national news

Where to from here?

An NIH panel charged with setting guidelines for HIV treatment seeks to chart a course for doctors, patients and policymakers

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by Bob Roehr

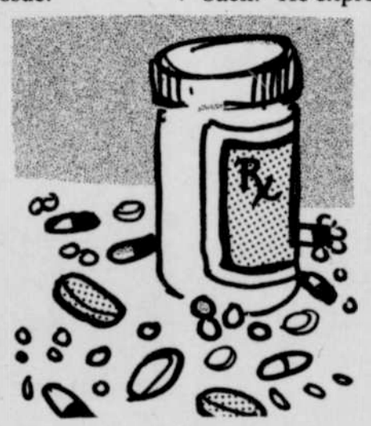
The National Institutes of Health Panel to Define Principles of Therapy of HIV Infection met in an exhaustive public meeting Nov. 13-14 in Washington, D.C. The 24-member group of clinicians, researchers and activists is chaired by Charles Carpenter, M.D. Their recommendations on how to use the new array of drugs is expected to be published in January.

Mapping the Frontiers

David Ho, M.D., of the Aaron Diamond Institute, said that the half-life of viremia, or viral presence in the blood, is only about six hours. He outlined the "rapid decay of viremia during the first 10 days of therapy, then a much slower decay in the second phase." That suggests the virus is largely cleared from blood during the first phase of therapy and only more slowly from other reservoirs of infection, primarily lymphoid tissue.

Ashley Haase, M.D., of the University of Minnesota, noted that triple combination therapy has had a "dramatic impact" on HIV in lymph nodes. But at least six months after therapy reduced plasma viral load below a detectable level, he still "found residue of the virus in lymphoid tissue."

"There are stages of infection when it might be more profitable to intervene," says Haase, adding that the "reservoir at early infection is smaller." He joined with Ho in suggesting "a rationale for early intervention."



Joseph Margolick, M.D., of Johns Hopkins University, talked of the "inflection point" where a rapid decline in CD4 cells occurs, which generally leads about a year later to an AIDS-defining condition. He says there is "evidence of emergence of new viral strains around the inflection point" in at least half the patients that researchers examined. But it is unclear whether viral mutations overwhelm the immune system or the system collapses and viral strains emerge that had been suppressed.

Janis Giorgi, Ph.D., of the UCLA School of Medicine, discussed a fairly recent discovery concerning the telomers of CD4 cells. Telomers are the multiply-repeated end patterns of chromosomes that sequence the other genes in cell replication. Telomers become shorter with age, thus inhibiting the cell's ability to replicate, whereas in cancer cells they become longer and hence "immortal," replicating wildly.

The telomers of CD4 cells in people with advanced HIV infection "reached the same length as those [which] are very old." That suggests they have undergone accelerated replication in fighting the virus, have rapidly aged, and have exhausted much of their ability to further replicate to fight disease.

Giorgi argued for early treatment, perhaps even "during the period before the immune response develops." She believes that the immune system shows some ability to rebound and even expel subsets of CD4 and CD8 cells that have been depleted. But that requires suppressing the virus for at least six months. It becomes much more difficult to restore the cells' subsets when the CD4 level falls below 50.

Viral Load Tests

Viral load tests have become indispensable in monitoring the effect of new therapies on the virus in clinical practice. The commercially available Amplicor test by Roche is sensitive down to 400-500 copies of the virus. The next generation will push the level of detection down to about 20-25 copies; it should be available in 1997.

Roche's Steven Herman, Ph.D., warned against fixating on individual numbers, particularly at the low threshold of accuracy of the viral load test. Changes in the 5,000-10,000 range "are really the 'noise' and variations of labs." What is significant is a three- to five-fold increase in viral levels that is sustained over time.

John Mellors, M.D., of the University of Pittsburgh Medical Center, compared HIV to meningitis, where conditions can change radically in just a few hours. With changes in HIV viral loads, he said, "nothing is going to happen overnight, in two weeks, or in two months. We can monitor and intervene over time."

Resistance and Compliance

Emilio Emini, Ph.D., of Merck Research Laboratory, warned, "HIV is genetically unforgiving. Once resistance begins to occur, there is no going back." He expressed worries about patients' failure to comply with the strict dosing pattern of protease inhibitors, which could lead to the mutation of viral strains resistant to those drugs.

But panel chairman Carpenter and others in clinical practice believe compliance is often tied to results. He used the example of AZT, where compliance has been a problem primarily when the patient has felt that the drug was not working for him or her. People who see results continue to take a drug on schedule.

That led panel member Valerie Stone, M.D., of Brown University School of Medicine, to suggest that the panel will have to include "quality-of-life issues" when formulating its recommendations. "For those who walk in feeling relatively well, it is difficult to convince them to take 17 pills a day."

Activist Mark Harrington is policy director of the New York-based Treatment Action Group and a member of the NIH panel. He believes that the panel's recommendations will include "use of viral load tests as a routine part of clinical management, and that protease inhibitors should be a part of the regimen."

But he cautioned, "It still may be an appropriate response for people who are healthy to wait for more drugs or for more research to come out." In light of potential problems of viral mutation and drug resistance, he said, "people might want to wait until they are really sure that they want to make a treatment decision and adhere to a very complicated regimen."

Gary Rose, treatment lobbyist with the AIDS Action Council, sees "the argument for resources becoming easier" with the establishment of these guidelines. "It becomes easier to say you have to have this early intervention Medicaid program because you have these standards."

Harrington concurs: "We hope this will lead to more appropriate coverage" by third-party payers. "All health care programs should pay for what is the best and most beneficial treatment regimen."