Thailand Weighs AIDS Vaccine Tests

The first large-scale tests could begin in Thailand next year. That prospect has rekindled a debate that preceded NIH's decision last year not to test the same vaccines in the United States

SAN PATONG, THAILAND—A visit to the AIDS ward of the only hospital in this district in northern Thailand provides a grim indication of the public health threat looming over this small nation. A nurse threads her way around the 40 beds jammed into the ward, many of which are occupied by patients whose diseases have progressed so far that their limbs are as thin as the metal tubing that frames the beds. The ward is always full. Two waiting rooms adjacent to it have been converted into makeshift wards themselves, each with 10 beds. Today neither has a free space. "We're asking for 90 beds," says the nurse, who is dressed in a traditional uniform, complete with angled hat. "But in the future, that's not going to be enough, either."

In 1987, Thailand was virtually HIV-free. But now an AIDS epidemic is raging in the country, as the crowded ward in San Patong Hospital, 20 kilometers outside Thailand's largest northern city, Chiang Mai, makes clear. Researchers believe that San Patong, a region of rice fields and simple stilt homes, has more HIV-infected people than anywhere else in Thailand. But because there is a long lag time between HIV infection and symptomatic AIDS, San Patong so far has only had a hint of the number of cases it soon will be experiencing. And the rest of the country may not be far behind.

PHOTOS BY DARROW MONTGOMERY

One step at a time. Prayura Kunasol says the planned tests may lead to a better vaccine.

Faced with this bleak outlook, Thailand is aggressively looking for ways to thwart HIV. Nowhere is this more pronounced than in the country's emerging role as the most important place in the world for testing AIDS vaccines. "There's probably more going on here than anywhere," says William Heyward, an epidemiologist with the U.S. Centers for Disease Control and Prevention (CDC) who is currently working for the World Health Organization (WHO) to help Thailand set up AIDS vaccine trials. Indeed, what happens here over the next few years could provide long-awaited answers on just how effective the leading first-generation vaccines really are. And it could settle some scientific arguments that have been raging in the United States over how best to proceed with vaccine development.

Hopes for answering those questions in the United States faded last year, when the U.S. National Institutes of Health (NIH) scrapped plans to spend nearly $30 million on large-scale tests in the United States of the two leading candidate vaccines after an expert panel concluded that they showed too little promise. That controversial decision left Thailand and other developing countries in the lurch. Whatever the merits of the decision for the United States, Thai researchers and officials feel that a different calculus applies here: In spite of an intensive education and public health campaign, infection rates are still high, and even a partially effective vaccine would be better than nothing.

Now these vaccines may finally get a chance to prove themselves—in Thailand. Although no decision has yet been made to stage large-scale efficacy trials here, the groundwork is being laid by teams of Thai researchers and scientists from Genentech and Biocine (a joint venture of Chiron and Ciba-Geigy), the two San Francisco Bay–area companies whose vaccines were put in limbo by the NIH decision.

Growing caseload. San Patong hospital's crowded AIDS ward.

In addition to launching the small safety trials that must precede efficacy tests involving thousands of people, these teams are working with dozens of foreign scientists and public health officials who are helping them confront a host of serious practical and scientific questions. Can efficacy trials with these vaccines be justified in the face of discouraging results from laboratory tests and data from limited human trials? Can groups of volunteers be found who have both a high infection rate and a willingness to participate in these and other trials that may be staged in the future (see box on facing page)? Can a vaccine made from the HIV strain prevalent in the United States provide protection against strains that are running rampant in Thailand? And if Thailand does decide to stage these efficacy trials, who is going to pay for them?

Why Thailand?

