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# HIV Vaccine Research & Development: Modeling the Path to Speedier Success

International AIDS Vaccine Initiative
and
The Bill & Melinda Gates Foundation

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This paper is a joint collaboration between the International AIDS Vaccine Initiative and the Bill & Melinda Gates Foundation. It was written by Holly Wong (IAVI), Chris Gingerich (University of Pennsylvania), Josh Michaud (Johns Hopkins University), and Katherine White, and edited by Patricia Kahn.

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To request additional print copies of this working paper or other information from IAVI please contact:

Publications Unit
International AIDS Vaccine Initiative
110 William Street, 27th Floor
New York, NY 10038 USA
Tel: + 1.212.847.1111
Fax: + 1.212. 847.1112
Email: pubs@iavi.org
Web: www.iavi.org

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# HIV Vaccine Research & Development: Modeling the Path to Speedier Success

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*IAVI's Policy Research Working Paper series disseminates important new research findings in order to promote the exchange of information and ideas that facilitate the effective development and global distribution of vaccines to prevent HIV infection.*

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## Acronyms and Abbreviations

| | |
|---|---|
| AIDS | Acquired Immunodeficiency Syndrome |
| BMGF | Bill & Melinda Gates Foundation |
| CAVD | Collaboration for AIDS Vaccine Discovery |
| CHAVI | Center for HIV/AIDS Vaccine Immunology |
| FTE | Full-time equivalent |
| HIV | Human immunodeficiency virus |
| HPV | Human papilloma virus |
| HVTN | HIV Vaccine Trials Network |
| IAVI | International AIDS Vaccine Initiative |
| IP | Intellectual property |
| MMV | Medicines for Malaria Venture |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health (United States) |
| POC | Proof of Concept |
| PD PPP | Product Development Public-Private Partnership |
| PV | Present value |
| R&D | Research and Development |
| RF | Rockefeller Foundation |
| TB | Tuberculosis |
| UNAIDS | The Joint United Nations Programme on HIV/AIDS |

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## Executive Summary

Developing a safe, effective HIV vaccine is one of the most urgent challenges ever to face international health research, since a vaccine offers the best long-term hope for reversing the AIDS pandemic and thereby saving millions, probably tens of millions, of lives.

However, the past two decades of steady but slow progress have shown that it is also one of the most difficult undertakings in science and international health, due mostly to the extraordinary ability of HIV to evade the immune system. So, despite major scientific advances in understanding HIV and AIDS during this time, most scientists now believe that it will take a number of additional years to design, test, and then manufacture on a large scale an HIV vaccine that meets the minimum standards for efficacy and duration of protection. In the best circumstances, a modestly effective vaccine may demonstrate "proof of concept" (POC) between now and 2008, but such a vaccine would still require several more years for additional testing and build-up of manufacturing capability before becoming widely available. If today's leading vaccine candidates perform poorly in these POC trials between now and 2008, scientists believe that it will take many more years to produce a successful vaccine to stop AIDS.

This long and unpredictable timeline creates its own set of problems. One is that it becomes more difficult to make meaningful estimates of how much funding will ultimately be needed. Another is that it complicates decision-making on how to use available funds most effectively, since it is hard to assess the impact of a particular action on the pace of the vaccine development process. Even so, as funders respond to calls for increased spending on HIV vaccines, it is critical to ensure that new monies are used in ways that can accelerate progress the most.

Against this background, the International AIDS Vaccine Initiative (IAVI) and the Bill & Melinda Gates Foundation (BMGF) launched a joint project to tackle these issues by taking portfolio modeling, a tool commonly used in the pharmaceutical and biotechnology industry, and applying it to the entire HIV vaccine development effort. This kind of modeling is a method of choice for decision-making in drug and vaccine development projects that involve many uncertainties and multiple factors.

In this study, we applied portfolio modeling to answer the following questions:

- Which activities are most likely to shorten the timeline for developing an effective HIV vaccine?
- How much time could be saved?
- How much will these vaccine "acceleration" activities cost?

Our approach identified the factors that most strongly affect the pace of HIV vaccine research and development (R&D), made the best possible estimates of the magnitude and impact of those factors, and used these numbers as input to the computer simulation model. The model then calculated the likelihood that an effective product would be developed and licensed within various time periods. We performed this analysis for the existing clinical development pipeline and for two scenarios in which increased funding channeled to carefully chosen activities is assumed to have led to improvements in the

development pipeline (referred to as the Status Quo, the Low-Improvement scenario, and the High-Improvement scenario).

The factors included in this analysis were the number of vaccine candidates currently in clinical development, the number of new candidates entering clinical development each year, the quality of these candidates (i.e., the chance that they will be successful), the duration of each clinical trial phase, and the cost of each phase. We based the costs of the Low- and High-Improvement scenarios on estimates of the additional investments required for applied research, clinical trials capacity, and other activities as identified by the HIV Vaccine Enterprise under its Scientific Strategic Plan. These investments were assumed to be incremental to the roughly $700 million already being spent annually on HIV vaccine R&D worldwide.

We estimated some of these data from current HIV vaccine research experience (e.g., the number of new candidates each year) and/or data from other vaccines. Other data reflect educated guesses by experts in the field consulted for this project—for example, defining a high-quality candidate remains uncertain as long as scientists do not know which immune responses a vaccine must induce in order to protect against HIV/AIDS.

These unknowns represent one important limitation of this analysis. Another is that the model cannot incorporate the potential effects of scientific discoveries that move the whole field forward, since discovery cannot be predicted or mandated to occur. Nevertheless, this type of modeling can be a valuable tool for thinking systematically about the main bottlenecks to faster progress, the key actions and investments needed to remove those bottlenecks, and their cost and potential impact on the timeline for achieving an effective product.

Our main findings and conclusions are the following:

**1. Investments that target critical bottlenecks in the pipeline, made alongside changes in the organization and management of vaccine R&D, can potentially reduce the time until an effective vaccine becomes available.** Under our more optimistic (High-Improvement) scenario, the model predicted a savings of anywhere from 5 to 22 years. Even under the less optimistic (Low-Improvement) scenario, strategic investments could advance the availability of a vaccine by 3 to 17 years. Using recent models of the impact of an HIV vaccine on the pandemic, having a vaccine five years sooner would translate into averting 10 to 15 million infections that would otherwise occur (IAVI, 2005b). Having a vaccine 15 or 20 years sooner would have an even greater benefit in human terms, saving many tens of millions of people from infection, illness, and premature death.

**2. The necessary improvements will come from steps that increase the quality and numbers of candidates in the pipeline, and decrease the time they spend in each clinical testing phase.** Activities most relevant to achieving these changes include intensifying vaccine discovery efforts, standardizing and optimizing laboratory methods used to evaluate vaccines in clinical trials, and reducing regulatory delays. While this list contains the main areas already receiving (or slated to receive) new funding and therefore does not represent new information, our findings point out that actions in these areas are

fundamental to accelerating the vaccine timeline and that future investments should be made with this objective in mind.

**3. Additional annual investment of $200 to $300 million beyond funds committed as of 2005 would be needed to support the necessary improvements.** Given current levels of funding for HIV vaccine R&D, this incremental investment is not unrealistic – and it could yield very large benefits. Indeed, in the long run, by saving time, these new investments may not add significantly to the cumulative cost of developing an effective vaccine, and might even lower it.

This analysis shows a potentially useful way of assessing possible new activities and funding targets in HIV vaccine R&D, in terms of their effects on the key factors in clinical development. More precise and reliable estimates will help strengthen the usefulness of this tool, which should be possible in the coming years as we learn more about the drug and vaccine development process, collect more precise information on other key variables (e.g., average cost of trials, average time in phase, positive effects of targeted research on the quality of vaccine candidates), and gradually accumulate more clinical data on HIV vaccine candidates. Given the continuing need for strategic funding decisions over the coming years, this way of thinking and the modeling approach itself can contribute to rationalizing and improving such decisions, so that the world can obtain an HIV vaccine many years earlier than would otherwise be the case.

# I. Introduction

A safe and effective HIV vaccine offers the best long-term hope for reversing the AIDS pandemic, which killed over 3 million people in 2005 and continues to expand in many parts of the world. Even though it is now over 20 years since efforts to develop a vaccine began, most experts believe that success is still at least a decade away, and possibly more.

Although this timeline often surprises people, it is actually not unusual; most vaccines in widespread use today took several decades (or longer) to develop, as shown in Table 1. In the case of HIV, the virus poses difficult—sometimes unprecedented—scientific challenges to vaccine makers, due to its highly sophisticated mechanisms for evading immune control. So, while it is always possible that a major scientific discovery will dramatically accelerate the pace of HIV vaccine development, the more likely scenario is that the world is still years away from having even a partially effective product.

**Table 1.** Developing vaccines: how long it takes.

| Infectious agent | Year vaccine licensed in U.S. | Year causal link to disease discovered | Years elapsed |
|---|---|---|---|
| Pertussis | 1948 | 1906 | 42 |
| Polio | 1955 | 1908 | 47 |
| Measles | 1963 | 1953 | 10 |
| Hepatitis B | 1981 | 1965 | 16 |
| Haemophilus influenza | 1981 | 1889 | 92 |
| Typhoid | 1989 | 1884 | 105 |
| Varicella zoster (chicken pox) | 1995 | 1953 | 42 |
| Rotavirus | 2006 | 1973 | 33 |
| Human papilloma virus (HPV) | 2006 | early '80's-mid '90's* | 12-25 |
| Malaria | none | 1893 | 112 and counting |
| Human immunodeficiency virus (HIV) | none | 1983 | 26 and counting |

*This range reflects the time from initial identification of HPV in some cervical carcinomas to the point of having conclusive epidemiological evidence for a causal link, in populations around the world.

*Sources:* AIDS Vaccine Advocacy Coalition, 2005; Children's Vaccine Initiative, 1993; Global Alliance for Vaccines and Immunization, 2006; National Institute of Allergy and Infectious Diseases, 1999.

These uncertainties make it difficult to estimate accurately how much time or money it will take to develop an effective vaccine, or to assess how the timeline and costs might be affected by different paths of action during the development effort. Yet without this information, it is harder for vaccine developers to make key decisions on research and development priorities or on how to allocate funding in strategic ways that accelerate and/or maximize the likelihood of success. The field is also deprived of input that could be especially valuable now that the HIV vaccine effort is expanding and many stakeholders are calling for new, more "rational" (i.e., objective and criteria-based) ways of making decisions about the clinical pipeline. Good estimates could also be valuable for sustaining public, political, and financial commitment, which is often difficult to secure when it comes to long-term goals—especially if policymakers, funders, and the public at large are unclear about what success is likely to require.

This project, undertaken by a team with joint support from the Bill & Melinda Gates Foundation (BMGF) and the International AIDS Vaccine Initiative (IAVI), sought to fill this information gap. Our objective was to bring a data-driven approach to analyzing which improvements in the vaccine development effort might accelerate progress the most. These findings can be used to inform ongoing discussions among researchers, funders, and advocates about whether, and how, increased investment can speed up the process. Additionally, they can begin to provide an analytic framework for supporting specific levels of investment, thereby reducing the field's reliance on educated guesses of how much is needed.

We chose to use a simulation model based on a portfolio management approach often used by the pharmaceutical industry to evaluate R&D efforts and to make decisions about resource allocation (Glickman et al., 2006; Schmid, 2004; Tiggemann et al., 1998). For example, Merck's Executive Vice President and Chief Financial Officer, Judy Lewent, has called the company's particular version of this approach "a key planning tool at Merck….and…integral to our strategic decision-making process" (Nichols, 1994).

To gather the information needed for this analysis, our team began by defining the main factors that determine the cost and rate of vaccine development, such as the number of candidate products in clinical evaluation, the average cost and time it takes to evaluate a candidate, the likelihood that a candidate proves worthy of advancing to the next phase, and several other factors (described in the Research Design section and in Appendix 1). This information was the basis for assigning estimated values to each of these factors, using the conservative assumptions that the level of spending on HIV R&D would not change, nor would there be major scientific breakthroughs (and referred to here as the Status Quo scenario). These estimates, in turn, were used as input data to the model. Computer analysis then calculated the probabilities that a successful product will be developed and licensed (referred to in this study as "vaccine debut") within a range of time intervals, given the Status Quo assumptions.

