



Update

EMBARGOED UNTIL
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Elaine Baldwin
(301) 496-5717

NEW ANTIBODY TEST GIVES EVIDENCE OF EARLY AIDS INFECTION

A new antibody test that gives early indications of infection with the AIDS virus is a promising alternative to commonly used blood screening tests, according to Alfred J. Saah, M. D., of the National Institute of Allergy and Infectious Diseases (NIAID).

Since March 1985, enzyme-linked immunosorbent assay (ELISA) kits have been used routinely to screen donated blood in the United States and many other countries to detect antibody against human immunodeficiency (HIV), the cause of AIDS. Dr. Saah had previously reported that some of the commonly used ELISA kits do not detect the low levels of antibody to the virus that occur in early infection.

Dr. Saah, who spoke today before the Third International Conference on AIDS, reported a comparison of the new antibody test, which utilizes a synthetically produced portion of the HIV envelope protein, against tests that are generally used to confirm positive results on ELISA screening tests.

Dr. Saah and his colleagues analyzed results of tests conducted on the blood of participants in a prospective study of 4,955 initially healthy, homosexual and bisexual males in four cities. The ongoing study, known as the Multicenter AIDS Cohort Study (MACS), is designed to trace the natural history of infection with HIV in these men. Participants in the study are seen every 6 months, and blood specimens are collected at each visit.

The regular visits have enabled the MACS researchers to detect early infection with HIV, and to do retrospective studies using the participants' frozen sera (blood samples) to test for indications of earlier infection.

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The investigators have been screening the sera of participants, using the ELISA and the Western blot, which also measures antibodies to the proteins, or antigens, of HIV. The Western blot is normally used by blood collection agencies to confirm positive results obtained by the ELISA.

In the current study, using the same blood samples, the investigators compared the new test, PENV9, in an ELISA format, against the Western blot and the radioimmunoprecipitation assay (RIP), which is more sensitive than the Western blot in detecting antibodies to HIV envelope proteins. Generally, scientists agree that the Western blot detects antibodies to core antigens earlier than to envelope antigens. Both the Western blot and RIP are complex and time-consuming procedures, whereas the ELISA is relatively simple. "Very few sera (blood samples) from early stages of HIV antibody production have been tested by both Western blot and RIP," Dr. Saah said.

The investigators identified 26 individuals who had Western blot results showing strong antibody reaction to core antigens. The Western blot did not show antibody to HIV envelope antigens in those sera. Tests of the same sera by RIP and PENV9 showed that approximately 85 percent were reactive to envelope antigens.

"Clearly, the best test to determine the sensitivity of any new serological assay is one that detects antibody in early infection," Dr. Saah said. "Our data show that PENV9 in an ELISA format is as sensitive as the Western blot and as specific as the RIP in detecting antibody in a large group of sera that are characteristically the most difficult to identify; that is, specimens near seroconversion."

Dr. Saah pointed out that the Centers for Disease Control had recently estimated that even with universal blood screening, some 50 persons a year are being infected with HIV through blood transfusions. "Use of the PENV9 or other tests using recombinant HIV envelope antigens would enable more precise blood screening for antibody to HIV early during seroconversion, without the need to resort to more complex procedures," he concluded.



Update

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Patricia Randall
(301) 496-5717

IMMUNOPATHOGENIC MECHANISMS AND IMMUNE RESPONSE IN HIV INFECTION

A number of mechanisms involved in the immunopathogenic effects of human immunodeficiency virus (HIV) infection are being studied by scientists at the National Institute of Allergy and Infectious Diseases (NIAID). Dr. Anthony S. Fauci, Director of NIAID and Chief of NIAID's Laboratory of Immunoregulation, reported progress in two major areas of research: a) defects in antigen-specific responses of CD4-positive lymphocytes (the immune system cells preferentially infected by HIV) without clearcut HIV infection, as well as the effect of HIV infection on expression of certain cellular genes, and b) how a latent or low-level chronic infection is converted to a productive infection.

