Policy Brief

International AIDS Vaccine Initiative

Developing and Delivering an AIDS Vaccine:

Issues and Answers

This brief provides an overview of the central policy issues that need to be addressed in order to speed the development and delivery of a safe and effective preventive AIDS vaccine. These issues can be tackled through concerted public actions - some of the ways to do so are outlined here. With increased and sustained political will, the global community can reduce by at least half the time that has typically been required for the global discovery and delivery of other vaccines.

AIDS is the greatest public health crisis of our time. Over 40 million people are now living with HIV or AIDS, and 14,000 more people are infected every day.[1] Life expectancy at birth has been reduced by up to 30 years in the hardest hit countries, from 65-70 years to less than 40. The epidemic has had a negative impact on economic growth in Sub-Saharan Africa - one recent study found that AIDS cost the region an estimated 11.7 percent of its GNP[2]. Ending the global AIDS epidemic is one of the greatest moral, technical, and economic challenges of our time, requiring a comprehensive global response that covers prevention, treatment, care and support.

An AIDS vaccine is the best hope to end the epidemic. Prevention programs such as education and condom promotion are slowing the spread of HIV and treatment helps people infected with HIV to live longer but these measures alone will not end the global epidemic. Vaccines to prevent disease rank among the most cost-effective public health interventions ever developed. Vaccines have helped eradicate smallpox, and effectively control many other diseases. A vaccine to prevent the spread of the HIV virus is scientifically possible, urgently needed, and must be a global priority.

[1] UNAIDS/WHO. *AIDS Epidemic Update 2003*. Geneva.
[2] Jeffrey Sachs, Ph.D., et al. *Macroeconomics and Health: Investing in Health for Economic Development* http://www3.who.int/ whosis/cmh/cmh_report/e/pdf/021-128.pdf

A new global paradigm is required to accelerate the development of an AIDS vaccine and assure its rapid distribution to all who need it. The active involvement of governments, the private sector, and community organizations in the North and South is essential to achieving this goal. Reaching this goal will require action on multiple fronts.

I. Accelerating AIDS vaccine Research & Development (R&D)

Where are we in the search for a vaccine?

The good news is that the prospects for the development of an effective AIDS vaccine are improving. Government agencies have raised their investment levels and industry involvement has increased.

As a result, a record number of vaccine candidates are in human trials. Currently, trials of 33 vaccine candidates are ongoing in 19 countries on six continents.

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Despite these advances, twenty-three years into the epidemic only one vaccine, developed by the biotechnology company VaxGen, Inc., has completed the later stage (phase III) trials necessary to determine if the vaccine is effective in humans. While the VaxGen candidate unfortunately failed to demonstrate effectiveness, it did show that large-scale trials for HIV vaccines are feasible. All but two of the remaining vaccine candidates now in trials are in the early stages of testing, and the current pipeline of candidates remains narrow and duplicative, focusing on just one approach to how an effective vaccine might work. New approaches and different candidates are urgently needed.

Further, there is a need for greater investment in developing vaccines suitable for use in developing countries and at affordable prices. And there are insufficient resources supporting clinical trials in developing countries hardest hit by the epidemic, resources which are necessary to determine if a vaccine will be effective in these settings.

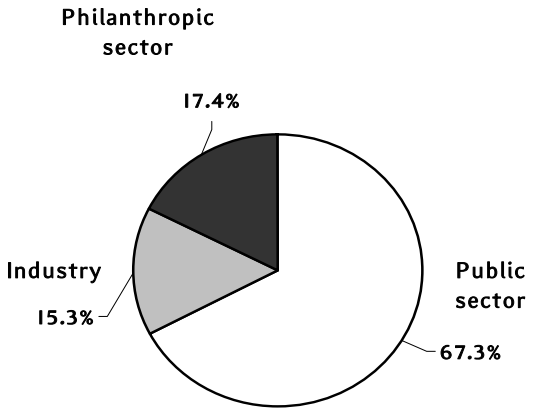
a. Increasing Public Sector Investment in R&D

How much is the world spending on AIDS vaccines?

Total spending on AIDS vaccine (R&D) has grown from roughly US$ 160 million in 1996[3] to an estimated US$ 549 in 2002[4]. But this still represents less than one percent of total global spending on health R&D annually.

