

## Accelerating the development and future availability of HIV-1 vaccines: why, when, where, and how?

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**An HIV-1 vaccine offers the best long-term hope to control the AIDS pandemic, especially in less-developed countries. To ensure its future availability we need to increase our research efforts today, including clinical trials. Although small-scale clinical trials of HIV-1 vaccines have been underway since 1987, the first phase III efficacy trials started only recently in the USA and Thailand. Initial results from these trials will be available within the next 2–3 years, and we must start planning now how vaccines should be used if found to be effective. In the meantime, the continuing promotion of the parallel development and assessment of other candidate vaccines is important. Financial mechanisms should also be developed as an incentive to industry and to ensure equitable distribution of future vaccines in less-developed countries. Moreover, a concerted effort is needed to ensure the development and future availability of appropriate vaccines for Africa.**

### Introduction

AIDS has been known for less than 20 years and today it is the most important infectious disease, being the most common cause of death in Africa, and the fourth most common worldwide. More than 2·5 million people died from AIDS in 1999, placing it above the other two major infectious killers, malaria and tuberculosis. Today almost 34 million people are living with HIV-1 infection or AIDS, 95% of them in less-developed countries, especially in Africa, which is home to more than 22 million of those infected. Meanwhile, HIV-1 continues to spread throughout the world. In 1999 alone, more than 5·5 million people became infected with HIV-1, at a rate of more than 15 000 new infections every day.<sup>1</sup>

A safe, highly effective, and affordable preventive vaccine offers the best long-term hope to control the pandemic, especially in less-developed countries. However, we must not expect that a vaccine will completely replace other HIV-1 preventive interventions, especially if the first generation of vaccines have only modest protective efficacy (say, <60%). These vaccines would need to be delivered as part of comprehensive HIV-1 prevention packages, including other health promotion and behavioural interventions. Moreover, the availability of even a modestly effective vaccine could reinvigorate social behavioural interventions, which may have to be redesigned around future vaccine delivery programmes, with strong community participation.<sup>2</sup>

Most of us recognise that vaccines are among the most cost-effective health interventions. Unfortunately, few people seem to appreciate the intense research needed for the development of vaccines, including multiple clinical trials. The same lack of understanding seems to exist among many international agencies, donors, and foundations, since they have been hesitant to adopt HIV-1 vaccine development as one of their priorities.

The global public and private expenditure on research related to HIV-1 vaccines in 1999 was estimated at less than US\$300 million globally, two thirds of which was provided by the US National Institutes of Health. Although this amount may seem high, it represents only a fraction of the 1999 global expenditure on drugs to treat HIV-1 infection and AIDS, which was about US\$3 billion in the USA and Europe alone. Additional financial support is required not only to develop new vaccine candidates, but also to strengthen appropriate infrastructures in less-developed countries where many vaccine trials will be carried out, and where future effective vaccines will have to be used as a matter of urgency.

The priority for making an HIV-1 vaccine widely available in the future lies in trying to develop such a vaccine through preclinical research, product development, and clinical trials today. This research process will not be easy, nor will it be fast, and it will require intense international commitment, collaboration, and coordination.

### The long path to an HIV-1 vaccine

Vaccine research is a long process that begins with basic research to identify potential immune correlates of protection, designs of appropriate immunogens, or vaccine concepts, and obtains safety, immunogenicity, and protection data in animals. The next step is to translate promising vaccine concepts into candidate vaccines that are appropriate for clinical evaluation in human volunteers.<sup>3,4</sup>

Preventive vaccines are tested on healthy human volunteers through sequential phases. Phase I and II trials provide safety and immunogenicity data, and are done among small numbers of volunteers at relatively low risk of HIV-1 infection. Depending on the results obtained, candidate vaccines may progress to phase III trials, to obtain definitive information about their efficacy in inducing protection against infection or disease. For scientific and statistical reasons, phase III trials have to be done in populations with a high incidence of HIV-1, many of which are located in less-developed countries. These are controlled double-blind trials, involving thousands of volunteers who, for ethical reasons, should also benefit from appropriate risk-reduction interventions.

