Hemophilia World

(FORMERLY AIDS CENTER NEWS)

Published by the World Hemophilia AIDS Center

This issue sponsored by Armour Pharmaceutical Company • DECEMBER 1986 — VOL. 3, NO. 3

Management of Pneumocystis Carinii Pneumonia in Aids

Julian Falutz, M.D. and Chris Tsoukas, MK.Sc., M.D., F.R.C.P.(C)

AIDS Services
Division of Clinical Immunology
Montreal General Hospital
McGill University
Montreal, Canada

Introduction

Significant advances in the diagnosis and management of the many infectious complications of AIDS have recently occurred. This review will address the diagnosis and treatment of *Pneumocystis carinii* Pneumonia (PCP).

Widespread asymptomatic contact with pneumocystis occurs at an early age and clinical evidence of disease in immunocompromised patients represents reactivation of this infection.

Sixty-six percent of all North American and European AIDS cases as well as 10-15% of African patients present with PCP. PCP is the initial opportunistic infection in over 70% of American hemophiliacs with AIDS.(1) Infection with this organism signifies severe immunocompromise. The median survival of AIDS paients with PCP is nine months.

Clinical Presentation

In non-AIDS immunosuppressed patients, PCP presents abruptly with persistent or spiking fever, minimal cough and tachypnea. Physical examination rarely reveals rales. Cyanosis is associated with extensive pulmonary involvement. AIDS patients with PCP typically have a longer and milder symptomatic period with slight, nonproductive cough, low-grade fever, and mild dyspnea.(2) Symptoms may persist for weeks or months prior to the actual diagnosis. Rapidly progressive respiratory distress is unusual. Physical examination of the lungs is frequently normal.

Investigations

The chest x-ray findings are variable and the initial x-ray in a symptomatic person can be normal or it may reveal a diffuse interstitial or alveolar pattern. Enlarged hilar or mediastinal lymph nodes may occur and it is unusual to find pleural effusions. Respiratory alkalosis, severe hypoxemia, and an increased alveolar-to-arterial oxygen difference are common. Diffusing capacity of carbon monoxide is low and flow rates can reveal a restrictive pattern.(3)

The pulmonary gallium scan serves as a useful adjunct in diagnosing PCP. A characteristic pattern of diffuse uptake, which can be graded, occurs in both non-AIDS and AIDS patients. This pattern of uptake may also be seen with cytomegalovirus pneumonia, histoplasmosis, and coccidiodes infections. Atypical mycobacterial infection does not generally cause diffuse gallium uptake. In patients at high risk for developing AIDS, a positive lung scan, even with a normal chest x-ray, is highly suggestive of PCP, and should lead to bronchoscopy to confirm the diagnosis.

Prior to AIDS, open-lung biopsy was the procedure of choice to diagnose PCP. This technique is now infrequently used; less invasive but equally effective techniques have replaced it. Fiberoptic bronchoscopy with bronchial lavage (BAL) or transbronchial biopsy (TBB) have similar diagnostic yields of greater than 80-90%.(4) As BAL gives the same results as TBB, without the added risk of a biopsy, this technique should be used initially. It may be used on an out-patient basis, or carried out at the bedside. It is easily performed in intubated patients, those who are thrombocytopenic or in patients with clotting abnormalities.(5) It is a relatively simple procedure, without significant risks or side-effects. Complications of TBB are pneumothorax, hemothorax, pneumomediastinum and hemorrhage. BAL associated complications are limited to transient fever and hypoxemia. Sputum induction as a means of making the diagnosis of PCP is currently being assessed.

Serology is not useful in the diagnosis of acute PCP. Seropositivity rates in AIDS patients with PCP do not differ from those of healthy controls, or in those with other pulmonary conditions.(6) Immunofluorescence techniques using monoclonal antibodies to PCP look promising.

Treatment

Empirical therapy of clinically suspected, yet not proven PCP, should be discouraged, as opportunistic infections other than with Pneumocystis may present with a similar clinical picture. The currently accepted treatment of proven PCP is with either trimethoprim-sulfamethoxazole or pentamidine. Success rates for both drugs are greater than 75% during the first episode of PCP.(7) TMP-SMZ has traditionally been the drug of choice, but either drug may be used initially with similar outcomes, same rates of resolution, and incidence of side-effects.(8) In patients with pre-existing renal insufficiency, TMP-SMZ should be used as pentamidine is nephrotoxic.

