Bulletin of the World Health Organization, 63 (4): 667-672 (1985)

The acquired immunodeficiency syndrome (AIDS): Memorandum from a WHO Meeting*

An International Conference on Acquired Immunodeficiency Syndrome (AIDS), sponsored by the United States Department of Health and Human Services and the World Health Organization, was held in Atlanta on 15-17 April 1985. More than 3000 participants from 50 countries attended. This conference was followed by a meeting organized by WHO on 18-19 April where the participants reviewed the information presented at the conference and assessed its international health implications, which are described in this Memorandum.

NATURAL HISTORY AND MODE OF TRANSMISSION

Since the first recognition of the acquired immunodeficiency syndrome (AIDS) in 1981, nearly 11 000 cases have been reported, mainly from the industrial countries. More than 80% of cases recorded to date have been reported from the USA. AIDS presents a major health problem in Haiti, and the reported incidence of the disease is increasing in Brazil and Canada. While six countries in Europe (Denmark, France, Federal Republic of Germany, Netherlands, Switzerland and the United Kingdom) have reported increasing numbers of cases since 1981, there have been relatively few cases from countries in Asia and the Western Pacific region (except Australia). Recent information indicates that AIDS may be a serious public health problem in tropical Africa; estimated incidence rates in some central African cities are comparable to those in New York or San Francisco, and cases have been identified in residents or migrants from over a dozen African countries.

In North America, Europe, and Australia, homosexual men account for at least 70% of the total detected AIDS cases. The disease has also been noted in intravenous drug abusers, haemophiliacs, recipients of blood transfusion, and the heterosexual partners or infants of patients or members of groups at increased risk of infection. Studies undertaken in Haiti and central Africa and among emigrants from these countries show that the disease is occurring mainly in the heterosexual population. Heterosexual contact in these populations is a major risk factor for transmission of infection.

The viral agent responsible for AIDS has been detected in blood, semen and saliva. Modes of transmission include sexual contact, contamination with blood from infected persons, and directly from an infected mother to her newborn baby. Large prospective studies on health care workers in contact with the blood of infected patients through needlestick injuries or mucosal exposure have documented only a single case of infection.

Studies of AIDS in the recipients of blood transfusions show a long time interval between exposure to the infection and onset of the disease. Mean intervals of 12 months in children and 29 months in adults have been noted. Estimates based on mathematical models suggest even longer incubation periods. The clinical outcome of known infection with AIDS-related virus within a period of 2-5 years of observation is as follows: 2-15% develop AIDS, 23-26% develop AIDS-related complex, and 60-70% remain asymptomatic. Most individuals appear to remain infected whether or not they develop symptoms.

THE AIDS VIRUS

The etiologic agent of AIDS is a retrovirus described in the scientific literature as LAV (lymphadenopathy-associated virus), HTLV type III (human T leukaemia virus or human T lymphotropic virus, type III), or ARV (AIDS-related virus). The definitive name will be a matter for approval by the International Committee on Taxonomy of Viruses in accordance with the rules governing the nomenclature of viruses. In this report the virus will be referred to as LAV/HTLV-III, which combines the two most widely used names.

The virus has a specific tropism for the OK T4+

* This Memorandum was drafted by the signatories listed on pages 671-672. A French translation of this article will appear in a later issue of *Bulletin*. Requests for reprints should be addressed to Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

subset of T lymphocytes and perhaps to an, as yet, undefined fraction of this subset. The virus has also been shown to be present in brain tissue of some patients, but it is not yet clear which types of cell are infected. The basis of the viral tropism for certain lymphocyte populations lies in part in the binding of the viral glycoprotein to the T4 molecule at the surface of the lymphocyte. The virus replicates in actively dividing T4 lymphocytes and can also be grown in cell lines derived from T or B lymphocytes. Like other retroviruses, the virus can remain in lymphoid cells in a latent, unexpressed state, and can be activated by such chemical agents as halogenated pyrimidines.

The mature virions that bud from the surface of infected cells are in the range of 100–140 nm and may have condensed, eccentric, round or bar-shaped cores. Three structural proteins are associated with the core, with relative molecular masses (M_r) of 24–25 000, 16–18 000, and 12–13 000. The major envelope protein is a glycoprotein of M_r 110–120 000. The protein in the outer part has an M_r of 65–70 000 and that in the transmembrane portion an M_r of 40–42 000. Besides these four major proteins, there is the polymerase reverse transcriptase characteristic of retroviruses with an M_r probably in the range of 70–100 000. On the basis of its morphology, certain characteristics of its genome structure, and the number and size of its structural proteins, LAV/-HTLV-III appears to be closely related to viruses of the lentivirus subfamily of retroviruses.

