Dying for a Vaccine

Money, media and a 10-year-or-bust mandate made the cause sexy. But with the first tests on deck, the risks are bigger than ever.

July 1, 1998 By Patricia Kahn

In 1984, when scientists finally nabbed HIV, it instantly raised prospects that a vaccine would follow. Even to hope that the new disease might soon join the list of deadly epidemics stopped cold by a vaccine was an awesome leap; if anything in medicine seems like a magic bullet, it's these tried-and-true weapons. But in the heady flush of success over identifying HIV, Margaret Heckler, then secretary of the Health and Human Services Department, blithely served up a science-fiction scenario of a quick fix when she said that a candidate would be ready to test within two years. After all, in the real world even a decade is turbo speed for a new vaccine.

Fourteen years later, a vaccine is nowhere in sight; in fact, even the fantasy has faded. During these years, while AIDS activists -- desperate to save lives -- pushed the National Institutes of Health (NIH) toward a massive research effort on treatments, there was no one fighting with such passion for a vaccine. In fact, many in the AIDS community cast a cold eye on the vaccine cause, fearful that research into, let alone development of, a shot that protected against HIV would dash the hopes of the already infected. Moreover, some scientists even grew skeptical that a vaccine was possible. And most drug companies steered clear, anticipating a long, difficult scientific path fraught with uncertain profits and a political and ethical minefield.

Now, with some big successes in anti-HIV therapy but the virus still spreading like wildfire worldwide, vaccines are starting to make a comeback -- although so far there's still more talk than action. Take, for example, President Clinton's 1997 call for an HIV vaccine within the decade, which invoked "can do" images of a man-on-the-moon-type effort. Yet he offered no Apollo-esque strategies to support it, nor has NIH come up with a concrete plan for trying to meet the deadline.

Is "10 years till a vaccine" remotely realistic? NIH top brass are wary. "I'll be happy if we can get a good candidate to the point of large-scale clinical trials in that time," says Dr. Carole Heilman, deputy director of the agency's Division of AIDS. Others are eager to go for it, but say that far more energy and focus are necessary. "The whole mentality of how we're looking has to change," says Dr. Margaret Johnston, scientific director of the International AIDS Vaccine Initiative (IAVI), a new nonprofit group dedicated to pushing vaccines forward. "We have to be much more aggressive. People haven't woken up yet to what making a vaccine really means."

Re-invigorating the national vaccine effort has been a rocky road since 1996, when a blue-ribbon

panel of AIDS researchers diagnosed the federal program as “in crisis”: It was deemed too small, of low priority and poorly funded, and too narrowly focused on basic science while neglecting targeted research. Added to this is not only the huge cost but the very slow and long development pipeline that leads promising vaccine candidates out of academic labs, into manufacture for human use, through early clinical tests for safety and ability to stimulate immune responses, and then finally into a Phase 3 efficacy trial, which tests if the candidate works.

Yet many scientists view the biggest obstacle as the formidable scientific challenge of HIV itself. A major mystery is that people usually show strong immune responses to HIV but still eventually get sick, so no one knows for sure which type of immunity a vaccine should stimulate to protect against disease. One emerging view suggests that a vaccine should aim at several arms of the immune system: The cells producing antibodies that destroy free virus in the blood, the cytotoxic T lymphocytes (CTL) that target already-infected cells, and also perhaps the dimly understood immune responses in the body’s mucosal membranes, including those lining the vagina and rectum -- ports of entry for sexually transmitted HIV -- and the gut, likely a key destination of HIV soon after infection. Another high hurdle: Since no animal immune system perfectly mirrors that of humans infected with the virus, there’s no way to know if a vaccine works without testing it in people.

Although daunting, none of this is new to vaccinologists, who rarely know all they’d like to about their prey. So they rely instead on educated trial and error, where experimental vaccines are tested in people and their designs improved based on the results. Another way they’ve sidestepped ignorance is to stick with the strategy that produced the very first vaccines and is still hard to beat: Take the whole virus, weaken or kill it so it can’t make people sick, and then count on the body’s own immune response to do the rest. But there’s a tradeoff because weakened whole-virus vaccines still carry a tiny risk of causing disease. For example, in the United States, there are about eight cases a year of vaccine-induced polio.

With HIV, fears about potential risks have steered researchers away from this traditional strategy and toward genetically engineered “designer” vaccines that are harmless because they use only parts of the virus. Again, there’s a price -- these vaccines, even if they work, may give weaker or less long-lasting immunity. Most types will also be expensive, adding to the problem of making an AIDS vaccine available to those most in need -- in developing countries, where over 90 percent of the world’s 31 million with HIV live.

