



# Update

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Elaine Baldwin  
(301) 496-5717

## **NIAID CLINICAL AND LABORATORY STUDIES SUPPORT COMBINATION OF ALPHA INTERFERON AND AZT IN HIV INFECTION**

Clinical researchers at the National Institute of Allergy and Infectious Diseases (NIAID) have achieved encouraging results in the treatment of patients with AIDS-related cancer by using a combination of alpha interferon and zidovudine (AZT). In addition, NIAID laboratory scientists have found that alpha interferon and AZT act at different stages of infection with human immunodeficiency virus (HIV), the cause of AIDS. Their findings were reported at the Fourth International Conference on AIDS in Stockholm.

Dr. Lawrence Deyton and his colleagues reported regression of tumors and persistently negative HIV cultures from the blood of several AIDS patients with Kaposi's sarcoma after treatment with the drug combination. In those patients who were able to tolerate the side effects of the treatment regimen, the results were at least as good, if not better, than previous experience with AZT or interferon alone.

AZT, an anti-retroviral agent, has been shown to prolong the lives of certain patients with AIDS. In previous studies conducted by NIAID scientists, AZT did not significantly reduce the tumors of patients with Kaposi's sarcoma, nor result in negative viral cultures; however, viral antigen levels decreased. At last year's International Conference on AIDS, in Washington, D.C., NIAID investigators reported that interferon used alone had anti-viral as well as anti-tumor effects in some patients with early HIV infection and Kaposi's sarcoma.

Dr. Deyton and his colleagues divided the 41 patients in their study into three groups, assigned to receive AZT at 250, 100 or 50 milligrams every four hours. The conventional

AZT dose is 200 mg. After a minimum of 6 weeks on AZT, each patient was started on subcutaneously administered alpha interferon, beginning at 5 million units. The dose was increased by 5 million units every 2 weeks, until toxicity developed (primarily a decrease in white blood cells). Patients were then maintained on the maximum tolerated dose of alpha interferon, which varied from patient to patient, while continuing to receive AZT. At 12 weeks, efficacy was evaluated.

Twenty-four patients have completed the study thus far; however, only 12 patients have been able to tolerate 12 weeks of interferon therapy. Of these 12, 6 had a greater than 50 percent reduction in Kaposi's sarcoma lesions and 5 had stable disease. Only 1 of the 12 had progressive disease while on therapy. In 7 patients, HIV cultures went from positive to negative, evidence of anti-viral activity of the treatment.

"Based on our current data," Dr. Deyton reported, "it appears that the most tolerable and effective dose of the combination is 100 mg. of AZT every 4 hours with 10 million units of alpha interferon daily. This regimen is capable of producing both anti-tumor and anti-retroviral effects. When the two drugs were combined, the anti-tumor response was approximately the same as that with conventional doses of alpha interferon alone, but the anti-retroviral response appeared to be better."

Moreover, Dr. Deyton added, by lowering the doses of both drugs, the investigators were able to reduce significantly the occurrence of adverse side effects that are commonly seen in patients treated with conventional doses of either AZT or alpha interferon. As many as 25 percent of patients receiving conventional doses of AZT experience anemia severe enough to require transfusions. Conventional doses of alpha inteferon often cause a flu-like syndrome, with severe fatigue, and can cause bone marrow suppression that often results in a need for dose reduction or discontinuation of therapy.

### **Laboratory Studies**

Results of NIAID laboratory studies reported by Dr. Guido Poli gave additional support to combining interferon and AZT in AIDS therapy. Dr. Poli and his colleagues compared the

ability of the two agents to affect HIV replication in chronically infected cloned promonocytes and lymphocytes (white blood cells).

These cells ordinarily express very low levels of HIV proteins; however, their viral activity can be increased 10 to 20 fold when the cells are stimulated by certain chemicals called phorbol esters (PMA). HIV activity is measured by an increase in the HIV viral enzyme, reverse transcriptase (RT).

The scientists reported that whereas AZT can easily block new infection of normal, uninfected cells, it failed to inhibit release of HIV from chronically infected, PMA-stimulated cells. In contrast, in interferon-treated cells, release of HIV was suppressed although viral proteins were still being made.

"Our research indicates that alpha interferon works primarily against either the assembly of viral particles or their release from infected cells," Dr. Poli said. "It appears to have little effect on proviruses that continue to be present in infected cells. AZT has a different mechanism of action; it can protect normal cells from new HIV infection. Because alpha interferon and AZT act selectively on different stages of HIV infection, it makes sense to treat AIDS patients with a combination of the two drugs."

Collaborating with Dr. Deyton were H. Clifford Lane, M.D., Anthony S. Fauci, M.D., Diane Lee, and Julie A. Metcalf, NIAID; Henry Masur, M.D., and Joseph A. Kovacs, M.D., Clinical Center, National Institutes of Health; Norman Salzman, M.D., Georgetown University, Washington, D.C.; Michael Baselar, Program Resources, Inc., Frederick, Md.; and Joseph Bigely, Burroughs Wellcome, Research Triangle Park, N.C.

Dr. Poli's colleagues include Thomas M. Folks, Ph.D., H. Clifford Lane, M.D., Anthony S. Fauci, M.D., Audrey Kinter, and Douglas Powell, NIAID; and Jan Marc Orenstein, M.D., Ph.D., George Washington University School of Medicine, Washington, D.C.

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