The acquired immune deficiency syndrome (AIDS) is a contagious viral disease with a very high fatality rate. Since the beginning of the AIDS epidemic in 1981 prevalence has increased exponentially, with a doubling time of 6–12 months. Around 18 000 cases have been reported, mostly from the industrialized countries, the highest prevalence being in the United States. By September 1985 a total of 1573 cases detected in Europe had been reported to the WHO collaborating centre on AIDS in Paris.

In the light of this problem, an International Conference on AIDS was organized in Atlanta, Georgia, USA with more than 3000 participants from 50 countries. Following this conference the WHO Regional Office for Europe convened a Consultation on AIDS Policies in Europe with the specific intention of formulating a policy on AIDS control in the European Region. One of the recommendations of that consultation was the preparation of guidelines for national public health authorities, providing them with a brief introduction to the problem and to the public health measures that can be taken to reduce the spread of infection.

These guidelines cover the magnitude of the problem in Europe, the virus and its mode of transmission, the major clinical features of the disease, laboratory tests, possibilities of treatment and prophylaxis, the role of blood and blood products, the public health importance of the disease, and control measures. This booklet is essential reading for anyone who needs to become quickly acquainted with the overall AIDS situation in Europe at the present time.

World Health Organization
Regional Office for Europe
Copenhagen

Guidelines on AIDS in Europe

First revised edition

The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this Organization, which was created in 1948, the health professions of some 160 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health problems of the countries it serves. The European Region has 33 active Member States,[a] and is unique in that a large proportion of them are industrialized countries with highly advanced medical services. The European programme therefore differs from those of other regions in concentrating on the problems associated with industrial society. In its strategy for attaining the goal of "health for all by the year 2000" the Regional Office is arranging its activities in three main areas: promotion of lifestyles conducive to health; reduction of preventable conditions; and provision of care that is adequate, accessible and acceptable to all.

The Region is also characterized by the large number of languages spoken by its peoples, and the resulting difficulties in disseminating information to all who may need it. The Regional Office publishes in four languages — English, French, German and Russian — and applications for rights of translation into other languages are most welcome.

[a] Albania, Austria, Belgium, Bulgaria, Czechoslovakia, Denmark, Finland, France, German Democratic Republic, Federal Republic of Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Morocco, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Spain, Sweden, Switzerland, Turkey, USSR, United Kingdom and Yugoslavia.

World Health Organization
Regional Office for Europe
Copenhagen

Guidelines on AIDS in Europe

First revised edition

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The guidelines on AIDS contained in this book were drafted by Dr H. Zoffmann, Statens Seruminstitut, Copenhagen, Denmark and amended and approved by the participants in the Consultation on AIDS Policies in Europe (see Annex 5). This first revision incorporates data up to 30 September 1985.

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FOREWORD

The etiological agent of the acquired immune deficiency syndrome (AIDS), at present threatening the health of the European population, has only recently been identified independently by Dr Luc Montagnier (Institut Pasteur, Paris) and then by Dr Robert Gallo (National Institutes of Health, United States). AIDS is caused by a retrovirus, termed lymphadenopathy-associated virus (Montagnier) or human T lymphotropic virus type III (Gallo). The name has yet to be finalized by the International Committee on Taxonomy of Viruses.

The origin of this virus is not yet clearly understood. The number of registered AIDS cases in the European Region at present is approaching 1600 and the epidemiological situation is disturbing; experts have estimated that about 100 000 Europeans may already be infected with the virus.

The following facts about the disease indicate the need for immediate joint action directed at the protection of the European population.

1. The case fatality rate is high, at least 50% of patients dying within a year of diagnosis.

2. The number of new cases is rapidly increasing, doubling every 6-12 months.

3. Known therapy is not effective.

4. Chemoprophylactic means are not available.

5. The development of an effective vaccine will probably take several years at least.

6. The long incubation period (up to six years, perhaps more) makes diagnosis difficult at the initial stage of the disease and makes the surveillance of the spread of infection difficult and uncertain.

7. Asymptomatic infection may persist for years.

8. The majority of European countries are as yet insufficiently equipped with reagents for specific serological tests for use in screening.

To formulate a Regional Office policy on AIDS control in the European Region, a Consultation on AIDS Policies in Europe took place in Atlanta, United States, on 19 April 1985, immediately after the International Conference on AIDS (14–17 April) and the WHO Global Consultation on AIDS (18 April). As a result of this meeting, five main activities were suggested.

1. The preparation of Regional Office guidelines on AIDS for public health authorities in Member States. These guidelines are presented herewith.

2. An appeal by the Regional Office to national counterparts for communicable diseases to direct the attention of national health authorities to the seriousness of the AIDS epidemic and to the appropriate control measures. This appeal has been made.

3. Strengthening of AIDS surveillance in the European Region through closer cooperation and collaboration of national institutions with the WHO collaborating centre for AIDS in Paris. Special appeals were made at the thirty-fifth session of the WHO Regional Committee for Europe in September 1985, following a circular letter on 30 May from the collaborating centre to all national counterparts for communicable diseases. A third appeal for all Member States of the European Region to join the surveillance programme has now been made.

4. The designation of new collaborating centres for virology and serology of AIDS in the Region. These would maintain reference reagents for LAV/HTLV-III antibody tests, provide laboratory training of staff to undertake these tests, provide reference facilities for positive sera, and coordinate the evaluation of antibody tests. Such centres have been or are being designated in Belgium, France, the Federal Republic of Germany, Greece, Hungary, Sweden, the USSR and the United Kingdom.

5. The designation of national collaborating institutions and of an individual (or office) responsible for AIDS surveillance and control. The Regional Office has launched appeals to the Member States to this effect.

Although progress in the control of AIDS greatly depends on the further development of basic research on virology, immunology and pharmacology, assertive public health measures are urgently required. It is hoped that these public-health-oriented guidelines will be useful for national health authorities and medically

qualified personnel in their efforts to prevent the further spread of AIDS in the European Region through currently available conventional measures.

J.E. Asvall
WHO Regional Director for Europe

Introduction

The acquired immune deficiency syndrome (AIDS) is a contagious viral disease with a very high fatality rate. AIDS was first recognized in 1981 in the United States and Europe, since when its incidence has risen rapidly, and cases are seen in many countries of the world. Nearly 18 000 cases have been reported, mostly from the industrialized countries, the highest prevalence being in the United States.

An International Conference on 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 Global Consultation on AIDS, organized by WHO on 18–19 April, where the participants reviewed the information presented at the conference and assessed its international health implications.[a]

In addition, a Consultation on AIDS Policies in Europe was held on 19 April to consider aspects of specific relevance to the European Region of WHO. This consultation recommended that the WHO Regional Office for Europe should prepare AIDS guidelines for Member States, specially designed for those not yet directly affected by the epidemic. The aim of these guidelines is to give a brief introduction to the AIDS problem and to the public health measures that can be taken to reduce the spread of infection.

Magnitude of the AIDS problem

Europe

Since the beginning of the AIDS epidemic in 1981, prevalence has increased exponentially, with a doubling time of 6–12 months. By September 1985, a total of 1573 cases had been reported to the WHO collaborating centre for AIDS in Paris (see Annex 1). Of these, 92% were in males and 42% were in the age group 30–39 years.

In the first half of 1985, an average of 27 new cases per week were reported to the collaborating centre. The recorded incidence of AIDS varies considerably among countries. The number of cases reported in 21 European countries and estimated rates per million

[a] The worldwide health implications of AIDS, as discussed at the Global Consultation, are described in Bulletin of the World Health Organization, 63: 667–672 (1985).

population are shown in Table 1. The highest rates were in Belgium, Denmark and Switzerland. Some 72% of the Belgian cases and 12% of the Swiss cases were in patients from Equatorial Africa, in contrast to Denmark where no African or Caribbean cases were reported. For comparison, the rate in the United States was 48.4 per million population in June 1985.

