

## The Search for Effective HIV Vaccines

Howard Markel, M.D., Ph.D.

In February 2003, after more than a decade of work, a team of scientists representing the biotechnology company VaxGen announced the results of the first phase 3 trial to test the efficacy of a vaccine against the human immunodeficiency virus (HIV). Despite the highest of hopes, their product, AIDSVax — which contains a synthetic monomeric glycoprotein based on glycoprotein 120 (GP120), the CD4-binding site on the outer coat, or envelope, of the virus — did not prevent HIV infection in the study cohort as a whole. It was a frustrating setback for HIV-vaccine research, a field that has endured a Sisyphean onslaught of disappointments. But if the virus that causes AIDS is persistent, the vaccine researchers are no less so. Indeed, on July 14, 2005, the National Institute of Allergy and Infectious Diseases (NIAID) announced a grant of more than \$300 million for a new Center for HIV/AIDS Vaccine Immunology. The center aims to address key immunology roadblocks to HIV-vaccine development and to design, develop, and test novel vaccine candidates.

As of this writing, two phase 2 trials that are testing therapeutic HIV vaccines are under way — these vaccines are designed not to prevent infection but, rather, by stimulating T lymphocytes that can identify and kill HIV-infected cells, to prevent or limit viral replication and delay disease progression. Although experts have not given up the ultimate goal of a preventive vaccine, they

are hopeful that a therapeutic vaccine will, at least, help stem the devastating tide of disease, disability, and death from AIDS.

Because the AIDS epidemic has occurred at a time when medical science is progressing at a rapid clip, unrealistic expectations or promises about its conquest have played a supporting role in

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this drama since the epidemic's earliest days. Historians have pinpointed April 23, 1984, as the moment of the most wildly optimistic prediction about an AIDS vaccine. At a press conference in Washington, D.C., at which the identification of the virus we now call HIV was announced, Margaret Heckler, the Secretary of Health and Human Services, proclaimed that a preventive vaccine would be ready for testing within two years.

Several scientists seated in the packed auditorium “blanched visibly” at Heckler’s declaration.<sup>1</sup> Their reaction was understandable. After all, it had taken 105 years to develop a vaccine for typhoid after the discovery of its microbiologic cause; the *Haemoph-*

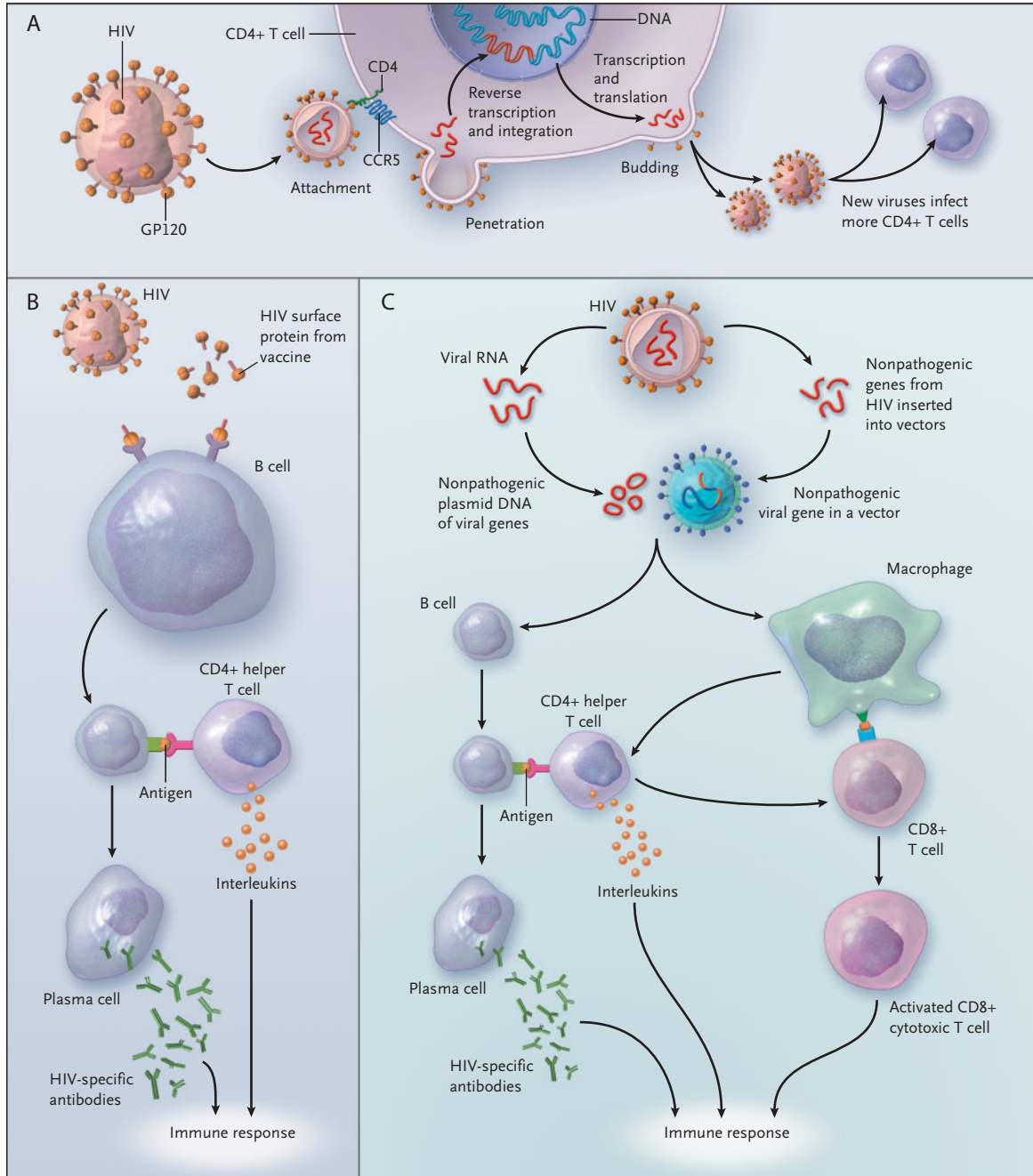
*ilus influenzae* vaccine took 92 years; pertussis vaccine, 89 years; polio vaccine, 47 years; measles vaccine, 42 years; and hepatitis B vaccine, 16 years.