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### Clinical trials of HIV-1 candidate vaccines

The first phase I trial of an HIV-1 candidate vaccine was undertaken in the USA in 1987. Since then, more than 6000 healthy volunteers have participated in 60 different phase I/II trials of 30 different candidate vaccines. Most of these phase I/II trials have been carried out in the USA, under the aegis of the National Institutes of Health, and in France, by the Agence Nationale de Recherches sur le SIDA.<sup>5</sup> Trials have also been done in several less-developed countries (table), notably Thailand, where eight HIV-1 preventive vaccine trials have been undertaken since 1994 including the current phase III trial (figure 1).<sup>6</sup>

The first candidate vaccines tested were based on the envelope glycoproteins gp120 or gp160 of HIV-1, an approach aimed at inducing neutralising antibodies.<sup>7</sup> Other candidate vaccines are designed to induce cell-mediated immunity, using live recombinant vectors (chiefly poxvirus-based vectors)<sup>8,9</sup> and more recently, DNA immunisation.<sup>10,11</sup> These multiple trials have shown that candidate vaccines are safe, and have also provided important information to improve subsequent vaccine designs.

Although most scientists agree on the necessity of doing multiple phase I/II trials of different vaccine concepts, there is substantial disagreement about criteria to proceed to phase III trials, especially on the desirable type or level of immune responses that the candidate vaccine should induce, and on the importance of protection in animals.

This disagreement could explain, at least in part, why it has taken 11 years from the first phase I trial of an HIV-1 candidate vaccine to the initiation of the first phase III trial.<sup>12</sup> In June, 1998, VaxGen (Brisbane, CA, USA) started a phase III trial of a gp120 candidate vaccine, involving 5400 volunteers in the USA, most of whom are men who have sex with men. The candidate vaccine is based on two variants of the B subtype of HIV-1 which are prevalent in the USA. A second phase III trial was launched by the same company in March, 1999, in Thailand, and uses a bivalent gp120 vaccine that, in addition to B-subtype protein, also includes gp120 derived from the E subtype, which is the most prevalent in that country.<sup>13</sup> This trial aims to enroll 2500 volunteers, most of them injecting drug users. Initial efficacy results from both trials are expected by the end of 2001.

These trials have already confirmed that even in the face of scientific disagreement, phase III efficacy trials



Figure 1: Volunteer receiving an HIV-1 candidate vaccine in Bangkok, Thailand

can be launched, provided that they use a well-designed protocol, have access to the necessary resources, and benefit from the commitment of all parties involved, especially the population from which volunteers are recruited.<sup>14</sup>

A phase IIb trial (an intermediate size proof-of-concept trial)<sup>15</sup> is being planned by the US National Institutes of Health. This trial will assess the protective efficacy of a canarypox-HIV-1 vector, either alone or boosted with gp120. The rationale for this trial, which will include up to 10 000 volunteers from the USA and other countries, is to assess the relative contribution of humoral and cell-mediated immunity in protection against HIV-1. This trial could start in 2001, with efficacy results available within 3–4 years.

After more than 12 years of HIV-1 vaccine research, only one candidate vaccine has moved to phase III trials; within the next 3–5 years we will have only one or, at the most, two possible effective vaccines—but of course this depends on the satisfactory completion of phase III trials. We must increase the chance of obtaining a usable vaccine by doing more basic research and more product development, to expand the pipeline of promising candidate vaccines for testing, including phase III trials.<sup>16,17</sup> Without phase III trials there can be no regulatory approvals, no products licensed, and no HIV-1 vaccines.

### Push and pull

There have been some discussions over the establishment of a multibillion dollar vaccine fund to purchase future vaccines against malaria, tuberculosis, and HIV-1 for less-developed countries. This pull mechanism would increase the market potential for these vaccines, and may provide the necessary incentive for industry to invest more money in research and development. Other financial mechanisms, such as tax-break incentives, are also being discussed.

These approaches are useful, although it is unlikely that pull mechanisms alone will produce an HIV-1 vaccine.<sup>18</sup> In addition to the real (or perceived) absence of commercial markets for future HIV-1 vaccines, there are also real (or perceived) limitations on the scientific knowledge that is required to develop effective HIV-1 vaccines. Gaps in our scientific knowledge dictate that complementary push mechanisms are implemented to support more basic and clinical research to synergise with the pull mechanisms.

