

KIDNAPPED IN GAZA: A REPORTER'S STORY By Joshua Hammer

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Seth Berkley, founder of the International AIDS Vaccine Initiative

**SPECIAL
REPORT
AIDS
AT 20**



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ATLAS**



\$232,000,000

The number of dollars the National Institutes of Health spent on research for an AIDS vaccine in the year 2000, up from \$82 million in 1993. In 2000, the NIH spent \$570 million on new drug therapies, up from \$431 million in 1993.

Can He Find A Cure?

A vaccine is our last, best hope of stopping the epidemic. Seth Berkley is trying to deliver the dream. BY GEOFFREY COWLEY

There was a time in the early '80s when AIDS was killing people with brutal efficiency, and no one knew what caused it. Was it swine-flu virus? The inhalants that gay

men were using to heighten sexual pleasure? There was no telling who would be stricken next, or what it would take to stop the new scourge. But as soon as researchers identified the AIDS virus in 1984, the ultimate solution seemed obvious. Science would vanquish AIDS just as it had polio, measles and smallpox: by immunizing people against it. In announcing the isolation of HIV, federal health officials famously predicted that a vaccine would enter clinical trials within two years and reach the

market within three. Seventeen years later experts still agree that a vaccine is our best hope of ending the pandemic. They also agree that we'll be lucky to have even a crude one on the market by 2007. At current rates, an additional 50 million to 100 million people will have contracted the virus by then—most of them in countries too poor to provide treatment—and millions will have died.

After two decades of frustration and neglect, the vaccine effort is moving back to center stage—and no one has pushed harder to get it there than Dr. Seth Berkley. Five years ago, at 40, Berkley assigned himself the grandiose task of delivering a yet uninvented vaccine to all the nations whose futures now depend on it. As head of the New York-based International AIDS Vaccine Initiative (IAVI), he lives as if removing the obstacles were his personal responsibility. Berkley

AIDS CRUSADER: Berkley has amassed \$230 million and used it to seed R&D projects on several continents. But creating a vaccine is only half of his mission. He wants to ensure instant worldwide access.

trained as a physician at Brown and Harvard, and cut his teeth as an epidemiologist in Brazil and Uganda, where he witnessed the emergence of AIDS in the 1980s. But he is more brash impresario than quiet country doctor. In any given week, he may call on a head of state in Africa, address a global health meeting in Oslo or Geneva, then fly to the U.S. West Coast to get Bill Gates or the directors of Yahoo behind his latest big idea. If he's home in time to press his case on a New York talk show, he is not only willing—he's jazzed.

As well he should be. Berkley has amassed a \$230 million war chest since starting IAVI, about the same amount the U.S. government spends on vaccine research in a year, and has used it to jump-start research projects on several continents. The vaccines in development are varied, and some are sure to fail. But by advancing them simultaneously, Berkley figures he can speed the search for a winner. His larger mission is to ensure that any vaccine capable of slowing the epidemic is promptly introduced—at affordable prices—in the hardest-hit regions of the world. That may sound obvious, but such quick action would be an unprecedented achievement, comparable in scale to creation of the vaccine itself. Berkley knows it's a moonshot, but he figures anything less would amount to surrender.

WHY IS A VACCINE so critical? Science has produced a flood of powerful AIDS drugs in recent years, and death rates have plummeted in countries with the means to buy and administer them. But even at discounted prices, these medications are far beyond reach for most of the world's 40 million HIV-infected people. The cost would exceed what some countries spend on all health services combined. Education, though critical, is not an adequate alternative—not in countries where a third of the population is already HIV-positive. "Prevention campaigns haven't fully worked on a global scale, and I'm not sure they ever will," Berkley says. "That's why you come back to the need for a vaccine."