But a more immediate worry in the vaccine field is how few candidates have even made it out of the lab and into the pipeline. And sadly, once in it, they don’t flow through: Of the more than two dozen products tested in Phase 1 safety trials, only three have made it to the next step, and none to Phase 3, a record that prompted Dr. William Heyward of the Centers for Disease Control and Prevention (CDC), to write in *The Journal of the International Association of Physicians in AIDS Care* (IAPAC), that the pipeline is more like a pipette.

The reason for this paltry trickle is one of the most contentious issues in the vaccine field. For many basic researchers, the bottom line is that current candidates are simply not good enough.

Even Dr. David Baltimore, the retrovirologist and Nobel laureate who chairs NIH's new AIDS Vaccine Research Committee, doubts that 14 years of R&D have produced anything worth large-scale tests. To him and others in the "theorist" camp, the key isn't "big trials now" but more basic research and small trials aimed at understanding what's needed for an effective vaccine. This is also the way to pull in drug and biotech companies, Baltimore says. "We need to face industry with real opportunities. Right now the pipeline isn't exciting enough -- we're testing concepts that are clearly outdated. Drug companies have made the reasonable judgment that the time isn't right."

But the "empiricists" -- mostly public health experts, epidemiologists and vaccinologists favoring more applied research -- counter that it's too soon to write off current candidates, since basic science can't predict which ones will pan out. "We don't know what works, end of story," says Dr. Seth Berkley, president of IAVI. "We have theories, but we don't know." Dr. Mary Lou Clements-Mann of Johns Hopkins University, a vaccine researcher and member of the FDA's vaccine advisory committee, agrees, saying, "I've seen vaccines moved from small- to large-scale tests much more rapidly, without answers as to why they might work." She adds, "After licensing, often we still don't know." Some lab tests can even be misleading, says Dr. Barry Bloom, an immunologist at the Albert Einstein College of Medicine and chair of the UNAIDS vaccine subcommittee. "If we went by animal models we wouldn't have the newest whooping-cough vaccine," he says. "If we'd used the same criteria as for HIV, it would never have gotten off the ground."

This long-simmering debate erupted last March when Dr. Jonathan Mann, former head of the World Health Organization's Global Program on AIDS, attacked the "theorists" in a passionate speech before Clinton's AIDS advisory council. Mann criticized the failure to mount efficacy trials as "unethical" and a "violation of human rights," and called on the NIH leadership to involve more people who have vaccine experience. And he accused the NIH of indifference to the people now getting HIV in this country, most of whom come from already-marginalized groups. "Very simply, if 40,000 college students were becoming HIV infected each year, it's obvious that field trials of AIDS vaccine candidates would have long been underway," he said.

But as polarized and ideological as the debate sounds, in practice there's a well-occupied middle ground, says José Esparza, vaccine team leader at UNAIDS Geneva. And he points out that opinions on efficacy trials reflect not only "theorist" vs. "empiricist" arguments but practical issues as well -- such as money. These tests take big bucks, and with limited funds it becomes a matter of "competing priorities," he says. Funding, in turn, reflects HIV vaccine research's low priority in the United States. "The fact of the matter is that the country with the financial resources and scientific know-how to develop the vaccine does not feel the urgency of the epidemic," he says. "The only solution is to increase funding for HIV vaccine research and proceed with parallel development of several vaccine concepts, including several large-scale efficacy trials."

Lurking in the shadows of this battle is the spectre of fallout from a large trial that fails, a common occurrence with experimental vaccines but much feared in the HIV field. Given the public attention to AIDS, a bust would give HIV vaccine trials "a bad name," says Baltimore. IAVI's Berkley disagrees. "Politically it's considered too risky to have negative vaccine trials," he says. "But why? With malaria, we've tested a lot of vaccines that didn't work. We need a big shift in mind-set." And

if a trial is well designed, says vaccinologist Clements-Mann, a negative result can give crucial information on how to make a better one.

That means a reality check on public expectations. “The public is looking for an immediate, spectacular success,” says immunologist Bloom. “But you don’t pull a vaccine out of a test tube and it works. It takes constant modification. You’re not going to get it right the first time. A 99 percent effective vaccine? I don’t see it on the horizon. But even 50 percent effectiveness would be enormously useful.”

Amid the clash of views, one vaccine is now inching its way toward that historical milestone -- the first Phase 3 trial, likely underway within a year or so. The figure behind the trial is Dr. Donald Francis, who, at the CDC in the early ’80s, was one of the first voices trying to awaken the world to the tragedy ahead. In 1993 he joined the HIV vaccine program at Genentech, a biotech behemoth based in South San Francisco. Researchers there had adopted the same strategy as nearly all early HIV vaccine makers -- focusing on a genetically engineered version of the so-called gp120 protein, which makes up the surface of HIV. These scientists had already succeeded in making a vaccine that prevented HIV from infecting chimpanzees. Early trials with small numbers of people found it to be safe in humans and able to stimulate a strong antibody response. The NIH’s National Institutes for Allergy and Infectious Diseases (NIAID) was prepared to pump $20 million into a Phase 3 trial.