However, the level of investment in HIV vaccine development has risen over the past several years and may continue to grow. The BMGF recently granted $287 million in new funds over five years, while the National Institute of Allergy and Infectious Diseases (NIAID)-funded Center for HIV/AIDS Vaccine Immunology (CHAVI)[1] has committed more than $300 million over seven years. IAVI has tripled its annual investment in the Neutralizing Antibody Consortium from $3 million to almost $10 million in the past year alone and expects this commitment to grow over the next five years. In subsequent steps of our analysis we therefore varied the Status Quo input values to reflect improvements that such new investments would hopefully yield in the vaccine development pipeline; this allowed us to estimate the potential impact of the improvements on the overall time until an effective vaccine is available.

However, it is important to note that this type of modeling has limitations. One is that while breakthroughs in immunology and HIV/AIDS science could significantly improve the design of vaccine candidates (and therefore speed the debut of an effective product),

[1] CHAVI is a new consortium of scientists collaborating on research that addresses some of the main scientific obstacles to HIV vaccine development. It was established through the U.S. National Institute of Allergy and Infectious Diseases (NIAID) in response to recommendations by the Global HIV Vaccine Enterprise, a consortium of independent organizations working to accelerate HIV vaccine development.

the potentially crucial role of these advances cannot be factored into this type of model, since it is not possible to predict when, or even if, such discoveries will occur. Another crucial caveat is that the results can be only as good as the input data, some of which are uncertain—reflecting the lack of sufficient information for making firmer estimates. Nevertheless, as industry's widespread use of this methodology shows, simulation modeling is a valuable tool for helping the field think systematically about the main bottlenecks to faster progress, the key actions and investments needed to remove those bottlenecks, and their cost and potential impact on the timeline for a successful vaccine.

Given these limitations, the main questions addressed by this project were:

- Can improvements to the vaccine development pipeline, catalyzed by strategic investments, accelerate the timeline for making an effective product?
- How much would strategic investments in HIV vaccine R&D shorten the timeframe for developing an effective vaccine?
- What level of investment, if aimed strategically at the critical bottlenecks, would be needed to shorten the vaccine debut timeframe?

The remainder of this report aims to answer these three questions. The main body of the report is geared to the non-expert reader, with additional detailed, technical information presented in Appendix 1.

# II. Research Design

## The R&D pipeline

To estimate the timeframe and costs of developing an effective HIV vaccine, our team customized a computer-based simulation model that derives timeline estimates based on specific assumptions about the main rate- and cost-determining factors during clinical development.

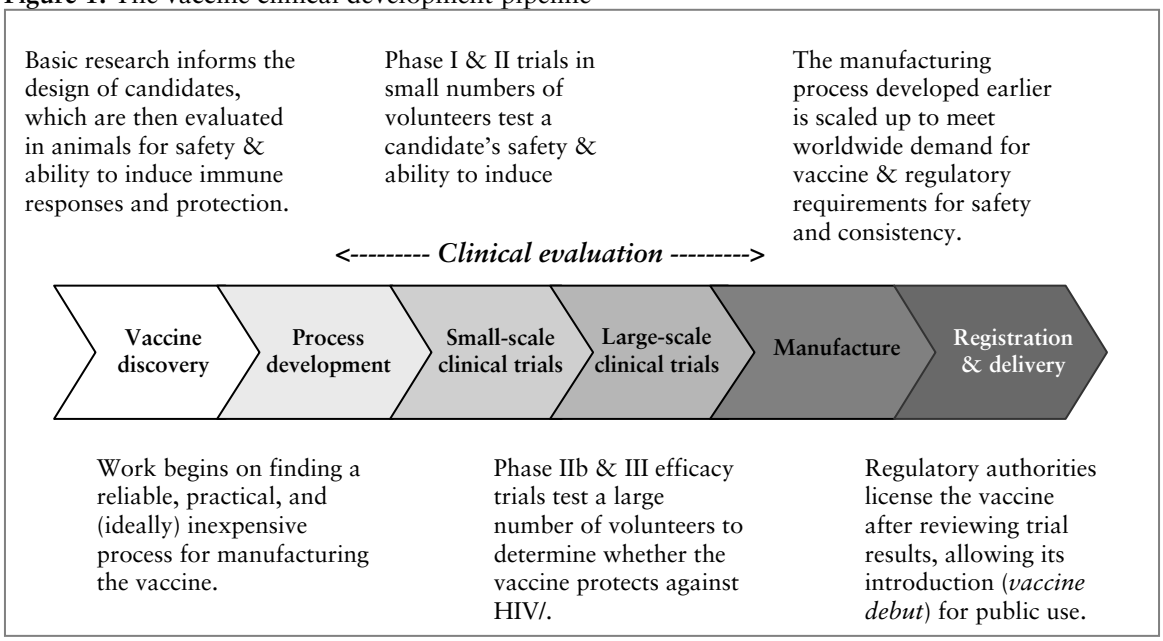
Clearly, no model can predict with great accuracy exactly how long it will take to make a vaccine. Moreover, on the surface, use of an imprecise modeling tool to make important decisions may seem counterintuitive, particularly to laboratory scientists accustomed to more exact measurements. Yet, as any scientist who has developed a product knows, the endeavor almost always involves many variables and a high degree of uncertainty, making it extremely difficult to predict outcomes. Despite these uncertainties, product developers—especially those in the private sector — must frequently make decisions about whether to invest (or continue investing) in a particular product, and if so, in what specific areas.

This need is what drives pharmaceutical companies to incorporate models into the decision-making process as a matter of routine, according to Mike Powell, a venture capitalist specializing in the biotechnology and pharmaceutical sectors (M. Powell, personal communication, March 2005). He notes that such an analytic approach "forces one to take a constructive look at all the steps involved, and think about what the real risks are." Merck's Judy Lewent described the value of the model as "[showing] us not only where we have competency gaps, but also where an increase in resources can help us reach our goals more quickly and where investments with only marginal returns can be cut" (Nichols, 1994).

## Identifying and estimating the key factors affecting the timeline

We began by looking at the three sequential, increasingly stringent clinical trial phases that all successful experimental drugs and vaccines must complete (see Figure 1), with the aim of identifying the factors that most strongly influence the time and cost.

**Figure 1.** The vaccine clinical development pipeline




The five factors we selected are defined in Table 2, below.

**Table 2.** Key pipeline attributes used in this study

| Attribute | Description |
|---|---|
| Current candidates | Number of unique vaccine candidates in each phase of the pipeline as of April 2005 |
| Pipeline flow | Number of new candidates entering Phase I studies in a given calendar year |
| Transition probability | Probability (in %) that a candidate successfully completes a given phase and moves to the next phase |
| Phase cost | Costs of all activities and studies for a candidate during a given phase of clinical trials |
| Time in phase | Estimated duration of each phase (including any delay before the next phase begins) |

In assigning specific input values to these attributes, we based our choices on the best information obtainable through a combination of published sources, historical experience, and expert opinion. (The experts we consulted are listed in Appendix 3.) Data from actual HIV vaccine trials were used when available; when they were not, we drew on data from the development of other vaccines or drugs, making modifications where appropriate through input from experts who helped assess the relevance of these data to HIV vaccine development. Nevertheless, we encountered many instances where there was some uncertainty about the best assumption to make; in these cases, we frequently relied heavily on expert opinion and made the more conservative assumptions (e.g., a longer time in phase or a lower probability of success). A detailed discussion of how we derived estimates for the various attributes under different sets of assumptions (different scenarios) is presented in Appendix 1.

Last, we defined "success" in this study as the development and licensure of a vaccine that prevents HIV infection and/or progression to AIDS in at least 50% of vaccinated people.

This is a relatively low level of efficacy, but one that reflects what could probably be licensed in most countries and therefore potentially represents a "first-generation" vaccine. However, this level of efficacy was not incorporated into the analysis in any direct way; rather, it was specified in discussions with experts about potential timelines and probabilities for success. We did not conduct a sensitivity analysis to determine how the level of efficacy would affect the model's predictions.

## Using the model to estimate the potential impact of improvements in the pipeline

The model was first used to derive a series of estimates based on the Status Quo assumptions. We then devised two alternative scenarios (designated the Low-Improvement and the High-Improvement scenarios) that both assumed more investment, and consequently some improvement in the attributes of the vaccine pipeline. Next, we analyzed the timelines and costs under the two improvement scenarios and compared them with results based on Status Quo assumptions, resulting in a series of predictions about the potential impact of targeted investments and a more robust pipeline.

In all cases, results from the model are expressed as probabilities. This is because incorporation of the uncertainty factor into the model generates results that represent not a single estimate but a range of possible outcomes derived by running the analysis 3,000 times. The likelihood of success is expressed as the probability that a vaccine will be licensed and introduced, and is calculated as the percentage of times in the 3,000 separate computer runs, all using the same input assumptions, that a given result (i.e., success within a given timeframe) was achieved.

# III. Results

## Question 1: Can strategic investments in research and development accelerate the timeline for making an effective HIV vaccine?

> *Investments targeted to critical bottlenecks in the pipeline, along with changes in organization and management of the vaccine effort, can reduce the time until an effective vaccine becomes available. Improvements will come from steps that increase the quality and numbers of candidates in the pipeline as well as decrease the time they spend in each clinical testing phase.*

Investment in HIV vaccine R&D is on the rise. However, it is not clear whether, and to what extent, these investments can be expected to translate into a faster pace of vaccine development, and thereby a shorter timeframe for success.

In this section we describe the main R&D areas being targeted by these new investments and present a qualitative assessment of which pipeline attributes they would affect most. This leads, in subsequent sections, to an analysis of their expected impact on the timeline and cost of developing an effective vaccine.

### Potential areas for investment

Discussions among HIV vaccine experts during 2004 and 2005 led to several key documents describing the major obstacles to HIV vaccine development, which also represent the most promising targets for new investments (Global HIV/AIDS Vaccine Enterprise, 2005a; IAVI, 2004). In particular, the Enterprise plan was developed through a process involving over 140 experts from 15 countries. Building upon the key actions and approaches laid out in that document, we sought guidance from our project's advisory panel and other experts to consider how investments in those selected areas might impact three key attributes of our model. Our focus was on the *relative* impact of such improvements, since it was not possible to directly link the amount of new funding to the precise level of improvement it would produce.

The results and conclusions of this process are summarized in Table 3 and discussed below.

1. **Accelerate vaccine discovery.** The vaccine field has struggled for more than two decades with fundamental scientific questions about HIV/AIDS and the immune system. Investing in research that can help answer these questions should enable researchers to resolve at least some of them — which, in turn, should fuel the design of better candidates with a higher probability of success, and thereby increase the flow of higher-quality candidates into the pipeline. However, the effects of these changes will need time to show an impact, since investments in vaccine discovery are likely to take five to ten years to be translated into new candidates ready for clinical testing.

**Table 3.** Expected impact of strategic investments on key pipeline attributes

| Purpose of investment | Anticipated effect | Pipeline attribute | | |
|---|---|---|---|---|
| | | Time in phase | Prob. of success | Pipeline flow |
| Accelerate vaccine discovery | Improve quality of candidates | - | + | + |
| Optimize & standardize lab tests for evaluating pre-clinical & clinical trials data | Enable comparison of results from ALL vaccine trials → identify best candidates | + | + | - |
| Boost regulatory capacity in developing countries | Reduce delays in regulatory reviews | + | - | - |
| Improve process development & manufacturing capacity | Ensure sufficient supply of consistent, high-quality vaccine lots | + | + | - |
| Expand clinical trials capacity & health care infrastructure in developing countries | Reduce difficulties & delays in testing efficacy of vaccine candidates | + | - | - |
| Resolve intellectual property issues that impede access to materials, methods, & information | Produce better vaccine designs and more easily identify best candidates | - | + | + |

2. **Optimize and standardize laboratory tests.** Even small variations in how researchers carry out laboratory tests during preclinical or clinical studies — for example, how they measure volunteers' immune responses in clinical trials — make it difficult to compare results from different trial networks or sponsors, since most of them use slightly different procedures and reagents. Shifting to a single optimized, validated protocol for each procedure would eliminate this obstacle, making it possible to identify the most promising candidates at each stage of development more efficiently, regardless of where the studies were done — leading to higher-quality candidates and to faster, more efficient evaluation of each candidate. One caveat is that in the absence of known immune correlates of protection, it is not possible to select only one laboratory assay to compare all candidate vaccines. Additional research is needed to understand the potential value of different assays to evaluate immune responses to candidate vaccines and their potential relevance in predicting protective immunity.

