WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTÉ

EB77/42
25 November 1985

EXECUTIVE BOARD

Seventy-seventh Session

Provisional agenda item 20

WHO ACTIVITIES FOR THE PREVENTION AND CONTROL OF ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Report by the Director-General

Acquired immunodeficiency syndrome (AIDS) has become a matter of increasing concern in a number of countries, particularly in Europe and North America. This report, updated from an information paper reviewed by the Programme Committee of the Executive Board in October 1985, assesses the current situation, describes the activities being undertaken by WHO, and indicates the course of future action to understand and control AIDS, including assurance of safe blood and blood products.

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Introduction

1. Since the first recognition of the acquired immunodeficiency syndrome (AIDS) in 1981, over 17 000 cases have been reported, mainly from the industrialized countries. Approximately half of these cases were reported in 1985 and over 75% were reported during the 1984-1985 biennium. More than 80% of cases recorded to date have been reported from the USA.

2. The number of cases reported to WHO up to 15 November 1985 is as follows:

Continent	Number of cases	Number of reporting countries
Africa	21	1
Americas	15 512	42
Asia	22	7
Europe	1 386	19
Oceania	132	2
TOTAL	17 073	71

There have been relatively few cases from countries in Asia and Oceania (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.

3. 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.

4. Cases of AIDS will still occur among the already infected haemophiliacs and those who have received contaminated blood transfusions; further infections through blood or blood products can now be greatly reduced by screening blood donations for antibody to the LAV/HTLV-III virus. Studies undertaken in the Caribbean 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.

5. The etiological 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.

6. The virus has a specific tropism for the OK T4+ 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 central nervous system cells 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.

7. LAV/HTLV-III has been detected in blood, semen and saliva. Modes of transmission include sexual contact, parenteral exposure to blood and blood products, and directly from an infected mother to child during the perinatal period. In the industrialized countries, intravenous drug abuse, and its accompanying problems associated with the sharing of contaminated needles, represent a major mode of transmission for LAV/HTLV-III infection. In the developing world, however, this represents a minor risk factor, if any. On the other hand, the use of unsterilized syringes and needles within and outside the health programme and the use of unsterilized instruments for tatooing and for scarification (for both ritual and medical purposes) poses a definite risk of transmission. There is no evidence that the virus is spread through casual contact with an infected individual, including contacts in a family setting, schools or other groups living or working together. Large prospective studies on health care workers in contact with the blood of infected patients through needle-stick injuries or mucosal exposure have documented only a single case of infection; two other cases are being investigated. There is no evidence of transmission by blood-sucking insects.

8. Studies of recipients of blood transfusions who developed AIDS show a long 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 LAV/HTLV-III within a period of 2-5 years of observation is as follows: approximately two-thirds will have no evidence of ill health; the remaining one-third will develop illness varying in severity from mild to extremely serious.

WHO network of collaborating centres

9. A meeting on AIDS was organized by WHO on 18-19 April 1985, immediately following the International Conference on Acquired Immunodeficiency Syndrome, Atlanta, GA, USA. The participants in the WHO meeting reviewed the information presented at the Conference and assessed its international health implications.[1] A key recommendation they made called on WHO to "establish a network of collaborating centres with special expertise in the field".

10. WHO acted on this recommendation by initially establishing the following collaborating centres:

- Division of Viral Diseases, Centers for Disease Control, Atlanta, GA, USA
- Institut de Médecine et d'Epidémiologie Tropicales, Hôpital Claude Bernard, Paris, France
- Department of Hygiene and Medical Microbiology, Max von Petternkofer Institute, Munich, Federal Republic of Germany
- Virus Laboratory, Fairfield Hospital, Fairfield, Victoria, Australia
- Unité d'Oncologie Virale, Institut Pasteur, Paris, France

11. The directors of these collaborating centres met in Geneva on 25-26 September 1985 to assess the up-to-date worldwide impact of AIDS and to advise the Organization on the development of a programme on AIDS in which they would take an active part (see below). Since then WHO has been extending its network of collaborating centres; at present the following centres are being established:

- National Institute for Biological Standards and Control, London, United Kingdom
- Faculty of Medicine, University of Singapore, Singapore
- Laboratory Centre for Disease Control, Ottawa, Ontario, Canada
- Institut Pasteur, Bangui, Central African Republic
- Central Public Health Laboratory, London, United Kingdom

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[1] See Bulletin of the World Health Organization, 63(4): 667-672 (1985).

