AIDS Update '96

New drugs, new tests, new optimism mark recent AIDS research

By JOHN TRAVIS

Imagine putting together a 50,000-piece jigsaw puzzle of an abstract painting—without a picture of the completed puzzle. First come the basics, such as identifying the four corners of the puzzle. After that, the puzzle solver painstakingly tries to marry piece after piece. As a rule, the jagged edges do not fit, and frustration mounts. On rare occasions, two pieces, maybe even three or four, snap into place and optimism emerges anew.

For more than a decade, immunologists, virologists, physicians, and other researchers have attempted to piece together something much more important than a jigsaw puzzle. Their obsession is the puzzle of AIDS, the deadly syndrome caused by the infectious agent known as HIV.

Investigators have recently fitted several new pieces into the AIDS puzzle. Two months ago, researchers at the Conference on Retroviruses and Opportunistic Infections in Washington, D.C., made headlines worldwide with presentations on potent drugs called protease inhibitors and on a novel way to predict HIV's impact in patients.

The protease inhibitors, in particular, stimulated a long-absent optimism among AIDS researchers. Attesting to this newfound hope is an editorial in the March NATURE MEDICINE entitled "AIDS—a treatable disease at last."

"We're clearly at the beginning of that era," agrees Douglas D. Richman of the University of California, San Diego, an organizer of the D.C. conference.

At the same time, Richman and other investigators stress that treatable doesn't equal preventable or curable. An international AIDS vaccine meeting 2 weeks after the D.C. conference barely caused a stir within the research community, largely because there has been little discernible progress in developing a preventive vaccine.

Even the much-publicized protease inhibitors, three of which have gained approval from the Food and Drug Administration, are not miracle drugs.

"We'd hoped to give [a patient] a drug, get rid of all the virus, and move on. We're not nearly at that point. . . . The best we can do is turn AIDS into more of a chronic disease," says Andrew Kaplan of the AIDS Institute at the University of California, Los Angeles (UCLA) School of Medicine.

In this roundup, SCIENCE NEWS describes some of the recent advances—and setbacks—that have made the last few months the most fascinating period in AIDS research in quite some time.

Surveying the enemy

It's tough to fight a war without knowing the size of the opponent's army, but that's the situation AIDS researchers have faced until recently. To measure the severity of an HIV infection, they were forced to rely upon secondary markers such as certain immune system cells within an infected individual.

These crucial CD4 cells are the target of HIV and usually decline in number as the virus slowly overwhelms a patient's immune system. However, CD4 cell counts don't necessarily provide an accurate indication of how much virus the body is battling. They're more accurately a measure of casualties rather than enemy soldiers.

That's why scientists are excited about directly measuring viral load, the quantity of HIV in a milliliter of an infected person's blood. To gauge viral load, investigators can now count the strands of viral RNA in a blood sample. HIV stores its genetic information in strands of RNA rather than DNA.

The researchers hope that monitoring changes in viral load will enable them to judge more quickly and accurately the effectiveness of new AIDS drugs. Moreover, viral load may prove much more powerful than CD4 counts at predicting the long-term survival of an HIV-infected person.

In one study presented at the D.C. conference, researchers analyzed blood samples taken in 1984 or 1985 from HIV-infected homosexual or bisexual men. At the end of a decade of follow-up, only 17 of 45 men whose viral load averaged less than 5,300 RNA strands had died of AIDS. But of 45 men whose average viral load exceeded 37,000, 34 had died (see table).

"There were striking, very convincing differences in the rates of progression to AIDS and death. . . . It surprised even me that one or two RNA determinations can look 10 years into the future," says study leader John W. Mellors of the University of Pittsburgh Medical Center.

Researchers caution that the new RNA assays haven't been approved yet for widespread use. At least three different companies are petitioning FDA for approval of slightly different versions, but no one has rigorously compared these tests' dependability and accuracy. That's vital before physicians can use them to determine the proper course of treatment for patients.

"It's still not clear what a result with one assay means compared to the same result in another assay. That could present a really large problem in clinical practice," comments David Burns of the National Institute of Child Health and Human Development's Pediatric, Adolescent, and Maternal AIDS Branch in Bethesda, Md. Investigators must also determine whether other factors, such as episodes of tuberculosis or pneumonia, might cause fluctuations in viral load, says Burns.