Starting date	Candidate vaccine	Subtype	Country	Number of volunteers
<b>Phase I/II</b>				
1993	Synthetic peptide MN-V3	B	China	23
1994	Synthetic peptide MN-V3	B	Thailand	24
	Synthetic peptide MN-V3	B	Brazil	30
1995	Envelope gp120	B	Thailand	30
	Envelope gp120	B	Thailand	52
1996	Recombinant V3 protein	B	Cuba	30
1997	Envelope gp120	B, E, B/E	Thailand	380
1998	Envelope bivalent gp120	B/E	Thailand	90
1999	Canarypox vector	B	Uganda	40
2000	Prime-boost canarypox vector plus gp160 or gp120	E + E	Thailand	130
	Prime-boost canarypox vector plus gp120	E + B/E	Thailand	125
<b>Phase III</b>				
1999	Envelope bivalent gp120	B/E	Thailand	2500

### HIV-1 preventive vaccine trials in less-developed countries

### What kind of science is needed?

A major conceptual problem for HIV-1 vaccine development is the lack of information on immune correlates of protection against HIV-1 infection or disease.<sup>19</sup> Animal protection experiments and natural history studies have failed to produce conclusive results, although most scientists believe that a combination of both humoral and cell-mediated immune responses may be needed for effective protection (which, in turn, could be improved if a mucosal immune component were added).

In the absence of known immune correlates of protection, different vaccine concepts must be developed and clinically tested in parallel. For many years the vaccine pipeline was basically limited to monomeric gp120 or gp160 proteins based on laboratory strains of the virus (dependent on receptor CXCR4 for cell entry), different synthetic peptides, and simple poxvirus–HIV-1 recombinant vectors. The first generation of envelope antigens achieved the induction of in-vitro neutralising antibodies in basically all the vaccinees. However, these antibodies are mainly directed against homologous laboratory-adapted strains of the virus, and their failure to significantly neutralise clinical isolates of HIV-1 (dependent on receptor CCR5) has been interpreted by some as an indication that these vaccines will not show efficacy in clinical trials.<sup>20–22</sup> In addition, the first generations of canarypox–HIV-1 vectors have inconsistently produced cytotoxic T cells in only 25–70% of the vaccinees.<sup>8,9</sup>

In an attempt to improve on these results, the HIV-1 vaccine pipeline is being expanded to include gp120 constructs based on clinical isolates of HIV-1, and conformational envelope antigens, with the goal of inducing neutralising antibodies against clinical isolates.<sup>23</sup> Likewise, to improve cytotoxic T-lymphocyte responses, new vaccine concepts are being pursued, including complex canarypox vectors expressing multiple HIV-1 genes,<sup>9</sup> different constructs of naked DNA vaccines,<sup>10,11</sup> and new live vectors, including the modified vaccinia Ankara (MVA) strain,<sup>24</sup> and vectors based on the Venezuelan equine encephalitis virus replicon.<sup>25</sup> Different candidate vaccine combinations are also being explored in an attempt to induce the best possible humoral and cell-mediated immune responses.

Most of these experimental vaccines are being tested in primate models, with different levels of success.<sup>26</sup> Immunisation with gp120, and to some extent with DNA vaccines, have been shown to protect chimpanzees against an HIV-1 challenge.<sup>27</sup> On the other hand, immunised monkeys are more difficult to protect against the simian immunodeficiency virus or chimeric simian–human viruses. In this system, immunisation very often results in partial protection, with decreased virus load and slower progression to disease. These animal studies are instructive, but their relevance in terms of vaccine-induced protection in human beings remains to be validated by phase III clinical trials.

Basic research and clinical trials (including efficacy trials) should be done as an iterative process, leading to gradual acquisition of new knowledge. Trials should be designed in such a way that they provide scientific information that could lead to the development of more effective vaccines. Careful judgement needs to be exercised in deciding how much science is essential to move products to large-scale trials, keeping in mind that the primary goal is not only the acquisition of new

scientific knowledge, but also the actual development of an urgently needed HIV-1 vaccine.

Major scientific issues to be addressed are related to the relative contribution of humoral, cell-mediated, and mucosal immunity for protection.<sup>19,28</sup> A primary scientific goal is the identification of potential immune correlates of protection, the Holy Grail of vaccine research (although some effective vaccines were developed without that information and it was not identified even after completion of the trials).<sup>29</sup> Perhaps, rather than thinking of one specific immune correlate of protection, we must work with the concept of multiple immune responses that, as a whole, could serve as effective immunological barriers against HIV-1.

We also need to understand the relevance of laboratory techniques currently available to measure vaccine-induced immune responses, including the importance of antibodies that fail to neutralise in-vitro clinical isolates of HIV-1, or the difficulties in finding consistent cytotoxic T lymphocytes among vaccine recipients. In addition, new laboratory techniques may have to be developed and validated to allow more sensitive and reproducible testing of the large number of samples that will be generated from phase III trials.

