

## THE SEARCH FOR AN HIV VACCINE

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HIV infections and deaths from AIDS continue to ravage many countries around the world, with most infected people living in the poorest nations.<sup>1</sup> In terms of morbidity and mortality, the HIV/AIDS pandemic is worse than the Black Death of the 14th century. The search for an HIV vaccine was seen as the logical solution to the burgeoning epidemic soon after the discovery of HIV, but early enthusiasm became muted as the realities of the challenge became evident.<sup>2-4</sup>

Nevertheless, there are scientific reasons why there is hope that an HIV vaccine will ultimately be developed. Firstly, studies of non-human primates that were given candidate vaccines based on HIV or SIV (simian immunodeficiency virus) have shown either complete or partial protection against infection with the wild type virus.<sup>5,6</sup> Secondly, successful vaccines have been developed against other retroviruses.<sup>7</sup> Thirdly, almost all humans develop some form of immune response to HIV infection, with some exposed people remaining uninfected or developing immune responses that are protective or that are able to control the viral infection over long periods.<sup>8</sup> Some people have remained free of disease for up to 20 years, often with undetectable viral loads.<sup>9,10</sup> A group of sex workers from Nairobi and South Africa has remained HIV-negative despite continuing high-risk exposure; resistance to HIV infection in these people is thought to be due to their ability to mount protective immune responses to HIV, rather than to any innate host genetic factors.<sup>11,12</sup> This group has provided insights into strategies for developing a vaccine.

### WILL AN APPROPRIATE HIV VACCINE EVER BE DEVELOPED?

The answer to this depends on a complex interplay of politics, science, institutions and their organisation, and public-private partnerships.

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### POTENTIAL DEVELOPMENTS

An effective, affordable, and accessible HIV vaccine is within reach

Equitable public-private partnerships between researchers, manufacturers, and distributors and partnerships between rich and poor countries are the best strategy for the development of the vaccine

Successful vaccine development entails adequate investment in the countries that carry the burden of the HIV/AIDS pandemic

If we fail to provide the world with an effective HIV vaccine, future generations will judge us harshly, because this failure will be due not to lack of ability or resources but to politics

### POLITICS

Many political realities will need to be accepted if the global health community is to develop an HIV vaccine:

- Vaccines are a public good and should be supported worldwide.
- Rich countries have the expertise and experience to develop and test HIV vaccines but do not have sufficient numbers of patients to conduct clinical trials of efficacy.
- Most poor countries have poor infrastructure and inadequate resources to conduct major trials of an HIV vaccine but are fertile ground for such trials. Thus, rich and poor nations are obliged to co-operate in the successful development of an HIV vaccine.
- Any trial of an HIV vaccine must take into account the history of exploitation and abuse of vulnerable people in clinical trials. All research has the potential to introduce unequal power relations between the researchers and the trial participants, particularly when the researchers are from a rich nation and the participants are from a poor nation.
- Rich countries want to do research in poor countries. Poor countries often have weak research infrastructure and regulatory institutions, allowing rich countries to exert more control over the research and over intellectual property rights.
- Most countries lack the political will and commitment – reflected in inadequate investment – to develop an HIV vaccine.

## SCIENCE

The current impressive knowledge of the genotypic, phenotypic, pathological and clinical aspects of HIV/AIDS reflects the substantial scientific discourse that has occurred around the world over the past two decades. However, the current knowledge base remains inadequate, in that it has failed to elucidate the most critical item on the HIV vaccinologist's wish list: the correlates of protection against HIV. Until these are defined with accuracy, as has been the case with other infectious agents, such as hepatitis B, the required 'height of the high jump bar' will remain speculative.

Another problem is that animal models for investigating candidate vaccines are inadequate. Results from studies of candidate vaccines in small animal models are invaluable, but their applicability to the development of an HIV vaccine in humans may be tenuous. Products that have an acceptable safety record in animal studies should be used as rapidly as possible in human studies, because human studies will give critical insights into the potential success or failure of a vaccine that far outweigh those from any animal data.

## INSTITUTIONS

Science has traditionally moved relatively slowly and cautiously in the transition from laboratory development of new agents to commercialisation. Yet in the case of HIV vaccines the scientific community is, for humanitarian reasons, under pressure to move with urgency. The scientific and corporate communities are being asked to 'think out of the box' and to break down traditional modes of operations, while still maintaining the highest values of science and ethics, in developing an HIV vaccine.

For almost a decade after the discovery of HIV a concerted and co-ordinated international effort to produce a vaccine was slow to develop. But a number of initiatives have helped to create a scientific framework for rapidly testing hypotheses and products. The International AIDS Vaccine Initiative (IAVI), whose mission is the development of and worldwide access to an HIV vaccine, has helped to keep the need for a vaccine high on the agendas of many governments. Following from IAVI's advocacy, changes in the scientific priorities of traditional institutions, such as the National Institutes of Health, the WHO, and the European Union's HIV vaccine platform, have also helped, as has the establishment of regional vaccine development programmes in poor countries, such as the South African AIDS Vaccine Initiative.