Table 1. Total number of AIDS cases reported in 21 European countries and estimated rates per million population[a]

Country	Number of cases				Rate
	October 1984	March 1984	June 1985	September 1985	
Austria	–	13	18	23	3.1
Belgium	–	81	99	118	11.9
Czechoslovakia	0	0	0	0	–
Denmark	31	41	48	57	11.2
Finland	4	5	6	10	2.0
France	221	307	392	466	8.5
Germany, Federal Republic of	110	162	220	295	4.8
Greece	2	7	9	10	1.0
Hungary	–	–	–	0	–
Iceland	0	0	0	0	–
Italy	10	22	52	92	1.6
Luxembourg	–	–	1	3	7.5
Netherlands	26	52	66	83	5.7
Norway	4	8	11	14	3.3
Poland	0	0	0	0	–
Spain	18	29	38	63	1.6
Sweden	12	22	27	36	4.3
Switzerland	33	51	63	77	11.8
USSR	–	–	–	0	–
United Kingdom	88	140	176	225	4.0
Yugoslavia	–	–	–	1	–
Total	559	940	1226	1573	

[a] Based on 1985 populations.

The distribution by patient risk group is shown in Table 2; 69% of cases were in male homosexuals or bisexuals. Compared to the distribution in the United States, few AIDS cases (6%) were recorded in intravenous drug abusers. Nevertheless, serological surveys have shown that LAV/HTLV-III infection is now spreading among intravenous drug abusers in some European countries. Some 3% of the cases were in haemophiliacs, and for 2% the only risk factor found was blood transfusion. Some of these patients had received transfusion overseas in Haiti and Martinique, the United States and Zaire. Seven per cent of cases were in people with no known risk factors; in this group, the male:female ratio was about 2:1.

Table 2. AIDS cases by patient risk group and geographic origin for 21 European countries,[a] 30 September 1985

Patient risk group	Origin				Total	
	Europe	Caribbean Islands	Africa	Other	Number	%
Male homosexuals or bisexuals	1031	4	11	39	1085	69
Intravenous drug abusers	90				90	6
Haemophiliacs	52			1	53	3
Transfusion recipients (without other risk factors)	30		5		35	2
Both homosexuals/ bisexuals and intravenous drug abusers	21		1	2	24	2
No known risk factor						
males	59	24	81	3	167	11
females	31	10	43		84	5
No information	16	1	16	2	35	2
Total	1330 (85%)	39 (2%)	157 (10%)	47 (3%)	1573	100

[a] Austria, Belgium, Czechoslovakia, Denmark, Finland, France, Federal Republic of Germany, Greece, Hungary, Iceland, Italy, Luxembourg, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, USSR, United Kingdom, Yugoslavia.

Surveillance

During the spring of 1984, a WHO collaborating centre for AIDS was established in Paris.[a] The functions of the centre are:

- to collate and consolidate information on the number of cases of AIDS in Europe and in other areas of the world, based on national reports;
- to present this information by epidemiological characteristics, risk groups and diagnostic categories;
- to ensure rapid exchange of information by publication at regular intervals of an information bulletin (this could also include information on current research or other pertinent data, with the particular purpose of indicating to research workers the types of studies being performed in the different institutions, thus avoiding duplication);
- to provide information about the possibilities of international collaborative studies, provision of reagents, exchange of material, important publications, and meetings on AIDS;
- to advise WHO on all relevant facts and progress on AIDS research.

To ensure simple and uniform reporting, the centre sends standard record forms to cooperating countries each quarter. In October 1985, 21 of the 33 countries in the WHO European Region were reporting to the centre.

At the Consultation on AIDS Policies in Europe, the value of the work of the collaborating centre was acknowledged, and it was recommended that the Regional Office should encourage all countries in the European Region to report to the centre.

In most countries, the reporting of AIDS cases is based on voluntary notification to the national health authorities. In a few countries, notification is compulsory. The consultation further recommended that the Regional Office should encourage the designation of national institutions for AIDS surveillance in all countries.

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United States of America

By 29 July 1985, 12 067 AIDS cases, involving 11 919 adults and 148 children, had been reported to the Centres for Disease Control (CDC) in Atlanta. Some 73% of the cases were in homosexual or bisexual men, 17% in intravenous drug abusers, 1.5% in blood transfusion recipients, 1% in haemophiliacs, 1% in heterosexual contacts of AIDS victims or carriers, and 6.5% in individuals with no known risk factors (1).

Recently, CDC published estimates of AIDS prevalence in certain high-risk groups, showing rates of 175–205 per 100 000 single men living in Manhattan, New York and San Francisco, and rates of between 200 and 270 among intravenous drug abusers in New York City and New Jersey. Prevalence among patients with severe haemophilia is estimated at 300 per 100 000 (2).

Other countries and regions

In Canada, 248 cases had been reported by 14 June 1985. The distribution by sex, age and risk group is similar to that reported from the United States.

In the Caribbean area, most cases are registered in Haiti, 340 having been reported by 31 December 1984. AIDS prevalence in Haiti is 60 per million population, which is the highest rate reported anywhere in the world. Compared to Europe and the United States, cases in females account for a significantly higher proportion, and heterosexual activity may be an important factor in the transmission of AIDS in Haiti.

In South America, 226 cases have been registered in 10 countries, including 182 cases reported from Brazil.

In Africa, cases of AIDS have been reported from several countries in the central part of the continent. Congo and Zaire have recently been identified as having a high incidence of AIDS. Contrary to both Europe and the United States, the male:female ratio is nearly 1:1, and the virus is widely spread in the community. Heterosexual activity seems to play an important role in the transmission of the virus. According to recent epidemiological data, the use of contaminated needles and syringes in health care facilities may also be a major factor in transmission.

No information is available from most countries in Asia, although six cases have been reported from Japan.

In Australia, 67 cases had been reported by March 1985. The distribution of cases by risk group resembles that reported from the United States.

The virus (see also Annex 2)

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

The virus has a specific tendency to infect a subset (OK T4+) of the T lymphocytes and has been shown to be present in brain tissue. The virus replicates in actively dividing T4 lymphocytes and, like other retroviruses, can remain in lymphoid cells in a latent, unexpressed state that can be activated. The virus is prone to mutation, and in particular the protein antigens of the envelope keep changing, which may create problems for the development of an effective vaccine.

LAV/HTLV-III is heat-sensitive. 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.

Mode of transmission

LAV/HTLV-III has been isolated from human blood, saliva and semen. Epidemiological data indicate that LAV/HTLV-III infection in humans is transmitted during intimate sexual contact and by blood and blood products. The infection may be transmitted from infected pregnant women to their children.

In the United States, cases of AIDS in individuals with no known risk factors have constituted a small and rather constant proportion of the total number of cases throughout the years, indicating a slight spread of AIDS from the risk groups to the general population. This also seems to be the case in Europe, where the proportion of indigenous AIDS cases in individuals with no known risk factors has been consistently low. Nevertheless, the spread of

LAV/HTLV-III infection outside risk groups has begun in both Europe and the United States.

In Africa, epidemiological information obtained recently suggests that exposure to contaminated needles and syringes in health care facilities may play a role in the transmission of LAV/HTLV-III infection. This may also apply to Haiti.

There is no evidence of LAV/HTLV-III transmission by casual social contact or by sneezing, coughing or the sharing of meals.

There is concern over the occupational risk for health care workers taking care of AIDS patients or handling specimens from them, but the additional risk is low (3). The virus can be transmitted by accidental needlestick injury (4). As at 26 September 1985, only one confirmed and two possible cases of transmission to health care personnel had been observed worldwide; these were caused by needlestick injury with contaminated needles (5). A few cases have been reported in health care workers with no known risk factor for acquiring AIDS, but there is no evidence that these were caused by exposure to AIDS patients.

Infection and major clinical features

The natural history of LAV/HTLV-III infection is still unknown. It is assumed that the infection in many cases will remain subclinical. Some infected individuals will develop transient or intermittent symptoms, and others will develop chronic lymphadenopathy with or without other symptoms, such as weight loss, diarrhoea and fever. It is estimated that 100 000 individuals in Europe and 0.5-1 million in the United States are infected with LAV/HTLV-III. How many of these will develop AIDS is unknown, but rates of between 5% and 20% have been reported.

The basic abnormality caused by LAV/HTLV-III infection is an impairment of the cellular immune response followed by a decrease of resistance to various infections, many of which are opportunistic, and/or the development of certain types of cancer.