And then NIAID wasn’t. In a stunning reversal, the agency pulled out. New data in early 1994 raised fears that differences among gp120 proteins in HIV strains directly from people and those grown in the lab -- used to make Francis’ vaccine -- might doom the vaccine to failure. Many voiced doubts about whether gp120s stimulated the “right” kind of antibodies. And even the chimp data didn’t convince everyone, since HIV can infect chimps but doesn’t give them AIDS. As scientists feverishly debated the meaning of the new findings, NIAID finally bailed out in June, saying that its limited funds should be saved for better candidates. The decision cast a pall over the whole field and led some companies to shrink or shut down their HIV vaccine work (including Genentech, which spun off Francis and the vaccine to a small new company, VaxGen).

Francis persisted, convinced that the vaccine’s ability to protect chimps meant more than the lab tests that gave NIAID cold feet. Now he’s ready once again, with his own funds -- $20 million raised privately so far -- and modified vaccines. These newest vaccines stimulate the type of antibodies NIAID wanted to see and, along with gp120 from the lab strain, contains gp120s representative of common strains at each of the two likely trial sites (Thailand and the United States). And he expects to get the official go-aheads soon. In the U.S., FDA approval for a Phase 3 trial is nearly certain, he says, once data from the ongoing Phase 2 trial are in. Meanwhile, in February an international group of scientists recommended to Thai officials that the Phase 3 trial there go forward. Together, the two trials would follow 7,500 high-risk volunteers for three years.

These trials-to-be have triggered the full range of reactions. Skeptics point to a growing belief that an HIV vaccine should induce strong CTL responses, and Francis’ doesn’t. “Seriously wanting” is how Dr. John Moore of the Aaron Diamond AIDS Research Center rates the vaccine. “I’m absolutely

certain that the vaccine's efficacy would be immeasurably low," he says. "There is also a moral issue," he adds, arguing, "It's simply not appropriate to immunize human volunteers with a protein that has no chance of protecting them from HIV." Others are more supportive of Francis' trials. "I'm delighted that VaxGen is moving ahead," says IAVI's Margaret Johnston. "It's important to know if gp120 works at all based on data rather than on what people see in a crystal ball. Any answer is worthwhile."

However the gp120 story ends, its cautionary moral -- don't put all your eggs in one basket -- has already spurred those in the vaccine field to pursue several other strategies. One is to put selected HIV genes into harmless viruses that infect the cells of vaccinated people and make them churn out HIV proteins, which should stimulate immunity. Since these viral "vectors" often evoke good CTL responses, some experimental strategies combine them with the antibody-stimulating gp120 for a one-two immunizing punch. And high hopes are pinned on the concept of vaccinating with HIV genes in the form of "naked" DNA. Although at least a decade away, this technology is a potentially revolutionary way to make vaccines cheaply and simply, which would be ideal for the developing world.

Increasingly, these new approaches turn on the old-fashioned idea of presenting the immune system with many different parts of HIV (working "top down" from whole virus) rather than the "bottom up" approach of selecting only one or two targets, as with gp120. This would hopefully give the wily, changeable virus fewer chances to evade immune attack. And that shift has sparked pockets of interest in a strategy long viewed as unthinkable -- using live HIV.

Estimated HIV Infections	
Sub-Saharan Africa	20.8 million
South & Southeast Asia	6 million
Latin America	1.3 million
North America	860,000
Western Europe	530,000
Eastern Asia & Pacific	440,000
Caribbean	310,000
North Africa & Middle East Asia	210,000
Eastern Europe & Central Asia	150,000
Australia & New Zealand	12,000
Global Total	30.6 million

Estimated HIV Infections: Sub-Saharan Africa
20.8 million

Estimated HIV Infections: South & Southeast Asia
6 million

Estimated HIV Infections: Latin America
1.3 million

Estimated HIV Infections: North America
860,000

Estimated HIV Infections: Western Europe
530,000

Estimated HIV Infections: Eastern Asia & Pacific
440,000

Estimated HIV Infections: Caribbean
310,000

Estimated HIV Infections: North Africa & Middle East Asia
210,000

Estimated HIV Infections: Eastern Europe & Central Asia
150,000

Estimated HIV Infections: Australia & New Zealand
12,000

Estimated HIV Infections: Global Total
30.6 million

Source: Joint United Nations Programme on AIDS (UNAIDS)