And so, after a mere 21 years, we continue to struggle to contain the pandemic of our age. This year, 34 candidate HIV vaccines are in the early phases of human clinical trials in 19 countries. But, as in 1984, a safe and effective preventive vaccine remains elusive.

Some delay can justly be blamed on inadequate funding. According to Mitchell Warren, executive director of the AIDS Vaccine Advocacy Coalition, in New York, “Last year, about \$680 million, primarily from the public sector but in smaller amounts from the private sector and philanthropy, went toward the development of AIDS vaccines — less than 1 percent of the total global spending on health-product research and development.”

During the past century especially, the major pharmaceutical companies have led the way in developing most vaccines. Yet when it comes to HIV, many of these companies have been slow to participate, in part because there is so much uncertainty about which approach is most promising (see diagram) and in part because the return on the massive investment required is likely to be small, especially as compared with the profits generated by blockbuster drugs such as statins or antidepressants.

“A substantial proportion of



**Approaches to HIV-Vaccine Development.**

The mechanism of normal HIV infection is shown (Panel A), along with the mechanisms of three types of potential vaccines: a subunit vaccine containing a synthetic protein from the CD4-binding site on the envelope of the virus (Panel B), a naked DNA vaccine, and a recombinant vaccine with a bacterial or viral vector (Panel C).

the entire investment in AIDS vaccines comes from the National Institutes of Health,” notes Dr. Anthony Fauci, the director of NIAID. “We need to overcome the scientific barriers to the point that leads industry to say we can afford to get involved. But . . . at the end of the day, we — and academe — must partner with industry. The government or universities do not manufacture vaccines, the pharmaceutical companies do.”

But even if we could vanquish the economic challenges, as well as the myriad cultural, social, and ethical problems that attend the development of any vaccine, there remains one Himalayan obstacle: the remarkable pathogenic power of HIV itself. Even now, scientists do not know the correlates of immune protection — the specific types of immune responses that an effective HIV vaccine must stimulate in order to prevent infection.

Typically, successful immune responses against viral infections include humoral and cellular components. The humoral reaction yields virus-neutralizing antibodies that prevent viral particles from infecting new cells. The cellular response mobilizes specific CD8+ cytotoxic T lymphocytes that target and kill cells that express viral antigens. Thus, an optimal HIV vaccine would elicit both types of responses.

