pathogenesis of the simian form of the virus, SIV, has helped scientists to discover the pathogenesis of HIV, the manifestation of the disease from SIV in simian monkeys is not predictive of the human AIDS experience[4]. Therefore, results of animal studies are not necessarily applicable to humans.

While these barriers hinder progress, what is known about the virus and its method of infection has encouraged various vaccine efforts from biotechnology companies. The HIV genome is RNA based and replicated through a DNA intermediate once the virus has penetrated the target cell. While most retroviruses have a genome that consists of only three coding regions (*gag*, *env*, and *pol*), HIV has four additional genes that regulate viral gene expression. The gene *env* in the envelope region, codes for a large surface glycoprotein, gp160. This molecule is split into two smaller proteins, gp120 and gp141, by a host cell protease as the virus particles separate from the cell membrane. Because *env* encodes the virus coat proteins, the most promising vaccine efforts have focused on recombinant proteins based on this gene[5,6].

Vaccine Development

Two types of immunogens are traditionally used for vaccine production: whole virus, either attenuated or killed, and purified viral proteins. With HIV, a killed virus might not be an effective immunogen because of the virus mutability, and a live attenuated virus may regain virulence and infect non-infected people. Therefore, most research has focused on developing vaccines based on viral protein subunits such as gp120 and gp160[7].

Most vaccine research has been based on one North American HIV-1 isolate, subtype B[8]. While phase I clinical trials (small-scale trials that focus on safety and immunogenicity) have been underway since 1987, the first phase III efficacy trials have begun only recently in the USA and Thailand. Since 1987, more than 60 phase I/II trials have been conducted, with a total of approximately 30 different HIV candidate vaccines[9]. At the present time, 19 HIV candidate vaccines are at different levels of clinical evaluation in the US, including recombinant proteins, synthetic peptides, nucleic acid vaccines and different recombinant live vectors[6]. The HIV candidate vaccine that has had the most success so far in Phase I trials is a gp120 product from VaxGen (Brisbane, California, USA)[6]. In 1998, the United States Food and Drug Authority (US FDA) approved this product for the first Phase III clinical trial[10]. This ongoing trial involves 5400 volunteers in the USA at high risk for acquiring HIV infection and utilizes a vaccine based on two variants of the B subtype of HIV-1 which are prevalent in the USA[6,10]. Efficacy studies of any vaccine are most useful when tested in a large target population. While the United States does have a significant population at risk for HIV, over 90% of the world's population at risk lives in developing countries[1,8]. Therefore, VaxGen also aimed to obtain approval to launch a second phase III clinical trial in Thailand.

Ethical Ramifications

Strains and Subtypes of Trial Vaccines

The ethical ramifications of an AIDS vaccine clinical trial in a developing country are great and need to be explored before proceeding with large-scale trials. While phase III trials have already begun, global ethical standards for HIV-1 vaccine trials are still in development and have yet to be officially enforced[11,12]. The antigenic variation of HIV is among the most important ethical considerations. The virus has two different strains (HIV-1 and HIV-2) and ten different subtypes (Figure 1). The worldwide prevalence of these subtypes is as follows: 23% A, 8% B, 56% C, 5%D, 5% E, and 3% others – F,G,H,J,NT[9]. The strain of the virus responsible for most of the new cases of AIDS in the world is HIV-2, in Africa[13]. However, as discussed previously, VaxGen's gp120 vaccine (AIDSVAX), is based on strains of the HIV-1 virus that are found in the United States[2,6,10]. While subtype B of the HIV-1 strain is predominant in the United States, in many developing countries, subtypes C and E are more prevalent[6,8,9]. It is probable that a vaccine that protects against subtype B will not protect against infection from all the other subtypes and may even facilitate infection by another subtype. Therefore, the vaccine on trial must be applicable to the subject population.

