AIDS RESEARCH

Virus From 1959 Sample Marks Early Years of HIV

Many AIDS researchers have long suspected that HIV-1—the version of the AIDS virus that causes most cases of the disease in the world—was lurking in the human population by the 1950s. Now, they have the first solid evidence to support that notion. A team led by David Ho, director of the Aaron Diamond AIDS Research Center in New York City, reports in the current issue of *Nature* that it has fished out and sequenced fragments of an early HIV-1 genome from a 1959 blood plasma sample. The sample came from a man living in what was then Leopoldville, Belgian Congo, and is now Kinshasa, capital of the Democratic Republic of the Congo. The results, if correct, would make this the earliest confirmed case of HIV infection.

The finding is not just a historical footnote. A comparison of the virus's genome with that of modern HIV strains is providing information on how much the virus has evolved—information that might help researchers design drugs and vaccines. And it may hold clues to how and when HIV jumped the species barrier from monkeys or chimpanzees to humans. "The implications for the origin of the epidemic and the future of drug discovery and rational vaccine design are striking," says virologist Steven Wolinsky of Northwestern University Medical School in Chicago.

Wolinsky, along with other experts who spoke with *Science*, gave a thumbs up to the study's technical accomplishments. "The data [are] very solid," says Beatrice Hahn, a molecular virologist at the University of Alabama, Birmingham. Ho and his colleagues, she says, have squeezed "about as much information as one could possibly get out of a sample that old and poorly preserved."

Almost as soon as HIV was identified in 1983, scientists began searching for the source of the infection. A group of British researchers suggested in a 1983 letter to *The Lancet* that a Manchester sailor who died in 1959 of AIDS-like symptoms may have been infected with HIV. Tissue samples taken from the sailor later tested positive for HIV, but most experts eventually became convinced that these findings were a result of laboratory contamination. A second tentative early sighting of the virus came in 1986, when André Nahmias, a virologist at Emory University School of Medicine in Atlanta, and colleagues from several U.S. labs screened some 1200 plasma samples from various parts of Africa that had originally been collected as part of a study of immune system genetics. One sample, dating from 1959, tested positive for anti-HIV antibodies.

Nahmias, who is a co-author on this week's *Nature* paper, jealously guarded this sample until better analytical techniques came along. Last year, he agreed to give some of it to Ho for analysis. After numerous attempts to detect HIV genes using the polymerase chain reaction, Tuofu Zhu, a postdoc in Ho's lab, finally managed to tease out four small fragments representing less than 15% of HIV's genome.

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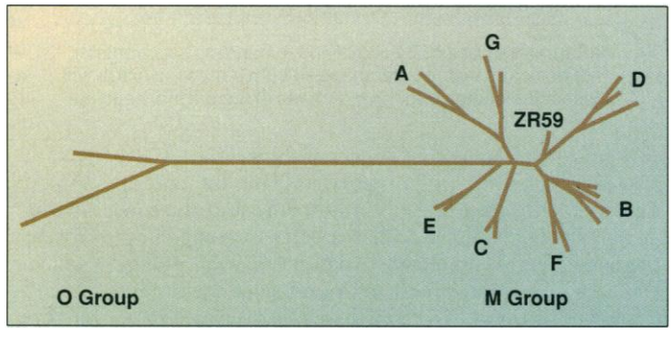
—Steven Wolinsky

Ho's lab sequenced these fragments and sent the data to Bette Korber of the Los Alamos National Laboratory in New Mexico and Paul Sharp at the University of Nottingham in the United Kingdom, both experts in deriving HIV phylogenies. Korber and Sharp determined independently that the 1959 strain, dubbed ZR59, evolved soon after the common ancestor of three common HIV-1 subtypes known as B, D, and F. Moreover, the analysis suggested that this common ancestor existed in the 1940s or early 1950s, and the authors speculate that the virus may have been introduced into humans shortly before that time.



SOURCE: ZHU *et al.*, *Nature*

Fossil virus? An early HIV-1 strain, ZR59, appears closely related to the common ancestor of modern HIV-1 subtypes B, D, and F.

Figuring out the evolutionary history of HIV has long been hampered by what researchers call its "starburst" phylogeny, that is, the rapid genetic variation the virus has undergone since it first infected humans. These new results shed light on the early history, researchers say, by helping narrow the window of time within which the virus could have jumped the species barrier. Moreover, by comparing the ZR59 sequence with viruses found today in nonhuman primates, researchers might be able to find common features that would identify which primate harbored the virus that originally infected humans. "[ZR59] may represent the status of HIV-1 soon after its transfer from primates to humans," says Francine McCutchan, a molecular biologist at the Henry M. Jackson Foundation for the Advancement of Military Medicine in Rockville, Maryland.

In addition, Ho says, the new data "help us put a time frame on this epidemic, to see how much HIV has evolved in the last 4 or 5 decades and understand where it is going." Having a better idea when the virus first infected humans also might help pinpoint the conditions that allowed it to later explode in the human population. For example, Ho and his team speculate that the virus might have spread rapidly after its first apparent introduction into humans in Africa through the use of unsterilized needles during vaccination campaigns or as a result of the dramatic social and demographic changes that swept the African continent in the late 1950s and early 1960s.

A better understanding of HIV's origins, Ho and others say, may also boost efforts to develop an AIDS vaccine, which are currently plagued with the problems posed by the genetic diversity of different strains, whose sequences can vary from each other by 10% or more. Knowing more about the common ancestor of these strains might help pinpoint those segments of HIV's genome that have changed the least over time, which could then become vaccine targets. "If subtypes B, D, and F belong to a common lineage, and [other subtypes] to another, the conundrum of selecting vaccine prototype strains from eight or more equidistant subtypes might be avoided," says McCutchan. A vaccine based on common features shared with HIV's early ancestors, she adds, may prove to be more universal in fighting the global epidemic than vaccines based on combining a cocktail of modern subtypes.

But whether or not ZR59 leads to better therapies, it at least gives researchers a more complete picture of the enemy. Says Ho: "We need to know what hit us."

–Michael Balter