Sequence studies indicate that the genetic variation of the AIDS virus is high, particularly in the region of the gene coding for envelope protein. Despite this variation, common epitopes appear to exist since in nearly all patients antibodies can be detected against proteins of a single prototype virus. All the viral proteins and their cellular precursors appear to be antigenic. Antigens most frequently recognized by the immune system are the core protein, and the envelope glycoprotein and its related cellular precursors or fragments. Antibody against the glycoprotein may be found at higher titres in AIDS patients despite a weak or absent neutralizing activity on virus infectivity.

LAV/HTLV-III, like many enveloped viruses, has been shown to be heat sensitive; exposing the virus in serum to a temperature of 56 °C for 30 minutes reduced infectivity by at least a hundredfold. The virus is readily inactivated by ether, acetone, ethanol (20%), sodium hypochlorite (0.2%), beta-propiolactone (1:400 dilution), sodium hydroxide (40 mmol/l), and glutaraldehyde (1%), but is relatively resistant to ionizing radiation and ultraviolet light. The inactivation procedures used in preparing hepatitis B vaccine from human plasma have been shown to inactivate LAV/HTLV-III.

APPLICABILITY OF LABORATORY TESTS

Laboratory techniques for detecting LAV/HTLV-III infection include procedures to isolate the virus, detect viral components (antigens, nucleic acid, or reverse transcriptase), and detect antibodies to specific proteins. These methods are of value for confirming a diagnosis of AIDS or the AIDS-related complex, determining the prevalence of infection in the community, screening blood intended for transfusion or fractionation, and evaluating various approaches to prevent or treat the disease.

A variety of assays are available for the detection of anti-LAV/HTLV-III. These include enzyme-linked immunosorbent assay (ELISA), solid-phase radioimmunoassay, immunofluorescence (IF), radioimmunoprecipitation, and Western blot assays. The tests most widely used for screening purposes are ELISA and immunofluorescence; both require relatively simple equipment and can be performed in most diagnostic laboratories in two working days. Serum that is repeatedly positive by ELISA or immunofluorescence should be tested by an additional method before the patient is informed of the results. The additional method may include the following:

(*a*) Repetition of the same type of assay (ELISA or IF) but using reagents obtained from a different source.

(*b*) Demonstration that the serum is positive with the test antigen but not with a control antigen prepared from uninfected cells.

(*c*) Use of techniques that detect antibody against one or more structural components of the virus. For example, radioimmunoprecipitation detecting antibody to the protein p-24, or Western blot assays that detect antibody against one or more of the core or structural proteins.

Countries that are about to or are considering whether to undertake serological testing should ensure that their laboratory personnel are adequately trained to do these tests and that centres are available to confirm the results.

Concern has been expressed in many countries about the confidentiality of results and the need to obtain informed consent from patients before performing the laboratory tests. The informing of antibody-positive individuals about their status calls for education of health care professionals, the general public, and the news media. Guidelines are needed to help health care professionals in interpreting the test results and on how to inform patients when the result is positive.

BLOOD TRANSFUSION AND BLOOD PRODUCTS

Infections due to LAV/HTLV-III can be transmitted by transfusion of whole blood, blood

cells, platelets, and factors VIII and IX derived from human plasma. LAV/HTLV-III has been recovered from almost all blood donors who were implicated in the transmission of AIDS. In some cases, the donors were still asymptomatic two or more years after the blood donation. There is no evidence to date that transmission can occur through other blood products such as albumin, immunoglobulins prepared by conventional Cohn fractionation for intramuscular use, or hepatitis B vaccines that meet WHO requirements. The recent introduction of heat treatment for factor VIII preparations has improved the safety of these products.

The median time interval between transfusion of blood containing LAV/HTLV-III and the diagnosis of AIDS in the recipient has been 4 years in adults. Consequently, transfusion-related cases of AIDS may continue to be identified several years after the establishment of serological screening of donors for LAV/HTLV-III. Transmission of infection to haemophiliacs can be reduced by the introduction of heat treatment of factor VIII and factor IX.

CLINICAL FINDINGS

The definition of AIDS given by the Centers for Disease Control for surveillance and reporting purposes has generally been accepted,[a] although it is recognized that many other clinical responses to infection by LAV/HTLV-III may occur. The most common disease manifestations are those of the lymphadenopathy syndrome and AIDS. More recently described is an acute mononucleosis-like syndrome of 3–14 days' duration with the appearance of antibody to LAV/HTLV-III in 2–8 weeks. An asymptomatic carrier-stage with these antibodies is also recognized. By careful documentation of the clinical responses of patients with LAV/HTLV-III infection, investigators have recently recorded a number of features of the disease in addition to those that fulfil the case definition. These include bacterial infections of the respiratory and gastrointestinal tract and neurological involvement in persons infected by LAV/HTLV-III. The observed neuropsychiatric symptoms may be severe, similar to those associated with subacute encephalopathy.