Unfortunately, HIV has a large menu of mechanisms that enable it to undermine immune responses. “HIV is astounding,” says Fauci. “Of the 60-million-plus people who have been infected

with it, there’s not a single documented case of someone who has ultimately cleared the infection from his or her body. The initial infection wipes out specific immune responses, the virus permanently integrates into the host cell’s chromosome and establishes what appears to be a permanent reservoir of infected cells, and . . . the antigens that induce broadly reactive neutralizing antibodies do not appear to present themselves in a way that allows the host to elicit a protective immune response.”

Moreover, the plasticity of the virus affords a steady stream of new variants by means of frequent mutation and, sometimes, recombination. Three major groups of HIV have been identified to date, and these have been divided into nine subtypes or clades. Consequently, any effort to create a vaccine must use the broadest possible range of HIV isolates from around the globe and will demand constant surveillance of the virus in ensuing years.

Another vexing problem has to do with an evolving understanding of the routes of infection. Although many people become infected through the bloodstream, 90 percent of HIV infections are contracted through sexual transmission, with the virus crossing the mucosal tissues that line the genital tract, the rectum, and other body cavities.

In April, researchers reported that within days after macaques become infected with simian immunodeficiency virus — a close relative of HIV — it destroys more than 50 percent of the memory

CD4+ T cells in their guts.<sup>2,3</sup> Studies of HIV infection in humans show a similar loss of intestinal memory CD4+CCR5+ T cells.<sup>4,5</sup> These findings have convinced many AIDS experts that the mucosal immune system in general, and the intestinal immune system in particular, is the primary site of viral replication and persistence, as well as the site of the loss of CD4+ T cells. Some now argue that, although the role of the gut in the pathogenesis of the infection is still poorly understood, vaccine strategies that target this type of immunity may revolutionize HIV research and therapy. Dr. Lawrence Corey, a vaccine researcher at the University of Washington, notes that “until now, we never felt the gut was that much different from, say, the bloodstream. But it is. It’s a major target for HIV in the first two weeks of infection, and we never see patients that early, making the concept of utilizing a therapeutic vaccine to stabilize or preserve immunity among HIV-infected persons . . . difficult.”

During the mid-1980s, scientists identified GP120 on the envelope of the virus as the CD4-binding site, the region that attaches to human cells and facilitates the entry of HIV. As a result, much energy was spent on developing a vaccine based on genetically engineered GP120 and the larger glycoprotein GP160 to prevent the acquisition of infection. This was the approach taken by VaxGen in designing its vaccine.

Although AIDSVax failed to

provide protection against infection, its failure held some critical lessons: the structure of the HIV outer envelope differs from the structure of monomeric GP120, and the outer membrane of circulating HIV strains hides its epitopes in a variety of ways that genetically engineered GP120 proteins do not mimic successfully. The viral glycoproteins appear to have a protective shield, consisting of variable loop sequences and extensive *N*-linked glycosylation, that makes them relatively resistant to antibody neutralization. There is little evidence suggesting that these difficulties can be surmounted anytime soon.

One of the sentinel observations of the natural history of HIV infection is that although some amount of T-cell depletion occurs in everyone who is infected, the virus is usually controlled for at least several years before it begins multiplying so rapidly that the immune system is destroyed. This temporary control corresponds to the presence of high numbers of T lymphocytes that can identify and kill HIV-infected cells. Such findings have led scientists to explore vaccines that stimulate these T cells, even though they do not prevent initial infection, in the hope of preventing or limiting viral replication and delaying disease progression.

A number of such vaccines are now being tested. Some are live-vector vaccines containing a bacterium or virus that has been modified so that it does not cause disease but can transport a gene or genes into the body that will make one or more HIV

proteins and confer some immunity. For example, a canarypox-vector vaccine containing HIV genes for both internal and envelope HIV proteins is being tested in a phase 3 trial in Thailand, but preliminary data on its immunogenicity are not encouraging.

Another vaccine, now in the early stages of a “proof of concept,” or phase 2B trial, contains replication-defective adenovirus type 5 that transmits the HIV genes *gag*, *pol*, and *nef* (which code for internal HIV proteins and may stimulate cellular immunity); this vaccine looks far more promising. The trial, a collaboration between Merck and the NIAID-funded HIV Vaccine Trials Network, is being conducted under the direction of Dr. Corey. So far, only about 250 people have been enrolled in the United States, Peru, Brazil, and the Caribbean, but the target is 3000 volunteers.