3. **Intensify and improve efforts in process development and manufacturing.** Process development, an expensive and often under-appreciated step in vaccine development, encompasses the myriad activities required to develop methods for producing vaccine candidates on a large scale, without which they cannot be made available globally. Equally important is the need for physical infrastructure (manufacturing plants) that can produce vaccines using these optimized processes, including the production of small lots of multiple candidate vaccines to be tested in clinical trials.

   Improvements in process development and manufacture should lead to positive changes in two key pipeline attributes. First, candidates would no longer face delay

or failure due to manufacturing or stability problems, thereby reducing time in phase. Second, ensuring early in its development that a vaccine candidate can be produced in sufficient quantities at the required quality standards would reduce the risk that a vaccine reaches Phase II or III but ultimately cannot be produced at large scale, a change that increases the probability of success.

4. **Expand clinical trials capacity and health system infrastructure in developing countries.** It is crucial to establish sufficient capacity for conducting large-scale vaccine trials in regions of the world that most need a vaccine. Much has been accomplished in the past decade, with trial sites now up and running in 20 countries. Yet more remains to be done. Investments in this area can reduce the time in phase for late-stage vaccine candidates, since strengthening clinical trials infrastructure helps avoid problems that delay large (Phase IIb and III) trials, such as lack of well-trained trial staff, volunteer recruiting strategies and capacity, and ability to deliver high-quality medical care.

5. **Strengthen regulatory capacity in developing countries.** Every clinical trial involving experimental medicines, vaccines, or procedures must undergo stringent expert review, both in the manufacturing country and the country where trials are planned, before the study can proceed, and then again prior to licensure. Yet many developing countries lack sufficient expertise, capacity, and/or systems to make these regulatory decisions in a timely, efficient manner. If left unaddressed, this problem will only worsen, since HIV vaccine development raises many novel regulatory issues. It is therefore crucial that health authorities in developing countries build sufficient technical capacity to evaluate products and trials expeditiously. Such improvements should minimize regulatory delays and thus reduce time spent in phase.

6. **Resolve intellectual property issues.** Finally, there is a need to address intellectual property issues that can slow progress of the R&D pipeline. One step that would catalyze progress is to find ways of allowing the exchange of certain patented information, materials, and methods across research entities without violating patents, especially during the early stages of vaccine development, when many patented materials do not yet have real commercial value. This would lead not only to more vaccine candidates entering the R&D pipeline, but also to better ones with a higher chance of success.

## Other avenues for accelerating vaccine development: Improving the organization and management of R&D

In considering the potential impact of increased investments on the pace of vaccine development, it is important to note that money alone is not enough. Rather, accelerating the timeframe for vaccine debut will also entail efforts to change organization and management processes within the HIV vaccine field. These issues have been extensively discussed among the major vaccine developers; for example, the Global HIV Vaccine Enterprise described the task of creating "new ways of doing business" as central to its role and has committed to working on establishing global processes across a range of activities, such as standards, performance criteria, data sharing, and communication.

Although it was not possible to model the specific impact of such changes, our study assumes that the necessary changes are implemented, paving the way for increased investments to have the desired effects of shortening time in phase and improving both the quality and numbers of new candidates in the pipeline.

Following is a brief summary of planned and proposed changes; for a more complete discussion, we refer readers to the *Global HIV Vaccine Enterprise Scientific Strategic Plan* (Global HIV/AIDS Vaccine Enterprise, 2005a) and the *IAVI Scientific Blueprint* (IAVI, 2004). Key elements include:

- **Establishing consortia of five to ten research groups to tackle long-standing scientific questions**, which often requires more expertise, effort, and resources than one or two groups can bring to bear. Modeled on IAVI's Neutralizing Antibody Consortium, this larger-scale approach — assuming it is well-funded and well-managed — is viewed as the best hope for resolving some key bottlenecks in vaccine discovery. The time is especially ripe, since many researchers believe that scientific knowledge and technology have reached a point where prospects for success are better than ever. If these efforts succeed, the knowledge gained should greatly improve vaccine makers' ability to develop rational principles for designing new and better candidates with a higher probability of success. In this regard, the BMGF recently established the Collaboration for AIDS Vaccine Discovery (CAVD), a network of 16 consortia, 11 of which focus on different approaches to developing novel candidate vaccines, with the other five providing centralized facilities to support comparative evaluation of immune responses, along with data and statistical analysis.

- **Improving the R&D decision-making processes**, which offers a significant opportunity to influence vaccine debut in two ways: (1) by shortening the time spent in the clinical development phases, and (2) in the long run, by significantly increasing the probability of success for the overall pipeline, since better decisions mean that the best candidates are more likely to move forward and the least promising are eliminated. Several vaccine developers are already working toward defining a clear set of criteria for advancing candidates to the next phase, but more can be done to coordinate these discussions across different groups in the field. As discussed above, investments in the availability and use of common procedures and reagents across labs, and possibly in head-to-head comparisons of leading vaccine candidates, will also boost these efforts.

- **Increased coordination among vaccine developers and sponsors** — a corollary to improved decision-making — is crucial to the goals of broadening the range of candidates and ideas entering the pipeline, and ensuring that these candidates pass through increasingly stringent decision gates as they progress. In practice this is not easy; even many pharmaceutical companies with large portfolios of candidates struggle to maintain such discipline. But adoption of this approach could bring significant efficiency gains to HIV vaccine development. Such coordination is not something individual developers can readily do on their own; they will need to reach agreement on standards and processes across the field. Various mechanisms for achieving this are under discussion; see, for example, the *Enterprise Scientific Strategic Plan* (2005a).

## Question 2: How much would strategic investments in HIV vaccine R&D shorten the timeframe for developing an effective vaccine?

> *Targeted investments, together with changes in organization and management of HIV vaccine R&D, could potentially shave anywhere from 5 to 22 years off the time needed to develop an effective vaccine — thereby averting between 9 and 68 million infections.*

Building on our assessment of how the recent investments in HIV vaccines are likely to impact the clinical pipeline (see previous chapter), we then used the simulation model to analyze whether and how the anticipated types of pipeline improvements could shorten the timeline for success.

We began by estimating the timeline for developing an effective vaccine under our Status Quo scenario, which assumes no change in the R&D investment level and no major scientific breakthroughs over time. Next, we compared this result with estimates derived from two alternative scenarios: a Low-Improvement scenario, which assumes a modest degree of improvement in the pipeline, and a High-Improvement scenario, which assumes greater improvement. In both cases, the improvements reflected:

- Greater flow of new candidates into the pipeline.
- Higher probabilities of success in moving from one clinical phase to the next (transition probabilities).
- Shorter duration of clinical development.

Our aim was not to make hard predictions about the number of years it will take to develop a successful vaccine, but to examine the relative magnitude of changes that might result under these different scenarios.

### The Status Quo timeframe

Estimates for the key pipeline attributes under the Status Quo scenario were derived largely through an analysis of the current pipeline, as described in Appendix 1, and are listed below in Table 4.

**Table 4.** Input assumptions for Status Quo scenario

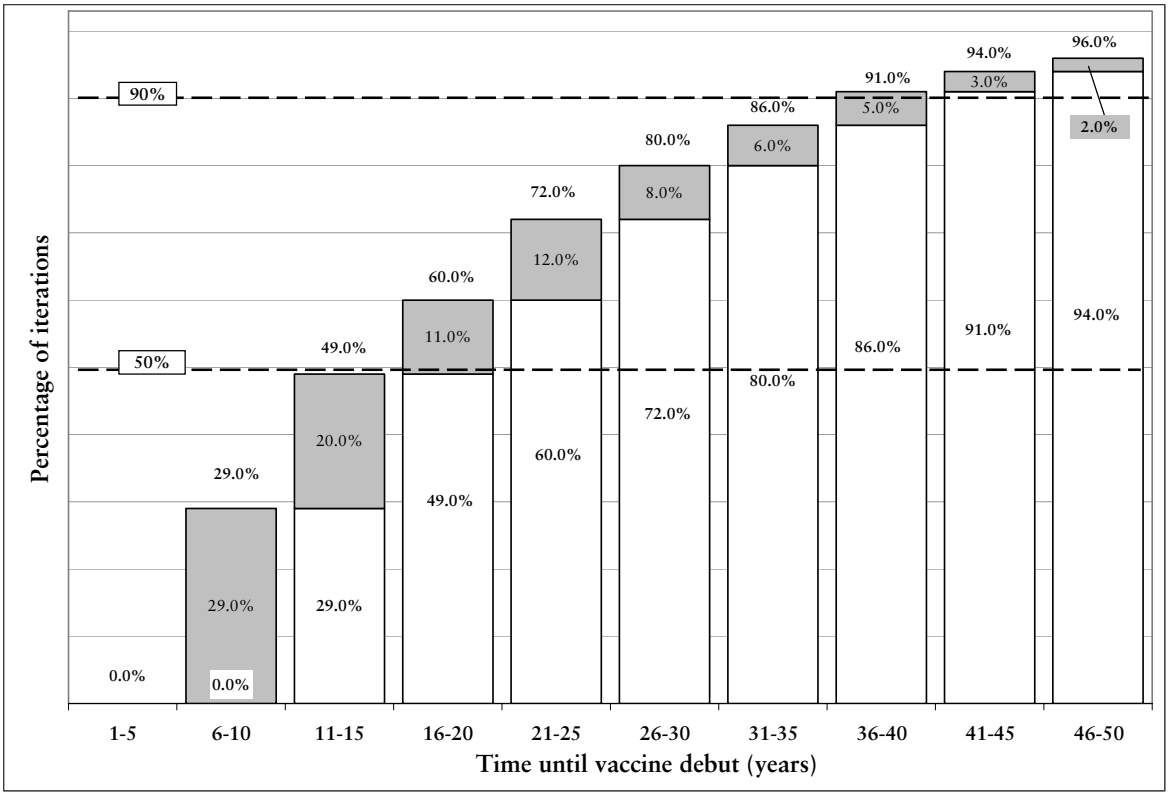
| Attribute | Phase I | Phase II | Phase IIb* | Phase III | Registration |
|---|---|---|---|---|---|
| Current candidates (number) | 22 | 2 | 1 | 1 | 0 |
| Transition probability | 20% | 38% | 15% | 65% | 95% |
| Phase costs (US$ millions) | $10m | $20m | $0-50m | $200m | $3m |
| Time in phase (months) | 24 | 24 | 0-48 | 60 | 18 |

* Some candidates are assumed to go directly from Phase II to Phase III studies, skipping Phase IIb.

Using these Status Quo estimates as input, our computer model generated a series of predictions about the likelihood that an effective vaccine will be developed within various periods of time.

Figure 2 shows the resulting vaccine debut timeframes, illustrating both the likelihood of success within subsequent five-year periods and the cumulative likelihood over time. For example, in 20% of model iterations, the time to debut is between 11 and 15 years, inclusive, while in almost half (49%) of the iterations, the time to debut is between 6 and 15 years. The 50% probability point falls at 16 years.

**Figure 2.** Timeframe for vaccine debut: Status Quo scenario




## Potential impact of pipeline improvements on time to vaccine debut

Next, we devised two alternative scenarios by modifying the Status Quo assumptions to allow for improvements to the pipeline, by degrees that our range of experts considered reasonable. These assumptions were then limited by "upper bounds" that could not realistically be exceeded — for example, the overall time a candidate spends in phase cannot realistically be shortened by more than two years, nor are transition probabilities for HIV vaccine candidates likely to exceed the high rates seen with some drugs.