According to the CDC surveillance definition (6), which has been adopted internationally, AIDS is:

- histologically verified Kaposi's sarcoma in individuals under the age of 60 years; or
- life-threatening or fatal opportunistic infections indicating cellular immune defect in individuals where no underlying cause of immune defect can be established.

CDC has recently adopted a revised case definition of AIDS for reporting purposes (Annex 4). The most important amendment to the definition is the introduction of laboratory testing for LAV/HTLV-III infection and for reduced cellular immunity, so that negative results on testing will lead to the exclusion of such patients suffering from AIDS. In the absence of test results, patients satisfying the above-mentioned clinical criteria will continue to be included. The clinical features of AIDS in Europe and the United States are similar.

In countries where appropriate diagnostic techniques are available, the surveillance definition for AIDS given by the Centers for Disease Control and published by WHO (7) was endorsed by participants at a recent meeting of the WHO collaborating centres on AIDS on 24-26 September 1985. Surveillance definitions are now being developed for use in countries where access to diagnostic techniques is limited.

Based on a report from the WHO collaborating centre in Paris (Annex 1), 65% of the recorded AIDS patients in Europe suffered from opportunistic infections alone, 20% from Kaposi's sarcoma and 13% from both.

A number of other symptoms have been considered as prodromal stages of AIDS. These include more or less chronic lymphadenopathy, excessive weight loss, fever and diarrhoea. These various clinical conditions have been termed lymphadenopathy syndrome (LAS) or AIDS-related complex (ARC). Some patients with LAS/ARC subsequently develop AIDS, but the exact proportion is unknown.

In infants, the clinical manifestations of LAV/HTLV-III infection resemble those seen in adults, although diarrhoea may be a more prominent symptom. Suspicion of AIDS in infants should be raised when one of the parents belongs to a risk group for AIDS, and either the mother or the infant has serological evidence of LAV/HTLV-III infection.

Mortality and case fatality

The case fatality rate in AIDS is very high. Over 50% of AIDS patients die within a year after diagnosis has been confirmed, and a further 30% within the next 2-3 years. The fatality rate is related to the symptoms: 56% in those with opportunistic infection, 25% in those with Kaposi's sarcoma, and 59% in those with both. In certain high-risk groups in the United States, the risk of dying from AIDS is estimated as similar to that from heart disease or cancer (2).

Laboratory tests

Demonstration of a reduced T-cell immune response is important to the diagnosis, since the majority of AIDS patients have a low number of T-helper cells. A decreased ratio of T-helper to T-suppressor cells may be an indirect indicator of reduced cellular immunity.

Tests for antibody against LAV/HTLV-III have recently been made commercially available. Demonstration of LAV/HTLV-III antibody gives strong support to the establishment of the diagnosis, since most AIDS patients and nearly all with LAS/ARC are antibody-positive.

Demonstration of antibody against LAV/HTLV-III is considered a specific and sensitive test for infectivity, since LAV/HTLV-III has been isolated from most of the antibody-positive individuals studied. Nevertheless, the correlation between infectivity and presence of antibody is not absolute. There is a low frequency of both false positive and false negative test results, and LAV/HTLV-III has been isolated from antibody-negative persons. A test for viral antigen, which might be more valuable than a test for infectivity, is being developed; it is unknown whether such tests will be more specific or sensitive than the currently available tests for antibody against LAV/HTLV-III.

A variety of assays are available for detecting 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 IF. Both can be performed in most diagnostic laboratories, require relatively simple equipment, and can be carried out in two working days. Serum that is repeatedly positive by ELISA or IF should be tested by an additional method before the final diagnosis is made. The additional method might comprise:

- a repeat of the same type of assay (ELISA or IF) but with reagents obtained from a different manufacturer;
- demonstration that serum is positive with the test antigen but not with a control antigen prepared from uninfected cells;
- the use of techniques that detect antibody against one or more structural components of the virus, e.g. radioimmunoprecipitation that detects antibody to the p-24 protein, 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 laboratory personnel are adequately trained to carry out these tests and that centres are available for performing any additional testing necessary. The Consultation on AIDS Policies in Europe recommended that WHO should establish collaborating centres for the virology and immunology of AIDS. These centres[a] should also be active in organizing regional training courses for laboratory personnel in relevant laboratory techniques.

Treatment

Specific antiviral treatment

Attempts have recently been made to develop drugs for treating LAV/HTLV-III infection (inverse transcriptase inhibitors, cell receptor blockers). The efficacy of these drugs in man is unproven. Studies are currently being carried out on small numbers of patients. Randomized controlled studies of the efficacy of these drugs on a multicentre and eventually international basis should be encouraged.

Treatment of the cellular immune defect

Many substances have been tried, e.g. interferon and immunomodulating drugs, but until now none has proved effective.

Treatment of opportunistic infections and AIDS-associated tumours

Treatment of patients suffering from the various symptoms of AIDS should be aimed especially at opportunistic infections. Clinicians taking care of AIDS patients should become familiar with the symptoms of these infections as they appear in AIDS patients and with laboratory procedures used in verification of the diagnosis. Many of these infections can be diagnosed only by an aggressive approach using invasive methods to obtain specimens suitable for microbiological and histopathological investigation, e.g. biopsies, endoscopies and extirpation of lymph nodes. To exclude underlying disease, the diagnostic procedures may also be extensive.

[a] Eleven such centres have been or are being designated in eight countries (Belgium, France, Federal Republic of Germany, Greece, Hungary, Sweden, USSR, United Kingdom).

For this reason, in countries where AIDS is infrequent, patients with suspected AIDS should be admitted to centres where the clinicians can get sufficient experience of the diagnostic procedures and of treating the various opportunistic infections. This may also be important because of the psychosocial problems related to AIDS.

Blood and blood products

LAV/HTLV-III infection can be transmitted by transfusion of whole blood, blood cells, platelets and factors VIII and IX derived from human plasma. There is no documentary evidence that transmission ever occurred 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 median interval between transfusion of blood containing LAV/HTLV-III and the diagnosis of AIDS in the recipient may be four years or longer in adults. Transmission of infection to haemophiliacs can be reduced by introducing heat treatment of factors VIII and IX.

Public health importance of AIDS

AIDS is a contagious disease. The AIDS virus, LAV/HTLV-III, is transmitted through sexual contact, by blood and blood products and from the pregnant mother to her child. In Europe, the virus has mainly been transmitted through intimate contact among male homosexuals and among intravenous drug abusers sharing needles and syringes. Heterosexual transmission is not yet a common feature of the spread of LAV/HTLV-III in Europe.

It is estimated that 100 000 people in Europe are infected with LAV/HTLV-III. The natural history of infection is unknown but is assumed to be long-lasting, perhaps for life. It is unknown how large a proportion of those infected will subsequently develop AIDS; between 5% and 20% has been reported. It is likely that the incidence of AIDS in infected individuals will increase further with time.

It is obvious that this contagious disease with a high fatality rate and an increasing incidence, together with the large number of LAV/HTLV-III-infected individuals who are potential AIDS patients, poses major problems for public health authorities. In many countries already involved, fear of AIDS in the community has generated a measure of panic and created a demand for emergency

measures. Furthermore, in countries such as those in Europe, the diagnostic and patient care procedures will be comprehensive and, consequently, costly. Thus, in countries where LAV/HTLV-III infection is spreading, AIDS may have a marked impact on the health economy. It has been estimated that in the United States the total cost so far of control measures and the treatment of AIDS patients has surpassed US $1500 million.

One of the most important public health questions in Europe today is which measures are appropriate to curb the spread of the virus. From an overall point of view, the spread of LAV/HTLV-III is still limited to certain risk groups, but future spread to the general community cannot be excluded. A two-part control strategy should be implemented: measures to reduce the spread of LAV/HTLV-III within the risk groups, and from the risk groups to the general population.

Control measures

The most effective control measures will be somewhat different from country to country, depending on cultural and administrative traditions. They will, however, involve health information, health education and health legislation.

The most important means at present available of limiting the spread of infection within risk groups and to the community at large is the provision of information about the infection and the disease, probable routes of transmission, and possible ways and means of reducing the risk of infection. This information should be widely disseminated in the community and in groups at increased risk of infection, and should be provided in layman's language.