Easing the load

While RNA assays for HIV may not be ready for the clinic, Mellors' study clearly implies that a lower viral burden delays the development of AIDS. That implication received strong confirmation from studies showing that drug therapies which reduce viral load can prolong good health.

Some of those ongoing trials test drugs, such as AZT (zidovudine), didanosine (ddI), and delavirdine, that target reverse transcriptase, the enzyme HIV uses to integrate its genetic material into host cells. In two trials of delavirdine taken with other inhibitors of reverse transcriptase, investigators have found that they can accurately figure the odds that a patient will maintain good health. They do this by combining the status of a patient's immune system (as demonstrated by CD4 counts) with measurements of viral load before therapy and 8 weeks into therapy.

According to data from these studies, antiviral treatments that reduce a patient's viral load by around 70 percent appear to halve that patient's likelihood of developing an AIDS-related illness or dying within a year or two, says William W. Feimuth of Pharmacia & Upjohn, the pharmaceutical firm in Kalamazoo, Mich., that makes delavirdine.

The greatest excitement at the D.C. conference surrounded reports on newer drugs, the protease inhibitors. These compounds target the virus' protease, a small, versatile enzyme upon which HIV depends to prepare the proteins needed for replication.

One study focused on ritonavir, a protease inhibitor recently approved by FDA for treatment of people with advanced AIDS. In a trial with 1,090 HIV-infected patients from around the world, investigators found that adding ritonavir to the normal drug regimen slowed disease progression significantly and reduced the number of deaths.

The patients, all of whom had severely compromised immune systems, as measured by CD4 counts, received either ritonavir or a placebo in addition to traditional AIDS drugs. The ritonavir reduced by half the number of patients progressing to AIDS during the course of the 7-month study. By the end of the study, only about 5 percent of the ritonavir group had died, compared to 8.5 percent of the placebo group, investigators reported.

"They showed a very convincing survival benefit," says Roy M. Gulick of New York University.

Gulick is testing another recently approved protease inhibitor, indinavir. At the conference in D.C., he presented results from a 24-week study of 97 HIV-infected people given indinavir alone, AZT and another reverse transcriptase, or all three compounds. Gulick monitored the safety of the drug regimens and their effect on viral load and CD4 counts. "There were very few side effects," says Gulick, noting that none of the complications observed was severe enough to warrant stopping a patient's treatment.

While all three drug regimens boosted patients' CD4 counts, the most impressive result of the study was the reduction in viral load produced by combining the three drugs. On average, patients enjoyed a 99 percent drop in their viral load, reports Gulick. "More than 85 percent [of the patients] had their viral load drop beyond our ability to detect it. It was quite dramatic," says Gulick. Furthermore, the viral load remained undetectable for most patients throughout the study period, says Gulick.

Investigators do sound a few notes of caution, however. "We're talking about virus in the blood. We're not talking about virus throughout the whole body," says Gulick. HIV probably remains at large in areas such as the lymph nodes, he explains. Furthermore, investigators warn, the protease inhibitors have not been tested long enough to establish their effectiveness and safety over many years.

Since HIV mutates rapidly, the major stumbling block for AIDS drugs is the development of resistance. AZT, for instance, generated great optimism in early trials but has turned out to have little long-term benefit.

"This new class of [protease] drugs is far more effective than the drugs we've had up to now, but I think it's unlikely that any of these drugs will ever actually cure anybody," comments Kaplan. "They'll never completely clear the virus from an infected individual. The best we can do is suppress the virus. Ultimately, everyone will develop some kind of resistant virus."

Kaplan's own research suggests that it will take no time for some people to develop resistance to current protease inhibitors. When he and his colleagues studied proteases used by the various HIV strains in 12 infected individuals, they discovered that many of the genes for the enzymes contained mutations that would provide resistance to known inhibitors.

"People who have never been treated with protease inhibitors already have viruses that are resistant to these inhibitors," says Kaplan. Furthermore, these resistant proteases are just as efficient in helping HIV replicate as the drug-sensitive versions, the investigators report in the March JOURNAL OF VIROLOGY.

One way patients may thwart resistance is to take a costly medley of AIDS drugs, including drugs such as AZT in combination with more than one of the new protease inhibitors.

"Everyone will be on combination therapy in the future," predicts Kaplan.