- Institute for Virus Research, Kyoto University, Kyoto, Japan

- National Bacteriological Laboratory, Solna, Stockholm, Sweden

- Office of Biologics, Bethesda, MD, USA

- One centre in Brazil to be named

The directors of the WHO collaborating centres are scheduled to meet again on 16-18 December 1985.

WHO programme on AIDS

12. The programme has the following components:

(1) Exchange of information;

(2) Preparation and distribution of guidelines, manuals, educational materials for the public, etc.;

(3) Assessment of commercially available LAV/HTLV-III antibody test kits; development of a simple, inexpensive test for field application; and establishment of WHO reference reagents;

(4) Cooperation with Member States in the development of national programmes/actions for the containment of LAV/HTLV-III infection;

(5) Advice to Member States on the provision of safe blood and blood products;

(6) Coordination of research, in particular on: (a) the development of therapeutic agents and vaccines; and (b) simian retroviruses.

Exchange of information

13. An important component of the programme is the participation of Member States and WHO collaborating centres on AIDS in the collection of data on the incidence of AIDS and the transmission of this information to WHO headquarters on a regular basis. Wherever possible, information on the gender, age, recognized risk factor (if any) and major clinical features should also be provided. Systematic collection of these data requires that a standard form be provided by WHO; this is at present under preparation.

14. WHO collaborating centres on AIDS provide data on the epidemiology and sero-epidemiology of LAV/HTLV-III infection in their regions to the regional offices and to WHO headquarters.

15. The WHO regional offices provide regular updates on: (a) the status of testing for LAV/HTLV-III infection in individual countries in their region; (b) legislation and policies introduced by Member countries to control the spread of the infection. All pertinent information is published in summary form on a monthly basis.

16. Meanwhile, because of the rapid changes in the world picture of AIDS and the need to involve the media for fast dissemination of information, updates and pertinent information published in the Organization's Weekly epidemiological record are provided, whenever necessary, to the WHO regional offices and the media by infonet, by facsimile or by telex. At the same time they are summarized on the automatic telex reply service.

17. Following WHO or other international meetings, special WHO reports are widely disseminated in extenso, and press releases are prepared for the public (and the media).

Preparation and distribution of guidelines

18. Although drugs to prevent and ameliorate disease manifestations of LAV/HTLV-III infections or a vaccine to protect those at highest risk of acquiring infection are the immediate goals of research in many countries, they are unlikely to be available for wide public health application within the immediate future. Meanwhile, prevention of AIDS will

depend totally on risk reduction programmes based on information/education. Credibility of these programmes depends heavily on laboratory-based diagnosis of the disease and the understanding of the natural history of the virus in specific countries and among specific populations. Prevention programmes can be undertaken immediately, based on current knowledge and best public health judgement. Guidelines/education materials on AIDS are being used effectively and are available from Australia and countries in North America and Europe; to be effective in other countries, however, these materials will have to be carefully tailored to meet specific needs. Three types of guidelines are of high priority, namely:

(1) Guidelines for the diagnosis, surveillance, prevention and control of infection with LAV/HTLV-III;

(2) Educational materials for high-risk groups and the general population, including adolescents, explaining mechanisms of transmission and possible preventive measures;

(3) Guidelines and manuals for health care personnel and other individuals who through their profession may be exposed to infection with LAV/HTLV-III.