This new framework gives the public and private sectors the chance to become partners in getting important academic, financial, and logistic support. Effective co-

ordination, maintenance, and expansion of these structures are essential. Equally important is the need for co-operation among these international bodies, to ensure that the efforts are not inhibited by organisational pride, traditions, or the desire to be first.

Levels of political will to support global initiatives to develop an HIV vaccine will largely determine the rate of their progress and success. Such political support will need to come from the highest levels of government and from global bodies such as the United Nations. Vaccines are but a part of the message of prevention that all governments should be endorsing, along with progressive policies on sex education, condom distribution, needle exchange programmes, and appropriate treatment. State and private sector funding of national and international vaccine programmes should be given the highest priority.

Political support for these programmes needs to be independent of other international crises. For example, our response to the events of 11 September should not deflect attention from the urgent need to develop a vaccine against the greatest threat ever to humanity from an infectious disease. Yet compare the rapid and committed response by the US government to the threat of anthrax with many governments' lack of support for development of an HIV vaccine over the past two decades.

## PUBLIC-PRIVATE PARTNERSHIPS

Political processes should seek to maximise the synergies between government and the private sector through public-private partnerships. Over decades the private sector has been the mainstay of vaccine production and distribution, and thus the private sector's expertise needs to be harnessed to produce and distribute an appropriate HIV vaccine.

Vaccines have never been as commercially successful as other medical treatments, and so entering the field of HIV vaccine development is a risk for companies. Most of the initial uptake of an effective vaccine will have to be in countries with a high prevalence; and as these countries are heavily indebted, they will not have the resources to buy and distribute the vaccine. Governments of the rich countries will have to work with IAVI, the World Bank, the United Nations, the WHO, and the private sector to ensure that commercial guarantees are in place to give the private sector an incentive to move into this field. These commercial agreements will have to give attention to:

- Setting limits on exploitation of intellectual property
- 'Guaranteed' markets
- Price controls in poor countries
- Limiting liability in the event of a small number of adverse events (such as with polio), and
- Ways to increase global manufacturing capacity.

Equally important will be the need for all countries, irrespective of wealth, to develop strategies to incorporate HIV vaccines into national vaccination programmes.

## WHAT WILL WE DO WITH AN HIV VACCINE?

### TARGET POPULATIONS

Even when we do develop an HIV vaccine, there is no guarantee that it will be used appropriately. This is why we should determine the rules for access to and distribution of the vaccine before making it widely available. The rules for distribution of an HIV vaccine must break with the present rules for access to new drugs and vaccines whereby priority is given to wealthy nations and people, who do not bear the burden of this disease. We see this problem in the current unequal access to antiretroviral drugs. HIV vaccines must be given firstly to the poorest and most vulnerable people in our global society. This will be a difficult challenge, as our current experience with polio vaccines in poor countries has shown, where warfare and social dislocation have often prevented the distribution of vaccines.

High-risk populations in rich countries will also need to be targeted. Commercial sex workers, high-risk gay men, haemophiliac people, injecting drug users, and children born to HIV-positive mothers will need to be protected (or partially protected) by these vaccines.

To ensure adequate manufacture and distribution of the vaccine, we will need accurate measures of the numbers of people in different regions that will require vaccination. This will be a difficult task that will need to involve governments and society.

How the vaccine will be used initially will be determined by the rates of full and partial protection given by the early generation of vaccines. If the early vaccines offer only marginal protection, there may be reason to use these only in high-risk groups and then wait for more successful vaccines to be developed for use in lower-risk groups. The same principle applies to any major side-effects: these will be tolerated by and be acceptable to low-risk populations only in the setting of very high predicted levels of protection.

Timing of administration of HIV vaccines will be complex and will need to take local factors into consideration. Decisions will need to be made whether to include HIV vaccines from birth in an expanded immunisation programme or whether to wait until pre-adolescence (or whether to immunise at both ages). Data on protection in these two settings of vertical and sexual transmission will help in these decisions.

### SUBTYPES OF HIV

The number of described HIV subtypes increases constantly, and their relevance to protective immunity remains unresolved. The possibility of immune responses to specific subtypes will continue to haunt HIV vaccinologists until adequate data confirm or deny that cross-protection can occur between subtypes. This matter will be difficult to deal with once a successful vaccine is identified in one or more geographical areas. For example, if a vaccine developed from the subtype B virus was found to be successful in an efficacy trial in the US, will this product then be seen as a compulsory alternative to a placebo arm in another study in a region in which subtype C is predominant? Because of their regional distribution, HIV subtypes have assumed a political and national importance, which could interfere with important international trials of efficacy.

### CONCLUSION

It is generally agreed that the development of an affordable, appropriate, and effective HIV vaccine is within reach – within 7 - 10 years. Vaccines are the only hope for the control and possible elimination of HIV infection, as was the case with smallpox and polio, which have been fully or partially eliminated by global vaccination programmes. How we distribute the vaccine will be a test of our international ethics and humanitarian objectives, and our generation will be judged by its success or failure in making a vaccine and ensuring equitable access to it.

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