### Subtype vaccines

Ten major genetic subtypes of HIV-1 (or clades) have been identified by the nucleotide sequence of their envelope genes, and these subtypes have a distinct geographical spread (figure 2). Most HIV-1 candidate vaccines have been based on subtype B strains, which are prevalent in the Americas and western Europe. Candidate vaccines have also been developed based on subtype E strains, for testing in Thailand.<sup>30</sup> Recent efforts have been directed toward the development of candidate vaccines for subtypes prevalent in other less-developed countries, notably against subtype C, which is responsible for more than 55% of all HIV-1 infections globally, and is the dominant subtype in southern Africa and India.

These efforts to develop candidate vaccines against different HIV-1 genetic subtypes are commendable, but we must recognise our lack of knowledge of the potential immunological relevance of HIV-1 genetic subtypes.<sup>31</sup> Research has already shown that genetic subtypes do not seem to strictly correspond to immunotypes (as defined by immunological relationships). More than one genetic subtype could share common protective epitopes, and it is also possible that more than one immunotype is contained within a single genetic subtype. The identification of vaccine-relevant immunotypes may also depend on what type of immune response is responsible for protection. In general, neutralising antibodies seem to be more strain specific, whereas cell-mediated immune responses are more cross-reactive.<sup>32</sup> That information is important to guide the design of new candidate vaccines, and to plan clinical trials, especially phase III trials.

At least for the initial phase III trials, attempts should be made to match the strains included in the candidate vaccine with those prevalent in the trial population. This could be particularly difficult in some African countries, where multiple subtypes are circulating concurrently. An alternative would be to design cocktail vaccines containing multiple subtypes. However, at some point in the future, we might have to carry out additional efficacy trials to explore the possibility of achieving cross-protection between different subtypes.