The clinical manifestations of LAV/HTLV-III infection in infants generally resemble those seen in adults, although diarrhoea has been observed to be a prominent symptom in some studies. Important elements that distinguish AIDS from other defined immunodeficiency syndromes include serum immunoglobulin levels in the normal or elevated range and evidence of predominant T-cell immunodeficiency. Suspicion of AIDS is also raised when one of the parents comes from a population group at risk for AIDS and either the mother or the infant has serological evidence of LAV/HTLV-III infection; infected women may be at risk of disease exacerbation during pregnancy.

Clinical differences have been observed between illnesses associated with LAV/HTLV-III in Africa and Haiti and those in other parts of the world in adults and children; in Africa, for example, weight loss, chronic diarrhoea, and fever are predominant and the prevalent opportunistic infections include candida oesophagitis, cryptococcal meningoencephalitis, and severe pneumonitis.

T-cell phenotypic markers (T4, T8, and the T4/T8 ratio) and delayed hypersensitivity responses are effective markers of immunological competency in AIDS patients. Reduction of T-cell numbers correlates with risk of the development of opportunistic infections characteristic of AIDS. A considerable number of other abnormalities in the immune system have been identified, including the presence of circulating immune complexes, serum inhibitors, increased levels of beta-2-microglobulin, and alpha-interferon.

VACCINE DEVELOPMENT

An effective vaccine is critically important for preventing the transmission of LAV/HTLV-III. The major aim of vaccination would be to prevent primary infection. Vaccination of persons with pre-existing infection is unlikely to be effective since this virus, in common with other retroviruses, induces persistent or latent infections. It is also unlikely that vaccination could ameliorate or prevent the clinical effects of this infection in already infected persons.

Antibodies in the serum of infected persons commonly react to most or all of the major structural proteins. The role of these antibodies in the natural disease is poorly understood. Some antibodies may be neutralizing, particularly those reacting with the transmembrane protein (p-41) and the envelope protein (p-65). It is these antigens that are likely to be of major relevance to vaccine development.

The extent to which LAV/HTLV-III isolates vary in their genetic and antigenic characteristics will critically influence the effectiveness of a vaccine. Nucleic acid variations in the *env* region include sites of potential glycosylation, which would be important in terms of vaccination. If frequent antigenic mutations occur in the virus envelope, as is the case with several other retroviruses, then vaccination may not be effective. Successful vaccination will depend on the presence of highly conserved regions of the viral antigens against which protective antibodies can be induced.

[a] See *Bulletin of the World Health Organization*, **62**: 429 (1984).

The choice of vaccine type is limited. A live-attenuated AIDS vaccine is unlikely since retrovirus genomes are integrated into the cell DNA. The development of a non-replicating vaccine also requires the resolution of certain problems, such as the selection of a cell line for producing the vaccine virus and of methods for purifying the viral antigens and freeing them from viral nucleic acid. Additional safety issues are raised by the use of human leukaemia cells, which are the cells now available for large-scale production of viruses.

Recombinant DNA technology may provide the most promising methods for vaccine development. Expression systems may be developed to yield large quantities of the required vaccine antigen in the absence of infectious virus. Other possible approaches to vaccine development include the use of recombinant vaccinia virus that expresses protective LAV/HTLV-III antigen and the use of anti-idiotype technology.

INFORMATION AND HEALTH EDUCATION

Control measures for AIDS will differ from country to country, but the most promising means of limiting the spread of LAV/HTLV-III infection is through education aimed at altering the behaviour and practices of certain individuals. Information about the disease, probable routes of transmission, and ways to reduce the risk of infection should be widely disseminated in the community and to groups at increased risk of infection. This information should be presented so that it can be easily understood. The public should be informed that there is no evidence of spread by the airborne route, by casual social contacts with infected persons (even within households), and by food, or to health care workers who are not in the high-risk group.

The highest prevalence of infection and disease in some countries is among homosexual or bisexual men, while in others heterosexual transmission is equally or more important. Risk factors include sexual contact with persons known to be infected, and the risk increases with the number of partners. The use of condoms may prevent the spread of infection, but this has not yet been documented.

Oral-genital contact and intimate kissing have not been shown to be risk factors. However, infection may be spread by these means, and persons with clinical, serological, or epidemiological evidence of infection may be advised accordingly. Similarly, the sharing of toothbrushes, razors, and other personal equipment that might transfer blood should be discouraged.

Infected women should be advised against getting pregnant because this may exacerbate the disease, and infection may spread to the fetus or infant.

