Why We Don’t Have An HIV Vaccine, And How We Can Develop One

The scientific obstacles remain formidable. But the economic challenges are just as real.

by Jeffrey E. Harris

ABSTRACT: Confronted with the recent high-profile failures of several clinical trials of promising candidate vaccines against HIV, many scientists have all but given up hope of producing a human-ready vaccine within the next decade. In this review I contend that although the scientific obstacles remain formidable, the economic challenges are just as real. The groundwork will be laid for a major scientific breakthrough in vaccine development only when there are new contractual structures that enhance private incentives for vaccine development; when we have clearly specified the rights to the profitable North American market; when we have established a system of liability protection for vaccine side effects; and when our clinical trials also test the behavioral consequences of vaccination. [Health Aff (Millwood). 2009;28(6):1642–54]

In the quarter-century since HIV was discovered, scientists have developed hundreds of candidate vaccines in laboratory animals, and more than a dozen have undergone at least early-phase testing in human subjects. Yet not a single candidate has been found to provide adequate protection against HIV infection in humans. Confronted with the recent high-profile failures of the AIDSVAX clinical trials in the United States and Thailand and the Merck/STEP trial in the United States, researchers have all but abandoned hope of producing a human-ready vaccine within the next decade. In his presidential address to the American Association for the Advancement of Science in February 2008, Nobel laureate David Baltimore bluntly summed up the scientific state of affairs: “There is still no AIDS vaccine and no hopeful candidate vaccine.” Even the recent press release from a trial in Thailand that Sanofi Pasteur’s ALVAC combined with booster doses of AIDSVAX reduced HIV infections by 31 percent has been received with skepticism, as previous trials of the two vaccine candidates, either alone or in combination, showed no protective effect.

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In this review I contend that the current pessimism concerning an HIV vaccine is misplaced. Although the scientific obstacles remain formidable, the economic challenges are just as real.

In its 2005 strategic plan, the Coordinating Committee of the Global HIV Enterprise endorsed the creation of a “global community of problem-solvers, more openly sharing information.” In its AIDS Vaccine Blueprint 2006, the International AIDS Vaccine Initiative (IAVI) emphasized “mechanisms such as ‘push’ and ‘pull’ incentives to reduce the risk of early-stage development in [research and development] and to ensure viable markets for AIDS vaccines.” Two years later, Global HIV Enterprise director Alan Bernstein underscored the importance of “maintaining and increasing industry involvement as full partners in the effort.”

These lofty objectives are easy to state. Economists are well aware of the enormous difficulties in designing incentive systems to foster cooperative action among parties with diverse interests. They understand all too well the conflicts inherent in regulatory schemes that promote the public welfare but impinge on individual rights. These problems of institutional design are just as difficult as scientific problems of vaccine design.

How Much Should We Invest In Vaccine R&D?

The scientific obstacles to the development of an HIV vaccine are relative, not absolute. How rapidly we overcome them may depend crucially on the size of our investment in vaccine research and development (R&D). In a world of trade-offs, more money for vaccine R&D will probably mean reduced investment in other prevention strategies as well as smaller budgets for antiretroviral treatment.

Annual worldwide investment in HIV vaccine R&D increased from US$327 million in 2000 to US$961 million in 2007, and then declined to US$868 million in 2008. Exhibit 1 shows the breakdown of investments in R&D for vaccines, microbicides, male circumcision, and pre-exposure prophylaxis in 2008. U.S. public funding has been the principal source of R&D investment in HIV vaccines, most recently contributing 71 percent of total global funding (Exhibit 2). The contribution of commercial sources, including pharmaceutical manufacturers and biotechnology companies, declined from 9 percent in 2007 to 4 percent in 2008, primarily as a consequence of the reduction in R&D investments by Merck, the developer of the STEP vaccine candidate. Concurrently, the contribution of the philanthropic sector has increased to 12 percent of total global funding.

Nearly US$900 million in vaccine R&D appears to be a substantial annual investment, especially in comparison to investments in R&D for other preventive strategies (Exhibit 1). However, for each alternative preventive strategy, we need to ask: What are the prospects of success, and what would be the implementation costs if the preventive strategy were adopted on a large scale? Recent clinical trials of a number of nonvaccine prevention strategies—including such microbicides as the diaphragm with lubricant gel; the SAVVY vaginal gel; cellulose sulfate gel,
and the vaginal BufferGel and PRO 2000 gel, as well as oral acyclovir for herpes virus have resulted in negative or equivocal findings. Thus, it is hardly obvious that R&D funds should be diverted away from vaccine development.