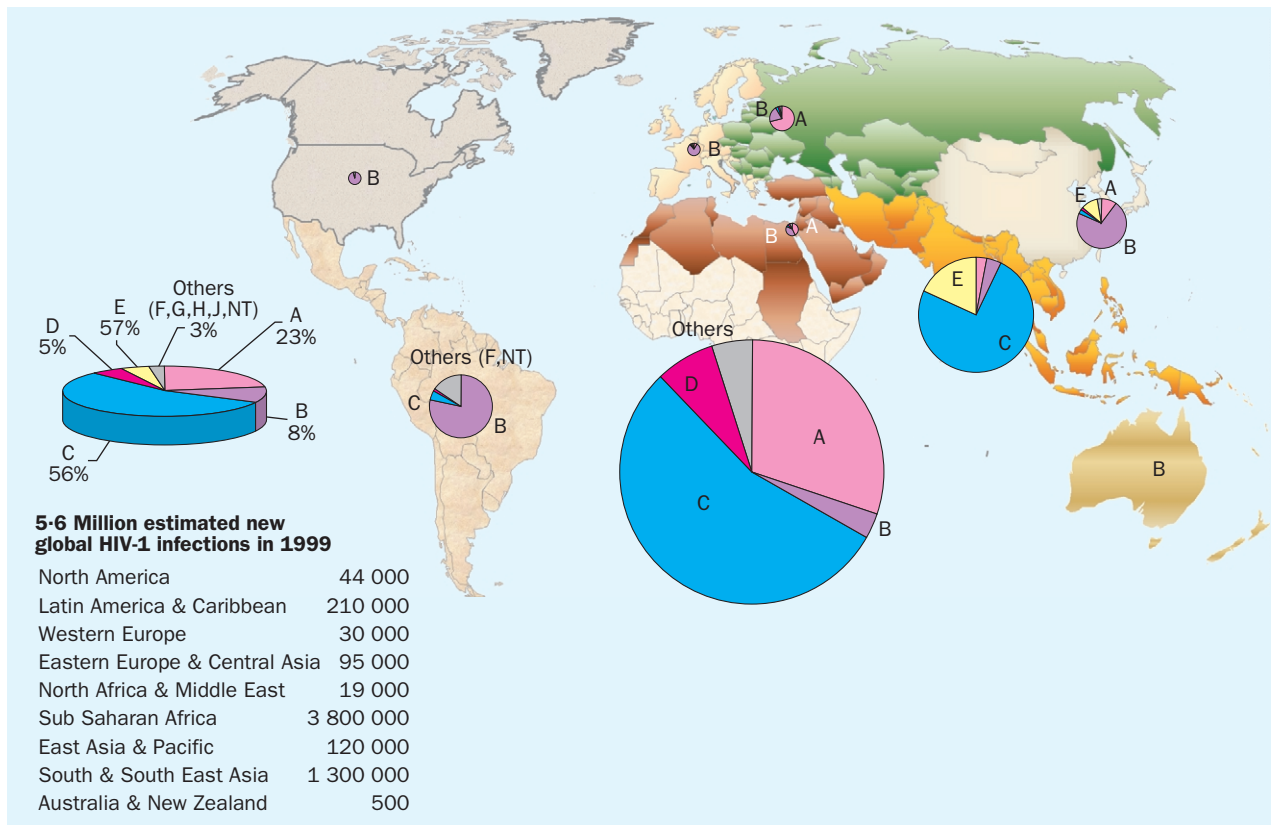


Figure 2: Distribution of incident HIV-1 env subtypes globally and by region (1999)

**The role of less-developed countries**

Multiple vaccine trials, including phase III trials, will have to be done in parallel to assess the protective efficacy of different candidate vaccines against different virus subtypes, and in populations that may differ in the route of transmission of the virus, or in genetic or health backgrounds. These trials will need to involve multiple partners from more-developed and less-developed countries,<sup>33</sup> and from the public and private sectors.

Trials in less-developed countries should be undertaken by local scientists, with the necessary collaboration from international partners, and with the full participation of local communities. Agencies and institutions should collaborate with host countries, to help strengthen the human and material infrastructures that will be needed to carry out trials that conform to the appropriate scientific and ethical standards.<sup>34-36</sup> Due attention should also be given to new concepts of developmental ethics and beneficiary justice.

Although decisions about HIV-1 vaccine trials will be the sovereign decision of each host country, a regional approach could facilitate the process by providing peer support and understanding. In addition, less-developed countries could pool their expertise and facilities together toward the common goal of allowing vaccine trials and future vaccine use.<sup>37</sup> A regional approach is being pursued by WHO-UNAIDS to assist in the development of a comprehensive African Strategy for AIDS Vaccines, as a technical component of the recently established International Partnership against AIDS in Africa (see website: [www.unaids.org/about/governance/files/PCB9-00.4-E.doc](http://www.unaids.org/about/governance/files/PCB9-00.4-E.doc)).

Different partners may have diverse motivations for their participation in the global effort to develop HIV-1

vaccines, including the acquisition of new scientific knowledge, profit, or public-health needs. They may also have different needs as regards visibility, funds, and desired roles. However, the tragedy of the AIDS pandemic imposes an obligation to approach this mission with an honest spirit of collaboration, avoiding unnecessary competition, duplication, or waste of limited resources, focusing on the urgent need to develop a safe, effective, and affordable vaccine.

**What should we do once we have an effective HIV-1 vaccine?**

The first opportunity to have an HIV-1 vaccine may be at the end of 2001. Although no-one can predict what would be the level of efficacy of the VaxGen candidate vaccine, it is imperative to plan now how that vaccine should be used if it is found to be effective.<sup>38</sup> Discussions and planning are needed to decide what level of efficacy will merit its deployment. Some early estimates have suggested that even vaccines with less than 60% efficacy could have a positive effect if used in populations with high HIV-1 incidence, especially if other preventive interventions are not widely available.<sup>39,40</sup>

Furthermore, the concept of efficacious vaccine needs to be agreed on. The original paradigm that HIV-1 vaccines need to induce sterilising immunity (completely blocking HIV-1 infection) is being replaced by the concept that vaccines could also be considered effective if they are able to modify infection (reduce viral load), as is the case in most animal immune-protection studies. Lower viral load seems to correlate with slower disease progression and with reduced potential for HIV-1 transmission, although the long-term effects are still unknown.

**Who is doing what?**

To address the many scientific, economic, ethical, and logistical challenges confronted in the search for an HIV-1 vaccine, no single institution or country will have all the answers. Only a truly international collaborative effort will provide the solutions, with different national and international agencies, non-governmental institutions, and the private sector using their comparative advantages. In addition to scientific challenges, which will be solved with necessary research, the financial challenges will require extra political commitment and support from governments, international financial institutions, and the private sector.