19. For this purpose WHO is collecting such guidelines/educational materials and will collate and distribute them to WHO collaborating centres and regional offices for review and comment. The final product will be published as a booklet (within the first quarter of 1986) and distributed to Member States. It will also be available worldwide. It is understood that it will require frequent updating; the Weekly epidemiological record will serve this purpose.

Assessment of commercially available LAV/HTLV-III antibody test kits

20. Infection with LAV/HTLV-III may be entirely silent for many years or may cause initially only an acute disease of limited duration. The laboratory diagnosis of an infection with LAV/HTLV-III therefore becomes of utmost importance. Such an infection may be identified by detection of antibodies to LAV/HTLV-III antigens (anti-LAV/HTLV-III), isolation of LAV/HTLV-III from blood tissues or body fluids, or identification of viral components by immunological or molecular techniques.

21. For routine large-scale testing, only the first approach, i.e. measurement of antibody to LAV/HTLV-III, is practical. The other techniques are used primarily for research purposes. Enzyme-linked immunosorbent assay (ELISA) for antibody detection is the method most frequently used for routine testing for LAV/HTLV-III infections. LAV/HTLV-III antibodies usually develop within weeks (rarely months) after infection and remain demonstrable possibly for life. LAV/HTLV-III antibodies and virus are often found simultaneously in the same individual, and a person with such antibodies must be considered to be a potential virus carrier.

22. ELISA test systems are highly sensitive ($>98\%$); however, not all reactive sera are indicative of LAV/HTLV-III infections because of non-specific reactions.

23. All sera reactive in an ELISA test should be tested in another system. Immunoblots (Western blots) have been most frequently used for this purpose, but other tests are also under evaluation. Non-specific reactions may also occur in the immunoblot assays, and careful evaluation by experienced laboratory personnel is needed.

24. In general, the percentage of "false positives" increases together with the sensitivity of the test systems. The acceptance of a relatively high percentage of "false positives" at this time appears prudent in order to detect all truly positive specimens among blood donors. A more specific, but also less sensitive assay system may be more appropriate for some epidemiological studies when confirmatory tests are not readily available.

25. Some laboratories also use immunofluorescence tests with LAV/HTLV-III infected and non-infected cells. Although this test appears somewhat less sensitive than immunoblot techniques, it is nevertheless a valuable additional test system which should be evaluated further.

26. To accelerate progress in the field of laboratory testing, WHO is undertaking the following:

(a) The establishment of international reference sera, available in a large number of aliquots, with antibodies to LAV/HTLV-III, for use in evaluating the sensitivity of immunoassays in respect to individual viral antigens and calibrated in antibody units. In addition, an international proficiency panel needs to be established;

(b) The distribution of LAV/HTLV-III virus for control purposes and for development of more simple and less expensive antibody tests, primarily for use in laboratories with limited technical facilities;

(c) Collection and characterization of additional isolates of LAV/HTLV-III and their free exchange through the WHO collaborating centres on AIDS;

(d) Development and characterization of panels of monoclonal antibodies to specific epitopes of LAV/HTLV-III and cDNA clones of reference for diagnostic and research work on AIDS.

27. The availability of screening tests for antibody to the LAV/HTLV-III virus, coupled with the finding that in some countries the large majority of those with the disease are either male homosexuals or intravenous drug abusers, raises the possibility of misuse of the test. Current test kit configurations have aimed at a very high sensitivity at the expense of some specificity in order to ensure the exclusion of blood which has any possibility of carrying the LAV/HTLV-III virus. Used in this way, the antibody test serves a clinically useful purpose, and the public health benefits in terms of a safe blood supply are generally perceived to outweigh the difficulties associated with false-positive reactions. It is therefore important for public health officials to be alert to the appropriate uses and the potential for misuse of the LAV/HTLV-III antibody test. In addition to screening blood, the antibody screening test has played an important role in research on the epidemiology of the disease. It can also be helpful as an adjunct in the diagnosis of persons with early signs and symptoms associated with AIDS, since the predictive value of positive test results increases substantially when it is used in persons with an increased risk for AIDS such as persons with symptoms. Meanwhile, WHO will organize collaborative studies for the comparative evaluation of candidate reference sera. Information will be collected on the performance characteristics of commercially available antibody test kits under field conditions. The results of these studies will be made available to Member States. Furthermore, WHO may enter into negotiations with a limited number of commercial producers to obtain kits at a price lower than the market price in the industrialized countries. These kits could then be made available to Member States.[1]