Consideration of implementation costs offers an even more favorable case for

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### EXHIBIT 1
Investment In Research And Development (R&D) For HIV Prevention, By Type Of Modality And Sector, 2008

<table>
<thead>
<tr>
<th>Type of Modality</th>
<th>Public sector</th>
<th>Philanthropic sector</th>
<th>Commercial sector</th>
<th>Total global investment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines</td>
<td>$620</td>
<td>104</td>
<td>28</td>
<td>868</td>
</tr>
<tr>
<td>Microbicides</td>
<td>$154</td>
<td>35</td>
<td>5</td>
<td>244</td>
</tr>
<tr>
<td>Circumcision</td>
<td>$4</td>
<td>4</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>PrEP</td>
<td>$21</td>
<td>21</td>
<td>1</td>
<td>44</td>
</tr>
</tbody>
</table>

**Public sector**
- U.S.: $620
- Europe: $69
- Other: $43
- Total public sector: $731

**Philanthropic sector**
- Philanthropic: $104

**Commercial sector**
- Pharmaceutical companies: $28
- Biotechnology companies: $5
- Total commercial sector: $33

**Total global investment**
- $868
- $244
- $11
- $44


**NOTES:**
- **Millions of 2008 U.S. dollars. PrEP is pre-exposure prophylaxis.**
- **Estimates for commercial-sector investment in vaccines and microbicides included ranges, which are omitted here.**
- **No investment reported.**

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### EXHIBIT 2
Distribution Of Sources Of Research And Development (R&D) In HIV Vaccines, By Sector, 2004–2008

<table>
<thead>
<tr>
<th>Year</th>
<th>U.S. government</th>
<th>Other public</th>
<th>Philanthropic</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>100</td>
<td>60</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>2005</td>
<td>80</td>
<td>40</td>
<td>20</td>
<td>20</td>
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<tr>
<td>2006</td>
<td>60</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<tr>
<td>2007</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>2008</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>


**NOTES:**
- **Commercial sources include biotechnology and pharmaceutical developers.**
- **Estimates for commercial-sector investment in vaccines included ranges, which are omitted here.**
- **Investments by pharmaceutical manufacturers and biotechnology companies exclude grants and contracts from public-sector agencies. These investments are attributed to the funding agencies.**
enhanced investment in HIV vaccines. The five-year cumulative cost of a program to circumcise twenty-six million men in sub-Saharan Africa was recently estimated at US$919 million if circumcisions were paid for by public funds. All nine of the clinical trials of pre-exposure prophylaxis in progress or planned in the United States and other countries will test the ability of the antiretroviral tenofovir, alone or in combination with emtricitabine, to prevent HIV infection. A cost-effectiveness study of pre-exposure prophylaxis in the United States pegged the wholesale price of tenofovir plus emtricitabine at $8,700 annually. If even half of this study’s target population of approximately 2.5 million high-risk men took these two drugs daily for pre-exposure prophylaxis, the annual cost in the United States would exceed $10 billion.

Recent estimates of the global investment required to achieve universal access to the remaining prevention modalities by 2010 (including voluntary counseling and testing, condoms, treatment of sexually transmitted infections, blood safety, and prevention of maternal-to-child transmission) total more than US$15 billion. Global demand for an HIV vaccine over the next three decades could cost US$1.6–US$3.8 billion per year. In the face of such implementation costs for HIV prevention, a US$900 million annual investment in vaccine R&D is hardly impressive.

**Why So Little Commercial Investment In An HIV Vaccine?**

Pharmaceutical manufacturers and biotechnology companies possess much expertise in vaccine development and commercialization. In fact, nearly all of the vaccines in worldwide use today are privately produced, commercial products. Yet the contribution of the for-profit sector to HIV vaccine R&D has been relatively small and is now in decline (Exhibit 2). From the economist’s standpoint, this comes as no surprise. The recent history of attempts to develop an HIV vaccine represents a textbook case in the economics of inadequate private incentives.