The resulting Low- and High-Improvement scenarios are summarized in Table 5 (see Appendix 1 for details on the rationale behind these choices), along with the vaccine debut timelines they predict. It is important to emphasize that the two scenarios do *not* reflect different assumptions about investments (i.e., that a smaller investment will yield the Low-

Improvement scenario and a larger one the High-Improvement one). Rather, the two scenarios reflect different possible outcomes for the same level of investment, an approach we took since it is not possible to directly link a specific investment level to a specific outcome.

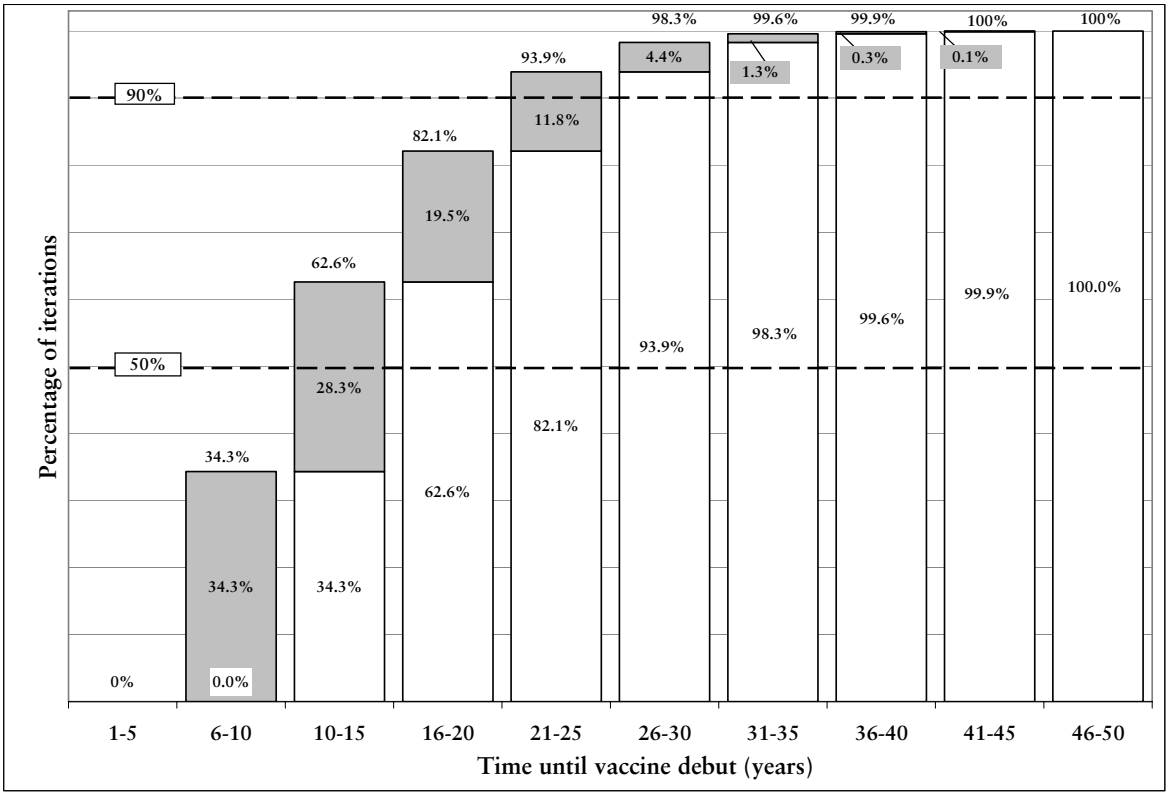
**Table 5**. Input assumptions for Low- and High-Improvement scenarios*

| Scenario | Time in phase | Probability of success | Pipeline flow |
|---|---|---|---|
| Low-Improvement | - 1 year | 10x increase | +5 candidates per year |
| High-Improvement | - 2 years | 20x increase | +10 candidates per year |

* The figures in the table indicate changes in each attribute relative to the Status Quo scenario.

The effects of these changes on the timeline to vaccine debut are shown in Figures 3, 4, and 5. Under the Low-Improvement scenario (Figure 3), our results suggest that the probability of getting a vaccine reaches 50% in 13 years — that is, three years earlier than under Status Quo assumptions — while the probability of finding a vaccine reaches 90% (approaching certainty) within 23 years, compared with 40 years for the Status Quo.

**Figure 3**. Impact of improvements on timeframe: Low-Improvement scenario




As illustrated in Figure 4, results within the High-Improvement scenario predict that the 90% debut timeframe can be reduced to less than 20 years — half the time of the Status Quo's 40-year timeframe estimate.

**Figure 4.** Impact of improvements on timeframe: High-Improvement scenario

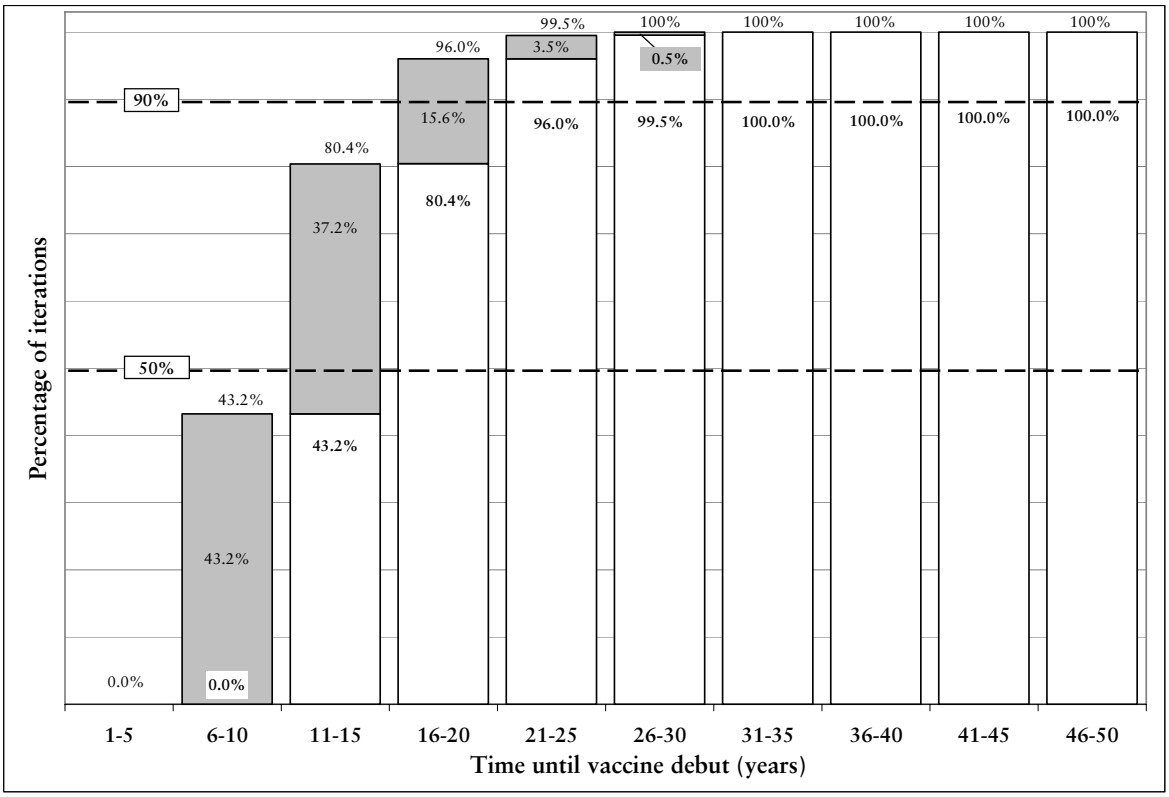
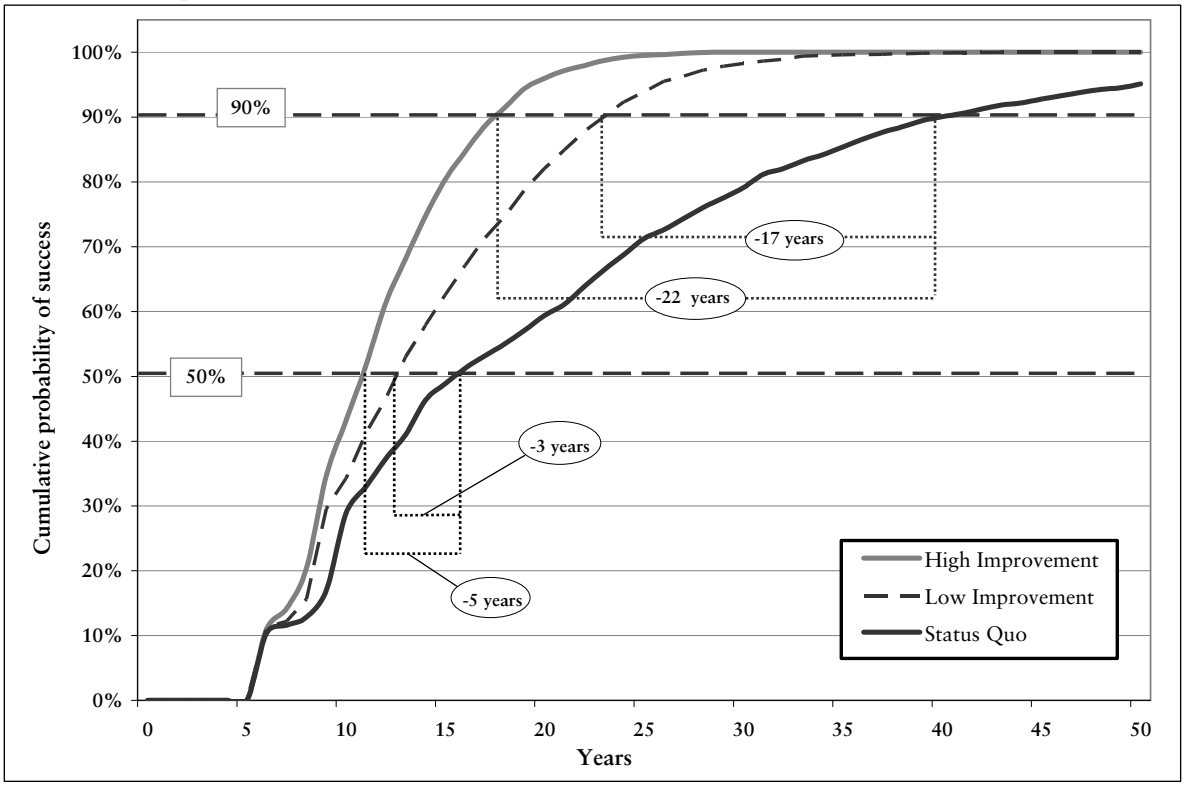



Figure 5 shows all three timelines on a single graph, so that the differences can be visualized more easily. Targeted investments could accelerate the timeline anywhere from 3 to 22 years.

**Figure 5.** Comparison of vaccine debut times under different scenarios




Note: Numbers inside the ovals represent the predicted time savings at the 50% and 90% levels.

## Potential impact of improved pipeline on the pandemic

Last, we examined the impact of these shorter timelines on the numbers of HIV infections prevented, using estimates of future infection numbers derived from an epidemiological impact modeling study recently undertaken by IAVI (2005b), which draws in part on a combination of other published epidemiological models. Results from this analysis suggest that the impact of the time saved under our two scenarios could be quite significant, as summarized in Table 6.

**Table 6.** Potential impact of an improved pipeline on the pandemic

| Scenario | Potential acceleration of success (# of years) | Potential # of HIV infections averted (millions of people)* |
|---|---|---|
| Low-Improvement | 3-17 | 9-53 |
| High-Improvement | 5-22 | 15-68 |

* Based on IAVI 2005b.

Results from the Low-Improvement scenario suggest that the timeline for success could be reduced by 3 to 17 years, as described above. Our epidemiological model predicts that even a vaccine with only moderate efficacy could avert about 30% of new infections globally over a 15-year period, corresponding to about 3.1 million infections per year. Therefore, a savings of 3 to 17 years could avert between 9 and 53 million infections.

