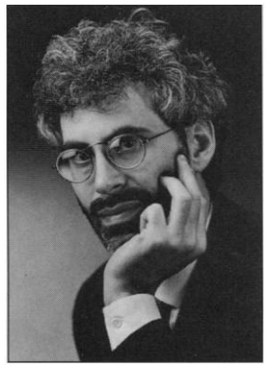
Infection With Selection: HIV in Human Infants

Fetuses can be infected only by their mother's virus, but some viral variants appear to be more infectious than others

Chicago—ACCORDING TO THE LATEST FIGURES from the World Health Organization, approximately 10 million people around the world are now infected with HIV, the virus that causes AIDS. With so many cases to study, you might think AIDS researchers would have figured out just how the virus gets from one person to another. In fact, they're still largely in the dark about the molecular mechanisms of HIV infection. Now, however, a small but growing group of molecular virologists, immunologists, and geneticists are studying the transmission of HIV from mothers to their infants in an effort to get a handle on why some exposures result in infection while others don't. Their unexpected results—which suggest that only a specific subset of viral variants are transmitted—could have a major impact on the design of prevention strategies.



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—Steven M. Wolinsky

One of the problems in studying AIDS transmission is that it's difficult to be there at the exact moment when it occurs. In a laboratory situation, working with a single viral strain infecting a white blood cell growing in culture, researchers can get some idea of the molecular steps involved in transmission. But in people, the story is far more complicated. An infected person may harbor dozens of viral variants capable of causing disease. The variants will be similar enough to constitute a single "strain" of HIV but will differ enough from their brethren to flummox an immune system that is trying to detect and destroy the virus. And HIV's prime target, the circulating white blood cells, behave quite differently in vivo than they do in the laboratory.

Steven M. Wolinsky, a molecular virologist at Northwestern University Medical School, decided to look at mother-to-infant transmission because it seemed to offer a relatively simple system to study. The first results from this approach appear on page 1134 of this issue of *Science*. Wolinsky set out to answer several key questions: Is one single viral particle enough to cause infection? If so, does that particle have to have some special molecular characteristic? And are there certain characteristics of the host immune state or cellular parameters that make one individual more susceptible to infection than another?

Even though there are a number of uncertainties about how and when the fetus is exposed to the mother's virus, one issue is straightforward. "You know exactly what virus is being transmitted from the mother to the fetus," says Wolinsky—something that is frequently not known with certainty in transmission after birth. Wolinsky and his colleagues at Northwestern, Los Alamos National Laboratory, the University of Miami, and New York University looked at viruses obtained from three mothers and their infants, who ranged in age from 2 to 4 months. Rather than attempt to study all 9500 base pairs of the viral genome, the researchers used the polymerase chain reaction technique to amplify two portions of the gene that codes for the viral envelope protein. Even so it was a daunting job of sequencing: The team sequenced approximately 41,500 nucleotide pairs in order to compare all the variants from each of the subjects.

One of the two portions of the genome Wolinksy and his colleagues looked at is known as the V3 loop. This portion of the protein that makes up the outer envelope of the virus is not only a highly variable region of the envelope, but is also thought to be the site crucial for immune recognition. The other segment, dubbed V4-V5, is also variable, but less so than V3.

As expected, the virus transmitted from a mother to her own infant was clearly more related to her virus than the virus in either of the unrelated infants. The V3 region nucleotide sequences varied between 0.5% and 6.1% for related pairs, and 10% to 17.3% for unrelated pairs. But Wolinsky's data showed a curious thing: Although each mother clearly had numerous viral variants in her body, only a subset of these variants showed up in the infant. In all three cases, the virus found in the infants was missing a site found in most but not all of the mothers' viruses where a sugar molecule attaches to a portion of the V3 region. Wolinsky says it is unclear what the significance of this missing sugar is, but because it is so rare, it suggests that some selection for it is occurring. In addition, although there were clearly viral variants that could be detected in the infants, the variability in the infant V3 and V4-V5 was far less than in the mother. Wolinsky concludes from this that only a few of the possible variants were passed on from mother to child.

Wolinsky is now trying to figure out just how this selection is occurring. He is also studying viral sequences and how they change over time in a large group of high-risk men who have been studied for years as part of the National Institute of Allergy and Infectious Diseases Multi-Center AIDS Cohort Study. Andrew Leigh Brown, a population geneticist at the University of Edinburgh, is studying cases of viral transmission among intravenous drug users infected in Edinburgh in the early 1980s. Although his data are still very preliminary, he thinks Wolinsky is on the right track. "We'd be willing to accept the general case that there is substantial selection going on at infection," he says. "But the exact nature of that selection may be different in infants from other cases of infection." Groups in Germany, Holland, Alabama, and the Centers for Disease Control in Atlanta are all trying to zero in on exactly what this selection phenomenon is, and how commonplace it is.

The clinical implications of viral selection at the time of transmission are enormous. If it turns out that specific features of some HIV strains make them more infectious than others, researchers will have a better idea how to target their prevention efforts. If, however, the specific nature of the selection Wolinsky found cannot be extended to other mother-infant pairs or other routes of infection, the picture gets even more complicated, and both effective therapies and vaccines will be far more difficult to design. Everyone agrees they need to study more examples of this selection phenomenon before they can be sure of its implications. "I'd like to see more instances where you can actually document transmission and have a look at this," says Dani Bolognesi of Duke University. "We're just too stupid to figure it out right now." ■ JOSEPH PALCA