HIV/AIDS RESEARCH

Tissue Says Blood Is Misleading, Confusing HIV Cure Efforts

DAWN BEACH, ST. MAARTEN—Three back-to-back talks at a meeting* here earlier this month provided fresh insights into why HIV is so difficult to eliminate from the body: Even when antiretroviral drugs (ARVs) knock down HIV to undetectable levels in blood, the virus remains active in tissues. "It's a beautiful story," said Steven Deeks of the University of California, San Francisco, who was not part of the new work. "We can no longer rely on the blood to inform us about what's happening with therapeutics." And this, Deeks says, could transform the approaches he and others take to curing the disease.

Sparked in part by the apparent cure of the "Berlin patient" (*Science*, 13 May, p. 784), Deeks and many others attending the meeting are exploring ways to seek out and destroy the tiny amounts of HIV left in the bodies of people who take powerful ARVs. The main obstacle to a cure is that reservoirs of cells that harbor latent HIV still persist.

Some researchers insist that ARVs have reached the limit of their powers and that other strategies are needed to wake up latent cells and purge the reservoir of virus harbored by long-lived cells. But others here argued that HIV continues to refill the reservoir and that ARVs have more work to do. Although the new findings triggered impassioned debates, even skeptics agreed the data were provocative.

A team led by Timothy Schacker, an infectious-disease specialist at the University of Minnesota, Twin Cities, analyzed five patients who had been infected for an average of 5.8 years, before and after starting ARVs. The researchers compared both levels of HIV and drug concentrations for 6 months in blood and tissue, including biopsies from the lymph node, rectum, and ileum. HIV dropped to undetectable levels in the blood of all men on average within 2 months. But lymphatic tissue, where much of the virus is trapped in a spider web of sorts formed by dendritic cells trapped in clusters of B cells, still had abundant HIV.

Collaborator Mario Stevenson, a virologist at the University of Miami in Florida, showed that HIV in the tissue continued to infect new cells there (the majority of which are CD4 lymphocytes) even after ARV treatment crippled virus in the blood. He was careful to point out that his assay indicated only that new cells were being infected; it could not directly detect the full cycle of "replication"—infection, integration of viral genes into the cell's chromosomes, followed by new virus production and entry into still more cells. Yet he reasoned that because "de novo infection" clearly was occurring, HIV must have successfully integrated in some cases. "At the very least, it provides the conditions for reservoir replenishment," he said.

A third collaborator, pharmacologist Courtney Fletcher of the University of Nebraska Medical Center in Omaha, offered a convincing explanation for the levels of virus in tissues. Using mass spectrometry and liquid chromatography, Fletcher found that concentrations of ARVs in tissues rarely reached what are considered therapeutic levels. "These data at least allow the hypothesis that fully suppressive concentrations of these antiretroviral drugs may not be uniformly achieved in the cells of the [gut] and the lymph node," he said.

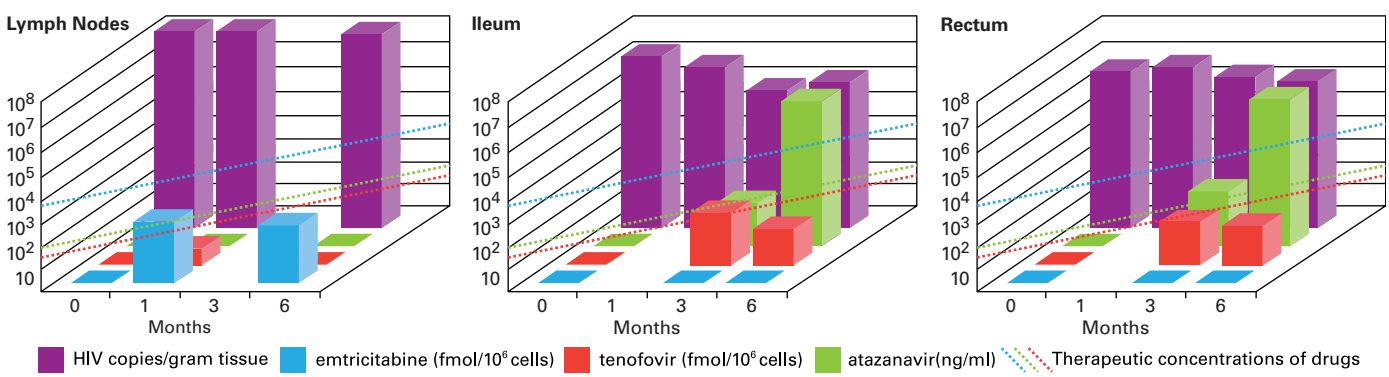
The team's combined data suggest that attacking HIV in the tissues might offer a novel way to shut a spigot that refills the reservoir. Fletcher explained that the key challenge may be to target cellular "transporters," proteins that move drug into cells and pump it out. Tinkering with cellular transporters may enable existing or new ARVs to reach therapeutic concentrations in various tissues, he suggested.

Virologist John Mellors of the University of Pittsburgh in Pennsylvania led the skeptic camp. Mellors accepts that a little de novo infection occurs but is unconvinced it could refill reservoirs. If replication really is taking place, on the other hand, that would make a compelling case that ARV levels in tissues are hampering cure efforts. To demonstrate ongoing replication, studies must show that HIV in tissue changes over time, either by becoming resistant to drugs or acquiring new mutations that have no obvious effect. Another presentation at the meeting by Sarah Palmer of the Karolinska Institute in Stockholm explicitly looked for viral changes in the tissues of eight treated patients who had fully suppressed HIV in their blood on ARVs and found none.

Schacker and co-workers stress that it's extremely difficult to prove that replication isn't happening with few samples. What's more, Stevenson argues that low levels of de novo infection might not lead to drug resistance or harmless changes in genetic sequence but could still refill reservoirs.

Steven Wolinsky, head of infectious disease at Northwestern University School of Medicine in Chicago, recently signed on with the Schacker team to do the genetic sequence analyses of the tissue samples. "I was bowled over when I learned the data that poor drug penetration into tissue plays an important role in ongoing infection," Wolinsky said. "It's a study we should have done 20 years ago."

–JON COHEN



Uneven levels. Treament reduced HIV in blood to undetectable levels in this patient, but had little effect in tissues.

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*The Fifth International Workshop on HIV Persistence During Therapy, 6–9 December.

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