TMP-SMZ may be given orally or intravenously. Survival is the same with either route of administration but relapse rates are higher with oral treatment. It is unnecessary to give folinic acid with TMP-SMZ to these patients. The

(continued on page 4)

From the Federal Republic of Germany

The Bundesgesundheitsamt (BGA) - the German counterpart of the Federal Drug Administration in the United States - has begun a survey of virus-inactivation methods used in preparation of all concentrates distributed in Germany. Information about side effects from the concentrates will also be solicited. This survey is in line with the recommendations made at the WHO meeting on the Safety of Blood Products held in April 1986.

Recent seroconversion to HIV antibody positivity by three hemophiliacs cannot be attributed to heat-treated concentrates. The three patients had changed from non heat-treated to heat-treated preparations within the possible HIV incubation period. •

HIV Antibody Prevalence United Kingdom

The AIDS Group of the United Kingdom Haemophilia Centre Directors reported an HIV seroprevalence of 59 percent in 1,268 patients with severe hemophilia A, 23 percent in 516 patients with moderate hemophilia A, and 9 percent in 220 patients with mild hemophilia A (British Medical Journal 293: 175, 19 July 1986). For patients with hemophilia B, the antibody prevalance was 8 percent of 174 severe, 4 percent of 115 moderate, and 3 percent of 29 mildly affected patients. Eleven (5 percent) of 215 patients with von Willebrand's disease were positive.

The prevalence of antibody was greater in patients who had received commercial factor VIII concentrates with or without other blood products. In this study, and others, it was evident that some batches of NHS factor VIII, not heat-treated, contained HIV. The overall prevalence of antibody in patients with hemophilia B (6 percent), much lower than that in patients with hemophilia A (44 percent), was closer to the prevalance in patients treated with only NHS factor VIII (10 percent). All factor IX concentrate used in the United Kingdom is supplied by the NHS. •

World Hemophila AIDS Cengter
Established under the auspices of the World Federation of Hemophilia and Orthopaedic Hospital
2400 South Flower Street
Los Angeles, CA 90007-2697 USA
Telephone: 213-742-1354
TELEX (VIA WUI): 6502283270
Director
Shelby L. Dietrich, ,M.D.
Editor
Donna C. Boone, M.S., M.S.
Contributing Editor
Carol K. Kasper, M.D.
Administrative Secretary
Ann Squibb

State of the Art

Hepatitis and Concentrates

Carol K. Kasper, M.D.

The transmission of hepatitis in blood products is a major concern in the management of hemophilia. We rejoiced at the advent of a vaccine against hepatitis B. Now our attention is turned to the prevention of hepatitis non-A non-B (NANB). Nearly all heavily-transfused persons with hemophilia have been infected, although only a small minority had clinical, icteric acute illnesses. A majority of all infected persons, including those who had clinical and those who had subclinical acute illnesses, develop chronic elevations of the liver transaminases. In some studies, a majority of those with elevated transaminases have had abnormal liver pathology on biopsy, usually chronic active hepatitis and, occasionally, cirrhosis. Thus, NANB in hemophilia is a serious problem.

Two major strategies to reduce the risk of NANB transmission are being employed. The first is to try to reduce the risk of getting an infected donor into the plasma pool. Unfortunately, there is no specific test for NANB, and blood banks must reply on so-called surrogate tests, including the donor's level of a liver transaminase (ALT, SGPT) and a test for antibody to hepatitis B core antigen (anti-HBc). The national Transfusion-transmitted Viruses Study (Aach et alia, New Engl J Med, 304:989,1981) showed that only five percent of recipients of single units of blood with ALT under 45 IU got NANB, whereas 42 percent of recipients of single units of blood with higher ALT levels got NANB. Further serologic data from the same study were analyzed by Stevens et alia (Ann Intern Med 101:735, 1984) who found that recipients of blood from donors who had anti-HBc had a two- to three-fold greater chance of getting NANB than recipients of anti-HBc-negative blood. Recipients of blood with both an elevated ALT and a positive test for anti-HBc had a 74 percent chance of getting NANB! The two surrogate tests overlap to some extent; positive tests for anti-HBc were three times as likely in blood with an elevated ALT than in blood with a normal ALT. Blood bankers are asking themselves whether ALT testing alone is reasonably adequate, or whether both tests should be done.

All blood and plasma collection systems in the USA have begun, or are soon beginning, ALT testing. The cut-off point for exclusion of blood with an elevated ALT is twice the upper limit of the normal range for some banks; other banks are choosing a lower cutoff, namely, two standard deviations above the normal mean. Some banks also plan to institute routine anti-HBc testing. Concentrates prepared solely from ALT-tested blood will be available towards late 1986.