- **Dimensions of risk.** Investment in HIV vaccine development is an extraordinarily risky enterprise for a profit-making firm. Three dimensions of risk are most critical. First, the demand for a vaccine is highly uncertain. It will depend not only on the vaccine’s efficacy, duration of protection, and price per dose but also on volatile political decisions by governments to implement large-scale vaccination programs. The innovative concept of an advance market commitment has been proposed as a means of reducing uncertainty in demand. In practice, this financing mechanism appears workable primarily for the procurement of a vaccine that has already been developed, as in the case of pneumococcal vaccine.

Second, international political pressures may prevent a successful HIV vaccine developer from charging enough to recoup its investment and manufacturing costs. For many other vaccines, regulatory authorities in various countries have permitted manufacturers to practice price discrimination—that is, charge higher prices in industrialized countries. But in the case of HIV, there is a genuine risk
“At least so far, the gains from HIV vaccine development have been an all-or-none proposition.”

that some countries may compel a successful developer to license the vaccine below cost to a generic manufacturer. Such compulsory licensing is already prevalent in the market for antiretroviral drugs.28

Third, at least so far, the gains from HIV vaccine development have been an all-or-none proposition. Although the scientific community learned a lot from the recent failures of the AIDSVAX and Merck/STEP vaccine candidates, the manufacturers of these vaccines were unable to convert any of these incremental advances in scientific knowledge into private gains. This inability is well known to economists as an example of the problem of public goods.

- AIDSVAX and VaxGen. The human immune system has two main lines of defense: antibodies and “killer” cells. Antibodies prevent infection. Killer cells control infection. Essentially all vaccines that medical science has thus far devised to protect against viruses induce the human immune system to produce neutralizing antibodies, which inactivate the viral invader before it can cause a lot of damage. Vaccines against such infections as measles and human papillomavirus (HPV) are stand-alone vaccines. Although adequate protection may require multiple doses to remind the immune system to make enough antibodies, no other intervention is required.

If there is to be a stand-alone vaccine that prevents HIV infection, then such a vaccine will likewise have to induce the human immune system to produce neutralizing antibodies against the most important subtypes of HIV.29 Unfortunately, the candidate vaccines so far tested in humans do not stimulate the production of broadly neutralizing antibodies.30 That was the principal explanation for the downfall of the two versions of the promising AIDSVAX vaccine that were recently tested in large clinical trials in the United States and Thailand.2

AIDSVAX was the product of VaxGen, a relatively small U.S. biotechnology company spun off from the larger firm Genentech in 1995. Both versions of AIDSVAX were purified forms of a signature molecule on HIV’s outer skin called gp120, which developers hoped would stimulate the immune system to produce neutralizing antibodies. The first candidate (AIDSVAX B/B) was derived from HIV subtype B, which is the dominant strain in North America, South America, Europe, Japan, Australia, and other locations where the virus is transmitted principally by man-to-man sex or sharing of drug injection equipment. The second (AIDSVAX B/E) was derived from subtype B and a hybrid strain circulating in Southeast Asia. By October 1999, VaxGen had enrolled more than 5,400 volunteers into a Phase III clinical trial of AIDSVAX B/B in North America and the Netherlands. By August 2000, the company had enrolled more than 2,500 volunteers into a separate Phase III trial of AIDSVAX B/E in Bangkok.31

Notwithstanding these favorable developments, VaxGen’s filing with the U.S.
Securities and Exchange Commission (SEC) in mid-2002 contained a revealing enumeration of “Risk Factors.”31 The ongoing trials might be unable to retain volunteers, or they might reveal unanticipated adverse reactions, or they might show no protection against HIV infection. Even if the vaccine proved effective, government inspectors might find fault with the company’s manufacturing facilities. Regulators might require additional clinical trials. A US$122 million joint venture with South Korean investors to manufacture more than 200 million doses of AIDSvAX annually might fall through. Contracts with government agencies might not be renewed. Even if a commercial product were brought to market, adverse publicity about side effects could damage sales and result in product liability suits.