Dr. Fauci and his colleagues demonstrated that exposure of CD4-positive lymphocytes to HIV in the absence of clearcut productive infection results in the suppression of responses to subsequent antigenic stimuli. This is not due to a presenting cell defect and can, in many cases, be overridden by mitogenic stimuli. This dichotomy between suppression of antigenic stimuli versus mitogenic stimuli is related at least in part to a negative signal given to the lymphocyte by HIV. In addition to the suppression of proliferative responses in CD4 lymphocytes resulting from non-infectious exposure to the virus, a clearcut downregulation of cellular gene expression occurs after infection with the virus. Specifically, HIV infection does not alter interleukin-2 (IL-2) receptor messenger (m)RNA expression but does inhibit mitogen-induced IL-2 mRNA expression. This dichotomy of effect on inducible IL-2 gene expression in the absence of effect on IL-2 receptor gene expression may play a role in the hyporesponsiveness of CD4-positive cells following non-cytotoxic infection with HIV. These observations provide further insight into the complex mechanisms, apart from a direct cytopathic effect, by which HIV induces immunosuppression.

The investigators also studied the complex mechanisms involved in converting a latent or chronic infection to a productive infection. They showed that in addition to the powerful mitogenic signals, a relatively

weak antigenic signal delivered to an infected cell is capable of converting a latent or chronic low-level infection to a productive infection. They also determined that other heterologous DNA viruses could induce upregulation of HIV expression in latently infected cells. Using a series of simultaneous cotransfection experiments, they demonstrated that the transfection of immediate/early genes of heterologous DNA viruses, such as herpes simplex virus, resulted in the upregulation of HIV promoter activity.

In addition, in order to study the physiological mechanisms whereby latently infected cells are induced to express virus, Dr. Fauci and his colleagues developed a model system of cloned, chronically infected promonocyte cell lines that responded to variety of cytokines by upregulation of virus expression. Of note was the fact that HIV infection of the cloned cell line resulted in both an upregulation of virus expression by cytokines as well as an upregulation of cellular gene expression, particularly IL-1 beta gene expression. These studies provide clearcut indication of the effect of virus on gene expression, as well as the effect of normal cellular gene function on viral expression. Thus, they have major implications for understanding the normal physiological mechanisms whereby chronically or latently infected cells are induced to express virus. These studies lend insight into the molecular basis underlying progression of the asymptomatic HIV carrier state to the immunosuppressed and ultimately diseased state.

Dr. Fauci and his colleagues have extended their studies on the immune response to HIV infection by demonstrating major histocompatibility complex-restricted, HIV-specific, cytotoxic T-cell responses in HIV-seropositive individuals. They demonstrated a gradation of responsiveness in that most HIV-seropositive healthy individuals manifested cytotoxic T-cell responses, and a substantial number of persons with AIDS-related complex also manifested some responses. A limited number of patients with full-blown AIDS who were studied did not exhibit cytotoxic T cell responses.

Cytotoxic T-cell responses were monitored in ten patients with AIDS who received bone-marrow transplants from their identical twins. However, at present it is too early to comment on either clinical or immunologic reconstitution. The bone-marrow recipients were also treated with AZT as well as syngeneic lymphocyte transfusions.

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Update

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Elaine Baldwin
(301) 496-5717

AZT MAY BENEFIT EARLY AIDS PATIENTS WITH KAPOSI'S SARCOMA

A study conducted by scientists at the National Institute of Allergy and Infectious Diseases (NIAID) indicates that the drug azidothymidine, or AZT, may benefit AIDS patients with Kaposi's sarcoma only. AZT, under the brand name Retrovir, was recently approved by the Food and Drug Administration for the treatment of advanced AIDS patients with a history of Pneumocystis carinii pneumonia, and patients with advanced AIDS-Related Complex (ARC). Dr. Robert Walker, NIAID, speaking today at the Third International Conference on AIDS, presented the first study of AZT's efficacy in treating patients at an earlier stage of infection.

Patients with early AIDS and Kaposi's sarcoma (KS) were chosen for the study because among persons with AIDS they have the most intact immune systems and their skin lesions can be easily evaluated for evidence of treatment efficacy. Furthermore, only limited therapeutic success has been achieved in patients with AIDS-associated KS, and the patients usually succumb to progressive disease or to an opportunistic infection.

An analysis of data from 36 KS patients enrolled in a randomized, double-blind, placebo-controlled trial showed that approximately 20 percent of patients receiving AZT for a minimum of 12 weeks experienced minor tumor regressions. Worsening of disease, measured by tumor progression, occurred in more patients receiving placebo than in patients receiving the drug. At the completion of the 12 week study, the patients on placebo were shifted to an open trial of AZT, and at least one patient has been receiving the drug for a year.