The second strategy to reduce the transmission of NANB in concentrates is to separate or inactivate viruses after collection of plasma. Hepatitis viruses are more resistant to inactivation than is HIV (HTLV-III/LAV). Plasma fractionators are developing more effective methods of processing and treating concentrates in an effort to eradicate NANB as well as AIDS in recipients. During the first two decades in which lyophilized concentrates were available, they were regarded as more likely to transmit viral infection than fresh or frozen blood components because of the large size of the donor pool. Now, some concentrates may be safer than fresh or frozen components because concentrates can be treated with viral inactivation procedures. •

The Use of Monoclonal Antibody in the Purification and Production of Antihemophilic Factor (Human) Factor VIII:C

Fred Feldman, Ph.D. and Michael B. Rodell, Ph.D.
Armour Pharmaceutical Company
Blue Bell, Pennsylvania

Since the late 1960's, replacement therapy using antihemophilic factor (AHF) concentrates has represented routine treatment and/or prophylaxis in the management of bleeding episodes in hemophilia A. Refinements of these concentrates have occurred since that time, resulting in the availability of products with improved solubility and reconstitution characteristics, longer shelf life, and better purity profiles.

Although these concentrates are recognized as truly being of a life-saving nature, some considerations must be made in assessing their benefit-to-risk ratio.

Within a very few years following their introduction into hemophilia treatment, the complication of hepatitis transmission associated with the use of these concentrates was noted. More recently, data and information became available linking AHF concentrates to the transmission of the human immunodeficiency virus (HIV), the AIDS virus. Consequently, manufacturers of these products have made major efforts and expended significant resources in developing ways and means to reduce such risks.

The most common approach taken to inactivate potential viral contaminants has been the incorporation of some form of heat treatment in the manufacture of AHF concentrates. Data published jointly by FDA and CDA scientists demonstrate the efficacy of this approach in the inactivation of HIV. As reassuring as this information is regarding that particulafr virus, the situation regarding the hepatitis viruses appears much less certain. The inability of some of the heat treatment methodologies to inactivate these viruses is known. Therefore, alternative approaches must be explored in attempting to minimize hepatitis virus transmission.

An additional cause for concern in the routine use of today's AHF concentrates is the fact that these products have a relatively low purity level when one compares their coagulant activity to the quantity of total protein present. Significant amounts of extraneous protein matter, devoid of coagulant activity, are in these concentrates. Patients are exposed to repeated infusions of non-therapeutically beneficial proteins; this may result in aberrations to their immunologic systems.

The application of biotechnology to attempt to resolve these problems has been employed in recent years, with two emerging technologies, recombinant DNA engineering and monoclonal antibody purification, coming to the foreground.

Genetic engineering research to produce a recombinant derived Factor VIII:C of high purity and safety is underway in a number of laboratories around the world. This activity involves the cloning of a Factor VIII:C gene and subsequent introduction of this gene into a suitable host cell capable of manufacturing (expressing) sufficiently high levels of Factor VIII:C. The desired protein, Factor VIII:C, must then be isolated and purified, since the host cell contains extraneous protein and other consituents that must be removed. Contaminating DNA molecules and viruses that may be present in the host system must be eliminated. Since exacting purification techniques will be required in order to accomplish this goal, the expression system used must be capable of producing high enough quantities of Factor VIII:C in order to have an economically viable process, as this protein is quite fragile and is easily degraded or inactivated.

Small amounts of Factor VIII:C produced via recombinant DNA technology have been shown to have suitable biological characteristics in hemophilic dog models. Yet to come is implementation of human clinical studies capable of demonstrating the safety and efficacy of Factor VIII:C derived from this bioengineering approach.

A second emerging technology being utilized in the production of Factor VIII:C involves the use of monoclonal antibody in the isolation and purification of this protein from human plasma. Monoclonal antibodies are proteins designed and constructed to have highly unique specificity characteristics, binding a particular biological entity by recognizing a finite portion of its structure (referred to as an epitope). These monoclonal antibodies can be generated by causing cell fusion to occur between myeloma cells and mouse spleen cells to form a hybridoma, screening for and selection of the particular hybridoma having the single clone of interest, injection of that hybridoma into mice, and harvesting of the resulting monoclonal antibody from ascites fluid.