Gulick, who concurs, notes that insurance companies and the rest of society will have to wrestle with difficult decisions stemming from the significant expense of combination therapy. Adding protease inhibitors to current regimens may drive annual drug costs of an AIDS patient to more than $10,000. Already, says Gulick, some insurance companies have balked at picking up the tab for the new drugs, despite the data attesting to their effectiveness.

How Viral Load Affects AIDS Progression

Average Viral Load*	Total HIV-Infected Patients	Deaths After 5 Years	Deaths After 7 Years	Deaths After 10 Years
< 5,300	45	0	2	17
5,300–12,900	45	1	6	25
12,900–37,000	45	10	22	32
> 37,000	45	23	31	34

* Measured in RNA strands per milliliter of blood. Data from J. Mellors.

A mother's burden

One of the more intriguing research uses of the new assays for viral load has been to examine the risk of HIV transmission from pregnant women to their babies. Studies in recent years have suggested that only between 15 and 35 percent of HIV-positive women will infect the babies they carry and that treatment with AZT can slash that risk by two-thirds.

Viral load assays have enabled investigators to test whether the amount of virus in a woman's blood determines the risk of mother-to-child transmission. Investigators in a UCLA study saw a clear increase in transmission risk associated with high maternal viral loads, they reported at the D.C. conference and in the Feb. 28 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. Furthermore, the women with low viral loads did not infect their infants.

Other studies haven't shown as conclusive a relationship between HIV transmission risk and maternal viral load, acknowledges UCLA's Ruth Dickover. "It's not necessarily a perfect predictor, but it's the best predictor that's available. . . . We've shown this is a very good research tool. It's too early to say if it can be used as a clinical tool," she says.

While a high viral load in the mother implies danger to the baby, a low viral load is no guarantee of safety, investigators warn. "I don't think there is a threshold for nontransmission," notes UCLA's Yvonne Bryson.

Bryson has also been at the center of another provocative issue surrounding infants and HIV infection. Last year, she and her colleagues reported evidence that a baby born to an HIV-infected woman was initially infected with HIV but later cleared the virus from its body (SN: 4/1/95, p. 196). Since researchers were skeptical that the developing immune system of a baby could fend off a virus that a mature immune system could not, the finding

ignited controversy and suggestions of laboratory error.

Two recent reports lend support to the validity of the observation, however. In the December 1995 issue of the journal AIDS, French researchers present evidence that 12 more infants appear to have successfully eliminated an HIV infection. Details of another 9 children who may have defeated HIV are reported in the Jan. 27 LANCET by a collaboration of investigators from Belgium, Italy, Sweden, and the United Kingdom.

Though neither of the new reports provides evidence as detailed as that in the Bryson paper, researchers are starting to accept the idea that the event may occur. "If this is a real phenomenon, then what does it teach us?" wonders Kenneth McIntosh of Children's Hospital in Boston.

It may be that the viruses cleared by these fortunate infants were in some way defective, he observes. A more provocative option, says McIntosh, is that there is something unusual about the immune response of certain infants. If so, researchers may be able to identify and exploit that protective element.

Jerom's legacy

A chimpanzee named Jerom holds a unique place in the annals of AIDS research. He was the first chimpanzee infected with HIV to develop AIDS. Researchers at Emory University's Yerkes Regional Primate Research Center in Atlanta euthanized Jerom in February after his health deteriorated seriously.

Since isolating HIV more than a decade ago, scientists have infected a variety of animals with the virus in search of a nonhuman research model of AIDS. The mouse, the most popular animal for biomedical studies, does not develop AIDS, even though HIV can replicate in rodents.

Investigators have had little success producing AIDS in species more similar to humans. Last year, a research team reported that a single baboon had come down with AIDS, but the group had infected the animal with HIV-2, not HIV-1. The latter, the much more common and aggressive form of the AIDS virus, does not infect baboons.

Scientists have always considered chimpanzees, the primate most closely related to humans, to be the animal with the best chance of developing AIDS from HIV-1. Since the mid 1980s, they have infected around 100 chimpanzees with the virus and anxiously waited.

While a number of infected chimpanzees showed declines in their CD4 cell counts, only Jerom came down with any of the illnesses associated with AIDS, says Harold McClure, head of Yerkes' AIDS research program.

