AIDS RESEARCH

# Results on New AIDS Drugs Bring Cautious Optimism

AIDS research ricochets from breathtaking optimism to stomach-wrenching disappointment so frequently that many people have become numb to new results. So the indisputably positive data about a new class of AIDS drugs presented in Washington, D.C. last week at the largest annual U.S. AIDS conference* has many AIDS researchers and HIV-infected people alike gauging just how excited they should feel. "Is this an advance?" asked Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID). "Yes. But those of us who haven't lost our long-term memories remember what happened with AZT," the first AIDS drug.

The advance Fauci was referring to came in presentations indicating that new AIDS drugs that act by blocking the activity of a protease enzyme needed for AIDS virus replication can reduce the amount of HIV in the patients' blood and, in late-stage patients, possibly decrease disease and death by as much as 50%. Adding further grounds for optimism, the finding that these drugs decrease viral load dovetailed with another encouraging result: Several other studies showed that people who had less HIV in their bodies fared better than people with higher viral loads. Although the benefit of a lower viral load might seem obvious, formal proof is just now emerging—and it promises to reshape the way clinicians manage HIV-infected patients.

But as the NIAID director recalls all too well, AZT, which targets another enzyme needed for HIV reproduction, reverse transcriptase (RT), generated similar excitement in 1986 when a study revealed that it could extend the lives of people who had already developed AIDS. Subsequently, however, AZT failed to show much benefit when given to HIV-infected people who hadn't yet developed symptoms. This apparently happened because, in time, HIV mutants cropped up that were invulnerable to the drug.

In spite of such worries, the 2400 people who got into the popular conference—many were turned away at the door—were much buoyed by the new results. "This is exciting news," said Lawrence Deyton, head of the HIV research branch of NIAID's Division of AIDS, although he added: "Now we have to go full steam ahead to demonstrate the durability of the clinical effect."

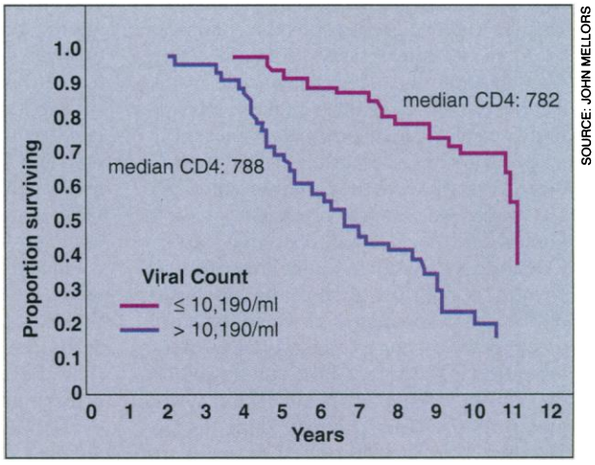
Much of the most exciting drug data revealed at the conference came out at a "late-breaker" session that capped off the gathering. One presentation there focused on a protease inhibitor called ritonavir, made by Abbott Laboratories of Illinois. As Abbott's John Leonard reported, ritonavir has been tested in 1090 AIDS patients from three continents, half of whom got the drug, while the rest received an inactive placebo. More than 80% of the study participants also took other anti-HIV drugs, and all had severely compromised immune systems, as indicated by counts of CD4 cells—a key component of the immune system—averaging about 30 per cubic millimeter of blood. (Normal CD4 counts range from 600 to 1200.)

In all, Leonard said, 33.1% of the placebo recipients developed an AIDS-related disease or died during the 7-month study; in contrast, only 15.3% of the treated patients had similar outcomes. And all of the patients had only minimal side effects, such as nausea and diarrhea. An analysis also showed that ritonavir decreased the patients' viral load sixfold through 16 weeks of the trial. But as the subsequent presentation by Roy Gulick from New York University revealed, that is a relatively modest effect.

Gulick and colleagues tested indinavir, a protease inhibitor made by Merck Research Laboratories, in 97 patients, who were equally split into three treatment groups: The control group received AZT plus 3TC, another RT inhibitor, while a second group got indinavir and a third got all three drugs. The ongoing study has not been conducted long enough to show differences in clinical outcomes in the patients, whose immune systems weren't as depressed as those of the patients in the ritonavir study. But the researchers did find huge differences in HIV levels following treatment.