About 67 percent of funding for AIDS vaccine research & development in 2002 came from government grants and research agencies, 17 percent from philanthropic sources, with the remaining 15 percent from the private sector (see Figure 1). Ensuring the development of a high efficacy vaccine will require significantly increased spending. IAVI has called for a doubling of resources to approximately US$ 1 billion per year.

b. Creating Incentives to Increase Private Sector R&D



Investment in AIDS vaccine R&D by Sector

Public sector sources such as international development agencies or national scientific research institutions account for the majority of funds invested in AIDS vaccine research.

*Includes a US$100 million multi-year challenge grant from the Bill & Melinda Gates foundation paid in a lump sum, which is expected to be spent over several years.

Source: IAVI. *Global Investments and Expenditures on Preventive HIV Vaccines: Methods and Results for 2002*. 2004

Why do we need the private sector to be involved?

Most vaccine product development expertise rests in private sector vaccine companies. These companies have traditionally played the leading role in translating important basic research - which is mostly carried out by government research agencies and academic institutions - into vaccines that can be manufactured at large scale for commercial use. But in the case of AIDS vaccines there is little incentive for private companies to invest in vaccine R&D. The potential market for an AIDS vaccine in industrialized countries is limited and the largest demand will be in countries least able to pay. As a result, industry faces a series of obstacles including scientific challenges, long development timelines and the lack of a paying market for AIDS vaccines, all of which could lower the return on investment.

[3] Rockefeller Foundation. *Accelerating the Development of Preventive HIV Vaccines for the World.* Summary Report and Recommendations of an International Meeting. Bellagio, Italy. March 7-11, 1994.
[4] IAVI. *Global Investments and Expenditures on Preventive HIV Vaccines: Methods and Results for 2002*. New York. 2004.

What can be done to increase private sector R&D?

Given the clear added value of industry expertise and the economic and social benefits of an AIDS vaccine, public policies aimed at increasing private sector involvement are critical. A combination of "push" and "pull" mechanisms is needed to spur new vaccine development. "Push" mechanisms support the immediate cost of R&D through subsidies and other incentives for private companies. "Pull" mechanisms provide an advance guarantee from funders that resources will be available to purchase and deliver a vaccine once it is developed. One challenge to effectively increasing industry involvement, however, is to create incentives that will be seen as sufficiently attractive to industry on the one hand, and politically feasible on the other (i.e., not seen as an unfair give away to financially successful pharmaceutical companies).

Push mechanisms

i) Government grants or contracts

According to a number of industry representatives, one of the best ways to increase pharmaceutical and biotech company involvement is through direct financial support for AIDS vaccine R&D, which helps to reduce the financial risk for the developer "up front". This may, in fact, be essential to increasing the R&D efforts of biotechnology companies, as many of them have difficulty raising funds to support AIDS vaccine R&D. While many governments provide direct support through grants or contracts, more is needed.

ii) Intellectual property

Intellectual property (IP) is the lifeblood of industrial investment in research. The need to protect IP rights as an incentive for private sector investment, however, must be balanced with the need to assure global access to life-saving health products. Several options have been proposed to address IP issues. In exchange for funding from public-private partnerships, philanthropic organizations and other funders, companies have entered into agreements that would allow them to retain rights to license the vaccine in wealthier markets but require them to sell at a much lower price or hand over to a non-profit development institution the rights to manufacture and sell the vaccine in poor countries.[5] Licensing arrangements and technology transfer between product developers and low-cost producers in developing countries could also accelerate large-scale vaccine manufacture.

iii) Tax incentives

Tax incentives are another option for spurring private sector investment. The United Kingdom has already implemented a tax credit for spending on R&D for vaccines and drugs against malaria, tuberculosis and strains of HIV/AIDS prevalent in developing countries, and Belgium and the United States have considered similar measures. The impact of these tax incentives now needs to be evaluated. Tax credits, however, are of limited use for biotech companies, many of which are unlikely to have revenue from current sales.

iv) Public support to prepare for clinical trials

The public sector can also assist in reducing the timeline and cost of development, by improving clinical trial infrastructure and regulatory and licensure measures in developing countries, and by supporting epidemiological analyses, which provides information needed for conducting AIDS vaccine trials.

Box 1.

R&D incentives in the United States for bioterror countermeasures

The Project Bioshield Act of 2004 ratified in the United States includes a package of incentives for accelerating the development of counter-measures against bioterror agents. This could set an important precedent for incentives for vaccines and drugs against AIDS and other diseases. The legislation includes: increased federal flexibility in awarding R&D grants and contracts to private sector developers, raising the per-contract cap from $100,000 to $25 million; measures to expedite the procurement and peer review process for these products; purchase pre-commitment market guarantees (up to $5.59 billion); and an allowance for emergency use of new products prior to FDA regulatory approval.