Diverse forces have led this tropical kingdom surrounded by Laos, Burma, Cambodia, and Malaysia to become AIDS Vaccine Central, but the strongest is the magnitude of the HIV epidemic here. Estimates suggest that as many as 1 million of Thailand's 60 million

CURRENT AND FUTURE GP120 VACCINE TRIALS IN THAILAND

Vaccine/subtype	Manufacturer	Collaborators	Participants	Status
gp120/B	Genentech	Mahidol Univ.	31	Ongoing
gp120/B	Genentech	Mahidol, BMA	~2500	Dec. '96?
gp120/B	Biocine	AFRIMS, RIHES	52	Ongoing
gp120/B & E	Biocine	AFRIMS, RIHES	~200	Spring '96?
gp120/B & E	Biocine	AFRIMS, RIHES	~2500	End of '97?

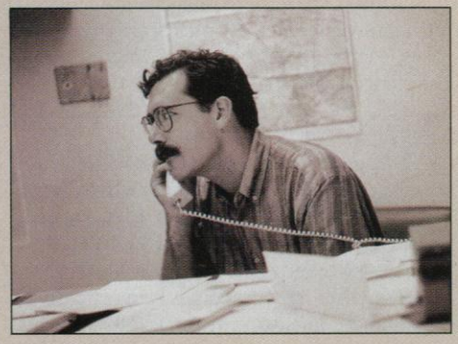
KEY: AFRIMS = Armed Forces Research Institute of Medical Sciences
RIHES = Research Institute for Health Sciences
BMA = Bangkok Metropolitan Authority

Searching for the Ideal Cohort

CHIANG MAI, THAILAND—Late on a Saturday night in this rapidly growing metropolis, Johns Hopkins University AIDS researcher Chris Beyrer tours the back streets he has come to know well since relocating here 3 years ago. "Hello," croons a woman in a short skirt sitting on a bar stool. Although it is September, the doorway to the bar is framed by small Christmas lights. "Christmas lights are pathognomonic for indirect bars," says Beyrer. Translation: Christmas lights at a bar are a distinctive signal that, in addition to drinks, sex is for sale.

Beyrer's assessment of the scene may seem clinical and detached, but that's his job. Beyrer is the Northern Thailand field director of the HIV Vaccine Efficacy Trials Network, or HIVNET, a project launched by the U.S. National Institute of Allergy and Infectious Diseases to help prepare the way for large-scale human trials at sites around the world. A chief aim of these projects is to identify groups of people, or cohorts, best suited to participate in such trials. And that effort is going strong in Thailand, because there's a good chance that these vaccines will get their first large-scale efficacy trials there (see main text).

As the studies that Beyrer and his colleagues have been conducting since 1992 attest, the optimum cohorts are not always obvious. Consider: These researchers have found that "direct" commercial sex workers (CSWs)—the ones who work in brothels—would not make good efficacy-trial participants, largely because they are hard to keep track of. But indirect CSWs, such as the ones at this bar and the many women who work in massage parlors, are less transient and may work out fine.



Balancing the numbers. Chris Beyrer is part of an NIH-funded program preparing the way for large-scale tests at sites around the world.

And that's not the only consideration in making such choices. The annual seroincidence, or rate of new infections, has to be high (at least 2%), but if it's too high (greater than about 15%), too many people will become infected before they've received their full series of shots, which can take 6 months. The number of participants needed for a statistically valid assessment of the efficacy of a vaccine depends in part on the percentage who show up for follow-up visits and the length of time that a trial runs—but researchers must keep in mind that if a trial runs more than a few years, too many participants will likely drop out.

Kenrad Nelson, the Johns Hopkins epidemiologist who is the principal investigator of HIVNET, and his colleagues have already learned much about which cohorts appear most viable. With the help of Chiang Mai University's Research Institute for Health Sciences, the Royal Thai Army (RTA), sexually transmitted disease (STD) clinics, hospitals, and the Red Cross, these researchers spent 18 to 24 months following 2710 HIV seronegative adults in four different cohorts: female CSWs, male STD clinic users, male RTA conscripts, and discharged RTA reservists. The STD clinic users had the best numbers: an annual seroincidence of 2.3% and an 18-month follow-up rate of 82%. Discharged RTA reservists had a similar profile. Indirect CSWs had a much less impressive follow-up rate of 54.1%, but their seroincidence of 4.9% considerably tilts the scales back in the right direction. With the direct CSWs, a seroincidence of 11.8% was deemed too close to the upper limit, and they had a dismal follow-up rate of 31.3%.

