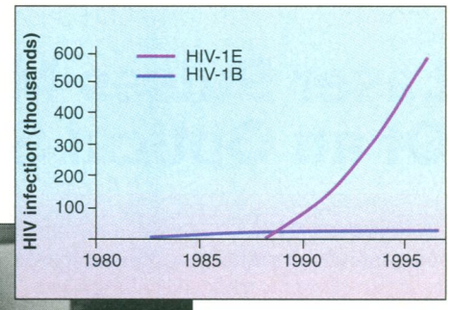
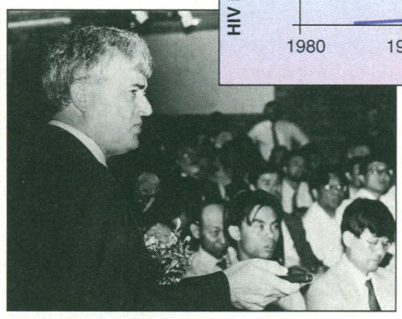
Differences in HIV Strains May Underlie Disease Patterns



CHIANG MAI, THAILAND—As the epicenter of the AIDS epidemic shifts from Africa to Asia, this Southeast Asian kingdom, which bills itself as "a golden wonderland," has emerged not only as one of the hardest hit in the region but as the one most willing to confront the disease. With as many as 1 million of its 60 million people already infected, Thailand—after some initial reluctance—has launched aggressive campaigns to curb the spread of HIV and to care for the thousands who have already progressed to symptomatic AIDS. Thailand has also emerged as a place that may provide answers to some of the most difficult questions facing AIDS researchers today.

This was made clear at a 5-day conference held here 2 weeks ago,* when researchers described many painstaking epidemiological studies tracking the course of the epidemic in Thailand, providing perhaps the most complete profile of the spread of HIV in any developing country (see box). And in one dramatic presentation, retrovirologist Max Essex of the Harvard School of Public Health in Boston revealed data, much of it gathered in collaboration with Thai researchers, that may help explain a long-standing conundrum: Why is HIV primarily transmitted through heterosexual intercourse in developing countries, while the main routes of infection in the industrial world are anal intercourse and the sharing of contaminated needles by injecting drug users? The answer, Essex argued, may lie in differences in the HIV strains in the developing and industrial worlds.


DARROW MONTGOMERY

Heterosexual transfer. Max Essex presenting data on preferential spread of HIV-1 subtype E strain in Thailand.

Essex noted that 10% or fewer of transmissions of HIV-1—the main type of the AIDS virus—occur through vaginal intercourse in the United States and Europe. In Thailand, the situation is just the opposite. "That suggests that something is dramatically different," said Essex. In collaboration with teams headed by Chantapong Wasi of Mahidol University and Vicharn Vithayasai of Chiang Mai University, Essex and his Harvard co-workers have begun to tease out biological explanations for that elusive "something."

For 5 years, researchers have theorized that the startling difference in transmission routes comes down to the substrains of HIV-1 spreading through a population. Specifically, in 1990, researchers tracking the Thai epidemic first recognized that what is now known as HIV "subtype E" almost exclusively infected Thai heterosexuals, while "subtype B," the strain that predominates in Europe and the United States, is found almost exclusively in Thai injecting drug users. Essex's new data show, for the first time, why subtype E may be preferentially transmitted through heterosexual sex.

HIV infects and destroys white blood cells, or T lymphocytes, that bear a CD4 receptor. Essex began by showing that 18 different subtype E and subtype B HIVs freshly taken from Thai patients all grew well in peripheral blood mononuclear cells, a mixture of cells that includes CD4+ T cells, which indicates that both could infect via the blood. Next, Essex took tissue from the vagina, cervix, breast, and penile foreskin and isolated the Langerhans' cells, which are common in the skin and play a critical role in turning on the immune system when they encounter foreign invaders. When he put the different virus subtypes on these Langerhans' cells, the subtype E viruses grew "quite well," while the subtype B viruses hardly grew at all. "There's a clear propensity for better infection [by subtype E HIVs] with those cells that line the female genital tract," Essex said.