The pharmaceutical industry, however, is reportedly less than enthusiastic, and US Senators Lieberman and Hatch have drafted a "Bioshield II" bill that contains more robust, but also more controversial, incentives.

[5] P.M. Danzon. "The Economics of Parallel Trade" Pharmacoeconomics, 1998; 13:293-304.

Pull Mechanisms

v) Market guarantees
The establishment of advance "purchase commitments" has been proposed to increase private sector investment. This involves a pre-commitment by donors to buy an effective vaccine if and when it is actually developed, up to a specified quantity and at a certain price per dose. Detailed model contracts have been developed and are being discussed. Some industry representatives have expressed interest in such market incentives.

vi) Purchase and delivery of existing vaccines
Supporting the purchase and delivery of existing vaccines is another pull mechanism that could help assure industry that there will be a market for AIDS vaccines in developing countries. The Global Alliance for Vaccines and Immunization (GAVI) is facilitating such work with funding from the Global Fund for Children's Vaccines. This fund currently has raised over a billion dollars to buy a range of childhood vaccines, and to build a market and strengthen vaccination infrastructure in poor countries. GAVI and the Vaccine Fund have had a positive impact on the number of vaccine suppliers active in the global market.

c. Preparing for Clinical Trials in Developing Countries

Why do we need to test vaccines in developing countries?

As there is no perfect animal model or known laboratory procedure to predict efficacy, only testing vaccines in humans will determine what works. In addition, as the virus strains circulating in different parts of the world vary, as does the genetic make-up of individuals, vaccine candidates must be tested in different populations and regions. Therefore, trials must be conducted in developing countries, which account for over 95% of all infections. Conducting clinical trials in partnership with the countries where a vaccine is needed most will help to build ownership of the vaccine and ensure that local needs are met, paving the way for eventual access.

How can we address the challenges involved with conducting efficacy trials in developing countries?

Conducting large-scale efficacy trials in developing countries requires significant preparation, including the recruitment of thousands of volunteers at high-risk of HIV infection. To facilitate recruitment, education and advocacy campaigns are necessary to increase knowledge and understanding of the potential benefits and risks associated with participation, and to prevent potential discrimination against trial participants within the community due to their perceived association with HIV. Trials must always be conducted in an open and ethical manner. Failure to adequately prepare communities or to communicate openly about the trial could result in a loss of crucial public support for vaccine research.

To effectively support clinical trials, more research and healthcare infrastructure is urgently needed. This includes training of local researchers and staff; development of informed consent processes and institutional review boards; counseling for volunteers and families; construction of laboratory facilities; and development of health services and referrals, including agreements on treatment for volunteers who may become HIV-positive during the course of the trial.

This challenge calls for a partnership between researchers, political leaders, community-based organizations and affected communities to initiate community outreach and education in the trial area at least one year in advance. Vaccine-related social behavioral research is also needed to assure that vaccine trials are well designed and to assess if and how vaccination may impact risk behavior. Such research can also inform the design of future delivery systems to facilitate high uptake of vaccines.

Clinical trials infrastructure and political support for such trials is currently being built in a number of developing countries. Vaccine "literacy" and awareness campaigns are under way in East Africa, for example, to persuade politicians and local communities about the importance of such trials. Several networks of clinical trials sites are also being developed in Africa, Asia and Latin America, with donor support. These efforts need to be stepped up in the coming years.

II. Ensuring Swift Global Access to AIDS vaccines

Formidable barriers also stand in the way of rapid global access to a vaccine once it is available. Historically, vaccines have taken up to 20 years or longer to reach low-to-middle income countries where they are most needed. For example, a vaccine against hepatitis B has been available since 1981; however today approximately 60 percent of the world's children still do not receive this potentially life-saving vaccine. And the experience with AIDS treatment shows what can happen if planning for access is not started well in advance. (Annex 1 presents more details of a typical timeline for vaccine product development and access.)

a. Preventing Unnecessary Delays in Regulation of AIDS vaccines

What's wrong with current regulatory systems?

Regulatory oversight is necessary to assure that only safe and effective products reach the consumer. But today's regulatory systems are not geared to facilitate rapid global access to AIDS vaccines. Traditionally, there is a gap of several years between initial licensure in an industrialized country and widespread licensure in developing countries.

What can be done to accelerate licensure of an AIDS vaccine?

Products are usually tested and approved in different markets sequentially, not simultaneously. This is largely due to economic factors, including the size and purchasing power of the intended market, as well as the cost of submitting licensure applications.