Information given to the public should be balanced and flexible, based on what is currently known about the spread of LAV/HTLV-III in particular countries. It should be stressed that there is no evidence of spread by casual social contact with infected persons, even within households, or by food, and that there is no evidence of spread to health care workers who do not themselves belong to a risk group.

Some of the following measures may be applicable in only some countries of the European Region; they should therefore be taken as examples only.

Preventing the spread of infection in groups with increased risk of infection

Homosexual and bisexual men should be informed about measures to reduce the risk of infection with LAV/HTLV-III. This information should be prepared and disseminated by the national health authorities in collaboration with the male homosexual community.[a] Special attention should be drawn to the fact that avoidance of multiple sexual partners is the most effective way of reducing the risk of LAV/HTLV-III infection. Although the protective efficacy has yet to be demonstrated, risk of infection may be reduced by the use of condoms. Although oral-anal and oral-genital contact and open-mouth kissing have not been shown to be as risky as anal intercourse, infection may spread by these means and their avoidance should be advised. The same considerations apply to the sharing of toothbrushes, shavers and similar personal articles. Intravenous drug abusers should be informed that the sharing of needles and syringes involves a special risk of LAV/HTLV-III infection.

People in high-risk groups should be urged to refrain from donating blood, plasma, body organs, other tissues or sperm.

Preventing the spread of infection from those known to be positive to anti-LAV/HTLV-III

Testing of healthy individuals for anti-LAV/HTLV-III should be done only after informed consent has been obtained. Individuals who have been tested for anti-LAV/HTLV-III on their own initiative and found positive should be offered individual counselling and psychosocial support. They should be informed that they are infectious through sexual contact and through their blood and semen. They should be encouraged to inform their sexual partner(s) about the risk. Sexual practices involving contact between mucous membranes and between semen and mucous membranes should be avoided. They should be urged to refrain from donating blood, plasma, body organs, other tissues or sperm. Personal articles such as shavers and toothbrushes should not be shared. When using health care facilities, they should make it known that they are positive to anti-LAV/HTLV-III.

Occupational restrictions on persons demonstrated to be positive to anti-LAV/HTLV-III seem unjustified.

[a] Information in English on the so-called "Safe Sex" campaigns may be requested from the health authorities in the United Kingdom and the United States.

Preventing the spread of LAV/HTLV-III in blood and blood products

Four means of control should be followed. First, the health authorities should appeal to individuals in high-risk groups to refrain from donating blood and plasma. This appeal should be disseminated in all possible ways and on all relevant occasions.

Second, where possible, blood donors should be organized in an attempt to establish a stable, voluntary corps of well informed and motivated donors. Expansion of donor activities in an attempt to be self-sufficient in blood should not include the use of blood taken in more casual settings, such as at places of work and during campaigns.

Third, screening of all donated blood and plasma for LAV/HTLV-III antibody should be considered. The feasibility of this measure should take account of local conditions, such as the level of LAV/HTLV-III infection in the population, the size of risk groups, the degree of organization of blood donors, and the financial resources available. Screening of blood should not begin before centres for further testing of blood positive for anti-LAV/HTLV-III have been established. Furthermore, to avoid individuals at risk donating blood simply to find out whether they are infected, antibody testing should be readily available in facilities separate from the blood donor service.

Fourth, European countries should be self-sufficient in blood and blood products. Risk of transmission of the virus may be substantially reduced by heat treatment of factors VIII and IX.

Preventing the spread of infection from identified risk groups to the community by routes other than blood and blood products

Information given to the public might mention that sexual contact between women and bisexual males and male intravenous drug abusers, and contact between men and female prostitutes, may pose a risk of infection with LAV/HTLV-III. The use of condoms should be encouraged.

Preventing the spread of infection to hospital staff and other health care workers

Evidence has accumulated that measures taken to avoid the transmission of hepatitis B virus are sufficient to protect staff against LAV/HTLV-III infection. Inadvertent needlestick exposure to LAV/HTLV-III-contaminated blood may, however, be a hazard for health care workers.

Specific prophylaxis

Passive immunization

Injection of immunoglobulin has so far not proved to be of any value in protecting against infection with LAV/HTLV-III.

Active immunization (vaccination)

An effective vaccine will be the ultimate solution to the problem of protection against infection with LAV/HTLV-III. Such a vaccine is not yet within sight, but the first step on the road to an immunological solution to the AIDS problem has been taken by isolating the causative agent. Many difficulties are foreseen, and a generally available effective vaccine is not expected to be licensed within the next five years. In any case, vaccination of people with pre-existing infection is unlikely to be effective. Amelioration or prevention of the clinical effects of infection by vaccination is also unlikely.

Chemoprophylaxis

This is a new field based on the specific natural history of LAV/HTLV-III infection. Whether it will succeed is as yet unknown.

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Annex 1

AIDS SURVEILLANCE IN EUROPE: situation at 30 September 1985

Report No. 7 from the WHO collaborating centre for AIDS, Paris

By 30 September 1985, 21 countries were taking part in the surveillance of AIDS in Europe by reporting their data to the centre. Since the previous report on 30 June 1985, three countries (Hungary, the USSR and Yugoslavia) have begun collaborating with the centre.

The sources of data in these countries are:

Austria	Federal Ministry of Health and Environmental Protection, Vienna
Belgium	Conseil supérieur de l'Hygiène publique, Ministère de la Santé, Brussels
Czechoslovakia	Institute of Virology, Bratislava
Denmark	Statens Seruminstitut, Copenhagen
Finland	Institute of Biomedical Sciences, Tampere
France	Direction générale de la Santé, Paris
Germany, Federal Republic of	Robert Koch Institute, Berlin (West)
Greece	Ministry of Health, Athens
Hungary	National Institute of Hygiene, Budapest
Iceland	General Direction of Public Health, Reykjavik
Italy	Istituto Superiore di Sanità, Rome
Luxembourg	Ministère de la Santé, Luxembourg
Netherlands	Staatstoezicht op de Volksgezondheid, Leidschendam
Norway	National Institute of Public Health, Oslo
Poland	National Institute of Hygiene, Warsaw
Spain	Ministerio de Sanidad y Consumo, Madrid
Sweden	National Bacteriological Laboratory, Stockholm
Switzerland	Office fédérale de la Santé publique, Berne
USSR	Ministry of Public Health, Moscow
United Kingdom	Communicable Disease Surveillance Centre, London
Yugoslavia	Federal Institute of Public Health, Belgrade

The collaborating centre uses the case definition of the Centers for Disease Control (CDC) in the United States. One source per country, recognized by the national health authorities, provides the information. The national data are noted on standard tables, and each source is responsible for the quality of the data provided.

The situation by 30 September 1985 (see Table 1 of the guidelines, p. 3)

A total of 1573 cases of AIDS have been reported to the centre; 347 new cases had been declared since 30 June by the 18 countries corresponding with the centre at that time,[a] i.e. an average of 27 new cases per week.

The greatest increases in the total number of cases were observed in the Federal Republic of Germany (75), France (74), the United Kingdom (49) and Italy (40). In four countries (Belgium, the Netherlands, Spain and Switzerland) an increase of 1-2 cases per week was noted. Of the 21 participating countries, five (Czechoslovakia, Hungary, Iceland, Poland and the USSR) have not declared any cases.

AIDS cases per million population were calculated from 1985 population estimates (Institut national d'Etudes démographiques, INED, Paris). The highest rates were noted in Switzerland (11.8), Denmark (11.2) and France (8.5). These are low compared with that in the United States (60).[b] The situation in Belgium is unusual, since 72% of the cases originate from Africa.

In Europe, the number of cases notified by the 15 countries collaborating with the centre on 15 October 1984 (Czechoslovakia, Denmark, Finland, France, the Federal Republic of Germany, Greece, Iceland, Italy, the Netherlands, Norway, Poland, Spain, Sweden, Switzerland and the United Kingdom) had increased from 559 cases at that time[c] to 1428 cases by 30 September 1985, an increase of nearly 160% in one year. The number of cases has doubled in these 15 countries in the last nine months.

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[a] Weekly epidemiological record, 60: 305-311 (1985).