Support for the crucial role of the Langerhans' cells in heterosexual transmission comes from data on SIV, HIV's simian cousin. Essex noted that Christopher Miller at the University of California, Davis, has reported that when he puts SIV in the vaginas of monkeys, the virus localizes in Langerhans' cells. The Pasteur Institute's Marc Girard and Patricia Fultz from the University of Alabama, Birmingham, have found that it is much easier to infect a chimpanzee vaginally with subtype E than with subtype B HIV. And Essex described new data from

* Third International Conference on AIDS in Asia and the Pacific/The Fifth National AIDS Seminar in Thailand, 17–21 September, Chiang Mai, Thailand.

Thailand Points the Way

Thailand has become a key destination for researchers trying to unravel the intricacies of the AIDS epidemic (see main text). And with good reason: Backed by a strong scientific community, relatively stable politics, and a sturdy infrastructure, Thailand is yielding the clearest picture yet of how the epidemic spreads in a developing country and how it might be combated. "The success or failure of the effort made by Thailand to counter the disease is being watched with great interest by many people around the world," conference organizer Nhatt Bhamaraprarati of Bangkok's Mahidol University told the 2546 attendees who came from 200 countries for the gathering.

The emerging profile of the spread of HIV in Thailand presented at the meeting is a sobering one. Because there is a long lag between HIV infection and symptomatic disease, Thailand—which had a minuscule number of HIV infections until 1988—has only seen the tip of the AIDS iceberg. And, as speaker after speaker at the conference emphasized, that iceberg is depressingly large. In the north of Thailand near Chiang Mai, for example, studies unveiled at the conference show HIV infection rates of 38% in commercial sex workers, 12% in Royal Thai Army recruits, and 16% among men using sexually transmitted disease clinics.

And Thailand may be a bellwether for other Asian countries. The World Health Organization estimates that although only 3 million of the 18 million HIV-infected people in the world are in Asia, that number has doubled since 1993—and the situation is getting worse. "It is expected by the year 1997 the annual number of new HIV infections in Asia will exceed those in Africa, and its share of worldwide cumulative HIV infections will increase to nearly 25% by the year 2000," said Peter Godwin, head of the Regional HIV Project at the United Nations Development Program.

–J.C.

Yichen Lu at the Virus Research Institute in Cambridge, Massachusetts, who has constructed different SIV-HIV hybrid viruses, called SHIVs, that differ in their ability to infect Langerhans' cells in test-tube studies. In Lu's experiments, monkeys given an intravaginal dose of the SHIV that favors Langerhans' cells were easily infected, while the ones given the SHIV that was nontropic for Langerhans' completely resisted infection.

Essex used this data as a springboard to hypothesize that there are two distinct HIV-1 epidemics. In developed countries, he argued, subtype B predominates and is spread primarily through blood and homosexual sex. In contrast, developing countries are experiencing "epidemic 2," which is driven by the other subtypes being spread primarily through vaginal sex (see table). "If other HIV-1 subtypes take hold in Western Europe or the U.S., we must predict a more significant heterosexual epidemic than we now see in the West," said Essex.

By and large, the response to Essex's presentation was enthusiastic. "I think he's on to something," said epidemiologist Sten Vermund of the University of Alabama, Birmingham. "I think it's highly plausible that E clade HIV could differ in its infectivity." John Mascola of the Walter Reed Army Institute of Research (WRAIR)—which first isolated subtype E—also found the talk provocative. "It's potentially extremely important," said Mascola. "Any single piece [of Essex's argument] is not compelling, but when he puts it together it makes a reasonably compelling case."

Still, some researchers had serious reservations about Essex's conclusions. Ann Duerr of the U.S. Centers for Disease Control and Prevention (CDC), in collaboration with Vinai Suriyanon and colleagues at Chiang Mai University, have been studying transmission rates between "discordant" couples—where only one is initially HIV-infected—in Chiang Mai. Although nearly 90% of these infections are subtype E, their work has shown that the rate of transmission is nearly identical to the rate found in a U.S. study that looked at discordant couples infected with subtype B. "The data I have on hand don't support [Essex's] conclusion," said Duerr, who cautions that they have not done a direct comparison of transmission rates of the two subtypes in their cohort.