In the techniques used by Armour Pharmaceutical Company, the monoclonal antibody isolated from mouse ascites fluid has specific recognition for the Factor VIII:R portion of the AHF complex (which also contains the coagulant component Factor VIII:C). In order to take advantage of this affinity, the monoclonal antibody is chemically coupled to a support matrix resin; this antibody-resin complex is packed into a suitable chromatography column. Resuspended cryoprecipitate, which contains the Factor VIII:R - Factor VIII:C complex and other proteins, is exposed to the column material; the monoclonal antibody binds to the Factor VIII:R moiety, thereby separating the AHF complex from other cryoprecipitate components. Subsequent to washing with appropriate solutions and/or buffers, the Factor VIII:C portion is cleaved from the Factor VIII:R by disrupting the connecting bonds of the complex. Factor VIII:C is then eluted from the matrix. Further purification steps, such as ultrafiltration and additional affinity chromatography, are employed to eventually yield a final product with high potency (100 AHF units per mL) and high purity (specific activity exceeding 3000, exclusive of albumin stabilizer).

This final product, derived from human plasma, represents a major advance in the isolation and purification of the specific protein, Factor VIII:C, that is responsible for coagulant activity in resolving bleeding episodes. To date, this concentrate has been evaluated in clinical studies, has been shown to possess excellent biological half-life and recovery when administered to hemophilic patients, and has been used to effectively manage bleeding episodes. •

Surgeon General's Report on AIDS

The report on AIDS from the Surgeon General of The U.S. Public Health Service is now available. Focusing on prevention, concise information about risks and transmission is also included. As part of a public education effort, some U.S. newspapers are distributing the report. Copies can be obtained by writing: AIDS, P.O. Box 14252, Washington, DC 20044, USA. •

PNEUMONIA IN AIDS (continued from page 1)

leukopenia and thrombocytopenia that occur frequently, are due to immunoligically mediated events, and not to bone marrow suppression.(9) In AIDS patients, as opposed to non-AIDs immunocompromised hosts, there is a very high (up to 75%) incidence of side-effects with TMP-SMZ, which often necessitate terminating treatment. Side-effects include erythematous and maculopapular rashes, with associated drug fever. Gastrointestinal upset, neutropenia, thrombocytopenia and hepatitis also occur.(10) Not all side-effects require stopping treatment. Hypersensitivity reactions, including skin rash and bronchospasm, may respond to antihistamine or adrenaline. Indications for stopping TMP-SMZ include: worsening status after 4-7 days of appropriate therapy, rapidly progressive leukopenia, thrombocytopenia, severe skin rash or hepatitis. Deteriorating renal function occurs infrequently, and does not require cessation of treatment. Doses should either be adjusted for the degree of renal insufficiency or serum levels should be used in guiding treatment.(11)

Upon discontinuation of TMP-SMX because of side-effects, the clinical response to pentamidine is good. Conversely, response to pentamidine is poor if treatment is changed for lack of beneficial response to TMP-SMZ.(10) Pentamidine may be administered intramuscularly or intavenously. The risk of thrombophlebitis or severe hypotension can be avoided by slowly infusing the drug intravenously in a large volume of fluid. Intramuscular injection may lead to the development of painful, sterile abscesses at the site of injection. Pentamidine, by either route, is associated with facial flushing, tachycardia, and dysgeusia. Delayed toxicities include renal insufficiency, severe fasting hypoglycemia, bone-marrow suppression, hepatotoxicity, drug fever, rash, hypocalcemia, and psychiatric disturbances.(11)

The optimal duration of treatment with either drug is not established. In non-AIDS patients, TMP-SMZ for 14 days is sufficient. In AIDS, treatment should be continued for a least 21 days.(8) Pentamidine is given for 14 days, but a longer course may be optimal. Simultaneous treatment with both drugs is unwarranted.

Clinical response to either drug usually occurs within 4-7 days. Improvement of the arterial blood gases and flow rates take longer. The chest x-ray findings may not resolve for 2-3 weeks. Indeed, the chest x-ray and lung gallium scan may then be interpreted as showing active disease even when the patient is well, having finished an appropriate course of treatment. Persistence of organisms obtained via TBB and BAL occurs in 60% of treated patients, and is of unknown significance.

A 25% mortality rate in first episodes of conventionally treated PCP, the high incidence of side-effects and the persistance of organisms in clinically resolved cases, has prompted the search for other drugs. Dapsone in combination with trimethoprim, resulted in a 100% initial response in 15 patients.(12) Side effects including gastro-intestinal intolerance, skin rash, neutropenia, anemia and transaminase elevation were seen frequently, but only required cessation of treatment in 2 patients. Repeat bronchoscopy showed organisms in 50%. Dapsone, as a single agent is less effective than either pentamidine or TMP-SMZ. Difluoromethylornithine (DFMO) was given to 60 patients unresponsive to conventional treatment. Forty-two of these responded to this drug after 14 days of therapy.(13,14,15) Side effects were few and reversible, however, severe thrombocytopenia was noted. Two other drugs, carbutamide and trimetrexate may prove to be of benefit.(16) The use of corticosteroids in acute PCP is controversial.