One of the biggest surprises was the RTA conscripts. "If we had a vaccine in 1993 to administer, they were the best cohort," says Hopkins' David Celentano, a behavioral scientist. Back then, their seroincidence was 3% and follow-up rate was near 90%. "But they're just not going to work." The problem is a Catch-22 that can potentially snare any cohort. Ethics demand that every AIDS vaccine trial volunteer be encouraged not to become infected. "You have to give them education, condoms, viricides—everything that might work," explains Nelson. This is precisely how the RTA has been treating new conscripts, and the seroincidence rates in one group studied for 18 months plummeted to 0.08%.

Despite all of the obstacles to setting up a cohort, Nelson—who has run various clinical trails in Thailand for 22 years—is not dismayed. Says Nelson: "I have great confidence that we can do an efficacy trial in Thailand."

–J.C.

people have been infected, about 90% through heterosexual sex. That's roughly the same number of infected people as in the entire United States, which has a population four times as large. And although Thailand has aggressively promoted the use of condoms and other preventive measures, new infection rates—a key parameter when evaluating the worth of a vaccine—are still frighteningly high in many populations. "We want to achieve a better intervention method, and we think the vaccine is the answer," explains Prayura Kunasol, the former head of Thailand's Communicable Disease Control department who is now helping to coordinate various AIDS vaccine trials.

The result, says Colonel Donald Burke of the Walter Reed Army Institute of Research (WRAIR), which is helping Biocine organize trials in Thailand, is an eagerness to push ahead with trials. "It comes down to what is the sense of urgency, what is the commitment, and what is the political will to control the epidemic," says Burke, who heads the entire U.S. military's AIDS research program and formerly helped develop a vaccine against Japanese encephalitis at the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, a 36-year-old collaboration between the Royal Thai Army and WRAIR. "These factors all weigh more heavily here than in the United States."

Epidemiologist Kenrad Nelson of Johns Hopkins University, principal investigator of an NIH-funded team that is helping ready Thailand for AIDS vaccine efficacy trials, adds that the Thai decisionmakers are much less fickle than their American counterparts. "If [the Thais] decide to study something, they carry through," says Nelson, who has conducted several rabies vaccine and leprosy drug trials in Thailand over the past 22 years. "That's one of the reasons Thailand is so out front."

Thailand's interest in AIDS vaccines is matched by Western researchers' interest in Thailand as a testing ground. The nation offers the big advantage of a relatively stable government—especially when compared to countries like Rwanda and Zaire, both of which once topped the list of potential AIDS vaccine efficacy trial sites. Thailand also has a long history of staging collaborative vaccine efficacy trials with the West, an independent spirit, and an educated and culturally homogeneous people. "The belief, the culture, it's very fertile for vaccines," says Prasert Thongcharoen, chief of the ethical

Money Matters

If Thailand decides to stage efficacy trials of the Genentech and Biocine AIDS vaccines (see main text), each test is expected to cost as much as $10 million. Right now, it's unclear who would pay for these studies, each of which would involve more than 2000 people and likely run for 3 years.

Both Genentech and Biocine say the financial risk is too great for them to foot the bills alone, but they would make a contribution. Thailand might, too, and there's talk of Japan and Sweden lending a hand. But the U.S. National Institute of Allergy and Infectious Diseases (NIAID), which currently spends nearly $500,000 a year helping Thailand prepare for efficacy trials, won't commit to spending money explicitly to test these two products. "They'd have to put a proposal in to us," says NIAID Director Anthony Fauci, who explains that it then would be a question of priorities. "Is it worth resources to test vaccines that most of the scientific community feels satisfied do not have a great chance of working?"

The U.S. Army, which now spends $3.5 million a year on AIDS vaccine research in Thailand and is intimately involved with the Biocine trial, is a more likely funder of efficacy tests. But the Army, too, has yet to make a hard-and-fast pledge to donate dollars. "We have an intellectual commitment in principle," says Army spokesperson Peter Esker, noting that "the financial details haven't been worked out."

