

tend to have more problems. There was a great deal of talk about preventive care, but what really happened, as far as I could see, was that successful HMOs were able to siphon off billions of dollars and become the corporations they are today by taking care of young, healthy, employed, middle-class people. Switching to HMOs became a way of protecting employers and their employees from the cost of taking care of the less-well — and the less-well-off — patients whose ever-increasing health care costs then had to be borne by a diminished pool of insurance purchasers. In a similar way, by excluding large categories of care and people with preexisting conditions, managed care made enormous profits, not a dime of which was ever returned to patients in the form of reduced premiums.

I can't help suspecting that underneath all these quality-improvement and pay-for-performance initiatives lies yet another scheme that will work out very well for insurers and very badly for providers and patients. The tens of thousands of dollars I'm going to lose out on for failing to achieve my electronic-prescribing or obesity-management goals has certainly caught my attention, but it's not

the big prize. The big prize will come from creating a multitude of grading systems that rate doctors against one another, making them increasingly dependent on quality-improvement goals and payments while distracting them from patient care and making reimbursement more complicated than ever. Overhead will go through the roof. My practice already needs a full-time nurse and receptionist dedicated exclusively to quality-improvement initiatives. The incentives for getting rid of sick and poor patients will be stronger than ever. During the past 25 years, I have stayed current and eagerly sought out and adopted every new advance that could possibly help me to help my patients, but from where I sit, these programs seem to have everything to do with money and power and next to nothing to do with improving care.

Meanwhile, U.S. doctors today have less and less to say about the care of their patients. All the complex lessons they learned in medical school are being swept aside for template care. Maybe I overestimate the next generation, but I can't imagine that young, creative people who are bright and talented enough to get into medical school will put up with this

nonsense for very long. They aren't becoming physicians so they can fill in checklists and be told by a phone-bank operator what they can and cannot do for patients.

The way things are going, I fear that soon, because there is no code or template for it, I'll have to stop being curious about my patients. Open-ended questions and waiting for patients to tell me what's on their mind will have to go. No one will die, but I, for one, will be a little lonelier. And if these so-called quality-improvement programs turn out to be elaborate cost-shifting schemes, many sick people will be deprived of medical care, and the overall costs for all of us will go up.

At a minimum, we should be working harder to determine whether these programs really will improve care before adopting what is a very radical and far-reaching change in the way medical care evolves and is delivered. If we adopt a multitude of quality measures that have not been validated, we are very likely to end up with more quality problems than we started with. We all went to medical school — if all else fails, we could try science.

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One Step Forward, Two Steps Back — Will There Ever Be an AIDS Vaccine?

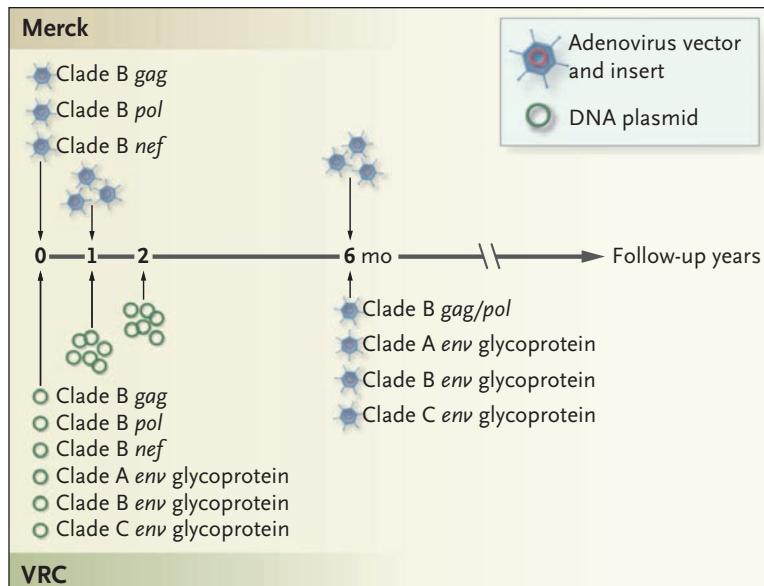
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In April 1984, when the human immunodeficiency virus (HIV) and AIDS were just beginning to be understood, a senior official in the Department of Health and Human Services stated at a press conference that there would be a marketable vaccine within “a min-

imum of two years, probably more like three years.”¹ This prediction has haunted the search for an AIDS vaccine, whose most recent setback was the announcement that a promising vaccine candidate, Merck's V520, was not effective and may actually have increased

some subjects' risk of acquiring HIV. Unfortunately, about a quarter-century after the discovery of HIV, there is neither a marketable vaccine nor a credible expectation about when there will be one.

A successful HIV vaccine would either prevent infection or reduce



Composition and Timing of Administration of the V520 Vaccine (Top) and the Vaccine Developed by the NIH (Bottom).

For the Merck vaccine candidate, a replication-deficient adenovirus type 5 was engineered to contain the *gag*, *pol*, or *nef* genes of HIV. This vaccine was given to volunteers at 0, 1, and 6 months. For the Vaccine Research Center (VRC) vaccine, a mixture of six DNA plasmids containing the *gag*, *pol*, *nef*, *env* A, *env* B, or *env* C genes is given to volunteers at 0, 1, and 2 months. At month 6, one injection of a different replication-deficient adenovirus type 5 is given; this was engineered to contain the *gag/pol*, *env* A, *env* B, or *env* C genes.

the viral load in persons who became infected, helping them to remain healthy and perhaps reducing their likelihood of transmitting the virus to others. But vaccine developers face many scientific challenges, including those posed by the genetic diversity and rapid changes of the viral envelope proteins and other features that allow HIV to elude immune control.² Critical immunologic responses that would prevent infection or control the virus are incompletely understood. Nonetheless, there has been considerable interest in vaccines, such as V520, that induce primarily T-cell responses, because numerous studies have provided evidence of the role of T-cell immunity in controlling HIV infection.

