

# HIV: Out of Sight but Not Inactive

HIV never really rests. Two new reports suggest that the AIDS-causing virus accumulates and actively replicates in the lymph nodes and related organs, even during the asymptomatic stage of HIV infection.

"The new findings demonstrate that significant viral activity occurs even during the prolonged period of apparent disease quiescence," says Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Md. A report by Fauci's team, one by Ashely T. Haase and his co-workers, and a related editorial on the HIV situation appear in the March 25 NATURE.

It is well known that HIV can be found in lymphoid tissues. However, this is the first time researchers have shown the extent and significance of HIV's presence in lymphoid tissues, which include the spongy lymph nodes, the spleen, the tonsils, and adenoids.

In the first report, Fauci and his colleagues collected lymphoid tissue from 12 people with HIV infection. Some of those people had the virus but showed no

outward sign of their infection and appeared healthy. Others had progressed to AIDS. Fauci's team used a powerful viral detector called polymerase chain reaction and other techniques in their study.

As expected, asymptomatic people showed little evidence of HIV in the bloodstream. However, lymphoid tissue removed from the same people showed high amounts of HIV as well as evidence of HIV replication.

That finding suggests that HIV not only hides out in the lymphoid tissues but actively replicates there, creating a dangerous reservoir of virus at a time when the person appears outwardly healthy, Fauci says.

Virologists know that soon after HIV infection, HIV begins to replicate, causing flu-like symptoms in many people. After that initial illness, the disease seems to go into hiding. During this time, the so-called follicular dendritic cells in the lymphoid tissues begin to trap the HIV circulating in the bloodstream. This immune mechanism clears most HIV from the blood, Fauci says. During this early,

asymptomatic period, CD4 T-lymphocytes (T-cells) migrate to the lymph nodes and become infected with the deadly virus. These T-cells are the major target of HIV.

As the disease progresses, more and more follicular dendritic cells die or become damaged. The lymphoid tissue's ability to ensnare HIV becomes limited, and the virus begins to spill out into the bloodstream, Fauci says. This is the period during which the number of T-cells begins to drop precipitously and people with HIV infection start to suffer from bouts of life-threatening infection.

The second paper adds to that view of HIV's progress. Haase, who is at the University of Minnesota in Minneapolis, and his colleagues obtained lymph node tissue from four HIV-infected people, including three who were asymptomatic. Using polymerase chain reaction and other techniques, Haase's team homed in on T-cells that had migrated to the lymph nodes. They showed that an extraordinarily large number of the cells had been infected with HIV. Indeed, Haase estimates that during the early stages of HIV infection, about 100 billion T-cells carry HIV but show no signs of viral replication. At the same time, approximately 1 billion T-cells contain actively replicating HIV.

The notion that HIV continues to reproduce even during the relatively symptom-free period of AIDS has led Haase and Fauci to conclude that a true state of latency in the disease does not exist. "I liken it to a constantly exploding volcano," Haase says. Even though the patient appears healthy, the virus never goes through a true period of total quiescence, he says.

Such findings may prompt AIDS experts to reconsider the policy of treating HIV-infected people only when some sign of deterioration appears. At present, clinicians give HIV-infected people antiviral drug therapy when their T-cell concentrations fall below 500 T-cells per cubic millimeter of blood, a point at which opportunistic infections begin to emerge.

The new findings suggest that treatment started right after infection might stand a better chance of stopping HIV's progress, says Dani P. Bolognesi at the Duke University Medical Center in Durham, N.C., who coauthored an editorial accompanying the reports.

Fauci warns that early treatment with available AIDS drugs could lead to resistance later on, a problem that could prove deadly if the virus outwits the first assault. Clinical trials must be done to prove that early treatment will benefit those with HIV infection, he adds.

— K.A. Fackelmann

## Kidney stones: Don't curb the calcium

It starts off innocuously, as a microscopic crystal floating in the tubules of the kidney. Over time, though, such invisible particles can grow layer upon layer, ultimately forming painful kidney stones that afflict one in nine people in the United States at some point in their lives. Because most kidney stones are made of calcium, physicians often recommend that patients who have already suffered from stones reduce their calcium intake. But a new study of more than 45,000 men challenges the traditional thinking, suggesting that low-calcium diets actually raise the risk of developing kidney stones.

In the March 25 NEW ENGLAND JOURNAL OF MEDICINE, a research team from the Harvard School of Public Health reports that men who ate a diet rich in calcium faced a 34 percent lower risk of developing kidney stones than did men who consumed a restricted calcium diet.

"This goes against everything we had been taught," says kidney specialist Gary C. Curhan, who led the calcium investigation. Curhan and his colleagues took their data from the Health Professionals Follow-up Study, a long-term investigation of diet and illness among male health care professionals age 40 through 75.

While it seems counterintuitive that consuming calcium could protect

against calcium-based kidney stones, Curhan thinks that a chemical called oxalate may explain the apparent puzzle. Oxalate is present in many foods, and it combines with calcium to form the insoluble crystals that make up most kidney stones.

Curhan suggests that a normal diet might provide enough calcium to tie up oxalate in the intestines, creating crystals that pass directly out of the body without harm. But a low-calcium diet would allow more oxalate to enter the bloodstream and eventually reach the kidneys, where it can form the crystals that lead to kidney stones.

That doesn't mean people should head to the local market and raid the dairy case with abandon. "The important thing we're trying to emphasize is not that adding calcium is necessarily going to help you but that for someone who has already had a stone, restricting calcium is not the right thing to do," says Curhan. He suggests people consume the recommended 800 milligrams per day.

He stresses that increasing fluid intake substantially cuts the risk of stones. The new study also hints that potassium may protect against developing stones: Men who ate a potassium-rich diet faced a 50 percent lower risk than did those who consumed the least amount of potassium. — R. Monastersky