The immediate cause of death in 55% of all AIDS patients is due to respiratory failure. Many of these deaths occur secondarily to overwhelming infection with *Pneumocystis carinii*.(17) The majority of patients with first episodes of PCP, and often second episodes, improve with appropriate treatment, yet 30% relapse by 6 months.(7,10) The high relapse rate and risk of respiratory failure, coupled with the poor long-term survival, has prompted the use of prophylactic therapy. The combination of pyrimethanine-sulfadoxine prevented relapse in 9 of 12 patients treated for 6 months.(18) Dapsone alone has been used for prophylaxis with encouraging preliminary findings. This drug is sulfa based, yet, few patients previously sensitive to TMP-SMZ developed side effects. TMP-SMZ, in low doses, significantly reduced recurrence of PCP.(19,20) The high incidence of side-effects, makes long-term administration of this drug difficult.

Conclusion

PCP is a cause of significant morbidity and mortality in hemophiliacs with AIDS. Conventional treatment, while effective in the majority, causes additional morbidity. Immediate therapeutic concerns are to improve their quality of life. It is hoped that by prolonging disease-free intervals, treatment aimed at reversing the underlying immune defects may then be initiated.

REFERENCES

1. National Hemophilia Foundation, AIDS Surveillance Update, October 1985.
2. Kovacs, J.A., Hiemeuz, J.W., Macher, A.M. et al. Pneumocystis carinii Pneumonia: Comparison Between Patients with the Acquired Immunodeficiency Syndrome and Patients with Other Immunodeficiencies. Annals Int. Med. 1984; 100:663-671.
3. Murray, J.F., Coleman, D.L., Dodek, P.M. et al. Correlation between Serial Pulmonary Function Tests and Fiberoptic Bronchoscopy in Patients with Pneumocystis carinii Pneumonia and the Acquired Immune Deficiency Syndrome. Am. Rev. Resp. Dis. 1984; 129:491-493.
4. Hartman, B., Koss, M., Hui, A. et al. Pneumocystis carinii Pneumonia in the Acquired Immunodeficiency Syndrome: Diagnosis with Bronchial Brushings, Biopsy, and Bronchoalveolar Lavage. Chest. 1985; 87:603-607.
5. Cohen, A.J., Philips, T.M., Kessler, C.M. Circulating Coagulation Inhibitors in the Acquired Immunodeficiency Syndrome. Ann. Int. Med. 1986; 104:175-180.
6. Maddison, S.E., Walls, K.W., Haverkos, H.W. et al. Evaluation of Serologic Tests for Pneumocystis carinii Antibody and Antigenemia in Patients with Acquired Immunodeficiency Syndrome. Diag. Microbiol. Infect. Dis. 1984; 2:69-73.
7. Haverkos, H.W. Assessment of Therapy for Pneumocystis carinii Pneumonia. Am. J. Med. 1984; 76:501-508.
8. Wharton, J.M., Coleman, D.L., Wofsky, C.B. et al. Trimethoprim-Sulfamethoxazole or Pentamidine for Pneumocystis carinii Pneumonia in the Acquired Immunodeficiency Syndrome. Ann. Int. Med. 1986; 105:37-44.
9. Hollander, H. Leukopenia Trimethoprim-Sulfamethoxazole and Folinic Acid. Ann. Int. Med. 1985; 102-138.
10. Small, C.B., Harris, C.A., Friedland, G.H., et al. The Treatment of Pneumocystis carinii Pneumonia in the Acquired Immunodeficiency Syndrome. Arch. Int. Med. 1985; 145:837-840.
11. Furio, M.M., Wordell, C.J. Treatment of Infectious Complications of Acquired Immunodeficiency Syndrome. Clin. Pharm. 1985; 4:539-554.
12. Leoung, G.S., Mills, J., Hopewell P.C. et al. Dapsone-Trimethoprim for Pneumocystis carinii Pneumonia in the Acquired Immunodeficiency Syndrome. Ann. Int. Med. 1986; 105:45-48.
13. Barlow, J.L.R., Roberts, N.E., Sjoerdsma, A. Eflornithine Hydrochloride (DFMO) in the Treatment of Pneumocystis carinii Pneumonia in Patients with the Acquired Immunodeficiency Syndrome. (Abstract) In: The International Conference on Acquired Immunodeficiency Syndrome. Paris: World Health Organization 1986; 38.