From their backwater in the HIV field, live but weakened ("attenuated") AIDS vaccines made a sudden, dramatic appearance in the headlines last September when IAPAC announced an initiative to push for a Phase 1 human trial by the year 2000. But that wasn't all. Recognizing the potential risk -- and the public fears -- of a live HIV vaccine, several IAPAC members volunteered to be the first guinea pigs, following the tradition of Louis Pasteur, Walter Reed and other vaccine pioneers. It was a vivid, startling gesture showing that the need for a vaccine was so great worldwide that people were willing to accept the risk of getting AIDS (although IAPAC considers this low). And since IAPAC's announcement, more than 270 people have volunteered to join them in rolling up their sleeves (a first trial would probably involve 10 or less).

IAPAC's attempt to put live vaccines on the agenda isn't a stab in the dark: There's already powerful evidence that they may work. In 1992, Ronald Desrosiers of the Harvard Medical School injected monkeys with a weakened version of SIV, a simian virus related to HIV, made by clipping out several genes. When the same animals were infected later with the intact, nasty SIV, they were fully protected from disease -- just as a good vaccine should do. No other vaccine candidate

has come close to matching this stellar performance.

Yet most AIDS researchers reacted to IAPAC's announcement with alarm, aware of then-emerging data that some attenuated SIV strains cause full-blown simian AIDS in baby monkeys and in a small proportion of adults. And even though IAPAC proposed using a more weakened strain, critics say that too little is known about HIV genetics to ensure that the virus can be made meek enough to not cause disease.

Whether a U.S. trial kicks off by the year 2000 or later depends on the FDA, whose primary concern is public safety, not necessarily the shortest road to an effective vaccine. Vaccinologist Clements-Mann ticks off some of the concerns: Could vaccinated people get sick from the attenuated virus years later? What happens when their immune systems weaken from age or illness? Is attenuated HIV transmissible, even at a low frequency? None of these questions can be tackled in short human trials.

IAPAC's deputy director, José Zuniga, acknowledges these fears. "I don't envy the FDA's position. We're not asking them to throw caution to the wind, to say we don't need more data. But we need to move from animals and ask what the vaccine does in humans." And he cites an accidental experiment in humans that suggests that a safe attenuated HIV is possible. Eight people, including seven in Australia, were found to be infected with weakened forms of HIV since the early '80s, without any apparent ill effects.

Yet for the FDA to even consider trials, and to ensure that potential volunteers are fully aware of the possible consequences, more animal data will be needed. Enter IAVI. Although the organization sees a trial in healthy volunteers as premature, it also believes strongly that the live-attenuated approach should be pursued, and have funded a pilot project to design a large safety study involving hundreds of monkeys. Similar studies were done for other live vaccines, such as polio. "I would consider enrolling in a trial if there was more data," says IAVI's scientific director, Margaret Johnston. "I'm not willing to make the leap of faith now."

In the meantime, Dr. John Sullivan of the University of Massachusetts has proposed an alternative plan for the first human trial, one that may be more acceptable to the FDA. Rather than vaccinating healthy volunteers, Sullivan suggests recruiting terminally ill cancer patients with still-intact immune systems. This plan, dubbed "a very reasonable first step" by IAVI's Johnston, could throw light on key issues, such as whether the chosen attenuated HIV strain replicates in humans, what types of immune responses it stimulates, and how its behavior in people compares to that of attenuated SIV in monkeys.

Researchers in Australia are also pursuing plans to test a live-attenuated vaccine within the next few years. Dr. John Mills, director of the Macfarlane Burnet Centre for Medical Research, is modeling his candidate on the naturally weakened HIV strain found in the seven Australians (who got it through blood from a single donor), with this speculative twist: He hopes to vaccinate with DNA only, not with whole virus. If that works, it would make vaccine preparation vastly simpler, safer and cheaper. With funding from IAVI, he's now working on safety studies in monkeys.

In the United States, despite both outside criticism and Clinton’s 10-year call, the NIH is sticking with its present strategy, beefed up with some extra funds and the involvement of big gun David Baltimore. Several new mechanisms are also in place to help researchers negotiate the arduous vaccine development pipeline. But there’s no specific 10-year plan, and a proposed NIH Vaccine Center, meant as a cornerstone of NIH’s born-again vaccine effort, has yet to get on its feet.

IAVI will likely shake things up when it presents its “scientific blueprint” for an HIV vaccine in 10 years at the World AIDS Conference in Geneva. Based on a 1994 brainstorming meeting of big vaccine players worldwide, the plan is “a very different approach from the basic science one,” says IAVI president Berkley. Its central elements: "Work on different things in parallel. Work top down. And go fast into humans -- don’t sit around and argue about animal mod

---