The potential impact of the High-Improvement scenario would be even more dramatic: If this scenario's somewhat greater enhancements to the pipeline can be achieved and lead to the predicted 5-22 year acceleration of progress, roughly 15 to 68 million infections would be avoided.

## Question 3: What level of strategic investments would it take to shorten the timeframe for making an effective vaccine?

*Additional annual investment of $200 to $300 million would be needed to support the pipeline improvements that could shorten the timeline to an effective vaccine. In the long run, by saving time, these investments may not add significantly to, and could even decrease, the cumulative cost of developing an effective vaccine.*

To expand on the encouraging finding that even modest improvements in the clinical pipeline could translate into millions of lives saved, we used the model to analyze how much funding it would take to realize these improvements, and how much it would ultimately take to succeed.

First, we assessed the estimated costs of finding an effective vaccine under the Status Quo scenario. Next, we estimated the funding increases needed to bring about the pipeline improvements considered the most promising investment targets for accelerating progress, as described in a previous section, and compared them with the total funding now committed to HIV vaccine development (as of mid-2005). [2]

### Costs for the Status Quo scenario

As a base figure to use for comparisons with the two Improvement scenarios, we first used the model to calculate the annual costs of funding candidates in the clinical pipeline. The figures resulting from each iteration of the model were then combined with the additional (known) annual research costs, both basic and applied, to determine the full R&D costs. In each iteration, we assumed that costs were incurred through (and including) the year that an effective vaccine was licensed for use; we assumed the cumulative cost would stop once this point was reached. Appendix 1 contains a more detailed description of how we derived these estimates.

Using this approach, the model estimated the average annual R&D costs under the Status Quo scenario at $744 million. Taking into account the model's estimated timeframe for success (using the probability distribution shown previously in Figure 2), this results in an average cumulative cost until success of $10.1 billion.

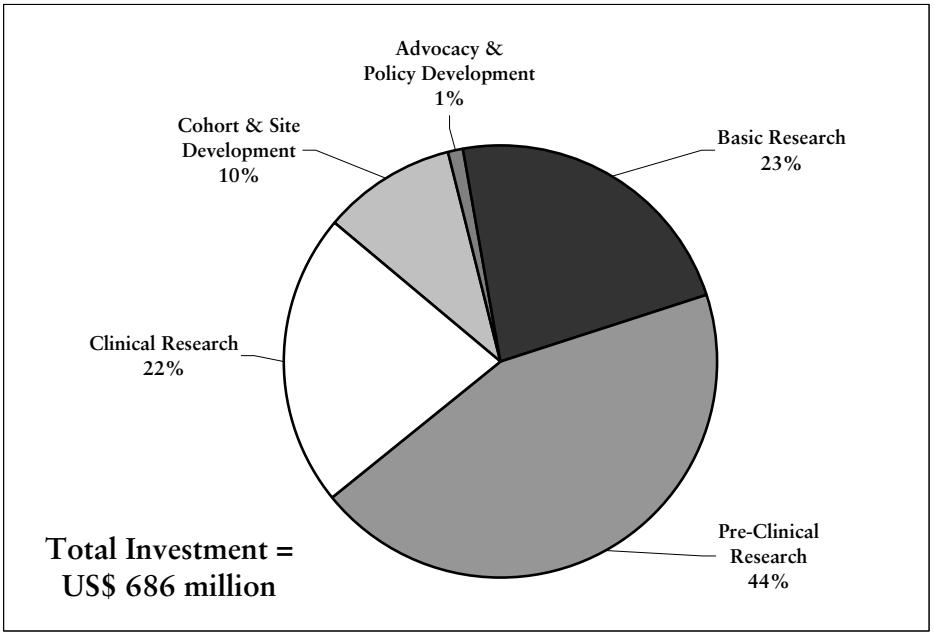
### Comparison with current funding levels

In 2004, R&D spending for HIV vaccines from the public, private, and philanthropic sectors was $686 million, according to the HIV Vaccines and Microbicides Resource Tracking Working Group (2005). As shown below in Figure 6, two-thirds (67%) of those

[2] This process had the inherent problem of requiring that correlations and cost comparisons be made between data sets carved up in different ways: the Enterprise's six scientific areas, NIH's specific budget categories, and the three key pipeline attributes used in this study. The analysis therefore required careful dissection of these categories in order for us to compare the same sets of costs, to the extent possible.

resources were devoted to basic and preclinical research and almost one quarter (22%) to clinical trials, with the remainder directed toward cohort development (10%) and policy and advocacy (1%).

**Figure 6.** Total HIV vaccine R&D funding by category (2004)




*Source*: HIV Vaccines and Microbicides Resource Tracking Working Group (2005)

This figure is close, but not exactly equal, to the model's estimate of $744 million. The difference reflects a slight divergence between the actual pipeline at a single point in time, and the Status Quo assumptions, which build upon known inputs such as the numbers and stages of candidates today, and incorporates some predicted values, such as numbers of new candidates flowing into the pipeline, their transition probabilities, and their time spent in phase.

## Comparison with costs of bringing a drug to market

Compared with the estimated cost of developing new drugs — such as the often-cited figure of $800 million for a single one (DiMasi et al., 2003) — a cumulative cost of $10.1 billion for an HIV vaccine may seem surprisingly high.

This disparity arises largely from the very different assumptions appropriate for our study compared to those used by DiMasi and his colleagues, reflecting differences in both the types of products being developed (and considering the extraordinary challenges in the case of an HIV vaccine) and in the states of knowledge in these two fields. For example, our Status Quo scenario assumed an overall probability of success that was one-thirtieth of DiMasi's figure for the drug pipeline. In addition, the estimated cost for each phase of HIV vaccine development was significantly higher than DiMasi's numbers, and the timeline was twice as long.

However, the Status Quo scenario that led us to the estimate of $10.1 billion reflects pessimistic assumptions about HIV vaccine R&D over the coming years — assumptions that are rapidly being superseded by positive developments in the field, thereby making a faster road to success appear more feasible. Most important among them are the new investments targeting key scientific hurdles to the HIV vaccine effort, along with changes in the organization and management of R&D. As discussed earlier, these steps should lead to improvements in several rate-determining attributes of the vaccine pipeline, which in turn should reduce the overall timeline.

## Accelerating progress: What will it cost?

Estimating the investment levels needed to achieve specific improvements to the pipeline was difficult, given the high level of uncertainty on several key points. We approached this task not through the simulation model, but relying instead on best estimates by the advisors to this project and by others in the HIV vaccine field. In particular, we drew on estimates made by the Enterprise Working Groups at an August 2005 meeting about critical investment needs. Table 7 summarizes the estimates we derived and the reasoning behind them.

**Table 7.** HIV vaccine R&D: Current and proposed new spending (all figures in US $ millions)

| Purpose of investment[a] | Resource tracking category[b] | 2004 spending[c] | New monies called for by the Enterprise[d] | Total |
|---|---|---|---|---|
| Vaccine discovery | Basic and pre-clinical research | $158 (basic) | $170(including new $110 committed by BMGF & NIH) | $670 |
| Laboratory standardization | Pre-clinical research | $302 (pre-clinical) | $40 | |
| Process development | Clinical research | $151 | $20-$40 | $171-$191 |
| Clinical trials capacity | Cohort & site development | $68 | $50-$140 | $118-$208 |
| Regulatory issues | Advocacy & policy development | $7 | $3-$5 | $12 -$16 |
| IP issues | Advocacy & policy development | | $2-$4 | |
| **TOTAL** | | **$686** | **$285-399** | **$971 - $1085** |

[a] These reflect the six strategic investment areas in the Global HIV Vaccine Enterprise Scientific Strategic Plan.
[b] These represent National Institutes of Health (NIH) budget categories. As the six strategic investment areas reach across multiple spending categories, we have identified only the primary category where such investments would fall.
[c] Data from HIV Vaccines and Microbicides Resource Tracking Working Group (2005).
[d] Based on an unpublished "Investment Menu" developed by an Enterprise Working Group (Global HIV/AIDS Vaccine Enterprise, 2005b) to estimate additional financial resources required to implement the recommendations of the Scientific Strategic Plan.
*Data reflect funding and commitments made as of August 2005.*

Using these estimated price tags for needs in each of the six scientific areas identified by the Enterprise, we then attempted to correlate the latter with the three pipeline attributes included in our analysis, so that ultimately we could tie the Enterprise's estimates of

required resources to the estimated costs of our two Improvement scenarios. We therefore added a financial perspective to our earlier examination of how increased investments in the six Enterprise-defined areas impact key pipeline attributes (see Table 3).

As discussed previously, advances at the **vaccine discovery** stage should lead to the design of better candidates, which is expected to have a big impact on both the R&D timeframe and the overall likelihood of success. (Better candidates would each have a significantly higher **transition probability** for each phase of clinical development, and therefore a higher overall likelihood of success.) These improvements would presumably also be catalyzed by the adoption of more streamlined, criteria-based decision-making processes for identifying the most promising candidates.

How much funding will it take to significantly impact vaccine discovery? The current level of global spending in this area is about $460 million per year; however, much of this goes into broader research on HIV rather than specifically to vaccine design. The "investment menu" developed by an Enterprise Working Group (Global HIV/AIDS Vaccine Enterprise, 2005b, unpublished) identified additional needs of $170 million per year for vaccine discovery ($110 million of which was committed in 2005). Addressing intellectual property (IP) issues can also contribute to vaccine discovery by, for example, allowing vaccine designers to use the optimal vector, HIV sequence, or methodology during this early stage of product development (when most candidate products have little commercial value), rather than being limited to those tools not restricted by patent protections. Furthermore, as scientific advances lead to higher- quality vaccine candidates, it will become both feasible and desirable to increase the **flow of high-quality candidates** into the pipeline. This could be accomplished in part through investments in basic and pre-clinical research, as well as through addressing IP issues. In the latter area, the Enterprise Working Group recommended additional investments of $2 to 4 million per year.

To improve **time in phase**, investments are needed in laboratory standardization, clinical trials capacity, process development and manufacturing, and regulatory issues. Current spending in these areas is generally counted under the rubric of clinical research, although some laboratory and process development/manufacturing costs may be categorized as preclinical research. In 2004, total global expenditures on clinical research were approximately $150 million.

In this area, the Enterprise Working Group estimated that additional investments of $113-225 million per year are necessary, including $50-140 million for clinical trials capacity, $40 million for laboratory standardization, $20-40 million for process development, and $3-5 million for regulatory issues. (Note that these figures explicitly exclude the cost of building manufacturing facilities.) Under our model, these annual costs would continue until a successful vaccine is licensed, although at least some costs might be one-time or time-limited investments that would be discontinued after improvements are achieved. However, for purposes of the model and analysis, the team counted all costs for each year until licensure of a first vaccine.

Overall, this results in the need for **an additional $175-$290 million** in investments (beyond the amounts already committed in 2005).

## Costs of success under the two improvement scenarios

Table 8 compares the expected costs of developing a successful vaccine under the Status Quo, Low-Improvement, and High-Improvement scenarios. As discussed earlier, the average annual cost on R&D under the Status Quo scenario is $744 million; the average cumulative cost until success is $15.5 billion; in present value terms (discount rate of 4 percent),[3] the cumulative cost is $10.1 billion.