The V520 vaccine consists of three injections of a recombinant, replication-defective adenovirus

type 5 vector that carries three HIV genes and was designed to elicit HIV-specific T-cell immune responses (see diagram). Adenovirus type 5 is a common cold virus and is generally considered harmless. The vaccine was evaluated in two trials involving volunteers who were HIV-negative but at high risk for infection. The HIV Vaccine Trials Network, which is funded by the National Institute for Allergy and Infectious Diseases (NIAID), in conjunction with the vaccine developer, Merck, conducted the STEP trial in the United States and abroad; the Phambili trial was conducted in South Africa. In September 2007, the STEP trial, which had enrolled 3000 subjects, was stopped after the data and safety monitoring board, at its first interim analysis, concluded that the vaccine neither prevented HIV infection nor reduced the amount of

virus in those who became infected. In October, the Phambili trial, which had enrolled only 801 subjects, was also stopped; the trial's monitoring board concluded that there was no reason to anticipate more favorable results. Participants in both studies were told whether they received vaccine or placebo.

Since there was only one HIV case in a female STEP subject (though there were more than 1100 women enrolled), post hoc analyses of the data have focused on men. As of October 17, 2007, there had been 49 HIV infections in men who were HIV-seronegative when they underwent randomization and who had received at least one dose of the vaccine, as compared with 33 infections in comparable men who received placebo. The men at greatest risk for HIV infection appeared to be those who both received the vaccine and had higher levels of immunity to adenovirus type 5 before enrollment. Despite the sobering preliminary analyses, it is unclear whether administration of the vaccine actually increased the risk of acquiring HIV. This will not be known at least until ongoing studies and data analyses are completed — and might remain uncertain indefinitely.

Even the preliminary findings, however, have immediate implications for future vaccine trials, particularly a study involving 8500 patients that had been scheduled to start in the fall of 2007 but is now on hold until at least the summer of 2008. That trial, known as Partnership for AIDS Vaccine Evaluation (PAVE) 100, will test a vaccine strategy developed at the National Institutes of Health (NIH) that has four components: three injections of an HIV DNA vaccine, followed by a single boost

with an HIV–adenoviral-vector vaccine (see diagram). The multiclade vaccine primarily elicits T-cell immunity and is another important test of the T-cell vaccine concept.

The NIH vaccine differs in many respects from the Merck product; notably, it entails one injection of adenoviral vectors, not three, and the other injections are only of DNA plasmids. However, the vector is also a recombinant, nonreplicating adenovirus type 5, although it is missing more genes than V520 and differs structurally from it in some other ways. The protocol is being intensively reviewed because of safety concerns, according to Gary Nabel, the director of NIAID's Vaccine Research Center, where the vaccine was developed. Although no decisions have been made, a redesign of the protocol is under way. For example, it is likely that the initial subjects will have no evidence of prior infection with adenovirus type 5. That requirement might preclude recruitment of subjects at some of the planned sites: in East Africa, as many as 95% of people may have antibodies against adenovirus type 5, as compared with less than half of people in the United States. A different type of adenovirus could be used in the vector, but making such a change could delay the study for an additional several years and necessitate rethinking of other aspects of the experimental vaccine as well.

The first large AIDS vaccine trials found that a recombinant glycoprotein 120 vaccine (based on the viral envelope) that induced neutralizing antibodies did not protect against HIV infection.^{3,4} The only ongoing large study of an AIDS vaccine is being conduct-

ed in Thailand, where a strategy of “priming” the immune system with a live recombinant canary pox vector containing HIV genes and then “boosting” it with a glycoprotein 120, thereby eliciting both B-cell and T-cell immunity, is being evaluated in 16,400 HIV-negative adults. The study started in 2003 and is expected to continue until July 2009. When the data safety and monitoring board last met, in July 2007, it recommended that the trial continue.

Unless an experimental vaccine turns out to be highly effective in preventing HIV infection, the results of one large phase 2B or phase 3 study are unlikely to lead to its licensure. A vaccine study that would be considered “successful” is more likely to be one that provides some of the missing information about the specific immune responses that protect against infection and that leads to additional large trials specifically designed to support the licensure of a refined vaccine. Such additional trials could easily take 5 years or more to complete.

In 2005, the global investment in HIV vaccine research and development was estimated at \$759 million, of which 88% was from governments, 10% from commercial firms, and 2% from philanthropy.⁵ The NIH spends about \$600 million a year on researching such vaccines; as of March 2007, it had supported 99 HIV vaccine trials involving 55 different products, 22 adjuvants, and more than 26,000 volunteers. PAVE 100 has a projected federal budget of \$137.5 million, as compared with \$32 million for the government portion of STEP. Although the STEP trial and others that failed to achieve their desired end points

have brought new knowledge, each disappointment also reinforces the view that a licensed AIDS vaccine is at least a decade away — and that is if things go well, which has not happened yet. Meanwhile, individuals and public health officials can only try to prevent HIV transmission through education and behavior modification, condom use, needle-exchange programs, and other effective, albeit imperfect, means that are already available.

According to Anthony Fauci, the director of the NIAID, “To be brutally honest with ourselves, we have to leave open the possibility . . . that we might not ever get a vaccine for HIV. People are afraid to say that because they think it would then indicate that maybe we are giving up. We are not giving up. We are going to push this agenda as aggressively and energetically as we always have. But there is a possibility — a clear finite possibility — that that's the case.”

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