The process of approval and the data required to obtain this approval vary between countries. As a result, vaccine developers are required to prepare and submit multiple applications. This can cause significant delays and higher vaccine development costs.

Action by regulatory agencies to streamline and coordinate dossier requirements and submission processes and develop fast track approval for life-saving products would significantly accelerate access and lower costs. Some progress has been made in standardizing regulatory approaches in Europe, Japan, and the United States, but more can be done to expand such harmonization efforts.

What can be done to improve regulatory capacity in developing countries?

Regulatory authorities in many low and middle-income countries have little experience and insufficient resources to review and approve new products, and as a result typically rely on prior approval by regulatory agencies in industrialized countries. The capacity of national and regional regulatory agencies in developing countries needs to be significantly strengthened, with technical and financial support from donor countries and multi-lateral agencies. In addition, countries with similar epidemiological and population characteristics could benefit by pooling their regulatory expertise. Some national regulatory agencies have expressed interest, and the World Health Organization (WHO) and others have begun to look at potential ways to facilitate such collaboration.

The European Medicines Agency (EMEA) has recently been given a remit to evaluate products that would not be used in the EU, but may be appropriate for some developing countries that lack evaluation capacity. This would be carried out in collaboration with WHO and country experts and could be helpful in supporting developing countries in making their own licensing decisions.

How effective will an AIDS vaccine need to be in order to be licensed?

An assessment of the potential benefits and risks of using a vaccine, which affects whether or not a product is approved, must be made by taking into account the local HIV burden. Methods for assessing such risks are urgently needed. Mathematical modeling shows that a vaccine that only protects some of the people who receive it could still have an important impact in reducing the epidemic in high incidence countries if administered to a large segment of the population. Locally appropriate risk benefit assessments can help ensure that such partially effective vaccines that are safe and would have a positive impact in controlling the epidemic could receive licensure.

Have the necessary guidelines and standards been developed to ensure licensure of an AIDS vaccine?

Several candidate vaccines in development incorporate new technologies for which no international consensus exists on how to assess safety, efficacy, and quality. Regulatory agencies in developed and developing countries need to come together to seek agreement on key scientific issues necessary for clinical trial and product licensing approval. Although there have been some efforts to address these issues, much more is needed. Meetings between regulators and vaccine developers show there are considerable challenges ahead in reaching consensus on guidelines for assessing AIDS vaccines. The WHO has played a leading role in this area.

b. Assessing the Potential Demand for and Use of a Vaccine

How many people will want to be vaccinated?

Estimating the number of people who would potentially benefit from an AIDS vaccine, the number of people willing to be vaccinated, and the willingness of national governments and the international community to support vaccine purchase and delivery costs are critical to planning for manufacturing and delivery. Such estimates and assessments will need to be considered in advance on a national, regional and global scale.

No vaccine is 100 percent effective. For the earliest AIDS vaccines, the degree of protection from infection will influence its uptake. Vaccines with high efficacy and a good safety profile are likely to be used more readily and widely. Assessments of the potential impact of a vaccine, taking into account both the local epidemic (e.g., rate of infection) and a vaccine's potential level of efficacy, can help determine which populations may benefit from its use and contribute to appropriate public financing decisions and related delivery strategies.

Some other key factors influencing individual and government demand include price, the duration of vaccine protection, number of doses required, socioeconomic factors (such as economic status, level of education, age, and perceived risk of infection) and the state of the current delivery infrastructure in different settings.

Individual, community and government perceptions of the need for a vaccine will also significantly affect acceptability and use, as could fears, myths and rumors about the vaccine (i.e., unfounded worries that the vaccine may cause infection). These issues need to be adequately addressed through local education and advocacy campaigns.

c. Developing Financing, Pricing, and Procurement Mechanisms

How much will it cost and who will pay?

Billions of dollars will be needed to purchase and deliver AIDS vaccines in low and middle-income countries affected by the epidemic. While some people will be willing and able to pay to be vaccinated, much of this funding will need to come from donor governments, multinational funding bodies like the Global Fund to Fight AIDS, TB and Malaria, and multilateral organizations like the World Bank. A vaccine funding pool that bulks together financial commitments could be one solution.

How much should developing countries pay?