[b] CDC AIDS activity: weekly surveillance report, 30 September 1985.

[c] Weekly epidemiological record, 60: 16-19 (1985).

Distribution of cases and deaths by disease category

These data are given in Table 1. The category "Other" (27 cases) includes four cases of progressive multifocal leukoencephalitis (Denmark 1, France 3); six cases of isolated cerebral lymphoma (France 3, Switzerland 1, United Kingdom 2); three Burkitt's lymphomas of the brain (Denmark 1, Federal Republic of Germany 2); seven non-Hodgkin's lymphomas (Federal Republic of Germany 4, Luxembourg 1, Norway 1, Switzerland 1); three B-cell lymphomas (Netherlands); and four unknown (Sweden).

Table 1. AIDS cases by disease category and number of deaths for 21 European countries,[a] 30 September 1985

Disease category	Cases		Number of deaths	Case fatality rate (%)
	Number	%		
Opportunistic infection	1025	65.2	575	56.1
Kaposi's sarcoma	309	19.6	77	24.9
Opportunistic infection and Kaposi's sarcoma	212	13.5	126	59.4
Other	27	1.7	14	51.9
Total	1573	100.0	792	50.3

[a] Austria, Belgium, Czechoslovakia, Denmark, Finland, France, Federal Republic of Germany, Greece, Hungary, Iceland, Italy, Luxembourg, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, USSR, United Kingdom, Yugoslavia.

Distribution by age and sex

The distribution of AIDS cases by age group and sex is shown in Table 2. Males accounted for 92% of the cases, and 42% of cases occurred in the age group 30-39 years. Among children under 15 years, 36 cases have been declared in 10 European countries (Table 3).

Table 2. AIDS cases by age group and sex for 21 European countries,[a] 30 September 1985

Age group	Sex		Total	
	Male	Female	Number	%
0-11 months	6	8	14	0.9
1-4 years	9	6	15	1.0
5-9 years	3	1	4	0.3
10-14 years	3	0	3	0.2
15-19 years	8	0	8	0.5
20-29 years	277	57	334	21.2
30-39 years	622	36	658	41.8
40-49 years	375	12	387	24.6
50-59 years	103	9	112	7.1
Over 60 years	21	4	25	1.6
Unknown	13	0	13	0.8
Total	1120	105	1226	100.0

[a] Austria, Belgium, Czechoslovakia, Denmark, Finland, France, Federal Republic of Germany, Greece, Hungary, Iceland, Italy, Luxembourg, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, USSR, United Kingdom, Yugoslavia.

Table 3. Paediatric cases[a] by risk group and country of diagnosis, 30 September 1985

Risk group	Country of diagnosis										Total
	AUS	BEL	FRA	DEU	ITA	NET	SPA	SWE	SWI	UNK	
Children of parents with AIDS or at risk of contracting AIDS	1	3	8	3	6		1		2		24
Haemophiliacs			2				2	1			5
Recipients of transfusion with blood or blood products			3			1				1	5
Unknown		2									2
Total	1	5	13	3	6	1	3	1	2	1	36

[a] Children under 15 years of age.

Distribution by geographic origin (see Table 2 of the guidelines, p. 4)

Cases of European[a] origin: 1330 (85%). Of these, 1228 patients were living in Europe before the onset of the first symptoms. Forty-two patients (3%) were living outside Europe: 13 in the United States, 12 in Zaire, three in Haiti, and one each in Bermuda, Brazil, Burundi, the Congo, Gabon, Ghana, Malaysia, Morocco, Nicaragua, South Africa, Togo and Venezuela; the country of residence was not specified for two patients.

[a] The word "European" refers to patients originating from one of the Member States of the WHO European Region.

Cases of Caribbean origin: 39 (2%). Of these, 37 patients were living in Europe before the onset of the first symptoms: 32 Haitians diagnosed in France, one in Belgium and one in Switzerland; one Dominican and one Jamaican living in the United Kingdom; and one of unspecified origin living in Switzerland. Two other Haitian patients diagnosed in France were living in Haiti.

Cases of African origin: 157 (10%). These cases were diagnosed in eight European countries and originated from 22 African countries (Table 4). Some 63% were from Zaire and 10% from the Congo. Among the remaining 20 countries, the number of cases varied from one to five. Eighty-six patients (55%) were living in Europe before the onset of the first symptoms; 66 were living in Africa and one in the United States. Two patients from Zaire, one from Burundi and one from Rwanda were living in other parts of the world.

Cases originating elsewhere: 47 (3%). Most of these patients originated from the American continent: 23 from the United States, four from Argentina, three from Brazil, and one each from Canada, Chile, Nicaragua, Peru and Uruguay. One patient originated from each of the following countries: Australia, Egypt, Israel, Lebanon, New Zealand, Pakistan, Thailand and Turkey; the origin of four others was unknown. Fourteen of these patients were not living in Europe before the onset of the first symptoms.

Distribution by risk group (see Table 2 of the guidelines, p. 4)

Of the 1330 European patients, 1031 (77.5%) were homosexuals or bisexuals.

Ninety patients (7%) were drug abusers and 21 (1.5%) both homosexuals and drug abusers. Of these 111 cases, 45 were diagnosed in Italy, 26 in Spain, 14 in the Federal Republic of Germany, 11 in France, seven in Switzerland, four in Austria, three in the United Kingdom and one in Sweden.

Of the 52 cases among haemophiliacs, 21 were diagnosed in the Federal Republic of Germany, 12 in Spain, nine in the United Kingdom, three in France, two in Sweden, and one each in Austria, Denmark, Greece, Italy and Norway. One haemophiliac from the Federal Republic of Germany was reported as being also a homosexual and a drug abuser.

Table 4. Distribution of AIDS cases in Africans by country of origin and country of diagnosis, 30 September 1985

Country of origin	Country of diagnosis								Total
	BEL	FIN	FRA	DEU	GRE	ITA	SWI	UNK	
Algeria			2						2
Angola			1						1
Burundi	4			1					5
Cameroon			2						2
Cape Verde			1						1
Central African Republic			3						3
Chad	1		1	1					3
Congo			13				2		15
Egypt			1						1
Gabon			3			1			4
Ghana				1				1	2
Kenya	1								1
Madagascar			1						1
Mali	1		2						3
Morocco	1								1
Rwanda	5								5
Senegal	1		1						2
Togo				1					1
Tunisia			1						1
Uganda								1	1
Zaire	71		21				7		99
Zambia		1			1			1	3
Total	85	1	53	4	1	1	9	3	157

For 2% (30 cases) the only risk factor found was blood transfusion. Of these, 15 were diagnosed in France, four in Belgium, four in the Netherlands, four in the United Kingdom, two in the Federal Republic of Germany and one in Italy. One patient diagnosed in the Netherlands had undergone heart surgery in the United States. One patient diagnosed in France had received blood transfusions in Haiti and Martinique; two diagnosed in Belgium had received transfusions in Zaire. One child diagnosed in the United Kingdom had received transfusions in the United States.

For 90 cases (7%) no risk factor was found (male:female ratio 2:1) and information was not obtained in 16 cases.

Of the 39 Caribbean cases, four were in homosexuals; no risk factors were identified for 34 cases (male:female ratio 2.5:1) and in one case no information was available.

Of the 157 African cases, 11 were in homosexuals. Five had received blood transfusions, and one was both homosexual and an intravenous drug abuser. No risk factors were identified for 124 (male:female ratio 2:1) and for 16 no information was available.

Among the 47 patients of other origins, 39 were homosexuals, two both homosexuals and intravenous drug abusers, one was a haemophiliac, and two had no risk factors. Information was not available in three cases.