VaxGen eventually developed a bivalent vaccine that also included gp120 derived from the E subtype of HIV; the subtype most prevalent in Thailand in addition to subtype C. A phase III trial was launched in 1999 in Thailand using this version of the VaxGen vaccine[9]. It is important to recognize, however, that the two candidate vaccines being tested in phase III trials are based on the major subtypes (B and E) present in the Americas, Europe and the Western Pacific Rim countries, where an adequate potential market is perceived to exist to justify the significant investment needed to develop, test and manufacture the vaccines. It was stated that for this reason, VaxGen has been able to support the development of these candidate vaccines entirely by private funding[6]. Unfortunately, these vaccines based on only B and E isolates may not be appropriate for use in Africa and South Asia, where most of new HIV infections are due to the A, D and C subtypes; and the strain most prevalent now in Africa is not HIV-1 but HIV-2. If subtype-specific gp120 proves to be essential for vaccine efficacy, as many expect, new candidate vaccines containing the relevant gp120 must be developed for these regions. In fact, from the global health perspective, Africa and South Asia are the two areas most in need of an HIV vaccine as most new HIV infections are occurring in those regions (Figures 1 and Table 1).

Financial incentives are needed, however, to encourage the pharmaceutical industry to develop vaccines that are useful primarily in these regions. The public sector demand for an HIV vaccine to be used in public health programs needs to be matched with the private sector requirement of profitability. To accomplish this, the public sector needs to provide appropriate funding to cover the cost of production and delivery of vaccines. Otherwise, it is unlikely that there will be sufficient motivation to develop vaccines specific to South Asia and Africa.

An ideal vaccine should protect against all strains rather than just those in any given geographical area. Therefore, current research needs to progress beyond the HIV-1 strain. It is known that given enough time the various strains will disseminate to regions where the vaccine will provide no protection. Therefore, even if the bivalent gp120 vaccine based on B and E subtypes did protect against the subtype E found in Thailand, this would not prevent people in Thailand from being infected by subtype C or other strains from other parts of the world. Nor would such a vaccine prevent infection in Africa from HIV-2[13]. Despite the fact that Africa has the greatest rate of new HIV infections in the world, it was not until August 2000, more than 12 years after research began on AIDS vaccines, that an experimental vaccine was developed that focused on

subtype A, the prevalent HIV-1 strain in Africa. However, no vaccine research has focused on the HIV-2 strain as yet, and the current vaccine based on subtype A is not expected to be available for the next 10 years[14]. Meanwhile, the epidemic continues to grow in Sub-Saharan Africa.

Given the increasing spread of HIV infection in developing countries, their representatives are eager to have any type of vaccine, regardless of efficacy or relevance to the specific population. Proponents of international vaccine trials argue that unless human trials take place, it will be not be known whether the vaccines are effective, and scientific progress will be hindered. Therefore, despite the genetic variability of the virus and the fact that Thailand has two subtypes of the virus, neither of which may be neutralized by the gp120 vaccine, Thailand representatives and U.S. researchers felt the trials needed to be commenced immediately[6,9]. Yet, in executing human trials, there are several ethical components that need to be considered.

The Immune Response and Adverse Reactions

The possibility that the vaccine will decrease immunity instead of confer protection is one ethical consideration. The immune response is not clearly defined for HIV, as the presence of antibodies does not necessarily protect against the disease. Vaccines such as AIDSVAX activate the antibody-producing arm of the immune response but do not elicit the killer T cells of cell-mediated immunity. Therefore, it is doubtful whether these vaccines will be able to eliminate or contain the virus[6,9]. Nevertheless, researchers argue that trials are needed in order to investigate whether vaccines against one subtype can protect against another, in which case Thailand provides an ideal testing environment; one of the high-risk populations in Thailand is composed of drug users, half of which carry subtype E of the HIV virus, and half of which carry subtype B. Immunity to HIV is not expressed through the typical immune responses. Therefore, it may not even be possible to gauge whether or not the vaccine induces immunity to HIV in a similar subtype population, much less a different one. Additionally, in a population afflicted with many endemic diseases, it will also be difficult to gauge any adverse reactions to the vaccine[15].

