AIDS RESEARCH

# High Turnover of HIV in Blood Revealed by New Studies

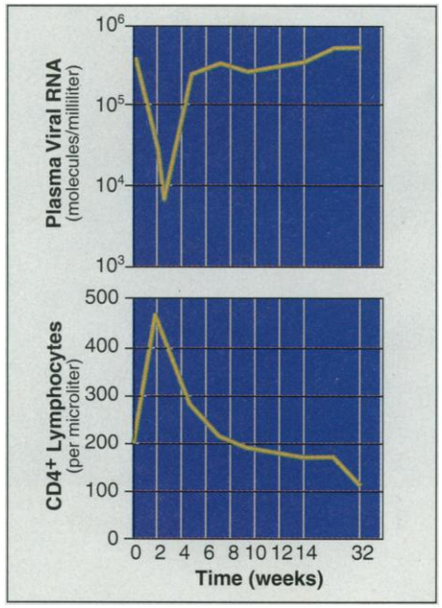
Over the past few years, AIDS researchers have reversed what was once conventional wisdom about the disease: that HIV is a virus present only in minute quantities in infected people. Today, improved techniques routinely net massive quantities of the virus. Beyond that, however, the details of the disease process have been murky. Now two research groups have pierced some of the murk. Using anti-HIV drugs as probes, the researchers perturbed what appeared to be a steady state of HIV in the blood, revealing that billions of virus particles are continuously produced by newly infected cells and then rapidly cleared. Experts in the field say these studies could have a broad impact on AIDS research, ranging from basic studies of the disease to methods of evaluating new drugs.

Although the new studies, which appear in the 12 January issue of *Nature*, were done by two independent groups of AIDS researchers teamed with mathematicians, they offer strikingly consistent findings. "We were very pleased when we found similar results—it must mean that the basic observations are correct," says George Shaw of the University of Alabama, Birmingham, leader of one team. Other AIDS researchers agree. "They're very impressive papers, and I think they are very solid," says Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases.

David Ho, head of the Aaron Diamond AIDS Research Center and leader of the second group, describes the work as capturing a motion picture of HIV's mortal combat with the immune system, rather than the snapshots that have been available to researchers until now. To date, studies of how HIV causes disease have largely focused on how much virus is present in the body at any given time, rather than the rate at which it is produced and cleared. But Ho and Shaw made the "turnover rate" of the virus—along with the turnover rate of the key immune system cells called CD4s, which are infected by HIV—the centerpiece of their work.

In essence, the two groups gave drugs that do not hinder production of new virus particles—but do block the capacity of newly made particles to infect other cells—and then observed the results. In Ho's study, the researchers gave an experimental drug from Abbott Laboratories to 20 HIV-infected people who initially had between 36 and 490 CD4s per cubic milliliter of blood (far below the normal range of 600–1200). The drug inhibits HIV's protease, an enzyme newly minted virus particles use to cut their surface proteins, which is a prerequisite for infectivity. The Shaw group studied 22 HIV-infected people with CD4 counts ranging from 18 to 251. These patients received either a protease inhibitor (Abbott's or one from Merck) or nevirapine, a drug that inhibits the viral enzyme reverse transcriptase, which enables HIV's genetic material, RNA, to infect a host cell's DNA.

Both groups analyzed plasma levels of HIV RNA—a proxy for the amount of free virus—after patients started taking the drugs. The drugs all cripple HIV's ability to produce infectious copies of itself, but researchers assume that none of the drugs has the capacity to eliminate virus already in the blood's plasma. Nonetheless, plasma HIV levels dropped exponentially when drug treatment began: Every 2 days, the level of plasma HIV was reduced by half (unfortunately, the effect was quickly reversed).




SOURCE: WEI ET AL. /NATURE

**Mirror, mirror.** Data from one patient after drug treatment show HIV dropping and CD4s rising.

The researchers did not focus on how the virus was being removed from the blood (a riddle that may involve everything from the immune system to the spleen and liver). Instead, they focused on the other side of the equation: Why wasn't HIV being replenished in the plasma? After all, there were cells that had already been infected with HIV prior to drug treatment, and those cells were capable of spitting out new virus particles after drug treatment began: Nevirapine has no effect on already infected cells, and although the protease inhibitors render new virions noninfectious, the new HIVs would still be detected in the plasma RNA assay.

The researchers conclude that already-infected cells are not capable of sustaining high levels of virus. For plasma HIV levels to remain high, they argue, many new immune system cells must be infected constantly. When drugs block new infections, plasma HIV levels fall. Rather than simply being the product of a constant high level of virus, says Shaw, the pathology seen in AIDS is "sustained primarily by a dynamic process where there are continuous rounds of de novo infection, replication, and turnover."

Both teams found the sharp drop-off in HIV levels. Ho's team went on to show that HIV decline is accompanied by a sharp increase in CD4 cells. By measuring post-drug rises in CD4s—the most dramatic of which was an increase of 600 in a month's time—they calculated that the total CD4 population in the peripheral blood in infected people is doubling every 15 days. The rapid rebound in CD4 count when virus replication is blocked, says Ho, leaves "no question to us that virus replication is the engine that drives CD4 depletion."

Although these studies say nothing about whether the new drugs tested help patients, the studies are revising views of how HIV operates. "The kinetics are a lot greater than we ever imagined," says AIDS researcher Steven Wolinksy of Northwestern University. University of Colorado immunologist Robert Schooley says he was most intrigued by data showing that the immune system can crank out hordes of new CD4 cells even in severely immunocompromised people. "There's a hell of a lot more immunological reserve than people would have thought," says Schooley.

Virologist Douglas Richman of the University of California, San Diego, a specialist in HIV drug resistance, says the new data challenge common wisdom that drug resistance is caused by HIV's high mutation rate. This is "a misconception," he says. HIV does not mutate any more frequently than other RNA viruses do; "drug resistance is a consequence of the high level of replication," says Richman, not of hypermutability.

Richman adds that these findings will change the way AIDS drugs are evaluated. At the moment, clinical studies typically begin evaluating a drug's effect on HIV levels 2 weeks after treatment begins. Given the rapid HIV turnover seen in this new work, Richman says, "if a drug doesn't have an effect by day 14," it isn't worth developing. And that is only one of the practical changes likely to result from the new HIV motion pictures that opened to rave reviews.

–Jon Cohen