Distribution of cases by risk group in the 16 countries having reported AIDS cases (Fig. 1)

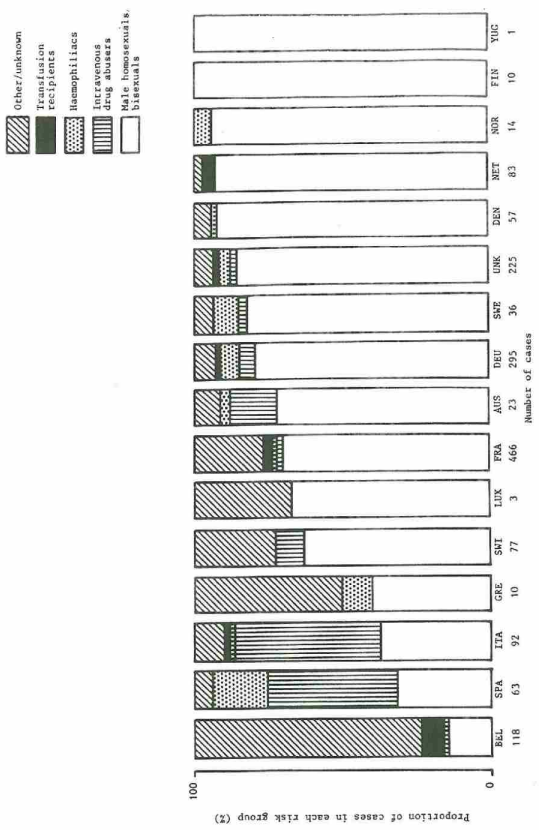
It is not possible to compare precisely the situations in the various European countries because of possible differences in the methods of data collection. Furthermore, in countries where the disease is still rare, the distribution may be modified with any increase in the number of cases. However, by examining these distributions, some interesting observations can be made.

Male homosexuals. AIDS patients belonging to this risk group account for 60–100% of the total number of cases in 12 out of the 16 countries. In four other countries (Belgium, Greece, Italy and Spain) they account for less than 50% of the cases.

Patients not belonging to any identified risk group. For the European countries as a whole, this group is second in importance. This situation is accentuated in four countries (Belgium, France, Greece and Switzerland), since these have a high proportion of patients originating from regions (such as equatorial Africa and Haiti) where AIDS has developed outside the principal risk groups.

Intravenous drug abusers. In Fig. 1, cases among heterosexual and homosexual drug abusers have been grouped together. The spread of AIDS in Europe has been particularly marked in this group. In October 1984, they represented only 2% of the total number of European cases and were reported by only three countries. By 30 September 1985, these cases represented 8% of the European total and were reported by nine countries, i.e. a significant increase of 6% ($P < 0.001$).

Fig. 1. Distribution of AIDS cases by risk group in 16 countries, 30 September 1985



Italy and Spain together declared 63% of the drug abusers with AIDS in Europe. Forty-five of the 92 Italian cases (49%) and 23 of the 63 Spanish cases (43%) occurred in this risk group.

Cases related to transfusion of blood and blood products. Ten countries have reported cases of AIDS among haemophiliac patients, and six have reported cases among other blood transfusion recipients.

Distribution of cases and deaths by half year of diagnosis (Table 5)

The number of cases diagnosed between January and September 1985 must be considered as provisional, due to the time required for the declarations to reach the national surveillance centres.

Table 5. Cases of AIDS and number of deaths by half year of diagnosis for 21 European countries,[a] 30 September 1985

Half year of diagnosis	Number of cases	Number of deaths	Case fatality rate (%)
Before 1981	21	11	52.4
1981: January-June	8	6	75.0
July-December	15	12	80.0
1982: January-June	28	19	67.9
July-December	52	45	86.5
1983: January-June	115	86	74.8
July-December	138	100	72.5
1984: January-June	214	126	58.9
July-December	316	185	58.5
1985: January-June	445	159	35.7
July-September	198	33	16.7
Unknown	23	10	43.5
Total	1573	792	50.3

[a] Austria, Belgium, Czechoslovakia, Denmark, Finland, France, Federal Republic of Germany, Greece, Hungary, Iceland, Italy, Luxembourg, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, USSR, United Kingdom, Yugoslavia.

The surveillance of AIDS in Europe began gradually in 1982; data obtained beforehand cannot be taken into account because of the unknown proportion of subjects lost to follow-up.

Half yearly incidence of AIDS

Apart from Czechoslovakia, Iceland, Poland (no reported cases) and Luxembourg (one case), the incidence of AIDS varied for the first six months of 1985 (provisional figures) from 0.3 cases per million population (Spain and the United Kingdom) to about three cases per million (Denmark and Switzerland). According to December 1984 data,[a] six-monthly incidence rates increased consistently in only six countries: Denmark, France, the Federal Republic of Germany, the Netherlands, Switzerland and the United Kingdom). Six months later, the situation has changed distinctly and the incidence rates show an increase in all the countries that have reported cases.

Review of public health measures related to blood donors

A questionnaire on public health measures related to blood transfusion was sent to 22 European countries (the 21 countries corresponding with the collaborating centre plus Portugal). Apart from the USSR, all the countries answered the questionnaire.

Systematic screening of blood donors for LAV/HTLV-III antibodies became effective in 16 of the 21 countries between June and November 1985. In 12 countries, screening is compulsory. In four others (Austria, Italy, the Netherlands and Sweden) it is only recommended, although the public health authorities of these countries consider that the recommendation is followed and that all blood donations are tested. In Austria, screening will become compulsory on 1 January 1986.

The test used in these countries is the enzyme-linked immunosorbent assay (ELISA). Confirmation of the results is usually by means of a second ELISA with a Western blot or immunofluorescence (IF) test. Portugal is the only country that does not yet use a confirmation test. The confirmation test is recommended in six countries (Denmark, Greece, Italy, the Netherlands, Sweden and Switzerland). For the other 10 countries, the confirmation test is compulsory.

Among the 16 countries that have taken measures related to blood donors, Portugal is the only one to have organized a national register of seropositive blood donors, for which confidentiality has been ensured. A national register is under consideration in Norway.

[a] Weekly epidemiological record, 60: 85-90 (1985).

Specialized consultations for the follow-up of seropositive subjects are organized or are being organized in 11 of the 16 countries (Austria, Belgium, Denmark, France, the Federal Republic of Germany, Italy, Luxembourg, Norway, Sweden, Switzerland and the United Kingdom). In Finland, seropositive subjects are followed up by the usual physician. Specialized consultations are under consideration in four countries (Greece, Hungary, the Netherlands and Portugal).

Information on seropositive subjects is systematic in five of the 16 countries (Denmark, Finland, Greece, the Netherlands and Switzerland) and is recommended in 10 of the remaining countries. No official recommendation concerning information on seropositive subjects has been made in Portugal. Systematic screening of blood donors is under consideration in five countries (Czechoslovakia, Iceland, Poland, Spain and Yugoslavia).

Eighteen countries have a national reference centre for confirmation. Luxembourg is, and Iceland will be, using a reference centre in a neighbouring country. Portugal has not as yet taken a decision.

Measures to exclude donors at risk have been taken in all the countries except Czechoslovakia, Finland and Portugal. These measures were initiated in 1983 for seven countries (Belgium, Denmark, France, the Netherlands, Norway, Sweden and the United Kingdom); in 1984 for Luxembourg; and in 1985 for Austria, Greece, Iceland, Italy, Poland, Spain and Yugoslavia. No data are available for Hungary.

Conclusion

Prevention of transmission of AIDS through blood transfusion is now effective in most European countries due to systematic screening for LAV/HTLV-III antibodies in blood donors. Even in countries where no cases of AIDS have been officially declared, setting up of screening is being studied; in Hungary, screening is already compulsory.

The AIDS epidemic continues to develop in the Region: an average of 27 new cases per week were notified between June and September 1985.

As in the United States, male homosexuals account for the highest percentage of the total number of cases (69%). The distribution according to risk group shows that there is a marked increase in cases among drug abusers. This group accounted for 2% of 421 European cases by July 1984 and 8% of the 1573 cases declared by September 1985. Over 40% of the cases in Italy and Spain occurred in this group. Several studies carried out in 1985 in

various European countries showed a high frequency (20-50%) of serological markers of infection with LAV/HTLV-III in drug abusers, indicating that the spread of infection has been rapid in this population. Information campaigns being set up in the countries of the Region should emphasize this aspect of the spread of AIDS.