Cooperation with Member States

28. WHO will undertake, on request, technical cooperative programmes with Member States. These could include, among other activities, the following:

(a) Organizing national and intercountry symposia/workshops, etc., on containment and prevention of AIDS;

(b) Providing specific technical consultancies;

(c) Promoting the development of national and regional laboratories for screening for LAV/HTLV-III infection and confirmation of results, providing training and follow-up in developing national/regional capabilities in:

- clinical diagnosis;
- laboratory diagnosis;
- applicable public health control measures;

(d) Establishing a mechanism to assist countries in obtaining the necessary material and equipment to establish laboratory diagnosis and epidemiological surveillance of AIDS.

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[1] The mechanism has still to be established.

Advice to Member States on the provision of safe blood and blood products

29. Several specific recommendations were made by the WHO group which met in November 1983, at which point the etiologic agent of AIDS had not yet been discovered.[1] Those recommendations remain valid even though additional measures to increase the safety of blood and blood products are now possible:

- educate the public and donors about AIDS;

- exclude donors who belong to high-risk groups;

- avoid non-essential use of blood and blood products.

30. In addition, the 1983 WHO meeting stated that, based on the information available at that time, albumin and immunoglobulin products are considered safe, as are hepatitis B vaccines which meet the WHO Requirements. Since then over 190 cases of blood-related AIDS have occurred in the USA and Europe. The identification of the LAV/HTLV-III virus in 1983/1984 led to the rapid development of screening tests for antibody to the virus, and the use of such tests has enabled blood collecting facilities to eliminate units of blood with antibody and which carry a risk of transmitting the LAV/HTLV-III virus. Initial results of screening in the USA showed that about 0.25% are positive in the screening test, but that when additional testing is done (such as the Western blot test), only about a quarter can be confirmed to have antibody to the virus.

31. Screening does, therefore, raise important issues relating to the use of "confirmatory tests" and the quality of data that should be available before donors are notified about test results.

32. In addition to screening donors for antibody to the AIDS virus, the introduction of appropriate heat treatment in the production of factors VIII and IX has apparently eliminated the risk of transmitting AIDS through those products, and the WHO consultants who met in April 1985 recommended the use of such products as a means of controlling the spread of AIDS in haemophilia patients.

33. That group also recommended that:

- where feasible, donors should be screened for antibody;

- antibody-positive units should not be used;

- donors should be informed about the screening in advance of donating;

- donor education and exclusion of high-risk groups should be continued.

34. WHO is convening a meeting in Geneva from 14 to 16 April 1986 to review data on donor screening and product safety. In addition, there will be discussions on issues related to donor screening such as confirmatory tests and donor notification.

35. Following the conference, a smaller group of experts will meet to develop an updated set of WHO recommendations. A group of experts will meet in Geneva in December 1985 to plan the April 1986 conference.

36. Although AIDS has become an increasingly important problem, it should not obscure the fact that other infectious agents which can be transmitted by blood are also of significance. Most important among those are the human T-cell leukaemia agent, HTLV-I, and non-A, non-B hepatitis virus.