(continued on page 5)

PNEUMONIA IN AIDS (continued from page 4)

14. Brennessel, D.J., Goldstein, J.A. Eflornithine Hydrochloride (DFMO) in the Therapy of Pneumocystis carinii Pneumonia in AIDS. (Abstract) In: The International Conference on Acquired Immunodeficiency Syndrome. Paris: World Health Organization 1986; 53.
15. Dietrich, D.T., Chachona, A., Greene, J. et al. Eflornithine Treatment of Resistant Pneumocystis carinii Pneumonia in AIDS patients. (Abstract) In: The International Conference on Acquired Immunodeficiency Syndrome. Paris: World Health Organization 1986; 53.
16. Anonymous. New Attack on AIDS Pneumonia. Med. World News 1986: June 23; 7.
17. Moskwitz, L., Hensley, G.T., Chan, J.C. et al. Immediate Causes of Death in Acquired Immunodeficiency Syndrome. Arch. Path. Lab. Med. 1985; 109:735-738.
18. Gottlieb, M.S., Knight, S., Mitsuyasu, R. et al. Prophylaxis of Pneumocystis carinii Infection in AIDS with Pyrimethamine-Sulfadoxine. Lancet. 1984; 2:398-399.
19. Hollander, H., Golden, J., Stulbarg, M. Recurrent AIDS-related Pneumocystis carinii Pneumonia: Frequency, Outcome, and Prevention. (Abstract) In: The International Conference on Acquired Immunodeficiency Syndrome. Paris: World Health Organization 1986; 51.
20. Shafer, R.W., Seitzman, P.A., Tapper, M.L. Successful Prophylaxis of Pneumocystis Pneumonia with Trimethoprim-Sulfamethoxazole in AIDS patients with Previous Allergic Reactions. (Abstract) In: The International Conference on Acquired Immunodeficiency Syndrome. Paris: World Health Organization 1986; 54. •

Hemophilia-Associated AIDS United States

As of September 15, 1986, 238 cases of hemophilia-associated AIDS had been reported to the Centers for Disease Control (MMWR 35: 669, October 17, 1986). Of the 238 patients, 212 (89 percent) had hemophilia A; 16 (7 percent), hemophilia B; 7 (3 percent), von Willebrand's disease; two, an acquired inhibitor to factor VIII; and one, factor V deficiency. Seven of the patients were female. Thirteen patients were known to have had other risk factors for AIDS in addition to a hematologic disease.

The first AIDS patient with underlying coagulation disorders was diagnosed in 1981. Since then the number of hemophilia-associated AIDS cases has increased each year but not at an exponential rate. However, in 1985, 92 percent of persons with hemophilia A and 52 percent of those with hemophilia B in a U.S. cohort had antibodies to the human immunodeficiency virus suggesting exposure to the virus or to virus particles. •

Meetings

III International Conference on AIDS, June 1-5, 1987 in Washington, D.C., U.S.A. More information from: International Conference on AIDS; 655 15th Street, N.W.; Suite 300; Washington, D.C. 20005, U.S.A.

Joint Meetings of the World Federation of Hemophilia and the International Society of Blood Transfusion with the XI International Congress on Thrombosis and Haemostasis in Brussels, Belgium, July 4-11, 1987. Lectures or symposia of special interest to hemophilia treaters are scheduled on July 9, 10 and 11. More information from: Dr. P.R. Rouffaer; Center for Thrombosis and Vascular Research; Campus Gasthuisberg; Teaching and Research; Herestraat 49; B-3000 Leuven, Belgium.

WHO Strategy Against AIDS

The World Health Organization (WHO) plans a multi-billion dollar strategy to deal with the worldwide problem of AIDS. The effort will be similar to but much more costly than, that used to eradicate smallpox.

The WHO plan is to help individual governments develop national AIDS programs, to act as an international clearing-house for AIDS-related information, and to provide direction for worldwide research into its causes and the search for a cure. A sizable effort will be directed, during the coming decade, into a newly formed unit focusing solely on AIDS. The AIDS strategy will be managed by Dr. Jonathan Mann.

Within the next five years, between one-half million and three million AIDS cases are estimated worldwide and as many as 100 million people may be infected with the human immunodeficiency virus. These numbers are based on the belief that the disease will continue to spread at the current rate in North America, Europe, and Africa and that larger numbers of infected persons will appear in Latin America. As of now, the virus has not appeared to any extent in Asia. Should that happen, the estimated number of cases would greatly increase.