Annex 2

THE VIRUS

L. Montagnier

There is now general agreement that the AIDS agent is a new retrovirus, described in the scientific literature as lymphadenopathy-associated virus (LAV), human T leukaemia virus or human T lymphotropic virus type III (HTLV-III) or AIDS-related virus (ARV). Without anticipating a definitive decision by the International Committee on Taxonomy of Viruses, it will be referred to here as LAV/HTLV-III, which combines the two most widely used names.

Main characteristics

Morphology. Three distinct aspects can be seen in ultra-thin sections of fixed infected cells:

- budding particles at the cell surface, with a crescent-shaped core separated from the plasma membrane by electron-dense structural material;
- immature free particles with a crescent-shaped core;
- mature virions, with a condensed, eccentric, round or bar-shaped core.

The size of the particles is in the range 100-140 nm.

Proteins. Three structural proteins are associated with the core, with apparent molecular weights in SDS gel electrophoresis under reducing conditions of:

- 24-25 thousand (referred to as p-24);
- 16-18 thousand (referred to as p-16);
- 12-13 thousand (referred to as p-12).

The major envelope protein is a glycoprotein of molecular weight 110-120 thousand (referred to as gp-110). It is bound to a hydrophobic transmembrane protein of molecular weight 41-43 thousand, referred to as gp-41.

Besides these five major proteins, there is the polymerase characteristic of retroviruses, reverse transcriptase, whose molecular weight is probably in the range 70-100 thousand.

A gag precursor of molecular weight 55 000 can be found, which is cleaved (probably by the virus-coded protease) into three gag proteins; a 40 000 molecular weight intermediate can also be found.

Cellular precursors of gp-110 with molecular weights of 150-160 thousand and 130 000 can be found.

Genome structure. Various isolates of LAV/HTLV-III have been cloned and sequenced. The genome has the classic structure of retroviruses, with two repeated regulatory sequences (long terminal repeat (LTR)) at both ends and three genes:

- gag coding for the three core proteins;
- pol coding for the polymerase and a protease;
- env coding for the envelope;

but has also new open reading frames, one lying between the pol and env genes (Q, P', A) and another overlapping the env gene and the 3' LTR, referred to as F, E', B. A small open reading frame, also lying between the pol and env genes, seems to be responsible for the transacting activity associated with the virus.

These two genes are expressed, since their specific m-RNAs have been found in infected cells, but the corresponding proteins have not yet been identified.

Relationship to other retroviruses

Sequence data have shown no relevant homology with the sequence of the HTLV-I-II/BLV group and with those of other animal retroviruses that have been published.

By its morphology, certain characteristics of its genome structure, and the number and size of its structural proteins, LAV/HTLV-III virus is close to the Lentivirus subfamily of retroviruses. Besides, the p-24 of LAV/HTLV-III has a common epitope with that of the major core protein of equine infectious anaemia virus, which is also related to the Lentivirus group.

Biology of the virus

Cell tropism. The virus has a specific tropism for the T4+ subset of T lymphocytes and perhaps to an as yet undefined fraction of this subset. The molecular basis of this tropism lies at least

in part in the binding of the viral glycoprotein to the T4 molecule itself, at the surface of the lymphocyte.

The virus can replicate only when the T4 lymphocytes are activated (by lectins, alloantigens or bacterial toxins) and actively replicate. It also grows - conveniently for mass production - in T4+ leukaemia cell lines (H9, CEM, HUT 78). Some viral strains have also been shown to grow in B lymphocytes transformed by Epstein-Barr virus (EBV), which may eventually express the T4 receptor. The virus seems also to replicate in monocytes. Virus has also been shown to be present in brain tissues, but it is not yet clear which type of cell is infected. As for EBV, it is possible that some cells which do not harbour any specific virus receptor may be infected by fusion with an infected T lymphocyte.

Cytopathic effect. The virus does not transform T4 lymphocytes, but instead inhibits their multiplication. Highly infected cells undergo fusion directed by the virus glycoprotein, giving rise to giant syncytia. Even though the virus does not destroy the cells, it may impair their function, for instance by binding to the T4 receptor or by some other mechanism. Like other retroviruses, the virus can remain in lymphoid cells in a latent, unexpressed state and can be activated by some chemical agents such as halogenated pyrimidines.

Antigenicity and genetic variation

All the viral proteins and their cellular precursors are antigenic. Antigens most frequently recognized by antibodies of patients are the p-24 core protein, the glycoprotein gp-110, and the transmembrane protein gp-41 and their related cellular precursors or fragments. Antibodies against glycoprotein have generally higher titres than those against internal core proteins and are more consistently found in AIDS patients. This high titre is in contrast with a weak or absent neutralizing activity on virus infectivity.

Sequence studies indicate that the genetic variation of the virus is high, particularly at the level of the envelope gene. Despite this variation, common epitopes do exist, since antibodies in nearly all patients can be detected by proteins of one virus prototype.

However, as has been shown for animal retroviruses, these variations may allow the virus to escape neutralizing antibodies and more generally the immune system. They may also constitute a severe obstacle to the development of a universal vaccine.

Virus inactivation

Physical agents. As with many enveloped viruses, LAV/HTLV-III is heat-sensitive: heating the virus to at least 56°C for 30 minutes reduces its infectivity by at least two logs.

When inactivation is followed by the disappearance of the reverse transcriptase activity, a nonlinear inactivation curve is observed. Inactivation in lyophilized preparations occurs more slowly, suggesting some virus protection in the dried state. It is also likely that some plasma proteins, such as clotting factors, diminish the heat sensitivity of the virus.

Like other retroviruses, the virus is relatively resistant to ionizing radiation and ultraviolet light. Partial inactivation of the virus has been observed by doses of 2.5×10^5 rads of gamma radiation and 5×10^3 J/m^2 of ultraviolet light at a wavelength of 254 nm.

Chemical agents. 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%). The treatments used to prepare hepatitis B vaccine from human plasma have been shown to inactivate LAV/HTLV-III virus.

Several products have been shown to have antiviral activity. Some of them (suramin, HPA23, phosphonoformate) are inhibitors of reverse transcriptase. Ribavirin (Virazole) also inhibits virus replication, presumably by suppressing viral protein synthesis.

These drugs are under clinical trial.

Annex 3

ELISA TESTS FOR SCREENING ANTI-LAV/HTLV-III ANTIBODIES

ELISA tests for screening anti-LAV/HTLV-III antibodies currently available in Europe include:

- Abbot
- Organon (ENI)
- Litton Bionetics
- ELAVIA (Diagnostic Pasteur).

Some differences exist between these tests, depending on the T-cell line used for virus production and the inclusion or non-inclusion of a test with a control cellular antigen. The ELAVIA test determines seropositivity on the basis of the difference in optical density measured on the viral antigen and a cellular antigen derived from the same cells used for virus production.

The results of an evaluation of the four tests in screening blood donors (specificity) or a panel of AIDS or pre-AIDS patients (sensitivity) are as follows:

Manufacturer	Cell line used to grow the virus	Sensitivity (%)	Specificity (%)	Country of evaluation
Abbott	H9	93.4	99.8	United States
ENI	H9	99.6	99.2	United States
Litton	H9	98.9	99.6	United States
Pasteur	CEM	99.9	99.9	France

Annex 4

THE CASE DEFINITION OF AIDS USED BY CDC FOR NATIONAL REPORTING

For the limited purposes of national reporting of some of the severe late manifestations of infection with human T lymphotropic virus, type III/lymphadenopathy-associated virus (HTLV-III/LAV) in the United States, CDC defines a case of "acquired immunodeficiency syndrome" (AIDS) as an illness characterized by:

- one or more of the opportunistic diseases listed below (diagnosed by methods considered reliable) that are at least moderately indicative of underlying cellular immunodeficiency;

- absence of all known underlying causes of cellular immunodeficiency (other than HTLV-III/LAV infection) and absence of all other causes of reduced resistance reported to be associated with at least one of those opportunistic diseases.

Despite having the above, patients are excluded as AIDS cases if they have negative result(s) on testing for serum antibody to HTLV-III/LAV,[a] do not have a positive culture for HTLV-III/LAV, and have both a normal or high number of T-helper (OK T4 or LEU 3) lymphocytes and a normal or high ratio of T-helper to T-suppressor (OK T8 or LEU 2) lymphocytes. In the absence of test results, patients satisfying all other criteria in this definition are included as cases.