A different and propitious candidate, which is being developed at NIAID’s Vaccine Research Center and is currently in a phase 2 trial, entails a combination approach: first, a vaccine is administered that uses naked DNA to prime an immune response to both internal HIV proteins and external HIV proteins; then, a booster shot involving an inactivated adenovirus vector is administered, which stimulates specific antibody responses to HIV envelope proteins and internal proteins. The hope is that this prime–boost strategy will be far more potent than the single adenovirus-vector or canarypox-vector vaccine and that it will ad-

dress some of the challenges posed by the diversity of envelope proteins found among the various HIV isolates throughout the world.

When asked whether changing the focus from prevention to therapy turns the concept of vaccination upside down, Dr. Gary Nabel, the director of the Vaccine Research Center, explains that what we are really doing is testing immune concepts. “I am an empiricist,” says Nabel. “I will look for any kind of protection we can get. In the end, we are searching to identify the critical immune parameters that will predict success in protecting against infection or disease. We need to define both variables.”

“These cellular-immunity-producing vaccines are primarily blunting mechanisms to dampen the progression of infection,” said Fauci, “but if they do work, we will be scrambling to produce one in combination with a vaccine that would induce neutralizing antibodies to protect against infection. This should be seen as a first step rather than an end point. No one is relying on these vaccines alone.”

But a comprehensive vaccine has yet to be found. Dr. James Curran, the dean of Emory University’s School of Public Health in Atlanta, was the director of AIDS research at the Centers for Disease Control in 1984 when he heard Margaret Heckler make her vaccine prediction. He recalls that afternoon well, and even today, despite our inability to predict with any certainty when we will have a vaccine, Curran counsels optimistic patience.

“Secretary Heckler was actually responding to a reporter’s question,” he said, “and I think her answer was a natural response that still occurs in an era of rapid scientific progress. Everyone understands we need a vaccine, and I think people back then were caught up with the enthusiasm of our initial successes. We now know that it is considerably more complicated.”

Dr. Markel is a professor of the history of medicine and a professor of pediatrics and communicable diseases at the University of Michigan Medical School, Ann Arbor, where he directs the Center for the History of Medicine.

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## Occupational Hazards

Ted Louie, M.D.

It was a gray Sunday in late February 1993, no longer cold enough for skiing or ice-skating but still chilly and windy enough to be oppressive. As a senior medical resident, I was glad to have a rare weekend off. Unfortunately, my fiancée, also a resident, had to do rounds that morning. She had started to cough and feel fatigued the night before, and I had tried to persuade her to stay home, but she wouldn’t consider it. That was Mei — strong-willed, no-nonsense, dedicated. When there was a job to do, she did it, with verve and passion and with a sweet but determined smile on her face.

I expected her to call me after rounds, but the whole morning went by while I waited restlessly. When the call finally came, Mei’s greeting was not the cheery one I was accustomed to.

“It’s Mei,” said a flat, distant voice. “I’ve been stuck by a needle.”

She had visited a patient who

was dying of AIDS, a gaunt, emaciated cocaine addict who had had intermittent fevers for many weeks. Residents are trained to do blood cultures in febrile patients as a matter of course. The intern was unable to draw the blood, so Mei did it. Ordinarily, she was among the best phlebotomists around, but this day, she was becoming feverish herself. Weak and shaky, she had inserted the needle into the patient’s vein, but as she withdrew it, she had miscalculated, and the blood-laden needle pricked her hand. She had disposed of the sharps properly and quickly washed the hand. Then the horror began to sink in.

We spent much of the remainder of the day on the telephone, talking to the emergency room physician, the chief resident, the infectious-disease fellow, and the infectious-disease attending. We both knew exactly what they would say — that zidovudine prophylaxis might be

of help, that it should be started quickly, that the chances of acquiring the human immunodeficiency virus (HIV) through a needle stick were relatively low — but we needed to hear all that repeated over and over, in soothing tones. The prescription for zidovudine was duly called in to the pharmacy, and I picked up the medicine. Mei now had a high fever and a dry cough. The antiviral drug made her feel worse. Every five hours, I roused her to take the pills; they gave her a headache, anorexia, and nausea and eventually turned her fingernails black. She curled back into a fetal position and slept fitfully, keeping the light on, waking with a start from time to time.

Until that fateful moment, Mei had never considered her own mortality. Patients might die around her, but like many young physicians, she felt somehow immune to their diseases. Now, as she replayed the accident in her mind thousands of times, while