At the study's start, all the patients had more than 20,000 copies of HIV RNA per milliliter of blood, as measured by the ultrasensitive polymerase chain reaction (PCR) assay. But after 24 weeks, the viral RNA had plummeted 200-fold and was undetectable in 86% of the patients who received all three drugs, although they likely still have small amounts of HIV because this PCR assay can't accurately detect fewer than 500 copies per milliliter. Only 40% of the people receiving indinavir alone had undetectable virus levels. And the researchers easily detected HIV in everyone taking just AZT plus 3TC. Again, there were few serious side effects linked to this protease inhibitor. "Certainly the response we have seen is very gratifying and the best of any [anti-HIV drugs] we've seen to date," said Emilio Emini, who heads anti-viral research at Merck Research Laboratories.

But a question that has long plagued clinical AIDS research (*Science*, 22 September 1995, p. 1666) concerns whether so-called "surrogate markers," such as viral RNA counts or CD4 counts—the current standard—can predict whether drug therapies help people live longer, healthier lives. Two substudies of large clinical trials, one presented at the meeting by Scott Hammer of the New England Deaconess Hospital in Boston and the other by William Freimuth of Pharmacia & Upjohn Inc., suggest that, yes, a drop in viral load does translate into a clinical benefit. But even more persuasive to many people at the meeting was a study led by John Mellors of the University of Pittsburgh that did not even directly address the question.




SOURCE: JOHN MELLORS

**Early warning.** High initial HIV levels spell trouble even when the starting CD4 counts are normal or near normal (above 500).

Rather than asking whether a drug's ability to decrease viral load is a valid surrogate marker, Mellors and colleagues at the Pittsburgh Multicenter AIDS Cohort Study assessed how viral load—regardless of treatment—affected a person's survival. Mellors analyzed blood samples collected every 6 months since as early as 1984 from each of 181 men, most of whom never took AZT (which wasn't available until 1987) or any other anti-HIV drug. After separating people by their initial viral loads and CD4 counts, Mellors assessed what happened to them over several years and found that the baseline viral load powerfully predicted survival, while CD4 counts did not.

In one particularly convincing example

* 3rd Conference on Retroviruses and Opportunistic Infections, 28 January to 1 February.

of this, Mellors and his colleagues divided the men into two groups, one including those with more than 10,190 HIV RNA copies per milliliter of blood and the other including men with fewer copies. After 10 years, he found that 70% of the people in the low viral-load group had survived, while more than 70% of the group with an initial high load had died—even though the two groups had nearly identical baseline CD4 counts. He closed his talk by quoting an infamous button that David Ho, head of the Aaron Diamond AIDS Research Center, made in 1993: "It's the virus, stupid." Ho, in turn, called Mellors' talk no less than "the most impressive thing at this meeting."

While Mellors was careful to note that his work does not prove that drug-induced drops in viral load lead to clinical benefit, he thinks the data clearly point in that direction. Others agree. The finding should transform the way doctors make key treatment decisions, said Douglas Richman, a clinician at the University of San Diego, California, who helped organize the meeting: "We'll get viral loads on everyone right away," as a guide to assessing their conditions and making treatment decisions.

This is undeniably an exciting time for AIDS researchers, but these high hopes are tempered by the realization that, so far, HIV in time has developed resistance to every drug—and every drug combination—thrown at it. And the goal of treatment is not a transient benefit, but a sustained one. Said NIAID's Deyton: "To those people who say, 'It's the virus, stupid,' we have to remember, 'It's the patient, stupid.' "

**–Jon Cohen**

ASTRONOMY

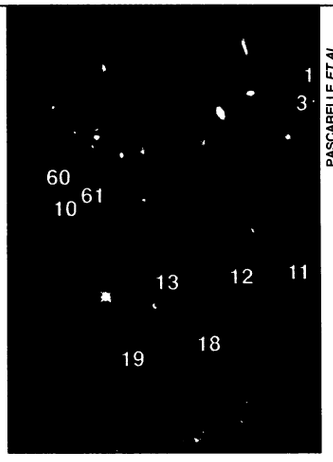
# Galactic Building Blocks Found?