In February 2003, VaxGen announced that AIDSvAX B/B did not reduce the incidence of HIV infection. Within days, the HIV Vaccine Trials Network decided to cancel another clinical trial of AIDSvAX B/B that had been in the works.32 VaxGen attempted to soften the blow by reporting an after-the-fact subgroup analysis indicating that black and Asian vaccine recipients developed higher levels of antibodies against HIV and lower rates of infection than unvaccinated black and Asian participants. But this finding may have had little if anything to do with race or ethnicity or with the vaccine itself, and may simply reflect the fact that participants with better innate antibody responses had greater resistance to infection.33

In November 2003, VaxGen announced that AIDSvAX B/E likewise showed no protection against HIV infection. Although government agencies continued to fund analyses of both clinical trials, no further contract support for AIDSvAX development was forthcoming. Initially, VaxGen had been able to parlay its technical expertise into separate government contracts to develop anthrax and smallpox vaccines. These contracts, too, were ultimately cancelled.34

There remain promising strategies to develop a protective vaccine that stimulates the adequate production of neutralizing antibodies,35 including antibodies to gp120.36 In fact, the negative findings of the two AIDSvAX trials have given researchers greater insight into the ways in which the signature chemical components of HIV evade recognition by the human immune system. It is unlikely, however, that any these advances will redound to the benefit of VaxGen. Even if the recently reported combination of AIDSvAX B/E and Sanofi Pasteur’s ALVAC turns out to have commercial value, it may come too late for VaxGen’s stockholders, as the company negotiated the rights to the AIDSvAX vaccine to Global Solutions for Infectious Diseases, a nonprofit foundation, in 2008.6

■ The Merck/STEP vaccine. The lack of success in developing a vaccine to stimulate production of neutralizing antibodies has led researchers to pursue the alternative strategy of developing vaccines to enhance the production of killer cells that would keep the infection contained.30, 37 The induction of killer cells was one of the novel features of the Merck vaccine employed in the STEP trial in the United States.4 Although no data are publicly available, Merck’s total investment in vaccine
R&D was likely to have been several hundred million dollars. Unfortunately, the STEP vaccine neither prevented recipients from getting infected nor controlled the reproduction of the virus once they were infected. The STEP trial was abruptly halted in September 2007 when the vaccinated group was found to have a higher rate of HIV infection than the unvaccinated group. As a direct consequence, the Phambili trial of the same vaccine in South Africa was cancelled, while the so-called PAVE-100 vaccine, which had been proposed by the U.S. Partnership for AIDS Evaluation for testing in Africa and the Caribbean, was also put on hold. Despite Merck’s continuing investment in prevention and treatment of HIV, its recent annual filings with the SEC make no mention of any specific plans to pursue the STEP vaccine.

Scientific and economic setbacks. Much has been made of the fact that the failures of AIDSVAX and STEP represent scientific setbacks. Perhaps even more important is the fact that they represent economic setbacks. Large pharmaceutical companies, scientist-entrepreneurs, and investors in biotechnology start-ups have observed how VaxGen and Merck incurred substantial sunk costs that could not be recouped by resale of manufacturing assets or marketing of intermediate technologies. There has been much talk about the need for sharing of preliminary data, biological samples, and laboratory techniques. From the economist's standpoint, what is most essential is a mechanism for sharing risk.

Containment Vaccines

The negative results of the STEP trial do not by themselves invalidate the concept of a vaccine that contains rather than prevents HIV infection. It is conceivable, in fact, that a containment vaccine could still serve as a stand-alone measure. It is entirely plausible that such a vaccine could greatly reduce the burden of HIV disease worldwide, especially if it reduced the probability that an infected person could transmit the virus to others.

Combination with pre-exposure prophylaxis. There is growing interest in the possibility that a future vaccine will be used in combination with other preventive strategies such as counseling to reduce risk taking among recipients who assume that they are fully protected. A logical step, in fact, would be to administer a containment HIV vaccine in combination with antiretroviral agents. Under such a scenario, we need to ask: How can we structure incentives so that containment vaccine developers and manufacturers of antiretrovirals act cooperatively?

In 2008 the total commercial-sector investment in pre-exposure prophylaxis was just over $1 million (Exhibit 1). The only pharmaceutical firm participating in clinical trials of pre-exposure prophylaxis was Gilead Sciences, the manufacturer...
of tenofovir and emtricitabine (the only two antiretroviral agents to be evaluated). Economists need to ask: Why only Gilead Sciences, and why only its two drugs?