This general case definition may be made more explicit by specifying:

- the particular diseases considered at least moderately indicative of cellular immunodeficiency, which are used as indicators of AIDS;

[a] A single negative test for HTLV-III/LAV may be applied here if it is an antibody test by ELISA, immunofluorescent or Western blot methods, because such tests are very sensitive. Viral cultures are less sensitive but more specific, and so may be relied on if positive but not if negative. If multiple antibody tests have inconsistent results, the result applied to the case definition should be that of the majority. A positive culture, however, would overrule negative antibody tests.

- the known causes of cellular immunodeficiency, or other causes of reduced resistance reported to be associated with particular diseases, which would disqualify a patient as an AIDS case.

This specification is as follows.

Diseases at least moderately indicative of underlying cellular immunodeficiency

In the following list of diseases, the required diagnostic methods with positive results are shown in parentheses. "Microscopy" may include cytology.

1. Protozoal and helminthic infections

- Cryptosporidiosis, intestinal, causing diarrhoea for over one month (on histology or stool microscopy).

- *Pneumocystis carinii* pneumonia (on histology, or microscopy of a "touch" preparation, bronchial washings, or sputum).

- Strongyloidosis, causing pneumonia, central nervous system infection or infection disseminated beyond the gastrointestinal tract (on histology).

- Toxoplasmosis, causing infection in internal organs other than liver, spleen or lymph nodes (on histology or microscopy of a "touch" preparation).

2. Fungal infections

- Candidiasis, causing oesophagitis (on histology, or microscopy of a "wet" preparation from the oesophagus, or endoscopic or autopsy findings of white plaques on an erythematous mucosal base, but not by culture alone).

- Cryptococcosis, causing central nervous system or other infection disseminated beyond lungs and lymph nodes (on culture, antigen detection, histology or India ink preparation of CSF).

3. Bacterial infections

- *Mycobacterium avium* or *M. intracellulare* (*Mycobacterium avium* complex), or *Mycobacterium kansasii*, causing infection disseminated beyond lungs and lymph nodes (on culture).

4. Viral infections

- Cytomegalovirus, causing infection in internal organs other than the liver, spleen or lymph nodes (on histology or cytology, but not by culture or serum antibody titre).
- Herpes simplex virus, causing chronic mucocutaneous infection with ulcers persisting more than one month, or pulmonary, gastrointestinal tract (beyond mouth, throat or rectum), or disseminated infection (but not encephalitis alone) (on culture, histology or cytology).
- Progressive multifocal leukoencephalopathy (presumed to be caused by Papovavirus) (on histology).

5. Cancer

- Kaposi's sarcoma (on histology).
- Lymphoma limited to the brain (on histology).

6. Other opportunistic infections with positive test for HTLV-III/LAV[a]

In the absence of the above opportunistic diseases, any of the following diseases is considered indicative of AIDS if the patient had a positive test for HTLV-III/LAV.[a]

- Disseminated histoplasmosis (on culture, histology or cytology).
- Bronchial or pulmonary candidiasis (on microscopy or visualization grossly of characteristic white plaques on the bronchial mucosa, but not by culture alone).
- Isosporiasis, causing chronic diarrhoea (over one month) (on histology or stool microscopy).

[a] A positive test for HTLV-III/LAV may consist of a reactive test for antibody to HTLV-III/LAV or a positive culture (isolation of HTLV-III/LAV from a culture of the patient's peripheral blood lymphocytes). If multiple antibody tests have inconsistent results, the result applied to the case definition should be that of the majority done by the ELISA, immunofluorescent or Western blot methods. A positive culture, however, would overrule negative antibody tests.

Known causes of reduced resistance	Diseases possibly attributable to the known causes of reduced resistance
Cancer of lymphoreticular or histiocytic tissue such as lymphoma (except for lymphoma localized to the brain), Hodgkin's disease, lymphocytic leukaemia or multiple myeloma	Any infection or cancer, if diagnosed after or within three months before the diagnosis of cancer of lymphoreticular or histiocytic tissue
Age 60 years or older at diagnosis	Kaposi's sarcoma, but not if the patient has a positive test for HTLV-III/LAV
Age under 28 days (neonatal) at diagnosis	Toxoplasmosis or herpes simplex virus infection, as described above
Age under 6 months at diagnosis	Cytomegalovirus infection, as described above
An immunodeficiency atypical of AIDS, such as one involving hypogammaglobulinaemia or angioimmunoblastic lymphadenopathy, or an immunodeficiency of which the cause appears to be a genetic or developmental defect rather than HTLV-III/LAV infection	Any infection or cancer diagnosed during such immunodeficiency
Exogenous malnutrition (starvation due to food deprivation, not malnutrition due to malabsorption or illness)	Any infection or cancer diagnosed during or within one month after discontinuation of starvation

Annex 5

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Atlanta, GA, USA, 19 April 1985

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7. Chronic lymphoid interstitial pneumonitis

In the absence of the above opportunistic diseases, a histologically confirmed diagnosis of chronic (persisting over two months) lymphoid interstitial pneumonitis in a child (under 13 years of age) is indicative of AIDS unless test(s) for HTLV-III/LAV are negative.[a] The histological examination of lung tissue must show diffuse interstitial and peribronchiolar infiltration by lymphocytes, plasma cells with Russell bodies, plasmacytoid lymphocytes and immunoblasts. Histological and culture evaluation must not identify a pathogenic organism as the cause of this pneumonia.

8. Non-Hodgkin's lymphoma with positive test for HTLV-III/LAV[a]

If the patient had a positive test for HTLV-III/LAV,[a] then the following histological types of lymphoma are indicative of AIDS regardless of anatomic site.

- Small noncleaved lymphoma (Burkitt's tumour or Burkitt-like lymphoma), but not small cleaved lymphoma.

- Immunoblastic sarcoma (or immunoblastic lymphoma) of B-cell or unknown immunological phenotype (not of T-cell type). Other terms which may be equivalent include diffuse undifferentiated non-Hodgkin's lymphoma, large cell lymphoma (cleaved or noncleaved), diffuse histiocytic lymphoma, reticulum cell sarcoma and high-grade lymphoma.

Lymphomas should not be accepted as indicative of AIDS if they are described in any of the following ways: low grade, of T-cell type (immunological phenotype), small cleaved lymphoma, lymphocyte lymphoma (regardless of whether well or poorly differentiated), lymphoblastic lymphoma, plasmacytoid lymphocytic lymphoma, lymphocytic leukaemia (acute or chronic) or Hodgkin's disease (or Hodgkin's lymphoma).

[a] A positive test for HTLV-III/LAV may consist of a reactive test for antibody to HTLV-III/LAV or a positive culture (isolation of HTLV-III/LAV from a culture of the patient's peripheral blood lymphocytes). If multiple antibody tests have inconsistent results, the result applied to the case definition should be that of the majority done by the ELISA, immunofluorescent or Western blot methods. A positive culture, however, would overrule negative antibody tests.

Known causes of reduced resistance

Known causes of reduced resistance to diseases indicative of immunodeficiency are listed in the left column, while the diseases that may be attributable to these causes (rather than to the immunodeficiency caused by HTLV-III/LAV infection) are listed on the right.

Known causes of reduced resistance	Diseases possibly attributable to the known causes of reduced resistance
Systemic corticosteroid therapy	Any infection diagnosed during or within one month after discontinuation of corticosteroid therapy, unless symptoms specific for an infected anatomic site (e.g. dyspnoea for pneumonia, headache for encephalitis, diarrhoea for colitis) began before the corticosteroid therapy
	or any cancer diagnosed during or within one month after discontinuation of more than four months of long-term corticosteroid therapy, unless symptoms specific for the anatomic sites of the cancer (as described above) began before the long-term corticosteroid therapy
Other immunosuppressive or cytotoxic therapy	Any infection diagnosed during or within one year after discontinuation of immunosuppressive therapy, unless symptoms specific for an infected anatomic site (as described above) began before the therapy
	or any cancer diagnosed during or within one year after discontinuation of more than four months of long-term immunosuppressive therapy, unless symptoms specific for the anatomic sites of the cancer (as described above) began before the long-term therapy

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