**Table 8.** Impact of Low- and High-Improvement assumptions on costs of developing an HIV vaccine

| Scenario | Years to success (at 50% and 90% probability) | Avg. annual cost (US$) | Avg. cumulative cost (US$) | Avg. cumulative cost (PV)* (US$) |
|---|---|---|---|---|
| Status Quo | 16-40 | $744 million | $15.5 billion | $10.1 billion |
| Low-Improvement | 13-23 | $1,067 million | $16.9 billion | $12.0 billion |
| High-Improvement | 11-18 | $1,140 million | $15.3 billion | $11.5 billion |

* PV, present value

We derived these annual cost figures from the model. They reflect each scenario's specific assumptions about new candidates entering the pipeline, transition probabilities, and time in phase. These figures are consistent with the annual investment level called for by the Enterprise ($971-1,085 million per year), although they are not identical.[4]

Under the Low-Improvement scenario, average annual cost is about $300 million higher than for the Status Quo, reflecting both the additional resources (strategic investments) described previously and the flow of new vaccine candidates with higher probabilities of success into the pipeline; both of these translate into more candidates in development, and therefore into additional costs. Under the High-Improvement scenario, average annual cost is only slightly more. The slight increase over the Low-Improvement scenario reflects somewhat higher numbers of new candidates entering the pipeline (10 more versus 5), as well as their higher transition probabilities (20-fold versus 10-fold increase).

Turning from the annual costs to the overall costs of success, even the modest differences among these three scenarios are partially erased: The average cumulative cost figures for the Status Quo, the Low-Improvement scenario, and the High-Improvement scenarios are $15.5, $16.9, and $15.3 billion, respectively. Interestingly, the fact that the High-Improvement cumulative cost is the lowest of the three suggests that more favorable conditions shorten the timeframe so significantly that the field ends up spending *less* money overall, even though more money is required each year until success is reached.

[3] **Present value** (PV) is the amount that a future sum of money is worth today, given a specified rate of return (interest). Because money earns a return, a given amount is worth more now than it will be in the future. By applying discounts to money being spent at different times, the amounts are all translated into today's dollars (i.e., present value), so they can be directly compared.

[4] The increased spend called for by the Enterprise is incorporated into the model, but we did not assume that all the new monies ($300-400K) are spent immediately; rather, we gradually phased in the increase over a period of five years.

Looking at the present value of these cost figures tells a slightly different story. In this case, the present value of the High-Improvement scenario ($11.5 billion) is higher than that of the Status Quo ($10.1 billion), reflecting the fact that the former concentrates high annual costs into the early years, counterbalancing some of the savings from the shorter timeline. Even from this perspective, the total cost of an effective vaccine under the High-Improvement scenario remains lower (by $0.5 billion) than the Low-Improvement scenario, again due to the shortening of the overall timeframe to success.

These figures have important implications for planning when and how to invest in HIV vaccine R&D. The additional investments that fuel the pipeline improvements obviously mean higher spending per year; however, these results suggest that the extra investment could have a significant impact on accelerating progress. Under the Low-Improvement scenario, we would spend $2 billion more in net present value terms compared to the Status Quo; however, the acceleration in timeline could be between 3 and 17 years. Under the High-Improvement scenario, if indeed the field can achieve the more significant impacts on the pipeline attributes identified in this chapter, additional spending of $1 billion over the Status Quo would accelerate the timeline by 5 to 22 years.

## IV. Conclusions

With every day adding 14,000 new people to the 40 million already living with HIV/AIDS, the dire need for effective new prevention technologies keeps growing. Yet one of the biggest hopes — a vaccine against HIV — still seems to be at least a decade, or possibly decades, away. Finding ways to speed up this process so a vaccine might be available sooner rather than later could save tens of millions of lives.

The HIV vaccine field now has 20-plus years behind it, along with ample proof that HIV is an especially difficult target for a vaccine, and that success, especially faster success, will require a larger-scale, more intensive effort. For the past few years, this scale-up has gradually been taking shape, fueled by an influx of new funds and fairly broad consensus across the field about what particular areas the scaled-up effort should target, and how.

Attracting and absorbing these new funds remains a process that requires fundamental decisions about which areas and activities to invest in, so that new funds can have the most impact on shortening the time needed to make a vaccine. The many uncertainties about how to develop a vaccine, plus the many different factors that influence the development timeline, make those decisions a challenge. Adding urgency to this task, stakeholders in the field have targeted the decision-making process itself as needing improvement, to make it more criteria-based and data-driven (Global HIV Vaccine Enterprise, 2005a). In this context, new strategies or tools that can help analyze these complex scenarios could provide useful support for making evidence-based decisions.

In this study we used computer-based modeling, which is widely used in the pharmaceutical and biotechnology sectors to analyze drug development scenarios involving multiple uncertainties and factors that vary. Our model incorporated data on the various factors that determine the development timeline of an HIV vaccine, and then estimated the likelihood of success within different timeframes. As with all such models, the results depend on the inputs and assumptions used; given the uncertainties surrounding HIV vaccine research and development today, many of the inputs to this model will be far from perfect.

Given the model's limitations, it is important to understand our results for what they are, and what they are not. No model, including this one, can predict just how long it will take to make an effective vaccine, since it is impossible to know when an important scientific discovery will occur — and success depends largely on that happening. Rather, the results were analyzed for any insights they might provide into the most effective ways to reduce the timeframe. We therefore focused on the *relative* timeline estimates, not on the absolute numbers, and on comparing outcomes of the three scenarios analyzed in this study: the Status Quo (where scientific knowledge and funding levels remain constant), the Low-Improvement scenario (which assumes a modest level of improvement in the vaccine pipeline), and the High-Improvement scenario (assuming a higher level of improvement).

Another key point in interpreting the model's results is that the degree of accuracy depends to a large extent on how well the critical rate- and cost-determining factors are identified and their values estimated. The main attributes we used were shown earlier in Table 2, and are repeated below.

**Table 2.** Key pipeline attributes used in this study

| Attribute | Description |
|---|---|
| Pipeline flow* | Number of new candidates entering Phase I studies in a given year |
| Transition probability* | Probability (in %) that a candidate successfully completes a given phase and moves to the next phase |
| Time in phase* | Estimated duration of each phase (including any delay before the next phase begins) |
| Phase cost | Costs of all activities and studies for candidate during a given phase of clinical trials |
| Current candidates | Number of unique vaccine candidates in each phase of the pipeline as of April 2005 |

* Attributes that are the focus of most of the analyses described below.

While we made the best estimates we could based on available data from HIV vaccines and other vaccine development processes, and incorporated input from a wide spectrum of experts, there is still some inherent uncertainty in these values, and they could undoubtedly benefit from further refinement.

With these caveats in mind, our main conclusions are:

**1. Investing new money in areas that can bring about positive changes in any of the three key pipeline attributes — pipeline flow, transition probability (i.e., chance of success in each clinical phase), or time in phase — along with instituting some recommended organizational changes in vaccine R&D, should significantly reduce the time until an effective vaccine becomes available.** For example, new investments leading to improvements on a par with the High-Improvement scenario could reduce the timeline by at least five years, and potentially up to 22 years — a substantial savings. But note that most of the acceleration (a savings of 22 years) is seen at the outer end of the timeframe, reducing it from 40 years to under 20; even under our best-case (High-Improvement) scenario, the early end of the timeframe advances much less (five years, from 16 to 11).

At first glance this can be a discouraging message that might create the impression that additional investment can wait, since success is probably relatively far off, even under optimistic scenarios. But that conclusion would be wrong. On the contrary: These findings suggest that the sooner new strategic investments are made, the more time they will ultimately save. Viewed in terms of the numbers of infections prevented, this latter message becomes clearer: Using a rough calculation based on the High-Improvement scenario and various epidemiological models (IAVI 2005b), shortening the timeline by 22 years could potentially mean 68 million fewer infections; even if only 5 years are saved, this still prevents about 15 million infections.

**2. Cost calculations also favor making additional investments now, since our results suggest that success in achieving certain pipeline improvements should not only result in a vaccine much sooner, but in the long run may not add significantly to the cumulative cost — and could even possibly decrease it.** This is because a shorter timeline reduces the total cost of making a vaccine. Thus, this approach makes sense not only from a public health perspective but also from an economic one. In the short run, we estimate the additional annual costs needed to fund the most relevant activities are about $200-$300 million per year beyond the funds already committed by the end of 2005.

**3. In asking *how* these improvements can be made, our results suggest that new investments aimed at accelerating progress should target areas of vaccine development that are most likely to improve the quality and number of candidates in the pipeline (i.e., transition probability and pipeline flow) and/or the time in phase.** Based on qualitative assessment, we also note which activities are most likely to bring about these improvements, focusing on the field's own list of highest-priority actions (drawn from key strategy documents written by the Enterprise and by IAVI).

- **To improve the quality of candidates in the pipeline** (i.e., increase their transition probability) — **crucial steps are: (1) increase activities in vaccine discovery, and (2) optimize and standardize laboratory evaluation of clinical trials samples to rigorously compare** *all* candidates to one another (which is not yet possible) and identify the best ones for advancement. Achieving these improvements will also require (3) **some reorganization of how this research is carried out**, for example, by tackling major questions through consortia of scientific groups rather than by individual groups. Better decision-making processes are also needed, especially with regard to selecting candidates to move forward and taking steps to lower IP barriers.

- **To streamline the clinical evaluation phases so that candidates spend less time in clinical testing, the key activities are: (1) expand clinical trials capacity** (to reduce delays caused by difficulties in getting trial sites started, training staff, and developing recruiting strategies), (2) **reduce regulatory delays, and (3) improve decision-making processes during research and development**. While this set of activities offers the most immediate opportunity to make modest improvements, it may have the least impact among the potential changes, since there is a limit to how much time can be shaved off the clinical testing process.

  The order and timing of these changes are also important, since it would be counterproductive to have more candidates flow into the pipeline if they are not of better quality and if some of the current inefficiencies in the development process remain.

Overall, these conclusions support the validity of decisions already made, in terms of recent funding commitments in the field, so in a sense, they reveal nothing fundamentally new. However, they serve to highlight the fact that improving these attributes is fundamental to an accelerated timeline, and that future investments should be made with such improvements in mind.

This brings us back to the model itself and to its potential value to the HIV vaccine field. This model-based analysis suggests a useful way of assessing potential new activities and funding targets — that is, in terms of their effects on the key rate-determining factors in clinical development. Increasing the model's usefulness will require better estimates of the pipeline attributes, which should become easier as more clinical data on HIV vaccines accumulate. Given the continuing need for strategic funding decisions over the coming years, perhaps this way of thinking, and/or the modeling approach itself, can contribute to rationalizing the process.

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# Appendix 1. Model inputs and assumptions

## Key model inputs

Below is a discussion of the specific values we chose for key model inputs (number of current candidates and cost per phase) and for each of the three pipeline attributes (pipeline flow, transition probability, and time in phase) that varied under the three scenarios tested (Status Quo, Low-Improvement, and High-Improvement). Also included are the assumptions and rationale behind each of the chosen values.

### 1. Number of current candidates

For purposes of this study, the team defined one candidate as a unique vaccine approach. This definition therefore included not only each individual product being tested, but also any vaccine approach that combined products in a unique way (such as a prime-boost strategy).

The numbers of current candidates we used as input for this study were derived from information about ongoing clinical trials, as documented in the IAVI Clinical Trials Database (IAVI, 2005a). These data were reviewed and refined to remove trials where a single candidate was being evaluated in multiple trials, and to eliminate candidates that would not be developed further or were being superseded by revised versions of the vaccine.

### 2. Phase cost

Costs for each phase of development were defined as the fully loaded cost (i.e., including both organizational overhead such as staff time and other general expenses, plus direct out-of-pocket costs) of all activities completed from the time the candidate begins a phase of development until it moves into the next phase. These costs included protocol design, clinical product manufacture, site preparation, conducting the trial, monitoring and evaluating the trial, and collecting and analyzing the data. Estimates for building or operating a manufacturing plant were not included. The values we chose are summarized below in Table A1.

**Table A1.** Estimates of phase costs

| Phase | Based on | Estimated cost (US$) |
|---|---|---|
| I | 2 studies of 50 volunteers each | 10 million |
| II | 2 studies with 200 volunteers each | 20 million |
| IIb (stand-alone) | Ongoing Phase IIb (HVTN/Merck) | 50 million over 4 years |
| IIb (rolling*) | — | 25 million over 2 years |
| III | 2 completed, 1 ongoing study | 100-200 million |
| Registration | | 3 million |

* With plans to expand into a Phase III study.