Appropriate pricing mechanisms are also needed. Tiered or differential pricing based on a country's ability to pay is one solution that has been used effectively for many other health products. Tiered pricing enables lower-income countries to receive lower prices, while governments and consumers pay more in wealthier countries. In this way, the private sector can obtain a reasonable overall return. It is also essential to improve procurement procedures for AIDS vaccines, so that supply requests last for several years and are backed by reliable payment from governments and donors.

d. Producing Sufficient Supply of Vaccine to Meet Global Demand

Will companies manufacture enough vaccine for the developing world?

Ensuring sufficient manufacturing capacity to supply vaccines at an affordable price for use by developing countries and soon after the vaccine's approval will require a new manufacturing paradigm. The economics of vaccine R&D and manufacturing have traditionally resulted in long delays in the introduction of vaccines into low and middle-income

countries. Commercial vaccine developers have in the past focused initially on predictable high profit markets in industrialized countries and have only supplied to developing countries much later. Public sector intervention will be necessary if this is to change.

What can be done to speed production to meet global demand?

Manufacturing is one of the most costly components of vaccine development. Building a large-scale facility to produce a sufficient supply of vaccines costs hundreds of millions of dollars and can take four to six years. If vaccine supply is to be ready as soon as possible after a vaccine license is awarded, then investments in bioprocess development (how a vaccine will be produced) and plant design and construction must begin well before the results of efficacy trials are available.

Most public sector and smaller commercial AIDS vaccine developers do not have access to the resources, expertise and facilities to invest in and undertake these essential manufacturing activities. The smaller developers of AIDS vaccines are finding it difficult to obtain good access to this bioprocess expertise and physical facilities. Currently, only large R&D based vaccine companies have all the experience, expertise, and facilities required for bioprocess engineering.

Public policy action is needed to overcome these barriers. Possibilities include using government subsidies to help small vaccine developers buy the bioprocess and manufacturing support they need. Another option is to have donors help to build a special bioprocess facility. Advance purchase contracts may also help to spur production. Once an AIDS vaccine has been proven to work well, donors could also help to move the manufacturing technology to a plant in a developing country, where manufacturing costs tend to be lower.

e. Distributing AIDS Vaccines in Developing Countries

Don't vaccine delivery systems already exist?

Unlike current vaccination programs, which primarily benefit children, initial AIDS vaccination efforts will be geared towards adults and adolescents, populations that are difficult to reach through current delivery mechanisms. Advance preparation is critical to assure that adequate delivery systems are in place when a vaccine becomes available. Several years of lead-time will be needed. A comprehensive delivery strategy must include transportation, venues for delivering vaccines (e.g. clinics, mobile units and community settings), storage facilities, maintenance of the cold chain (if the vaccine requires refrigeration), education and marketing appropriate to specific populations, and linkages between voluntary counseling and testing (VCT) and vaccine delivery. Preparing for access should also include action to build necessary human resources.

As no vaccine will be 100 percent effective, an AIDS vaccine must be combined with other prevention practices, such as condom use and avoidance of needle sharing.

What can be done to make sure a vaccine is used?

Knowledge of AIDS vaccines and their potential benefit will have an impact on whether governments make vaccine introduction a public health priority. It is important that AIDS advocates, community groups and vaccine developers work to increase awareness.

In addition, to make sure that AIDS vaccines are supported by the public and that individuals are willing to be vaccinated, local campaigns will be needed to educate communities on the characteristics, advantages, risks and limitations of AIDS vaccines, and to also address potential discrimination against those who seek to be vaccinated.

III. Conclusion

Efforts to accelerate the development and swift global introduction of an AIDS vaccine must be part of any comprehensive response to the epidemic. Governments in both the North and the South must step up to the challenge imposed by HIV, and mobilize their best human, technical and financial resources for this effort. In particular, they must address the key constraints to accelerated R&D and rapid access to an AIDS vaccine. Expanded political commitment, increased funding, and sound policy choices can all help to overcome these constraints. A number of policy options are outlined in this briefing paper. Others remain to be creatively designed and energetically implemented by governments, the private sector, and civil society, including affected communities and individuals living with HIV/AIDS.

About IAVI: IAVI (www.iavi.org) is a global not-for-profit organization working to accelerate the development of a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI also works to assure that a vaccine will be accessible to everyone who needs it. IAVI's major financial supporters include the Bill & Melinda Gates Foundation; the Rockefeller, Sloan and Starr foundations; the World Bank; BD (Becton, Dickinson & Co.); the European Union; and the governments of Canada, Denmark, Ireland, the Netherlands, Norway, Sweden, the United Kingdom and the United States.

Policy Brief
The Policy Brief series outlines key public policy issues in the research, development and eventual distribution of HIV vaccines.
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