Informed Consent and the Risk of Infection in Untreated Subjects

Another ethical concern is consent. Informed consent is absolutely necessary for any experimental trial in the United States. One of the primary conditions of using human subjects for experimental trials, according to the Declaration of Helsinki adopted by the 18th World Medical Assembly in 1964, is that human subjects should not

Figure 1: Global distribution of HIV subtypes and strains (all except Africa have only HIV1)

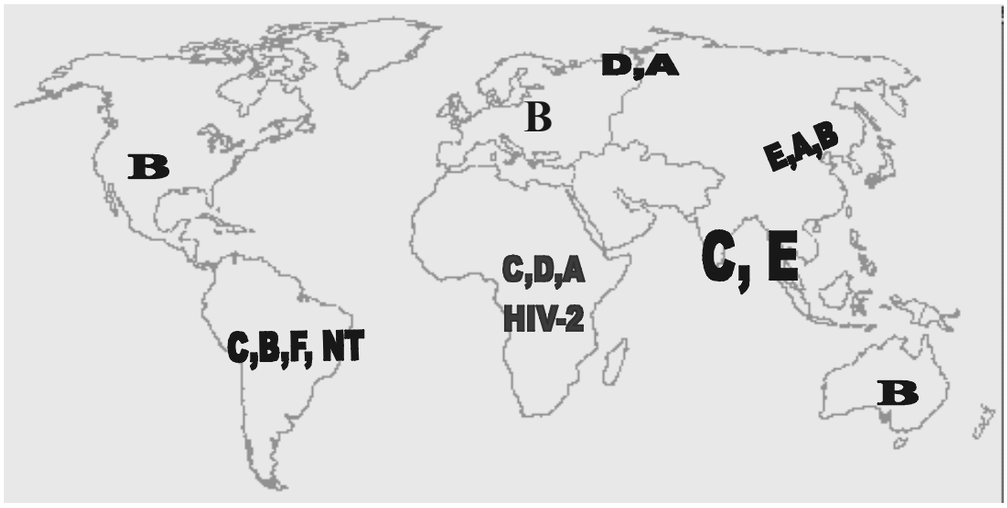

Table 1: Rates of new HIV infections occurring per year worldwide according to UNAIDS estimates[1]

Sub Saharan Africa	3.8 million
South and South East Asia	1.3 million
Latin America and the Caribbean	210,000
East Asia and the Pacific	120,000
Eastern Europe and Central Asia	95,000
North America	44,000
Western Europe	30,000
North Africa and the Middle East	19,000
Australia and New Zealand	500

be used until successful experiments in animals have been completed[15]. The problem with HIV is the lack of a relevant animal model for human AIDS. With that in mind, informed consent becomes an even more pressing concern for any clinical trial. Many industrialized countries have established their own ethical guidelines for human experimentation but this is rarely the case for developing countries[12]. Considerations that are mandatory in the United States may be swept aside in countries that have less stringent legal codes. Therefore, the Declaration of Helsinki and the most recent UNAIDS guidelines for HIV preventive vaccine research can be influential in providing ethical guidelines for vaccine trials in developing countries.

The UNAIDS guidelines include 18 points explaining ethical requirements for HIV vaccine trials. These guidelines are the result of a working group meeting of consultants coordinated by WHO where a consensus was reached that the ideal efficacy trials in developing countries would be controlled, double blind and fully randomised. The meeting concluded with the resolution that the geographical sites for trials should have adequate resources for education about preventing HIV infection. These ethical guidelines for the entry of vaccines into phase III trials were officially issued in May 2000, but have yet to be enforced[11]. The guidelines acknowledge, "Some countries do not currently have the capacity to conduct independent, competent and meaningful scientific and ethical review"[11]. This is due to poor government infrastructure in many developing countries, as well as political instability that may contribute to the lack of human rights considerations, and consequently lack of ethical guidelines for human experiments. Illiteracy, language and cultural barriers, and diminished personal autonomy (especially for women in some countries) can also contribute to the lack of adequate informed consent in certain developing countries. Hence, the UNAIDS guidelines stipulate that in this event, the sponsor of the vaccine trials must ensure that an adequate structure is developed within the host country before trials can take place: "HIV preventive vaccine trials should only be carried out in countries and communities that have the capacity to conduct appropriate, independent and competent scientific and ethical review"[11].