The disease has spread through the population in a different pattern in Africa than it has in the United States. However, the modes of transmission are the same: by sexual contact, by exchange of blood, and from mother to child.

One of the major problems in combating AIDS is the perception in many parts of the world that it is a disease of the wealthy, affecting only those in "rich" nations. This perception is false. •

Wider Use of AZT to Treat AIDS Patients

Azidothymidine (AZT). the most encouraging of six experimental drugs used in clinical trials to treat manifestations of AIDS, has been made more available to AIDS patients under a strict protocol defining entry criteria, follow-up procedures, and laboratory studies. AZT is the first drug shown to prolong the survival of AIDS patients although it is neither a cure nor a breakthrough drug and its long-term toxic effects are unknown.

The drug, developed and manufactured by Burroughs Wellcome Co., has been used in a U.S.A. study involving AIDS and AIDS-related complex patients in 12 centers nationwide. Data from the first 32 weeks of the study indicated that those patients receiving AZT were living longer than those in the control group who were receiving placebos. However, the study's limited duration makes it impossible to determine how long AZT may prolong survival.

Scientists believe that AZT stops the growth of the AIDS virus by disrupting the chemical chain needed for viral replication inside the body of an AIDS patient. The drug appears to be capable of crossing the blood-brain barrier. Because the AIDS virus has been found in the brain, and has resulted in severe neurological problems for many AIDS sufferers, it must be attacked at the brain level. •

SELECTED ABSTRACTS

Annual Meeting
American Society of Hematology
December 6 -9, 1986

PREDICTIVE VALUE OF T HELPER LYMPHOCYTE COUNTS IN HEMOPHILIACS WITH HIV ANTIBODIES. M.E. Eyster, J.J. Goedert, M.H. Gail. The Pennsylvania State University School of Medicine, Hershey, PA and The National Cancer Institute, Bethesda, MD.

The primary target cells of the human immunodeficiency virus (HIV) are the T helper (T_H) lymphocytes. Severely depressed T_H counts are universally found in patients with AIDS, and there are strong indications that the absolute number declines progressively following HIV infection. To determine whether T_H counts were predictive of AIDS, lymphocyte subsets were performed by flow cytometry at the time of regular clinic visits on a cohort of 80 seropositive hemophiliacs in whom estimated dates of seroconversion could be ascertained from stored frozen sera. Serial T_H counts were available on nine patients prior to the diagnosis of AIDS, and in all nine the values declined steeply during the 12-24 months prior to the onset of opportunistic infections. The mean slope was -28.6 ± 8.7 cells/month versus -8.3 ± 3.4 cells/month for the seropositive patients who did not develop AIDS ($p = .005$). Ten cases of AIDS occurred 24 to 95 months after seroconversion, for a cumulative incidence of 19.5% ± 7.9% at six years after seroconversion. Older age at the time of seroconversion was associated with a significantly higher incidence of AIDS (p for trend = .02). Platelet counts less than 100,000 cells/mm^3 were also associated with increased risk of development of AIDS ($p < .01$). T_H counts were significantly lower in hemophiliacs destined to develop AIDS within two years ($p < .01$). A steep decline in T_H cells preceded the development of AIDS, and an absolute T_H count below 200 cells/mm^3 was associated with an approximate 50% probability of the development of AIDS within two years. It is concluded that T_H cells fall progressively after seroconversion, and that a very rapid decline heralds the onset of full blown AIDS. These findings have important implications for future treatment strategies during the long latency period of two to eight years or more from the appearance of HIV antibodies until the development of AIDS in hemophiliacs.

TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION TO HOUSEHOLD CONTACTS OF PERSONS WITH CONGENITAL HEMATOLOGIC DISORDERS. E. Operskalski,* and the Transfusion Safety Study Group (intr. by Carol B. Hyman, M.D.) University of Southern California, Los Angeles, and other participating institutions.

The Transfusion Safety Study is collecting data concerning the transmission of transfusion-acquired infections from patients with congenital hematologic disorders to household members. Of 233 patients for whom information is presently available, 128 (55%) were anti-HIV-positive. The 128 positive patients lived in 123 households with 174 members; 16 contacts were positive by EIA and immunoblot.