Where possible, input assumptions were based on actual experience within the AIDS vaccine field. There are ample data available for Phase I, but only very limited experience

for later stages of development (Phase IIB and Phase III). At the same time, expert advisors were critical of extrapolating assumptions from trials for drugs and other vaccines; estimates for these later phases are therefore less solid than those for Phase I.

- **Phase I** development costs were assumed to be $10 million, based on two studies with approximately 50 participants each. (This includes direct costs estimated at $25,000 per participant, fully loaded costs of approximately $100,000, and the cost of the vaccine.) These estimates are in line with an internal IAVI costing exercise and are similar to estimates from the HIV Vaccine Trials Network.

- **Phase II** development costs were assumed to be $20 million, based on a minimum of two studies with approximately 200 participants each and including the cost of supplying vaccine. (Direct study costs were estimated at $30,000 per participant.) These estimates are in line with IAVI's costing exercise and are similar to estimates from the U.S. HIV Vaccine Trials Network (HVTN) and VaxGen's Phase II study.

- **Phase IIb** trial costs are likely to vary significantly, depending on the protocol design and the numbers and locations of trial sites. For a stand-alone Phase IIb study we assumed a cost of $50 million over four years, while a rolling Phase IIb (i.e., one that will gradually be expanded into a Phase III licensure trial) was estimated at $25 million over two years. This latter number was based on the assumption that a rolling Phase IIb adds only an additional two years to a stand-alone Phase III trial (i.e., seven years for these two studies together). The $50 million estimate is in line with the expected cost for the ongoing trial by the HVTN and the pharmaceutical company Merck (the only Phase IIb study launched to date), which aims to enroll about 1,500 volunteers, and is within the $25,000 to $35,000 range estimated by our experts for fully loaded costs per patient. This trial is likely to be on the higher end of this range, since it has many trial sites spread over many countries plus additional costs incurred by its use of central laboratories to evaluate safety and immunogenicity data. (For example, transporting volunteers' blood samples to the central laboratories costs $2,000 to $5,000 per volunteer).

- **Phase III** trial costs are subject to an even wider degree of variation, based on the size of the trial, the protocol, and the number and locations of sites. In making our estimates, we first considered the number of volunteers to be enrolled, using the assumption that a trial seeking licensure would require between 8,000 and 16,000 volunteers. This was based partly on the size of ongoing trials: The Aventis-Sanofi Phase III trial in Thailand has enrolled 16,000 participants, while the combined size of the two completed VaxGen Phase III trials was about 8,000. It is worth noting that many experts expect the size of Phase III trials to increase in the future as more trials are conducted in areas with lower HIV incidence.

  In making our estimates for Phase III, we considered the full cost of a single trial, the cost of the vaccine itself, and the costs of developing both the vaccine production process and the tools for testing product stability and release prior to licensure. We included these latter expenses because a Phase III trial seeking licensure must use vaccine made by a process very similar to the one that will be used post-licensure for full-scale manufacturing. Estimates for developing the manufacturing process and supplying the trial with vaccine range from $5 to 50

million. However, we did not include the cost of building a full-scale factory, even though factory design and construction are critical for achieving registration. Our reasoning was that with the cost expected to be anywhere from $70 to $500 million, it is unlikely that this investment will be made each time a candidate enters Phase III. Given the high degree of uncertainty about when this investment would be made and how much it would be, we did not include it anywhere in the model.

Putting these considerations together, we arrived at Phase III trial costs between $100 and $300 million — a wide range that reflects the wide variation in possible vaccine and trial approaches. These figures are consistent with several benchmarks that our team considered, including the ongoing Thai Phase III trial (estimated to cost $190 million for the trial and product, which means approximately $12,000 per participant), an ongoing rotavirus trial of 6,600 children with reported direct costs of over $100 million (taking place where there was already significant infrastructure), and Phase III trial costs of $150 million for the two VaxGen trials.

One last point is that a single Phase III trial might not be sufficient for licensure; some experts believe registration will require both a Phase IIb and a Phase III or, alternatively, two Phase III trials. If more than one Phase III is required, this would significantly increase the costs and the timeline (assuming trials are sequential, not concurrent) for Phase III development.

- **Registration costs** were estimated at $3 million, with the assumption that dossier preparation and submission require between 10 and 15 person-years of effort and that the fully loaded cost of a full-time equivalent (FTE) employee for this work is about $250,000.

## Pipeline attributes

For the remaining three properties included in this analysis (pipeline flow, transition probability, and time in phase), we first estimated values for the current state of the pipeline (Status Quo). We then varied these estimates under two alternative scenarios designed to assess how various actions would change the timeframe and cost of developing an effective vaccine. These values were summarized earlier in Table 6, which is shown again below.

**Table 6. Summary of Low- and High-Improvement scenarios ***

| Scenario | Time in Phase | Probability of success | Pipeline flow |
|---|---|---|---|
| Low-Improvement | - 1 year | 10x increase | +5 candidates per year |
| High-Improvement | - 2 years | 20x increase | +10 candidates per year |

* The data in the table reflect changes in each attribute relative to the Status Quo scenario.

**1. Pipeline flow**

During the years 2003 and 2004, 16 and 13 new candidates, respectively, entered the clinical development pipeline. Most of this project's expert advisors predicted that these numbers will decline in the near term, to be followed by a slate of new candidates based on novel vaccine concepts (i.e., differing from the concepts behind the present batch of products). The consensus was that it would take at least two years for these new candidates to emerge, with a steady flow expected within ten years. These considerations led to the following estimates of how many new candidates will enter clinical trials during the 50-year time period considered in the Status Quo scenario (see Table A2).

**Table A2.** Estimated number of new candidates entering Phase I over the next 50 years

| Year of scenario | No. of candidates |
|---|---|
| 1 | 10 |
| 2 | 7 |
| 3-10 | Random number between 3 and 10 |
| 11-50 | Steady flow of 10 candidates per year |

In asking what increases in the number of new candidates we should build into the Low- and High-Improvement scenarios, we were guided by our initial intention to examine the impact of doubling funding for HIV vaccine R&D, and modeling this rise in spending by increasing the flow of candidates into the pipeline. However, many experts consider it highly unlikely that a doubling of funding would lead to a doubling of candidates, and indeed, with decreasing marginal returns, more resources per candidate would be required. Nonetheless, we felt it was useful to understand the potential impact of doubling the number of candidates on the overall timeline, and therefore chose the following changes in flow scenarios:

- **Low-Improvement scenario:** increase of 50%, corresponding to five more candidates per year
- **High-Improvement scenario:** increase of 100%, corresponding to ten more candidates per year

**2. Transition probability**

The transition probability is the likelihood that a candidate will successfully pass from one phase of development to the next, expressed as a percentage. In the Status Quo scenario, all transition probabilities remain constant throughout the 50-year duration of the simulation.

To estimate the Status Quo transition probability, the team used three different types of information: data on AIDS vaccine candidates evaluated so far (drawn from AIDS vaccine databases), historical benchmarks (i.e., data from other vaccines), and expert input.

- **Historical AIDS vaccine data:** A limited number of vaccines have made the transition from Phase I to Phase II, and only two to Phase III. The limited data available (up to April 2005) lead to estimates of 20% for the probability of

transition from Phase I to Phase II and 38% for the Phase II to Phase III progression.

- **Struck's analysis:** Mark Struck's article "Vaccine R&D success rates and development times" (Struck, 1996a), a widely quoted source of information on transition probabilities and timelines for vaccine development, documents probabilities of 72% in Phase I, 79% in Phase II, and 71% in Phase III. His analysis is based on clinical studies between 1983 and 1994 and uses data from commercial databases that monitor drug development. Several experts we consulted questioned the relevance of these data to AIDS, based on their view that many of the earlier vaccines were easier to develop, and therefore their transition probabilities are overly optimistic relative to expectations for AIDS vaccines.

- **Tufts Center for the Study of Drug Development:** Tufts maintains a database on viral vaccines covering a wide range of infections and containing information on timelines and success rates. Again, our experts expressed concern that the data were overly optimistic for application to AIDS vaccines. Overall, the Tufts data showed transition probabilities of 92% in Phase I, 57% in Phase II, and 76% in Phase III.

Taking all these factors into consideration, the team derived transition probability estimates for HIV vaccines as follows:

- **Phase I and II:** Based on the available data and expert advice, we assumed a transition probability of 20% for Phase I and 38% for Phase II.

- **Phase IIB and III:** Determining the transition probabilities for Phase IIb and Phase III was more challenging, given that only one IIb trial (now ongoing) and three Phase III trials have been launched so far. Based on discussions with a range of experts, the team made a best guess that the probability of moving directly from Phase II to Phase III (i.e., without going through Phase IIb) is 10%.

  However, it looks increasingly likely that Phase IIb trials (rather than Phase III) will become the next step for at least some candidates that look promising in Phase II. In this case, we assumed that the transition probability will be the same as for Phase III. (In other words, a candidate's probability of transitioning through Phase IIb and Phase III is the same as its probability of transitioning through Phase III alone.) The team also assumed that the risk of failure will be much higher in Phase IIb than in III, and that a candidate successfully passing through Phase IIb into Phase III would have a much higher probability of advancing to Registration. Using the Struck benchmark for Phase III transition probability as an upper limit, the team assumed the transition probability at Phase IIb to be 15% and for Phase III to be 65%. However, we retained the 10% estimate for the current candidates in Phase III.

- **Registration:** In both the drug and vaccine fields, benchmarks for transition probabilities for Registration range between 90% and 100%. There is likely to be intense political pressure to approve an AIDS vaccine following a successful Phase

III trial. As such, our team assumed that Registration carries a 95% transition probability, which is conservatively in line with data from Struck.

Turning to the Low- and High-Improvement scenarios, both assumed significant changes in transition probability (10-fold and 20-fold, respectively) over the 50-year time period analyzed in this study. To arrive at these values, we started once again with historical success probabilities for vaccines against a variety of diseases (Struck, 1996a), and then modified them to the circumstances of AIDS vaccines and the different scenarios for accelerating progress.

However, making these estimates was more difficult than for the other two attributes. One big uncertainty was how to model the effects of growing scientific knowledge on the pipeline, in particular on transition probability. One approach is to view progress mostly as the result of a landmark discovery (or series of discoveries) that dramatically changes the field and the overall pipeline probability of success. This "lightning bolt" scenario would be reflected in the model by major improvements in transition probabilities for candidates developed after the big discovery. Another approach views scientific progress as an iterative process with slow but steady improvements, and would be incorporated into the model by increasing the transition probabilities for candidates gradually over time. Based on advice from our expert panel, we used the latter, iterative approach for this study.

Another uncertainty was how to extrapolate transition probability data from other vaccines to HIV vaccines and our hypothetical scenarios. The most comprehensive information on vaccines (Struck, 1996a) estimates the overall probability of success for an individual vaccine at 39% — almost 50 times the pipeline probability under our model's Status Quo assumptions, perhaps reflecting the fact that these earlier products were easier to make than an HIV vaccine. Therefore, we considered these probabilities as an upper boundary beyond which HIV vaccines are very unlikely to progress. Narrowing the range further, it is also unlikely that the pipeline probability of success for an HIV vaccine will exceed that for drugs, suggesting that an overall pipeline probability of 21.5% (the estimate of DiMasi et al., 2003, for a new drug) — approximately 30 times the model's Status Quo assumptions — is a more realistic upper limit. These data are shown below in Table A3.

**Table A3.** Total probability of success for clinical development (Phase I to Registration)

| | **Probability of success** | **Relative to Status Quo** |
|---|---|---|
| Status Quo | 0.7% | - |
| Low-Improvement scenario | 7% | x10 |
| High-improvement scenario | 14% | x20 |
| Drugs[a] | 21.5% | x30 |
| Vaccines[b] | 39% | x50 |

[a] DiMasi et al. (2003)
[b] Struck (1996a)

Mindful of these upper limits, we therefore selected the following transition probability values:

- **Low-Improvement scenario:** The pipeline probability was increased yearly until it reached ten times the original level, over the 50-year timeframe of the model.
- **High-Improvement scenario:** The pipeline probability was increased yearly until it reached 20 times the original level.