Unfortunately, the AIDS virus has a way of foiling that approach. Most pathogens

leave us stronger if they don't kill us, because they prime our immune systems for future encounters. HIV doesn't work that way. As far as we know, no one has ever recovered from the infection and gained protective immunity. The result is that vaccine developers don't know quite what they're looking for. They can only hope that immunity is possible and guess at the best ways to achieve it. "Developing drugs was relatively straightforward once we had the virus and could study it in a test tube," says Dr. Anthony Fau-

prise could accomplish when the incentives were right. "A lot of the public-health community thinks companies are evil and ought to give things away," he says. "That's fine as a short-term strategy, but pretty soon no one's making new products." His solution was to create a nonprofit venture-capital firm. IAVI would invest in companies or academic labs with good ideas, then do everything possible to help them succeed—orchestrate clinical trials, coordinate regulatory approvals and work to establish purchase funds and distribution systems. In return, IAVI's partners would pledge to sell (or license) their products simultaneously in rich and poor countries, and to offer break-even prices in the developing world while reaping higher profits elsewhere.

Berkley assembled a powerful board of directors (the current chairman is Lee Smith, the former president of Levi Strauss International) and proceeded to wow governments and foundations with his smooth, impassioned pitch. His big break came in 1999, when he met with Bill Gates and emerged with a pledge for \$25 million, the largest private gift any AIDS group

had ever received. Gates has remained a vocal ally, pledging an additional \$100 million as a challenge grant this year. IAVI now has support from five governments and employs 50 people worldwide. Its spacious home office overlooks New York Harbor from atop Manhattan's financial district and exudes the spare elegance of a successful New Economy start-up. Any Davos regular would feel at home there.

To date, IAVI has invested \$20 million in R&D efforts at five companies. Its goal is to have eight to 12 AIDS vaccines in development by 2007 (an effort that will cost \$500 million), and to have at least two in large-scale human trials. Getting one of these vaccines onto the global market within a decade would require streamlining some countries' regulatory procedures, but Berkley is on the case. He recently launched a Web-based petition to present to the United Nations later this month (Yahoo, MSN and RealNetworks have all signed on as sponsors), and he's securing commitments from legislators around the world to help standardize regulatory requirements. "If we could speed the process by even six months," he marvels, "millions of lives might be saved."



CASUALTY OF WAR: Nkosi Johnson, who was known as the Ryan White of South Africa, died just last week of AIDS. He was 12 years old.

ci, director of the National Institute of Allergy and Infectious Diseases. "But until recently, the opportunities for applied vaccine research just haven't been there."

Nor have the dollars. Though the United States and Europe spend more than \$3 billion a year on drugs to treat HIV infection, the whole world spends just \$350 million a year on AIDS vaccine research—chump change when, as Berkley puts it, "the greatest plague since 1347 is upon us." Pharmaceutical companies have had good reason to be wary. Gauging a vaccine's effectiveness requires inoculating thousands of healthy volunteers and tracking them for years. Even a successful vaccine is less profitable than a drug that people take every day. And the populations with the greatest need are typically the least prepared to pay. "From the standpoint of maximizing return on investment," Berkley concedes, "you'd stay far away from a vaccine."

Berkley conceived IAVI with exactly these problems in mind. After returning from Uganda in 1989 he joined the Rockefeller Foundation, where he eventually became associate director for health sciences. In that capacity he supervised health programs for 30 countries and saw what private enter-

Eight Routes to a Vaccine



Live attenuated HIV: Weakened version of the virus triggers a robust immune response, but the vaccine itself could cause AIDS. Human tests unlikely.



Whole killed HIV: Safer than live virus but less effective because virus doesn't generate proteins. Vaccines based on pieces of HIV are easier to prepare.



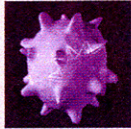
Recombinant HIV proteins: Molecules mimicking HIV's outer surface trigger the production of antibodies, but the antibodies may not block infection.



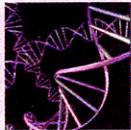
Peptide epitopes: Tiny fragments of HIV proteins are easy to make and safe to use, but may not elicit a broad-enough response to handcuff the virus.



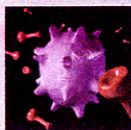
Live bacterial vectors: Genetically altered bacteria generate HIV proteins, which the immune system learns to recognize and destroy. Safe, simple.



Live viral vectors: Harmless viruses are engineered to generate HIV proteins, which elicit an immune response. More stable than bacterial vectors.

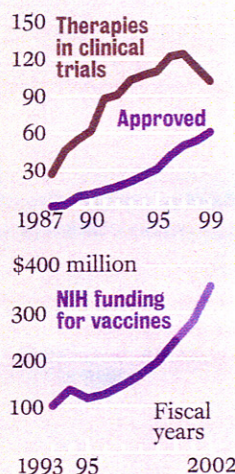


Naked DNA: HIV genes are introduced into the recipient's cells, which then produce the viral proteins needed to activate the immune system.