A scientifically reasonable answer is that these two drugs are long-acting medications that need be taken only once daily. They have a low propensity toward the development of resistance and a low incidence of side effects. An economically reasonable answer is provided in a fact sheet on a clinical trial of tenofovir plus emtricitabine (marketed as Truvada) in HIV-negative high-risk women in Kenya, Malawi, Tanzania, and South Africa. “Gilead Sciences, which makes Truvada, is providing the drug free for this clinical trial,” the fact sheet reads. “If Truvada is found to be safe and effective for HIV prevention, Gilead Sciences will make a good-faith effort to provide Truvada for this use. The company has also provided technology transfer of Truvada to companies that produce generic drugs.”

Therapeutic or preventive? A more telling answer is that antiretroviral medications are a safe and profitable investment as therapeutic agents, but they are a risky and potentially unprofitable investment as preventive agents. Once people are infected with HIV, they have a much higher willingness to tolerate drug side effects, to accept the possibility that the drug may not work, and to pay a larger percentage of the drug’s cost. HIV-infected individuals are, in short, good customers. The same need not be true for individuals who are free of disease. A seriously ill patient with advanced HIV disease may find it entirely acceptable to take an antiretroviral drug that may cause nausea, fatigue, impaired kidney functioning, and even fatal lactic acid buildup in the blood. By contrast, the occurrence of serious side effects in otherwise well individuals might expose the manufacturer to legal liability.

The developer of a containment vaccine may very well need the cooperation of a drug manufacturer to carry out clinical trials and ultimately bring the product to market. Achieving such cooperation will require careful specification of the property rights of vaccine developers and drug manufacturers, who would otherwise have strong economic incentives simply to market their product as a stand-alone therapy for people with advanced HIV disease. This is an example of the difficult problem of designing complex transactions when the parties would benefit from cooperative action, but where property rights are not well defined—a problem first described in 1960 by Nobel Prize–winning economist Ronald Coase. As economists well know, grandiose expressions of cooperation will not suffice. Each party to the transaction wants to know: What’s in it for me?

Should We Rethink Our Standards For Human Testing?

Adequacy of nonhuman testing. Nonhuman testing has proved strikingly inadequate to assess candidate HIV vaccines. Test-tube analyses of the ability of antibodies to neutralize HIV have not proved to be consistently reliable indicators of their ability to neutralize HIV in the human body. Animal models of retroviral infection, including models in nonhuman primates, have not so far accurately predicted the human response to many vaccine candidates. Consequently, we may need to re-
Should we lower the threshold for ‘go’ versus ‘no-go’ decisions about proceeding with human testing?"

assess our standards for screening vaccine candidates and instead move more rapidly to early-phase human testing. This will require careful reassessment of the rights of human subjects to participate in potentially risky clinical trials, particularly in settings where the incidence of HIV infection is very high.

Monkeys constitute the most important species for testing candidate vaccines against HIV. Because monkeys do not contract HIV, researchers have instead produced experimental infections by injecting one of two genetically related viruses—simian immunodeficiency virus (SIV) or simian-human immunodeficiency virus (SHIV)—into the animal’s bloodstream. To be sure, HIV is also transmitted in humans by the blood-borne route through needle sharing, transfusion, and maternal-to-child transmission. However, the vast majority of natural human HIV infections entail the invasion of a mucosal barrier—that is, the tissues lining the vagina, the penile urethra, or the rectum. There is mounting evidence that the human body’s first-line immune response at the mucosal surface is essential in preventing HIV from passing quickly to distant organs and causing long-lasting damage. Yet this critical step is bypassed in experimental monkey models.

This is not to say that animal models are useless. Still, we do not yet know the magnitude and breadth of the neutralizing antibody response or the killer-cell response required to protect human beings, and animal models are unlikely to give us the answer. It is hardly comforting that the Merck/STEP vaccine stimulated a killer-cell response in monkeys infected with SHIV, but not in monkeys infected with SIV. This discordance has engendered considerable debate as to which primate model, if any, closely mimics HIV infection in humans. Inevitably, we must ask: Given the peculiarly human characteristics of HIV infection, why not expand clinical investigation and early-phase testing in human subjects?

Trials of nonvaccine preventive measures. The Institute of Medicine (IOM) recently concluded that many apparently negative trials of nonvaccine preventive measures were marred by inadequate statistical power, primarily because the baseline HIV incidence was overestimated during trial design. The need to perform evaluations in regions with sufficiently high HIV incidence applies just as well to vaccine trials. This leads us to ask: In regions of the globe where the incidence of HIV is highest and where other preventive and therapeutic options are least available, should we lower the threshold for “go” versus “no-go” decisions about proceeding with human testing?