Aside from government and industry sources, Thailand might also get a helping hand from the International AIDS Vaccine Initiative, a new group being set up by the Rockefeller Foundation's Seth Berkley to speed R&D. The group, conceived in think tanks he convened over the past year and a half, does not plan to fund trials outright. Rather, explains Berkley, he hopes the group can help countries negotiate deals with lenders, like the World Bank. "The world is not set up to solve this kind of problem," says Berkley of what he sees as the lackluster drive to develop AIDS vaccines. Another new nonprofit, the Albert B. Sabin Vaccine Foundation, may also help fund the trials if it can meet its goal of building a war chest of at least $50 million.

If either vaccine is shown to work, a different kind of money problem would have to be solved: Thais may not be able to afford the vaccine. Although specifics are in short supply, both companies promise to work with Thailand to cope with that problem—if and when it comes up.

–J.C.

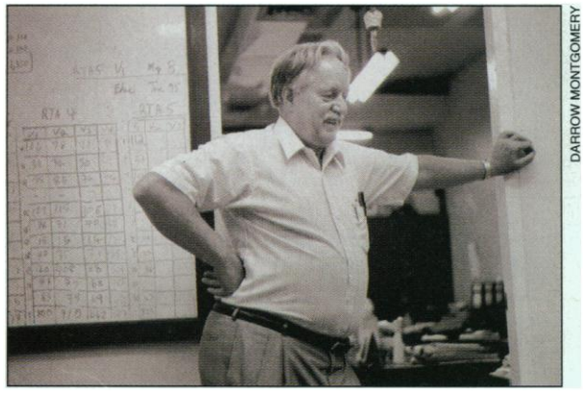
board of Thailand's National AIDS Prevention and Control Committee that approves AIDS vaccine trials.

Companies besides Genentech and Biocine are taking notice. "We trust them, and we trust what they do," says Jean-Louis Excler of France's Pasteur Mérieux-Connaught, which has a broader AIDS vaccine R&D program than any company in the world. "They have very skilled people." Pasteur Mérieux-Connaught is now testing various AIDS vaccines in small-scale human tests in both the United States and France, and Excler says the company hopes to begin similar-sized trials in Thailand next year of whatever proves to be the most promising of these approaches.

Trying time

At the moment, Thailand is host to two small-scale trials designed to test whether the Genentech and Biocine preparations are safe and produce an immune response in Thai recipients. A team led by Sricharoen Migasena, director of the Vaccine Trial Center at Mahidol University, began administering the Genentech vaccine in February to 31 "recovering" injecting drug users (IDUs) in Bangkok. A second team, led by Sorachai Nitayaphan at AFRIMS in Bangkok and Chirasac Khamboonruang of the Research Institute for Health Sciences at Chiang Mai University, began injecting 52 volunteers with the Biocine vaccine in August.

If these tests confirm results of similar trials done in the United States, which have involved a total of more than 1200 participants, the companies and their Thai collaborators hope to move on to large-scale trials to test whether the vaccines are effective. Genentech aims to start testing its vaccine on 2500 or so Thai IDUs by the end of 1996; Biocine hopes to have a modified version of its preparation in roughly the same number of people by the end of 1997.



DARROW MONTGOMERY

Experience. Johns Hopkins epidemiologist Kenrad Nelson has collaborated with Thai researchers for 22 years.

Company scientists are confident that these trials will happen. "We went to work in Thailand at the request of the government," notes Biocine's Anne-Marie Duliège, who heads the company's clinical work on HIV vaccines. "That's very, very important." Duliège's counterpart at Genentech, epidemiologist Donald Francis, is particularly heartened by what he sees as the Thais' appreciation of the trial-and-error, empirical nature of vaccine development. "When I talk to these people, they speak my language," says Francis. "When I talk to people at the NIH, they don't understand me."