Investigators injected HIV-1 into Jerom several times between 1984 and 1987 and first saw a drop in his immune cells in 1991, says McClure. That drop was temporary, but about a year ago, the chimp's CD4 cells began a steady decline. Eventually, says McClure, Jerom experienced anemia, pneumonia, and chronic, often severe diarrhea—conditions typical of AIDS.

Last summer, when it became obvious to Yerkes researchers that Jerom had developed AIDS, the investigators transferred some of his blood to another HIV-infected chimpanzee in an attempt to speed AIDS development in another animal. The CD4 cells of that animal have dropped dramatically since the transfusion, though no AIDS symptoms have yet appeared, says McClure. Investigators suggest that after spending years in Jerom, the virus has evolved to became more virulent than the version of HIV that was originally injected into either chimp.

Since chimpanzees are an endangered species and AIDS appears to take as long to develop in them as in humans, some researchers question whether additional AIDS research funds should be spent on the animals. "The chimpanzee is not going to be a very useful model," contends Richman.

McClure is not ready to dismiss the primates as a research model, suggesting that chimpanzees used in AIDS research should come from breeding colonies and not from the wild. The observation that AIDS develops at the same pace in humans and chimpanzees indicates that their immune responses to HIV may be almost identical, he says. Consequently, vaccine developers should rigorously test preventive vaccines in chimps before beginning trials in humans, McClure argues.

Despite its indecisive role in the controversy over using chimpanzees as animal models, Jerom's development of AIDS provides a direct lesson in another area. "It proves HIV causes AIDS," says McClure.

That statement may seem obvious, but a few researchers, as well as a host of vocal nonscientists, continue to propound theories that HIV infection does not directly produce AIDS. Among their many proposals, these individuals contend that drug abuse or AZT therapy is the actual culprit behind the immune destruction in AIDS patients.

Jerom never received AZT treatment, notes McClure. In addition, he wryly observes, "this animal was not a drug abuser."

Rejecting aid from a baboon

Another experiment concerning HIV and a primate made news recently. When Suzanne T. Ildstad, an investigator at the University of Pittsburgh, stepped to the podium at last month's American Association for the Advancement of Science (AAAS) meeting in Baltimore, there appeared to be more journalists than scientists in the audience. The media intensity stemmed from Ildstad's involvement in a controversial attempt to rescue the immune system of Jeff Getty, an HIV-infected AIDS activist.

Because baboon immune cells are not susceptible to infection with HIV-1, the investigators had hoped that a cross-species transplant of baboon bone marrow would reconstitute Getty's ravaged immune system. Ildstad had recently discovered a class of cells derived from bone marrow that she expected would facilitate acceptance of the foreign tissue.

In this initial trial, however, the baboon facilitator cells were apparently unable to prevent Getty's immune system from rejecting the bone marrow transplant. Eight weeks after the transplant, Ildstad and her colleagues could find no evidence of surviving baboon immune cells. "If there is a take, it's at a very low level," says Ildstad.

Ildstad and her colleagues have yet to submit a report on the experiment to a peer-reviewed journal; they decided to release their results early because of rumors that the transplant had helped Getty. The patient has indeed seen an improvement in his condition, including an increased number of CD4 immune cells, says Ildstad. Yet the investigators don't attribute this recovery to the presence of baboon bone marrow. They warn that Getty's improvement may be temporary. The stress of the operation and preoperative procedures may have stimulated his immune system, they suggest.

Illdstad claims that the procedure did not transfer any infectious agents from the donor baboon to Getty, a concern raised by opponents of cross-species transplants. "There's absolutely no evidence for baboon-derived infection," she says.

If given permission by the FDA, Ildstad intends to try another baboon bone marrow transplant in which she'll use stronger drug regimens to prevent immune rejection of the graft.

Experience counts

As the failed baboon bone marrow transplant demonstrates, not all pieces of the AIDS jigsaw fall into place as neatly and quickly as investigators and patients would like. Though hope has risen that the new protease inhibitors will turn AIDS into a treatable disease, investigators note that it's important not to overlook basic factors that may also extend the life of HIV-infected people.

At the D.C. conference, Mari M. Kitahata of the University of Washington in Seattle presented a simple study with this powerful message. Of 403 men diagnosed with AIDS between 1984 and 1994, those treated by physicians who had little or no experience handling AIDS patients generally survived about a year less than those treated by physicians with significant experience. When it comes to the puzzle of AIDS, the availability of advanced drugs and of veteran physicians who know how to use them are both crucial. □