Unblinding the blind. In the classic clinical trial, both the subjects and the experimenter are blinded as to who receives the intervention or the placebo. As the recent IOM report noted, this research design does not measure how the experimental subjects might have changed their risk-taking behavior if they knew they had re-
ceived the intervention. Thus, a prostitute who thinks that she is being protected by a microbicidal gel may decide not to insist on a condom. In fact, one hypothesis explored in the aftermath of the Merck/STEP trial was that men who thought they received the real thing engaged in riskier sexual practices.

To assess the behavioral response to vaccine interventions, we need to design clinical trials that have both blinded and unblinded arms. That way, the effect of the subject’s knowledge of his treatment can be directly measured.

**Is All Of The Money In A Subtype-B Vaccine?**

The scientific community is well aware of the enormous challenges posed by the genetic diversity of HIV. It is widely recognized that one vaccine may have to be tailored to subtype B, which dominates in North America, Europe, Australia, the Caribbean, and much of South America, while another may have to target subtype C, the dominant strain in the southern cone of Africa and in India. Still other vaccines may have to target types A, F, G, H, J, and K, which are highly prevalent in the remainder of sub-Saharan Africa, as well as a hybrid of A and E circulating in Southeast Asia.

Economists have a different take on this alphabet soup of genetic diversity. The AIDSVAX B/B and Merck/STEP vaccines were targeted to subtype B, which is seen among injecting drug users and—more importantly—among men who have sex with men. The latter population constitutes a consumer group with a substantial willingness to pay for HIV prevention. Consequently, there is a much stronger private incentive to market a subtype B vaccine than any of the remaining subtypes. It should come as no surprise that in July 2002, with the AIDSVAX trials still in progress, Genentech reserved the right to market AIDSVAX B/B in North America. In short, subtype B is where the money is.

A recent International AIDS Vaccine Initiative (IAVI) report noted that “whenever IAVI grants rights to industrial partners to develop and distribute vaccines arising out of IAVI-sponsored collaborations, those partners must agree to a set of ‘access commitments.’ These commitments provide that any vaccine will be promptly registered, manufactured in adequate quantities and distributed at reasonable prices in the developing world.” Although a commercial firm that participates in an IAVI-sponsored collaboration may agree in advance to practice price discrimination in developing countries, it will surely insist on retaining the rights to sell the subtype B version of its vaccine in North America.

**Who Bears The Risks For Vaccine Side Effects?**

We have not squarely confronted the problem of risk bearing for vaccine side effects. In the United States, the National Vaccine Injury Compensation Program has proved to be an effective system of government-based insurance against the risks of childhood vaccines. But the case of HIV vaccine-related risks is likely to be far more complex. In particular, many candidate vaccines contain live non-HIV
viral “vectors” that may themselves increase the possibility of unanticipated side effects. The adenovirus-5 (AD5) vector, which was employed in the Merck/STEP trial, was initially thought to be a harmless common cold virus. Yet some scientists have raised concerns that AD5 enhanced the risk of contracting HIV infection, particularly in uncircumcised men.\textsuperscript{3, 4, 48, 50}

The IOM’s very first Committee on a National Strategy for AIDS (of which I was a member) noted in 1986, “Unless problems of vaccine liability are dealt with swiftly and effectively, no manufacturer may be willing to produce HIV vaccine for use in the American market.”\textsuperscript{51} This observation is as apt today as it was nearly a quarter-century ago.

**How Do We Get There From Here?**

The view that an HIV vaccine is unattainable and that investing heavily in vaccine R&D is simply shoveling money into a bottomless pit is just plain wrong. But investment has to do more than fund research. It has to change incentives.

New public-private contractual structures are required to reduce economic risks for vaccine developers. These include rewarding firms for intermediate endpoints rather than all-or-none-payment for vaccine delivery; clearly specifying rights to the profitable subtype B market in North America; providing antiretroviral manufacturers with stronger incentives to participate in joint ventures involving containment vaccines; and establishing a system of liability protection now rather than later. To proceed more rapidly to human testing, new institutional arrangements are required between manufacturing countries and testing countries, where HIV incidence is highest. Clinical trials need to include blinded and unblinded arms to assess the effect of a recipient’s knowledge of vaccination. Instituting these changes will be every bit as important for HIV vaccine development as getting the science right.

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**NOTES**