One factor within the informed consent dilemma is that before running any clinical trial, the volunteers must receive counselling to understand the rationale behind the experimental treatment, and to be educated about methods of reducing their risk of infection. The vaccine is targeted at a high-risk population. To measure appropriately the efficacy of the vaccine, researchers would need to hope that the volunteers ignore the counselling and instead engage in high-risk activities. Hence, counselling may not be related to the goals of clinical trials, but is necessary for conducting any randomised trial. The UNAIDS guidelines include this consideration, stating that appropriate risk-reduction counselling and access to prevention methods should be provided to all vaccine trial participants[11]."

Most vaccines currently in use such as those for polio, tetanus, diphtheria, measles, hepatitis B, and influenza prevent disease without actually preventing infection. Similarly, few of the candidate HIV vaccines appear capable of preventing infection. The expectation that HIV vaccines will in fact prevent infection is encouraging the scientific community to hope that these vaccines will prevent disease. In developed countries, it will be ethically required that individuals in vaccine trials who are found to have acquired HIV infection after being vaccinated will be offered antiretroviral therapy, which usually dramatically reduces virus levels. If vaccines cannot achieve protection against infection, however, treatment with antiretrovirals will compromise the ability of the trial to measure the efficacy of the vaccine in preventing disease. However, delaying the drug treatment until viral loads can be determined at several time points presents another ethical problem.

Because of these complications, determination of the protective efficacy of potential HIV vaccines may only be possible with trials in developing countries where the resources are not available to provide antiretroviral drugs. It is that situation where an effective treatment exists but is not made available to subjects who are infected during the course of a vaccine trial that makes clinical trials in developing countries most unethical.

Cost and Ethical Imperialism

Ideally, the populations of participant countries should receive the benefits of whichever product they help develop. In the case of AIDS vaccines, the product should be available at little or no cost to the participating country, and should address the needs of the population. Ethically speaking, vaccine trial sponsors must make successful vaccines available to the countries in which they are tested. Otherwise, an imperialistic trend is established whereby industrial countries are exploiting the resources of developing countries for a product that is exclusively available only to populations in richer countries.

The price of a new vaccine will depend on the size of the market. A small market will lead to higher prices than a larger market. Production costs of the HIV vaccine could be US$10 or more per dose, with distribution costs adding additional expenses[6]. Even at a price of US$10 per dose of vaccine, health ministers in poor countries could still be reluctant to purchase the vaccine, as this would exhaust their average health budget. The current average cost of the Expanded Program on Immunization (EPI) immunization program (inclusive of all 6 vaccines) is US$20-25 per child (US$1.50 for vaccine cost, plus US$20 for delivery)[6]. Given the sensitivity of vaccine production costs to volume, the marginal cost of production would be much lower than the average production cost, providing the opportunity for tiered pricing

wherein the public sector in developing countries might obtain the HIV vaccine for much less than US $ 10 per dose.

While the size of the epidemic in the developing world may be perceived as justification for trials of a partly effective vaccine developed in the United States, the possibility that this might just be an effort to "dump" the vaccine in external markets must be considered. Companies may be seeking to recover the costs of already produced vaccines by sending them to the developing countries. Vaccine production is in general a large investment and without domestic trials, biotechnology companies stand to lose on their investment, in addition to the many doses of vaccine that have already been produced. With international trials, the vaccines can be used but developing countries cannot afford the high price at which a vaccine would be sold in the United States. If a vaccine that is not approved for trials in the home country is "dumped" in other countries to recover investment, it should be donated free of charge in exchange for the clearance to run trials on that country's population. Generally, the WHO subsidizes vaccines for the developing world; the question is whether companies will consider providing AIDS vaccines at affordable prices as they have offered other vaccines, such as the childhood vaccines included in EPI, in the past. If the world market alone is used to distribute vaccines, they will end up being allocated to populations and regions based on the ability to pay just like any other commodity. As it is, many developing countries cannot even afford to implement the new antiretroviral drug therapies. With a current cost of about $12,000 to $15,000 per patient each year in the United States, the only public health measure available to developing countries is counselling against behaviours that increase the risk of the disease[12]. In addition to whether the vaccine will be available at subsidised prices, the question of whether companies will be willing to assume the cost of providing antiretroviral therapy to volunteers in developing countries, who are infected during the course of the vaccine trial, is also one to consider.