Francis's comment reflects his frustration over NIH's decision not to support efficacy tests of these two vaccines in the United States. That decision was preceded by an intense scientific debate, which is now being replayed with some new twists as Thailand moves toward its own judgment on large-scale testing.

The central issue in this debate is whether any vaccine of the type made by Genentech and Biocine is likely to confer enough protection to warrant the expense of efficacy trials, which even in Thailand might run as much as $10 million apiece (see box). Both vaccines are made from genetically engineered versions of HIV's surface protein, gp120; the hope is that the vaccine will prime the immune system to recognize the protein on live HIV and mount an attack on the virus before it can establish a permanent infection.

Three years ago, that hope seemed well founded to many AIDS researchers, in part because test-tube studies showed that antibodies taken from people who had been vaccinated with gp120 could "neutralize" HIV that had been grown in lab cell lines, rendering it noninfectious. But in late 1993, researchers revealed that the same antibodies were largely incapable of neutralizing HIV freshly taken from patients. These results fueled skepticism already raised by research with similar vaccines against HIV's simian cousin, SIV: Preparations made from the SIV equivalent of gp120 have consistently failed

to protect monkeys from infection.

Some researchers have contested the relevance of these results, noting for example that both the Genentech and Biocine preparations appear to prevent chimpanzees from becoming infected with HIV-1—even though antibodies from the chimps could not neutralize fresh isolates of HIV in the test tube. But on 17 June 1994, a panel advising the National Institute of Allergy and Infectious Diseases (NIAID) recommended nixing the proposed U.S. trials. NIAID Director Anthony Fauci took the panel's advice, saying NIAID would wait until more promising vaccine candidates moved through the pipeline before staging large-scale trials in the United States.

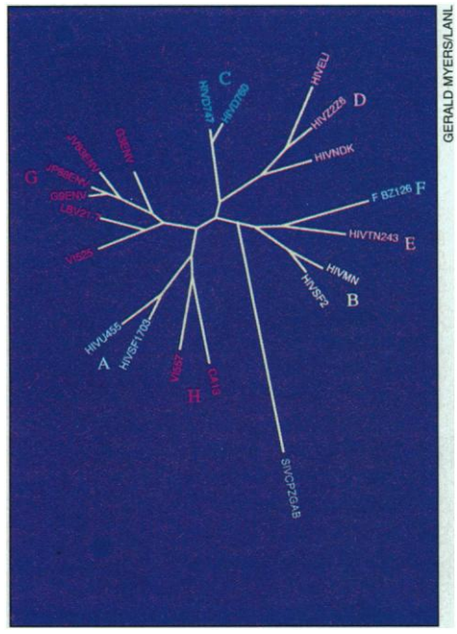
Biochemist John Moore of the Aaron Diamond AIDS Research Center believes that recent findings support Fauci's decision. Moore and colleague Ruth Connor recently studied a handful of cases in which volunteers who participated in safety and immunogenicity trials of the Genentech and Biocine vaccines in the United States subsequently became infected with HIV. As Moore reported last month at a Paris AIDS meeting, 14 of these "breakthrough" cases had received their full doses of vaccine. Although Moore is careful to note that these data do not prove that the vaccines are ineffective—this was not, after all, a properly controlled efficacy trial—he says the vaccines "clearly have not protected these people from infection." SIV vaccine developer Ronald Desrosiers adds that "there's no way you can look at that data and not be discouraged."

In spite of such findings, Desrosiers and many other researchers believe that gp120 vaccines shouldn't be written off without a clinical trial to determine whether they provide at least a limited degree of protection. "It could be that the vaccines are 70% effective, and that would be consistent with the breakthroughs," says Desrosiers. José Esparza, chief of AIDS vaccine development at WHO's Global Programme on AIDS, says that given the impact of the AIDS epidemic in developing countries, the negative data aren't compelling enough to discard the gp120 approach. "Lab assays and animal models will never be a substitute for clinical trials," says Esparza. "The only way past this impasse is to agree we have to combine field trials with animal and lab research." Adds Biocine's Duliège: "Every single person in the field of AIDS vaccines needs to know whether envelope-based vaccines work or not."