Transmission of infection among intravenous drug abusers is due to the contamination of needles, syringes, and other equipment. Efforts should therefore be directed against the intravenous injection of illicit drugs and the risks in sharing of needles and syringes should be made known. In the developing countries the use of syringes, needles, and other instruments without sterilization may play a role in transmission of the disease.

Infected persons with haemophilia should be advised about the risk of transmission of AIDS to their sexual partners. The risk of transmission by contaminated blood can be reduced by routine screening of blood donors for antibodies to LAV/HTLV-III. A similar approach should be used to reduce the risk of transmission by organ or tissue transplantation and by artificial insemination.

CONCLUSIONS AND RECOMMENDATIONS

Considering that there was now sufficient information to permit national health authorities to take action in order to decrease the incidence of AIDS among high-risk groups, the participants submitted the following conclusions and recommendations:

(1) At the international level, action should be taken to:

—establish a network of collaborating centres with special expertise in the field. The centres should assist in the training of health staff, the provision of reference panels of sera and other reference preparations relevant to diagnosis and research, the evaluation of diagnostic tests, and provision of advice on the production of working reagents. They should also assist in the preparation of health educational material and the organization of studies to determine the natural history of the disease and the extent of infection in different parts of the world.

—coordinate global surveillance of AIDS using a compatible reporting format and the currently accepted case definition; these data and other important developments on the disease should be disseminated as widely and rapidly as possible.

—assist in the development of an effective vaccine, and when appropriate, the development of international requirements for the vaccines; the evaluation of candidate vaccines should be actively supported.

—encourage and assist in periodic serological studies in countries where AIDS has yet to be recognized, and ensure the collection of comparable data and representative selections of sera; since

LAV/HTLV-III infection precedes disease manifestation in individuals, early recognition will require serological studies in the known high-risk groups.

(2) In countries, action should be taken to:

—inform the public that LAV/HTLV-III infection is acquired through heterosexual and homosexual intercourse, sharing of needles by intravenous drug abusers, transfusion of contaminated blood and blood products, transmission from mothers to their babies, and probably through repeated use of needles and other unsterile instruments that pierce the skin or mucous membranes. Information should be provided about the risk of LAV/HTLV-III infection and AIDS, especially to those men and women who may be at increased risk because of multiple sexual partners. There is currently no evidence of spread of LAV/HTLV-III by casual social contacts even within households. Provision of timely and accurate information on these points is recommended.

—ensure that health care workers are informed about AIDS and LAV/HTLV-III infection, the modes of transmission and clinical spectrum, the available programmes of management including psychosocial support, and the methods for prevention and control.

—assess the risk that AIDS poses to each country's population and establish the methods of diagnosis, surveillance, and laboratory testing, including specific tests for LAV/HTLV-III.

—screen, where feasible, potential donors of blood and plasma for the presence of antibody to LAV/HTLV-III; when the latter is present, this blood should not be used for transfusion or for the manufacture of products where there is a risk of transmitting infectious agents. Potential donors should be informed in advance about this screening procedure.

—reduce the risk of transmission of LAV/HTLV-III, which might be present in concentrates of factors VIII and IX, by heat treatment or other proven methods of inactivation.

—inform potential donors of organs, sperm, or other human material about AIDS and encourage groups at increased risk of infection to exclude themselves from donating. Whenever possible, serological testing should be performed before these materials are used. This is particularly important when donor material is collected from an unconscious or deceased patient on whom relevant information may be lacking.

—refer individuals who are seropositive to LAV/HTLV-III for medical evaluation and counselling. Such people should be encouraged to inform their doctor or health care attendant of their status.

—develop guidelines for the total care of AIDS patients and for handling specimens from them in hospital and other settings. These guidelines should be similar to those which are in use for the care of patients with hepatitis B.

—develop codes of good laboratory practice to protect staff against the risk of infection. These recommendations may be based upon those found in the *Laboratory biosafety manual*.[b] The level of care required for working with specimens from patients infected with LAV/HTLV-III is similar to that required for specimens from hepatitis B patients. The use of class II biological safety cabinets is recommended. These cabinets are adequate for containment of other agents such as herpes and hepatitis viruses, mycobacteria, and protozoa that may be present in the specimens. For work involving production and purification of LAV/HTLV-III, the P3 biosafety containment level must be employed.

—collect and store serum samples from representative laboratory workers at the time of employment and at regular intervals thereafter, in order to be able to assess the risk of laboratory-acquired infection and the effective observation of biosafety guidelines. Countries should provide this information to WHO for collation and dissemination. Provision of serum samples and testing should be carried out with the informed consent of the subjects.

—maintain the confidentiality of the positive results of serological testing and the identity of these AIDS patients. Serological testing should be undertaken with the informed consent of the patient.

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[b] *Laboratory biosafety manual*, Geneva, World Health Organization, 1983.

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