- The President of the USA recently pledged additional support to accelerate the availability of vaccines in less-developed countries.
- Additional resources have been committed for HIV-1 vaccine research to the US National Institutes of Health, including funding for its new Vaccine Research Center.
- HIV-1 vaccine research is also being done by other US agencies, including the Walter Reed Army Institute of Research (Rockville, MD), and the Centers for Disease Control and Prevention (Atlanta, GA).
- Research agencies in other countries, especially the Agence Nationale de Recherches sur le SIDA (France), the Medical Research Council (UK), and the National Institute of Infectious Diseases (Japan) are also sponsoring HIV-1 vaccine research.
- The Bill and Melinda Gates Foundation has committed more than US\$1 billion to vaccine activities, including a US\$750 million contribution to the Geneva-based Global Alliance for Vaccines and Immunization.
- The pharmaceutical industry is also rising to the challenge, pledging donations of existing vaccines for less-developed countries, and doing more research to develop new vaccines.
- The New York-based International AIDS Vaccine Initiative is using a social venture capital approach to promote the development of new HIV-1 candidate vaccines for less-developed countries.
- The AIDS Vaccine Task Force of the World Bank recognises that the technology for an HIV-1 vaccine is an international public good, and is exploring financial mechanisms to ensure the equitable distribution of the results from HIV-1 vaccine research, especially in less-developed countries.
- The European Commission is funding HIV-1 vaccine research through EUROVAC, and has prioritised funding for economic studies on HIV-1 vaccines.
- WHO and the joint United Nations Programme on HIV/AIDS recently launched a WHO-UNAIDS HIV Vaccine Initiative, to continue activities initiated by WHO in 1989. The Initiative will focus on international coordination and collaboration, setting international norms and standards, and facilitating the conduct of trials in developing countries, serving as “honest broker”, and assisting in training and capacity building.
- Increasing numbers of less-developed countries, including China, Kenya, South Africa, and India, are assuming the challenge of contributing to the global effort to develop and evaluate HIV-1 vaccines. This is a very positive development, because without their full participation, less-developed countries could be left out of the benefits of future HIV-1 vaccines.

After obtaining positive data from phase III trials, subsequent phase IV effectiveness trials may still be required, to generate information on the best use of the vaccine in public-health programmes. New vaccination strategies may have to be developed, to access the appropriate target population, which in many less-developed countries will probably focus on young adults and pre-adolescent children. An appropriate cost-effective delivery system should be part of the calculation. Phase IV trials could also provide the timeframe that may be needed to scale-up vaccine production for large-scale use of the vaccine.

Many decisions will have to be made concerning whether and how the vaccine should be used, and these decisions might have to be made with substantial levels of uncertainty. Regulatory authorities will have to consider standards for vaccine licensing (ie, level of protective efficacy, virus load modification).<sup>41</sup> Industry will have to decide whether the level of efficacy achieved warrants vaccine production, or whether additional research is needed to improve efficacy. Target countries will need to assess the effect of the introduction of an HIV-1 vaccine in the overall HIV-1 prevention effort. Early planning will also be required to estimate the number of vaccine doses needed, according to different scenarios of vaccine efficacy and vaccination strategies. Financial institutions and international agencies will need to be involved, to explore and initiate mechanisms to support future vaccine production and distribution. In the long term, a comprehensive set of strategies will have to be explored to ensure vaccine availability in less-developed countries, and issues relating to intellectual property rights, transfer of technology, and local production will have to be resolved.

However, we must ensure that vaccines are developed for those residing where the needs are greatest. A disturbing scenario could be drawn from the ongoing VaxGen phase III trial, which uses gp120 proteins based on B and E subtypes. With all the caveats discussed above, an effective subtype B vaccine could be antigenically appropriate for most more-developed countries. If proven effective, the candidate vaccine against subtypes B and E being tested in Thailand could be appropriate for use in most south-east Asian countries. Unfortunately, our present state of knowledge suggests that, even if trials in the USA and Thailand show subtype-specific efficacy, these vaccines will not be appropriate for use in Africa, where subtypes C, A, and D are prevalent, and for which a cocktail-vaccine approach should be considered.

To avoid the scenario that has occurred with other vaccines, in which those people in most need are often the last to receive immunisation, strategic planning is needed to develop purchasing mechanisms and delivery systems. Planning will also be needed to ensure that vaccine use in the northern hemisphere does not jeopardise vaccine availability in the southern hemisphere. This situation must be prevented at all costs. The ultimate irony would be that a vaccine developed in collaboration with less-developed countries could actually contribute to increasing the gap and inequalities that the AIDS pandemic has created.

We thank our colleagues for the many discussions we have had over many years. Some of the concepts expressed in this paper belong to the collective wisdom of the HIV-1 vaccine community, and we do not claim ownership over them. Although we assume full responsibility for the content of the paper, we received useful comments from Barry Bloom, Win Gutteridge, Lisa Jacobs, Saladin Osmanov, Claire Pattou, Peter Piot, and Michael Scholtz.

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