**3. Time in phase**

Estimates for the duration of each phase were derived from data on current and previous AIDS vaccine candidates, modified through expert input. Theses revisions were necessary to accommodate the observation that development phases (especially early ones) often overlap, rather than always proceeding in a strictly linear manner where one phase ends before the next one begins.

- **Phase I:** Based on historical experience and the Struck benchmarks, the team estimated Phase I at 24 months. There was some concern that this might be overly optimistic, given recent history and the tendency for some candidates to "languish" at this stage. On more detailed examination, however, the sluggish candidates often turned out to be early versions of vaccines that had been modified and/or are advancing in other Phase I studies.

  The current pipeline includes 22 candidates in Phase I, some of which entered clinical trials prior to 2005. To represent the status of the current pipeline, the team assumed that half of the candidates were at the beginning of the phase and half were 12 months into the phase.

- **Phase II:** Based on historical experience and the Struck benchmarks, Phase II was estimated as 24 months. The current pipeline includes two candidates in Phase II, one of which the team assumed to be early in Phase II and the other 12 months into it.

- **Phase IIb:** Current estimates for the HVTN/Merck Phase IIb trial are approximately four years; however, this could stretch to five years if recruitment of volunteers proceeds more slowly than expected. Assuming that future Phase IIb trials will have a similar size and design, we assumed 48 months as the duration of a complete Phase IIb trial. In the case of a Phase IIb that rolls into a Phase III trial, the team assumed that the combined Phase IIb/III trial would last at least seven years. Assuming 60 months for Phase III development, the expected duration of a rolling Phase IIb was estimated at 24 months (i.e., half of a full Phase IIb). As of April 2005, we assumed the candidate in the HVTN/Merck trial to be at the beginning of the phase.

- **Phase III:** This estimate includes the time needed to establish clinical sites, recruit the trial population, run the trial, analyze the data to determine if the results justify seeking registration, and develop the process for vaccine production (assuming that limited investment in manufacturing capacity has been made previously), along

with the tools for analyzing stability and release at licensure. It assumes only one trial per candidate.

Based on the previous experience at VaxGen, the current Thai trial, and the potential number of participants needed for future Phase III trials, the team estimated Phase III development at 60 months. The current pipeline includes only one candidate in Phase III, and we assumed that this candidate had completed one year of development (i.e., four years until completion of the phase).

- **Registration:** Benchmarks for Registration range from 12 to 18 months for both vaccines and drugs, with some potential for fast-track approval within six months. Registration for vaccines is often at the slower end of this range, due to the complexities associated with gaining approvals for biologics, and can extend longer if approval requires "bridging studies" beyond Phase III — which would happen, for example, if the manufacturing process for full-scale production post-licensure differs significantly from that used during the Phase III trial. However, we balanced this possibility against the expectation that an AIDS vaccine will be fast-tracked in any regulatory review. The team therefore assumed 18 months for registration.

For the two Improvement scenarios, we recognized that there is a limit to how much time could be shaved off the clinical development stage, since vaccine trials involve monitoring volunteers over months or years, depending on the phase, trial design, and regulatory requirements. Time savings during this stage would come mostly from streamlined decision-making about which candidates to advance, and from eliminating delays caused by process development issues, manufacturing problems, or slow recruitment of trial volunteers. For our test scenarios we therefore chose "time in phase" values that represent only modest improvements: the Low-Improvement scenario trimmed one year off the Status Quo total development time of 14.5 years, while the High-Improvement scenario cut two years (see Table A4). However, the limitation in time savings achievable at this stage means that, although reducing time in phase would have an almost immediate impact on reducing the debut timeframe, it also offers the smallest contribution of the three attributes we analyzed to the overall shortening of the vaccine debut timeframe.

**Table A4.** Time in phase under the Status Quo and the Low- and High-Improvement scenarios

| Scenario | Phase I | Phase II | Phase IIb | Phase III | Registration | Total |
|---|---|---|---|---|---|---|
| Status Quo | 2 | 2 | 4 | 5 | 1.5 | 14.5 years |
| Low-Improvement | 1.75 | 1.75 | 3.75 | 4.75 | 1.5 | 13.5 years |
| High-Improvement | 1.5 | 1.5 | 3.5 | 4.5 | 1.5 | 12.5 years |

* Number of years a candidate takes to complete one phase and move to the next.

## Costs for each scenario

To determine costs of the HIV vaccine R&D pipeline, we recorded the annual costs for funding all of the candidates in the pipeline, combined with annual research costs (basic

and applied) for each iteration of the model. These costs were included for all years up through and including the year of vaccine success, and were used to produce the following figures:

- **Average annual cost:** The average (calculated for each iteration of the model) of the total annual costs for year 0 through the year of success.

- **Total cumulative cost:** The sum (calculated for each iteration of the model) of the total annual costs for year 0 through the year of success.

- **Average cumulative cost:** The mean of the total cumulative costs calculated for each iteration of the model, calculated across all 3,000 iterations.

These three measures were calculated for each of the Status Quo and the Low- and High-Improvement scenarios.

## Appendix 2. Expert panel members

**Dr. Supamit Chunsuttiwat**
*Senior Specialist in Disease Control, Ministry of Public Health, Thailand*

Dr. Supamit is Co-Principal Investigator of the Prime-Boost HIV Vaccine Phase III Trial being conducted in Thailand. Prior to his work on the Prime-Boost HIV Vaccine project, Dr. Supamit served in several positions from 1985 through 2000 in the Communicable Disease Center at the Ministry of Public Health, including Director, Division of General Communicable Diseases; Director, Technical Coordination Center; and Section Chief, Viral and Rickettsial Disease. Dr. Supamit earned his medical degree and MPH from Mahidol University in Bangkok.

**Dr. Patricia Danzon**
*Professor, Health Care Systems, Wharton Business School, University of Pennsylvania*

Dr. Danzon is an internationally recognized expert in the fields of health care, pharmaceuticals, insurance, and liability systems. She is a member of the Institute of Medicine and the National Academy of Social Insurance, and is also a Research Associate of the National Bureau of Economic Research. Board memberships include the Board of the International Health Economics Association. She has served as a consultant on international health care issues to the World Bank, the European Commission Working Group on Pharmaceuticals, the New Zealand Treasury, the Asian Development Bank, and U.S. Agency for International Development. In the U.S., her consulting experience includes work for the American Medical Association, the American Hospital Association, the Insurance Services Office, the Institute for Civil Justice, the Alliance of American Insurers, and the Pharmaceutical Manufacturers' Association. Professor Danzon received her Ph.D. in economics from the University of Chicago.

**Dr. Melinda Moree**
*Director, Malaria Vaccine Initiative (MVI)*

Dr. Moree develops and directs the overall strategy and implementation of MVI. Leading the team in advancing malaria vaccine development, she ensures adequate funding to fulfill MVI's mission, the highest quality for all program activities, continued commitment to existing relationships, and the forging of new, focused partnerships. Dr. Moree previously led business development for MVI and helped define the financial and non-financial basis for public-private development efforts. An earlier association with the Program for Appropriate Technology In Health (PATH) included two years as an international health consultant and liaison between PATH and USAID. Dr. Moree has both public and private sector experience in product development and technology transfer. Prior to joining PATH, she was Manager of Advanced Research at EKOS Corporation. Dr. Moree received her Ph.D. in medical microbiology from the University of Maryland at Baltimore.

**Dr. Mike Powell**

*Managing Director, Sofinnova Ventures Inc.*

Dr. Powell joined Sofinnova Ventures in 1997. In his 20 years of pharmaceutical development experience, he worked on 20 clinical products and authored almost 100 papers and books, including a 1,100-page treatise on vaccine design. Prior to joining Sofinnova Ventures, he was Group Leader of Drug Delivery at Genentech (1990-97), where his focus was developing new therapeutics. In 1987 he was part of the founding team of Cytel; as Director of Product Development, he was responsible for the company's early growth that culminated in a successful IPO. Before this he was Scientist and Project Team Leader at Syntex Research. Mike received his Ph.D. in physical chemistry from the University of Toronto in 1981, and completed his post-doctorate work in bio-organic chemistry at the University of California, where he was subsequently a faculty member (1981-84).

**Dr. Jim Tartaglia**

*Vice President, Research and Development-Canada, Sanofi Pasteur*

Dr. Tartaglia is responsible for ensuring that all R&D at Sanofi Pasteur functions operate with maximum efficiency to contribute to the launch of new or improved products, and oversees the company's global HIV vaccine program. Prior to joining Sanofi Pasteur-Canada, he held the position of Executive Director of Research at Virogenetics Corporation of Troy, New York, a former subsidiary of Sanofi Pasteur. While at Virogenetics, he helped develop the poxvirus vector technology as an immunization vehicle for both veterinary and human application. Prior to joining Virogenetics in 1990, he worked as a Research Scientist with the New York State Department of Health and a Post-doctoral Fellow at Roche Institute of Molecular Biology in Nutley, New Jersey. Dr. Tartaglia is an inventor on over 20 patents relating to recombinant vaccines and has authored over 115 publications in the areas of molecular virology and recombinant vaccine technology. He received his Ph.D. from the Department of Microbiology and Immunology at the Albany Medical College.

**Piers Whitehead**

*Vice President, Corporate and Business Development, VaxGen Inc.*

Mr. Whitehead joined VaxGen in July 2002 and is responsible for many aspects of VaxGen's commercial development, including negotiating and managing partnerships and alliances, product sales, and corporate strategy. Mr. Whitehead was formerly a Vice President of Mercer Management Consulting, where he headed that firm's San Francisco office. There he led marketing, strategy, and manufacturing projects, with an emphasis on global health and vaccines, for such clients as the Global Alliance for Vaccines and Immunization (GAVI), UNICEF, and several pharmaceutical and biopharmaceutical companies. Mr. Whitehead received his M.A. in classics at Oriel College in Oxford.

## Appendix 3. List of people consulted

- Steve Black, Director, Vaccine Study Center, Kaiser Permanente
- Supamit Chunsuttiwat, Senior Specialist in Disease Control, Ministry of Public Health, Thailand
- Vaila Clements, Vice President of Corporate Development, Quintiles Transnational
- Patricia Danzon, Professor, Wharton Business School, University of Pennsylvania
- Joseph DiMasi, Director of Economic Analysis, Tufts Center for the Study of Drug Development
- Laura Efros, Director of Vaccine Public Policy, Merck & Co., Inc.
- Mark Feinberg, Vice President, Policy, Public Health and Medical Affairs, Merck & Co., Inc.
- Don Francis, Executive Director, Global Solutions for Infectious Diseases
- Garry Johnson, Director of Corporate Development, Quintiles Transnational
- Peggy Johnston, Director for HIV/AIDS Vaccine Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health
- Mark Mitchnick, R&D Director, International Partnership for Microbicides
- Melinda Moree, Director, Malaria Vaccine Initiative
- Mike Powell, Managing Director, Sofinnova Ventures Inc.
- Janice Reichert, Senior Research Fellow, Tufts Center for the Study of Drug Development
- Steve Self, Director of Statistical and Data Management, HIV Vaccine Trials Network
- Larry Smith, Fiscal Manager, HIV Vaccine Trials Network
- Jim Tartaglia, Vice President, Research and Development, Sanofi-Pasteur, Canada
- Banks Warden, CFO, HIV Vaccine Trials Network
- Mitchell Warren, Executive Director, AIDS Vaccine Advocacy Coalition
- Judy Wasserheit, Director, HIV Vaccine Trials Network
- Piers Whitehead, Vice President, Corporate and Business Development, VaxGen
- Wendy Woods, Vice President, Boston Consulting

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Upperhill Road
PO Box 340 KNH 00202,
Nairobi, Kenya

IAVI—Europe
Herengracht 208
1016 BS Amsterdam
The Netherlands

IAVI—Headquarters
110 William Street
New York, NY 10038
United States

IAVI—India
193 Floor 1, Jorbagh
New Delhi, 110003
India

IAVI—Southern Africa
6 Aubury Park, Unit 0006
Magalieszicht Ave,
Dunkeld West 2196
South Africa