Galaxy formation has been a puzzle with all the pieces missing. Many theorists who study the formation of structure in the cosmos think that galaxies formed from the "bottom up," with small structures merging into larger ones. But these subgalactic clumps of gas and newborn stars have eluded observers probing the distant universe to get a glimpse of galaxies' early history. Presumably, the clumps are too dim and too far away to image clearly from Earth. The orbiting Hubble Space Telescope (HST), however, may have finally revealed the missing galaxy pieces.

In a poster presentation at last month's meeting of the American Astronomical Society in San Antonio, astronomers Sebastian Pascarelle, Rogier Windhorst, and Stephen Odewahn of Arizona State University in Tempe and William Keel of the University of Alabama, Tuscaloosa, reported detecting a field of what appear to be tiny nests of star formation. "They may be the building blocks we've been looking for," said Pascarelle, who presented the team's results. Both the objects' size, roughly 1/30th the diameter of the Milky Way, and their distance from Earth, some 12 billion light-years away, imply that these are the primordial star clumps from which present-day structures like the Milky Way were formed—although some astronomers say that other features of the clumps raise doubts about this interpretation.

The team began to suspect it might have found something unusual during a routine spectral scan from a ground-based telescope, the Multiple Mirror Telescope at the University of Arizona, of the patch of sky around a distant radio-emitting galaxy, designated 53W002. Because the universe is expanding, the further an object is from Earth, the faster it recedes and the more its light spectrum shifts to longer, or redder, wavelengths. For 53W002, the redshift is 2.4, indicating that it is roughly 12 billion light-years away. But that galaxy turned out to have company that was equally far away. While looking at the spectrum of a dim object in the same field as 53W002, "we realized, 'Oh my goodness, we have another 2.4 redshift here,' " Windhorst recalls—the implication being that they had found a star cluster of some sort in the deep reaches of space.

The ground-based observations couldn't tell them anything about the second object's shape or nature. But further observations by the HST, with its unparalleled seeing, showed that it was just one of 18 tiny, faint clumps of stars. Once HST pinned down the objects' positions, the group could aim the ground-based telescope at four more of them and take spectra to confirm that they are at the same redshift as the first. That implied that the objects form a cluster, scattered across a million or so light-years of space.




**Distant parts?** This cluster of small dim clumps of stars (*indicated by numbers*) may be merging to form a galaxy.

The Hubble images showed that each member of the cluster is only some 1500 light-years across. That size, Jeremiah Ostriker of Princeton University points out, is consistent with the idea that the clumps are newly formed galactic building blocks. It's just the size at which theory predicts that gravity could overcome thermal pressure in the gases left over from the big bang, drawing them together to form the pieces that later assembled into full-sized galaxies. In addition, the clumps have a blue tint, the result of ultraviolet radiation that has been redshifted into the visible spectrum. Because this high-energy radiation is a marker of hot, short-lived stars, this may mean that the clumps are sites of vigorous star formation, as expected for pieces of an embryonic galaxy.

Theorists like Ostriker welcome the observation. Along with separate work, such as galaxy surveys on much larger scale structure in the cosmos, he says, it shows that theory and observation are "all coming together." But some astronomers say they are skeptical that the starry clumps are galactic building blocks. They point out that spectra of three of the four confirmed cluster members have features indicating that they contain weak, active galactic nuclei (AGNs)—copious emitters of light thought to be the result of matter falling into a black hole. Because present-day spiral galaxies don't have these central engines, this finding may cast doubt on the idea that the clumps are destined to become an ordinary galaxy.

And even aside from the AGNs, the collection of clumps might not be a typical progenitor of the galaxies of today, adds Joel Primack, a cosmologist at the University of California, Santa Cruz: "Just seeing one serendipitous observation of this kind doesn't tell us much." And Lennox Cowie, an astronomer at the University of Hawaii, says that because the find was "targeted"—linked to the radio galaxy—and not part of a random search across the sky, there is no way to know whether the cluster is typical. "It's rather a particular region to start off with," he says.

Windhorst, however, notes that some theories say transient AGNs like those in three cluster members could be common in young galaxies. And he says that additional data—which he declined to discuss because the paper on the find is under review—show that the field they surveyed "is not peculiar, at least not grossly so. ... We have other reasons to believe" that clusters like this will be "the rule and not the exception."

To resolve this issue, the team is looking forward to the additional observing time it has won on HST. More observations, Pascarelle says, "would tell you how universal this is"—and whether the researchers have indeed managed to find the pieces of which galaxies are made.

**–James Glanz**