A question of type

As Thai officials weigh these arguments, they will also have to confront another hotly debated issue: Are vaccines developed from one strain of HIV likely to provide protection against other strains? By analyzing the genetic sequences of HIV's surface protein, researchers have established that there are at least eight "genotypes" of HIV, which are designated as subtypes (or clades) A to H, and at least two of these subtypes are circulating in Thailand.

Until recently, Thai IDUs were infected almost exclusively with the B subtype—which is also the predominant subtype in North America and Europe—while a subtype E HIV has been spreading rapidly by heterosexual transmission through the rest of the Thai population. Recent studies have indicated that these patterns of infection are changing: As first reported in the August issue of the journal *AIDS* by the CDC's Marcia Kalish and co-workers and separately by Mahidol University's Chantapong Wasi and colleagues, subtype E is becoming increasingly common in Bangkok IDUs, accounting for more than 40% of the most recent infections.



HIV's family tree. At least eight subtypes, or "clades," of the AIDS virus have been identified by analyzing the sequence of its surface protein. B subtypes are most common in North America and Europe. Intravenous drug users in Thailand are mostly infected with a B subtype, although an E subtype is spreading rapidly in the general population and increasingly among drug users. This clade diagram was constructed by Gerald Myers and Bette Korber of Los Alamos National Laboratory.

Researchers are divided on whether antibodies raised against one subtype of HIV are likely to neutralize other subtypes of the virus—or even slightly different versions of the same subtype. Indeed, at a recent meeting in Chiang Mai, different groups reported conflicting results on both those questions. The Genentech and Biocine trials might provide a clinical test, however.

The two companies are planning different strategies. Both are testing B-subtype vaccines to establish whether they are safe and can stimulate immune responses in Thai recipients, and Genentech wants to conduct efficacy tests of its current vaccine in Bangkok IDUs. Biocine, on the other hand, is also developing a subtype E–based gp120, and it hopes to test a vaccine containing both B and E gp120 on a broader population.

The recent spread of subtype E among Thai IDUs is leading some AIDS vaccine researchers to question the wisdom of Genentech's proposal to test only a B subtype vaccine in this population. "I think this trial is inappropriate," says Moore, who adds that even if the Genentech vaccine does show some efficacy in the IDU population, it may not prevent heterosexual transmission, the main problem in Thailand.

Other researchers see merit in sponsoring two different approaches. "I support the [Genentech] trial, especially as far as [the early phases]," says epidemiologist Khanchit Limpakarnjanarat, adjunct director of the HIV/AIDS Collaboration, a joint project of the Thai Ministry of Public Health and the CDC that is helping to stage the trial. "There are serious questions that we're concerned about, but subtype B is still prevalent in this population." WHO's Heyward is even more enthusiastic. "This is a great scientific and public health opportunity to move ahead and learn a lot with a single trial," implores Heyward.

Despite the pessimism about gp120 vaccines, observers are confident that the Thais will stage real-world tests of at least one of them. Prayura, former head of the Thai CDC, says he "acknowledges" that these vaccines have a low likelihood of working, but he is still interested in testing them. "We look at the development of a vaccine like this: It will start with low efficacy, and from that knowledge we can design a better one," says Prayura. "But without a trial, no one can say the vaccine can be proven good or not good."

There is certainly no giddy optimism here that these vaccines will protect the majority of people who receive them. Rather, researchers and officials like Prayura hope that whether the preparations work or not, they will illuminate how to make the next generation of vaccines and put to rest lingering questions about strain variability, the meaning of various immune responses, and, ultimately, the value of genetically engineered gp120. "Some people are content living the life of perpetual uncertainty," says WHO's Heyward. "I'm not." And that sentiment seems to be widely shared among Thai researchers, as they watch hospitals like San Patong struggle to cope with a steadily increasing number of patients who are sick and dying from AIDS.

–Jon Cohen