All patients entering the study had a minimum T4 lymphocyte count of 200 cells per cubic millimeter in peripheral blood and were culture-positive for the human immunodeficiency virus (HIV). Patients were randomized to receive oral drug, high-dose intravenous drug, low-dose intravenous drug, or placebo, every four hours for 12 weeks. Throughout the study, HIV cultures remained positive in all groups of patients. No significant changes were noted in immunologic status.

The investigators also observed that although no patients had signs or symptoms of neurologic dysfunction, HIV was isolated from the spinal fluid of approximately half of the patients. The significance of this

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finding is unclear, Dr. Walker said. He also said that fewer positive cerebrospinal fluid cultures were seen in the patients on AZT than in the patients on placebo.

Twenty-five percent of the patients receiving AZT developed transfusion-dependent anemia.

The study was conducted by Dr. H. Clifford Lane, Dr. Henry Masur, Dr. Joseph A. Kovacs, Dr. Walker, Ms. Stephanie Carlson, Dr. Thomas Folks, and Dr. Anthony S. Fauci.

Dr. Lane, who is Deputy Clinical Director, NIAID, said, "Based on these encouraging results, and laboratory studies on the anti-retroviral properties of alpha interferon, the NIAID research team has begun a Phase I study to evaluate the combination of AZT and alpha interferon."

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Update

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Ann London
(301) 496-5717

CYTOTOXIC T CELL ACTIVITY PROVIDES CLUE TO AIDS VACCINE

White blood cells that kill other cells infected by invading virus may play a key role in a vaccine for AIDS. Cytotoxic T lymphocytes (CTL) are an integral part of the human body's defense system against infection by viruses. When stimulated in certain ways, CTL can attack and destroy virus-infected cells. Scientists at the National Institute of Allergy and Infectious Diseases (NIAID) are trying to determine the mechanisms that stimulate CTL to act against cells infected with HIV, the retrovirus that causes AIDS. These studies mark an important step toward developing a vaccine to prevent an HIV-infected person from progressing to full-blown AIDS.

Dr. Scott Koenig and his colleagues had previously examined CTL activity against HIV in three different groups of people. They studied seven healthy HIV-seropositive individuals, nine patients with AIDS, and seven HIV-seronegative persons, who were used as controls. Two of the AIDS patients had received bone marrow transplants from their HIV-seronegative identical twins.

The blood of two of the seropositive healthy individuals showed CTL activity. However, none of the AIDS patients' blood showed cytotoxic activity against HIV, except for the two who had received bone marrow transplants. There was no CTL activity in the blood of either HIV-seronegative individuals or AIDS patients who had not received transplants.

In the present study, Dr. Koenig and other NIAID scientists attempted to determine which proteins of HIV are the target for CTL responses. The composition of the study population was the same except for the addition of patients with AIDS-related complex.

The researchers used recombinant vaccinia viruses to infect cells with HIV. The recombinant vaccinia viruses were made by inserting genetic material from HIV into vaccinia virus, the virus used for smallpox vaccination. These particular recombinant vaccinia viruses expressed proteins from either the envelope (surface) or gag (core) region of HIV.

The recombinant vaccinia virus-infected cells were used as target cells to determine whether CTL in the blood of the study group participants were able to kill target cells containing HIV envelope or gag proteins. Cells that were infected with a vaccinia vector expressing the protein beta galactosidase alone were used as a control.

The scientists found that in most cases CTL acted against the cells containing HIV envelope protein. This is an important step toward determining which specific proteins of the HIV genome can stimulate CTL-mediated immune responses to HIV and toward developing vaccines that can stimulate specific cell-mediated immune responses to HIV.

The next phase of this research is to expand the study longitudinally by adding more subjects and conducting it over a longer period of time. By doing so, the researchers hope to determine if the presence of CTL gives healthy HIV-seropositive individuals protection from eventually developing AIDS.

These findings were presented at the III International Conference on AIDS held this week in Washington, D.C. The research team included Drs. Koenig, H. Clifford Lane, Alain H. Rook, and Anthony S. Fauci, Chief, Laboratory of Immunoregulation; Drs. Patricia Earl and Bernard Moss, Chief, Laboratory of Viral Diseases.

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