Combinations: Researchers hope that cocktails incorporating more than one element will elicit the broad immune response needed to ward off infection.

THE STATE OF THE RESEARCH



CHARTS ARE ADJUSTED FOR INFLATION. SOURCES: PHRMA, NIH. RESEARCH BY JOSH ULICK. ILLUSTRATIONS BY BRIAN CHRISTIE.

No one expects the first generation of AIDS vaccines to work perfectly. But with 15,000 people contracting HIV every day, even a partially effective immunization could work wonders. So far the only candidate to reach large-scale human testing is AIDSVax, a compound owned by VaxGen Inc. of Brisbane, Calif. Developed in the late '80s, this vaccine uses a protein from HIV's outer surface to elicit antibodies against the virus. Ideally these antibody molecules would latch onto HIV whenever it entered the bloodstream, disabling it before it could infect healthy cells. Few experts expect that tactic to work by itself (the virus's outer envelope is an ever-changing target), but VaxGen has inoculated 8,000 high-risk HIV-negative volunteers in the United States, Europe and Thailand over the past three years to find out. After getting the vaccine or a placebo, and being counseled in risk reduction, the participants are tested periodically for HIV. The trials are scheduled to run for one to two more years, but the company is hoping for signs of success this summer.

Most newer vaccines—including compounds developed by Merck, the Harvard AIDS Institute and others—elicit a different response, known as cellular immunity. Researchers got interested in this approach in the mid-'90s, after noticing that certain people exposed to HIV either don't become infected or survive indefinitely without getting sick. Some have genetic mutations that can't be medically induced, but others may

be mounting immune responses worth emulating. In studying a group of Nairobi prostitutes who remained free of HIV despite years of constant exposure, Oxford University researchers Andrew McMichael and Sarah Rowland-Jones noticed that the women all had white blood cells designed specifically to kill HIV-infected cells.

The Oxford researchers had never fancied themselves vaccine developers. But with IAVI's backing, they concocted a vaccine to trigger the same kind of response they'd seen in the prostitutes. Large clinical trials are still several years off, but researchers in Britain and Kenya are now testing the vaccine for safety. Like many of the compounds now under investigation, it consists of two shots. The first contains nothing but snippets of HIV's genetic material. When taken up by a person's cells, this "naked DNA" generates harmless viral proteins. The immune system, sensing trouble, then sends forth white blood cells called cytotoxic lymphocytes, or CTLs, to destroy the affected cells. This skirmish teaches the immune system to recognize HIV, but it doesn't mobilize a large fighting force. To boost the response, the researchers administer a second shot that combines the HIV genes with a virus called MVA, which gets a bigger rise out of the immune system. The result should be a large standing army.

IAVI's other development partners include AlphaVax of Durham, N.C., Targeted Genetics of Seattle, Therion Biologics of Cambridge, Mass., and the University of

Maryland's Institute for Human Virology. Each is pursuing a different route to cellular immunity, and all are collaborating with researchers in Africa or India. The technical hurdles are still high, as are the political ones. The companies, agencies and scientists Berkley has pulled into his tent are not all natural allies. They're competitors at heart, with a knack for dissension and backbiting. And Berkley himself is not everyone's idea of a hero. Treatment activists accuse him of paying too little heed to people who are already sick, and some health officials view him as a cowboy whose brash demands for fast action flout scientific tradition. Meanwhile, citizens' groups fearful about vaccine safety are warning that universal AIDS shots are just around the corner.

We should be so lucky. No one is close to having a vaccine ready for universal use, and no one is suggesting that we abandon care or treatment to speed the search for one. But as the AIDS pandemic expands, the need for a vaccine grows ever clearer. By pushing the cause so aggressively, Berkley has helped draw the right players back into the game. He claims not to care who wins if he can just quicken the pace. "We're creating an atmosphere where it may be easier for others to succeed," he says, extending his palms. "We're saying, 'Look, here's a huge moral challenge. The world needs to put something together. What can we do? What incentives will really work?'" If we're lucky and persistent, the third decade of this plague will bring answers. ■