To avoid the scenario that has occurred with other vaccines in which those people in most need are often the last to receive immunization, strategic planning is needed to develop purchasing mechanisms and delivery systems. Planning is also needed to ensure that vaccine use in industrial countries does not jeopardize vaccine availability in developing countries. This situation must be prevented at all costs. Currently, the countries hardest hit by the AIDS epidemic are the least able to pay for a vaccine should one become available. The ultimate irony would be if a vaccine developed in collaboration with, and tested in a developing country, was made available to developed countries at a price too expensive for those countries which need the vaccine the most. This scenario would only contribute to increasing the gap and inequalities that the AIDS pandemic has created.

The Ideal Vaccine

The ideal vaccine, according to the Bellagio Conference on HIV Vaccines in March 1994, should be able to protect against all subtypes of HIV and from all routes of exposure[8]. The vaccine should be safe in both the short and long term, preventing the reversion to infectious HIV and immunosuppression in those vaccinated. Heat stable and simple to administer, the vaccine should also be safe to deliver without prior screening for HIV infection and it should provide long-lasting protection with a minimum number of doses to eliminate possibilities of "missed opportunities". This occurs when potential candidates for vaccination do not complete the full vaccination course because of the need to return for subsequent doses and booster shots[8]. Recent data has revealed that a live attenuated vaccine does protect monkeys from infection with SIV[9]. Despite the difference in disease manifestation in monkeys and humans, this indicates the possibility that the best immunity against HIV-1 will come from a whole virus product, rather than a viral subunit. Among the many vaccines with the potential to be "magic bullets", the most promising may well be one which combines various subtypes such as the bivalent vaccine on trial in Thailand. One study presented at the Tenth International Conference on AIDS in Japan in August 1994, showed that HIV-1 isolates can be grouped into a minimum of 5 subtypes based on the *env* and *gag* genes. A multi-component vaccine such as one suggested by this study is needed to address the global diversity of the virus[16]. At the same time, this vaccine should also be effective against the various modes of transmission of HIV. Unfortunately, the current vaccines in large-scale trials do not meet any of the ideal vaccine criteria as they have narrow efficacy against different HIV strains, are expensive, require multiple doses, may not confer lifelong protection and require boosting, and have low to moderate efficacy[6].

Conclusion

With the increasing rate of HIV infections, particularly in developing countries, the need for an intervention is clear. An affordable, available HIV vaccine remains the best long-term strategy against the AIDS epidemic. However, current vaccines in clinical trials are limited to the pattern of the epidemic in industrial countries. These vaccines do not meet the needs of developing countries that are hardest hit by the epidemic. South Asia and sub-Saharan Africa are two regions where the highest numbers of new HIV infections are occurring, yet there is no vaccine available that addresses the pattern of the epidemic in these populations. Not only is a vaccine needed that addresses the needs of these countries, but the vaccines that are currently in trial need to adhere to universal ethical guidelines. Unless such a vaccine can be developed and administered in a clinical trial that includes the relevant subtypes prevalent in the population included in the trial, 2) is safe

and highly effective in both the short and long term, maintains confidentiality of the volunteers due to the stigma attached to HIV and AIDS, adheres to a universal informed consent standard, and is available at minimal or no cost, large-scale trials in a developing country of a vaccine manufactured in an industrialized country are unwise.

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