Another wrinkle to Essex's theory, as William Heyward of the World Health Organization pointed out, is that subtype B is predominant in the Caribbean, Central America, and Brazil, and these regions all have primarily heterosexual epidemics. Essex countered that this discrepancy may be because anal intercourse is more common in these countries, although he offered no data to support that contention.

WRAIR's Donald Burke, who heads the U.S. military's AIDS program, said his group is now gearing up to do assays of different subtypes' ability to infect different cell types. Until the hypothesis gains more support, says CDC epidemiologist Timothy Mastro, who is based in Bangkok and heads the HIV/AIDS Collaboration, "the data are too thin to say it's true." But he notes: "The fact that there is this remarkable separation [of subtypes] is hard to explain."

–Jon Cohen

TWO HIV-1 EPIDEMICS

Category	Epidemic 1	Epidemic 2
Location	West (U.S., Europe)	South (Africa, S.E. Asia)
Cause	HIV-1B	HIV-1C, -E, -D, -A
Number infected	~1.5 million	15–20 million
Epidemic status	Plateau or decreasing	Increasing
Exposure route	Blood, rectal bleeding	Vaginal intercourse
Exposure cell	Monocyte, lymphocyte	Langerhans' cell

SOURCE: MAX ESSEX

ENDANGERED SPECIES

Minimum Population Grows Larger

When it comes to saving endangered species, Noah's ark offers little practical guidance. As population geneticists have long known, a single breeding pair can't provide enough genetic variability to allow a small population of their progeny to survive an array of environmental onslaughts or an accumulation of deleterious traits. But just how large a population must be to ensure long-term survival has been a matter of some debate. Back in the early 1980s, researchers estimated that at least 500 randomly mating individuals would be required. New studies of the genetics of small populations offer a much more sobering estimate: They suggest that a species must number 10,000 or more to maintain its evolutionary viability.

That's grim news for modern-day Noahs. Recovery goals for many endangered species are in the hundreds, so the new figures imply that current efforts—even if successful for years or decades—won't prevent extinctions hundreds of generations from now. "The implications are that in the very long run, our recovery plans may allow genetic damage to accumulate. Well down the road, we could lose what we've been trying to save," says Robert Lacy, conservation geneticist at the Chicago Zoological Society.

When researchers originally estimated the population size needed for long-term survival, they focused primarily on variation in quantitative, polygenic traits, which are determined by the effects of many different genes; height in humans is a common example. Such genetic variation, which arises by mutation, is important because it is the raw material of evolution. Over many generations, natural selection will favor the few beneficial mutations that allow species to adapt to changes in climate, pests, food, or other environmental factors. In the 1980s, researchers concluded that 500 randomly mating individuals (comprising what geneticists call an effective population) could supply enough variability.

"Well down the road, we could lose what we've been trying to save."

—Robert Lacy

Now population geneticist Russell Lande of the University of Oregon, Eugene, argues that these calculations underestimated the critical population size because they failed to consider the effect that these mutations have on the fitness of organisms. Lande's analysis, published in the August issue of *Conservation Biology*, is based on recent work in which other researchers, particularly geneticists Maria López and Carlos López-Fanjul of Complutense University in Madrid, studied mutations in quantitative traits such as the number of bristles on the abdomen of the fruit fly *Drosophila melanogaster*. The Madrid workers found that the most extreme mutations—those causing dramatic changes in bristle numbers—often had lethal side effects and so had no chance of spreading in the population.

Only mutations with little effect on fly survival and reproduction, the so-called quasi-neutral mutations, could be maintained in the population. But these mutations typically had much smaller effects on the trait, causing only about 10% of the total genetic variation in bristle number. To produce the same amount of variation from quasi-neutral mutations—rather than from all mutations as done in the original calculation—requires 10 times as many individuals, says Lande. This implies that the effective population size needed to preserve a species' evolutionary potential is 5000, not 500. Because the vagaries of mating make a population's effective size much smaller than