37. It is especially important, in view of the potential for transmitting infectious agents through blood, that re-use of unsterile needles be strongly discouraged. Limited epidemiological studies and extensive experience with the use of jet-injection guns for mass

[1] Bulletin of the World Health Organization, 62(3): 419-432 (1984).

inoculation in many millions of individuals over more than 20 years indicate that the transmission of parasitic, mycotic, bacterial and viral diseases, including hepatitis B and hepatitis non-A, non-B, from human to human by this means has not been confirmed. However, limited laboratory studies evaluating the risk of transmission from different types of jet injectors are at present under way. It is anticipated that WHO will support more extensive research studies in this area.

Coordination of research

Antiviral agents

38. Major efforts are under way to develop therapeutic modalities for AIDS and ARC patients. Reverse transcriptase, which is unique for retroviruses and does not appear to be a constituent of normal host cells, offers an excellent target for antiviral agents. This was the rationale for selecting some of the agents currently under study. Suramin, HPA 23 and ribavirin have all been reported to inhibit viral replication in patients. However, the virus has reappeared when medication was stopped. This is probably due to the incorporation of the viral genome in host cells and may present a problem in eradication of the virus with antiviral agents. Maintenance treatment for extended periods may be required after viral replication ceases.

39. Other agents under study include azidothymidine and foscarnet. To date very few patients have been treated with azidothymidine but preliminary results are encouraging. To date no clinical benefit has been observed in patients treated with any therapeutic agent, other than temporary cessation of viral replication. Interferon has proven somewhat effective in control of Kaposi's sarcoma and studies are proceeding in AIDS patients at increased dosages.

40. Candidate drugs require careful study within the framework of classical drug evaluation and under the guidelines of national control authorities. Once a candidate agent is identified and preclinical studies indicate safety, studies to determine the pharmacology, toxicity and tolerated dosages must precede studies to determine benefit. Anecdotal studies claiming benefit for drugs without evidence of statistically proven efficacy do considerable harm to the patients by creating false hope and to therapeutic trials in general.

41. If at all possible, placebo-controlled studies in ARC patients should be encouraged. Such studies will yield an answer on the efficacy of a drug more quickly and in fewer patients than the use of historic controls.

42. WHO, through its network of collaborating centres, can play an important role in keeping close watch on developments in the area of antivirals and act as coordinator of collaborative action and/or clearing-house for information.

Vaccine development

43. The most effective way of controlling an infectious disease is through prevention. The classical method of prevention is through the use of vaccines. Multiple approaches to LAV/HTLV-III vaccine development are currently under way, and include the purification of selected envelope components from disrupted virus and the production of envelope proteins by recombinant nucleic acid technology. No attempts are being made to develop live attenuated or whole virus inactivated vaccines. These preparations would contain viral nucleic acid and the potential for nucleic acid to integrate into cell DNA, switch on cellular transforming genes, or recombine to generate new transforming viruses cannot be excluded.

44. One important issue involves the matter of viral heterogeneity. Considering the diversity of membrane antigen configurations in various viral isolates, it will be necessary to determine if immunization with a given preparation is capable of evoking antibodies protective against all virus variants.

45. As research on vaccine development is being pursued, efforts are being made to improve the methods available for vaccine evaluation. These include developing better assays for virus neutralization and developing the most appropriate animal models. Work in all of these areas is proceeding rapidly and data should be available for presentation and discussion in the coming months.

46. As with antivirals, WHO can play a major role in coordinating collaborative action on vaccines as well as serving as a clearing-house for information.

T-lymphotropic retroviruses of simians

47. T-lymphotropic retroviruses of simians have been described which show some antigenic relationships with LAV/HTLV-III viruses of human origin.[1] These agents provide potentially valuable models for the study of control and treatment of AIDS.

Programme structure

48. Several divisions in WHO headquarters, Geneva, and corresponding structures in the regional offices take an active part in the programme; the overall coordination is provided by the Division of Communicable Diseases at headquarters. The Secretariat will be strengthened to cope with the increasing requirements of the WHO programme on AIDS in 1986-1987.

[1] Weekly epidemiological record, 35: 269-270 (1985).

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