Type of contact	Relationship	(+)/Total
Sexual	Homosexual	1/ 1
	Heterosexual	12/56 (21%)
Non-sexual	Parent	0/71 (0%)
	Sibling	0/18 (0%)
	Offspring	3/21 (14%)
	Other	0/ 7 (0%)

These data provide further evidence of relatively high risk of HIV infection of sexual contacts. The three anti-HIV-positive children are all infants born to anti-HIV-positive wives of infected hemophiliacs.. Passively acquired antibody has not been excluded for two; the third was positive at ten months of age. Thus, vertical transmission may be a very important mechanism of perpetuating the HIV reservoir.

IMMUNOLOGIC AND SEROLOGIC FOLLOW-UP STUDY OF A COHORT OF HEMOPHILIACS: G.F. Gjerset,* R.B. Counts, J.A. Hansen,* P.J.Martin, and the Transfusion Safety Study Group (TSS). Puget Sound Blood Center, University of Washington and other participating institutions.

Thirty-two hemophiliacs have been evaluated since 1983 to determine prognostic indicators in relation to AIDS. Eleven of the 32 were treated only with cryoprecipitate or plasma (1,672 - 15,455 donors/patient). Using evaluations of these patients by the TSS in 1986, T4 lymphopenia (absolute T4 ≤ 200/mm3) was assumed to indicate progressive disease. In 1983, 14/27 had anti-HIV antibodies (HIV+); 4 of the 14 (28%) now have T4 lymphopenia. Of the 13 who were HIV- in 1983, 7 now are HIV+ and 2/7 (28%) have T4 lymphopenia. T4 lymphopenia was also seen in 1/6 patients remaining HIV- in 1986. Low T4 counts in 1986 were not significantly correlated with duration of HIV seropositivity, type of treatment, hepatitis B serology, alanine aminotransferase or cumulative dose of clotting factor. The T4/T8 ratio measured in 1984 was correlated with T4 counts both in 1984 (not shown) and in 1986 ($p < .02$, Table 1). In 1984, some of the patients had increased HLA DR positive T cells (%DR+ T, defined as % of non-B lymphocytes reacting with monomorphic DR antibody 7.2). This 1984 finding was not correlated with T4 lymphopenia in 1984 (not shown), but was strongly correlated with T4 lymphopenia in 1986 ($p < .02$, Table 2). In contrast, the 1986 %DR+ T was not correlated with T4 lymphopenia in 1986. Thus, increased DR+ T and a low T4/T8 ratio appear to precede T4 lymphopenia. Since the ratio is often low in HIV+ individuals, the presence of DR+ T cells may identify patients at particular risk for developing T4 lymphopenia. Our data are consistent with the idea that lymphocyte activation plays a role in the pathogenesis of AIDS and that HIV seropositive patients may remain stable > 3 years when evidence of chronic in vivo lymphocyte activation is absent.

Table 1.

		T4 (1986)	
		≤200	>200
T4/T8 (1984)	≤1	7	5
	>1	1	10

Table 2.

		T4 (1986)	
		≤200	>200
%Dr+T (1984)	<10	2	9
	>10	6	2

HIV STATUS AND T CELL SUBSETS IN CONGENITAL COAGULATION DISORDERS. L.M. Aledort and the Transfusion Safety Study Group. Mount Sinai Medical Center, New York, N.Y. and other participating institutions.

It has been suggested that chronically transfused hemophiliacs have T cell abnormalities independent of their Human Immunodeficiency Virus (HIV) status. This altered immune status may make the recipient more susceptible to infection with HIV. The Transfusion Safety Study (TSS) group has data on 332 hemophilia and Von Willebrands (VW) disease patients and 238 controls consisting of untreated coagulation defects and/or household members. The incidence of HIV positivity is 83%, 57% and 24% for Factor VIII (FVIII), Factor IX (FIX) concentrates and unpooled product recipients respectively. The percent of T4 cells in all groups studied (FVIII, FIX and VW patients) were significantly lower in HIV positive as compared to HIV negative patients (26 vs 42) ($p=0.0001$). HIV negative recipients of blood products also differed from negative controls but were much closer (42 vs 46). The percent of T8 cells were significantly elevated in FVIII and FIX and VW HIV positive versus negative recipients ($p=0.0001$). Similar significant differences were seen between HIV negative recipients and controls but values were closer as above. T4/T8 ratios demonstrated significant differences in all groups treated ($p=0.001$) when comparing HIV positivity with HIV negativity. However, FVIII concentrate recipients who are HIV negative have significantly lower T4/T8 when compared to controls, ($p=0.0001$) and single pooled FVIII deficient recipient patients ($p=0.0264$). This T cell abnormality may predispose FVIII concentrate recipients to infection with HIV and thus a higher incidence of HIV antibody in this large group of patients which comprises 72% of all patients followed.