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AIDS in The Netherlands

CLINICAL AND MICROBIOLOGICAL DATA ON 36 CASES


Summary
On 31st December 1984, 36 patients with AIDS fulfilling the CDC case finding criteria, had been treated in two academic hospitals. All of them had antibodies to LAV/HTLV-III. A description is presented of the clinical features, laboratory data and the many microbiological complications. The prognosis in patients with opportunistic infections was extremely poor; that in patients with only Kaposi's sarcoma was considerably better. Neth J Med 1985;28:487.

Introduction
In the spring of 1981 an unusual clustering of Kaposi's sarcoma and Pneumocystis carinii pneumonia was recognized in previously healthy homosexual men in New York City and California. Soon the clinical spectrum broadened, with many different so-called opportunistic infections, and in these patients evidence of a defect in cellular immune responses was found. It was not until February 1983, over 5 years after onset of disease in the first recognized cases, that 1,000 patients with AIDS were reported to CDC, but thereafter there was a near doubling of cases every 6 months.

The highest proportion of cases (73 per cent) was seen in homosexual or bisexual men, but soon other risk groups were identified: intravenous drug users (17 per cent of cases), Haitian immigrants to the USA (3 per cent), haemophiliacs (1 per cent), receivers of blood transfusions (1 per cent), sexual partners of patients or persons at risk (1 per cent). AIDS was also recognized in children from parents at risk (64 cases up to December 1984). For the 26 per cent of all cases with a risk factor that does not apply to women (i.e. homosexual males or patients with haemophilia), 76 per cent have been males and 24 per cent females (US figures).

Six months after the first American reports, the first report on European AIDS cases appeared, and today AIDS is recognized in countries all over the world. A large number of cases appear in Central Africa (especially Zaire; with 40 per cent female patients), and in Haiti, although it is possible that AIDS has been present unrecognized for a long time in Central Africa, the recent epidemic form is new there, too.

The epidemiology of AIDS soon suggested an infectious - i.e. viral - aetiology. Extensive evidence has now been accumulated that infection with a newly discovered retrovirus called lymphadenopathy-associated virus (LAV) or human T-cell lymphotropic virus III (HTLV-III), plays a crucial role in the pathogenesis of AIDS and related disorders. The LAV/HTLV-III virus shows tropism for the OKT4 subset of T-cells and, through a destructive action on these cells, brings about the permanent immune deficiency resulting in opportunistic infections and probably certain cancers. Antibodies to HTLV-III-related antigens can be found in up to 100 per cent of patients with AIDS. Besides AIDS the clinical spectrum of HTLV-III infection also encompasses symptom-free individuals, flu-like illness, persistent generalized lymphadenopathy, so-called AIDS-related complex, and autoimmune disease.

Total case fatality rate for AIDS patients in the USA so far is 47 per cent, but, since most cases have been diagnosed in the past 2 years, this is certainly an underestimation of final mortality. Of patients reported more than 3 years ago, 81 per cent have died.

In The Netherlands the first cases were diagnosed in 1982. At the end of 1984, 42 cases meeting CDC criteria had been reported. In this paper we describe the clinical, immunological and microbiological data on 36 of these patients.
AIDS was diagnosed in accordance with the CDC surveillance definition, which demands two criteria: 1) the presence of a reliably diagnosed disease at least moderately predictive of cellular immunodeficiency; and 2) the absence of an underlying cause of the immune deficiency or of any defined cause of reduced resistance to the disease.

Included in our study are all patients admitted before 31st December 1984 either to the Academic Medical Centre, University of Amsterdam (30 patients) or to the Leiden University Hospital (6 patients), in whom AIDS was diagnosed before 31st December 1984. In each case the diagnosis of Kaposi’s sarcoma was proven histologically. Pneumocystis carinii pneumonia and other infections were confirmed by culture results and/or histological examinations and/or a diagnostic serological profile, except for 3 cases of Toxoplasma gondii encephalitis, which were diagnosed on the basis of typical CT-scan abnormalities and striking radiological and clinical improvement upon anti-toxoplasmosis therapy.

T-lymphocyte membrane phenotypes of peripheral blood lymphocytes were determined by a cytofluorometric method (Coulter Epics-C) using monoclonal antibodies to mature T-cells (leu-4 or OKT3) or to helper/inducer (leu-3 or OKT4) and suppressor/cytotoxic (leu-2 or OKT8) T-cell subsets and a fluorescein-conjugated goat anti-mouse IgG. Ratios of helper/suppressor lymphocytes lower than 0.8 were scored as depressed.

All material for histopathological studies was processed according to a protocol. A postmortem was performed in 22 cases. As soon as possible after death, mostly within 2 hours, tissue specimens were collected from all affected organs for microbiological studies. In order to ensure optimal immunohistochemical, electron-microscopic and histopathological studies, fragments of tissue from all organs were fresh-frozen in liquid nitrogen and fixed in Karnovsky’s fixative and in 4% buffered formalin respectively. Routinely, 5 μ paraffin sections of all organs were stained with haematoxylin-eosin, PAS, PAS following diastase digestion, Grocott’s stain, Ziehl-Neelsen stain, and the elastic Van Gieson stain, covering all opportunistic infections and malignancies. Biopsy material from living patients (intestinal tract, lungs, lymph nodes, etc.) was processed in the same way.

Antibodies to HTLV-III were measured using an ELISA developed by W.J.A. Krone and others at the department of virology, University of Amsterdam, using a H\textsubscript{3}-HTLV-III cell lysate.

### Methods

### Results

The mean age of our patients was 39.5 years (range 23-57). All patients were males, all except one being homosexual or bisexual men with an active sexual life. The one exception was a heterosexual monogamous man who had received several blood transfusions during heart surgery in the USA, 4 years prior to the first symptoms of AIDS. Thirty-one of the patients were of Dutch nationality. The great majority reported sexual contacts in the USA or with persons from the USA. Four patients had Kaposi’s sarcoma only: 24 patients (67 per cent) had opportunistic infections and 8 (22 per cent) had both Kaposi’s sarcoma and opportunistic infections. Table I lists the prodromal complaints; 32 of the 36 patients had one or more complaints; only 3 patients with cutaneous Kaposi’s sarcoma and one patient presenting with acute cryptococcal meningitis reported no previous symptoms. Malaise and fatigue were almost invariably present, followed by unexplained weight loss and unexplained fever. The mean interval between onset of symptoms and diagnosis of AIDS was 9.7 months (range 0.5-36). Table II lists the infections or malignancies considered as evidence of the existence of AIDS. Most frequently Pneumocystis carinii pneumonia led to diagnosis, followed by Kaposi’s sarcoma.

At examination at the time of diagnosis most patients had signs of recent weight loss. Weight/height\textsuperscript{2} was low: 19.6 ± 1.6 kg.m\textsuperscript{-2}; 40 per cent had fever and 40 per cent were dyspnoeic. Lymphadenopathy (two or more non-adjacent enlarged lymph nodes) was found in 36 per cent, hepatosplenomegaly in 25 per cent. Dermatological abnormalities were seen frequently: half the patients presented with a candida infection of skin and/or mucous membranes, a quarter with Kaposi’s sarcoma and 15 per cent with herpes infection.

<table>
<thead>
<tr>
<th>TABLE I: PRODROMAL SYMPTOMS IN 36 AIDS PATIENTS</th>
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<tbody>
<tr>
<td><strong>Prodromal symptoms</strong></td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Malaise and fatigue</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Night sweat</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Neurological or psychiatric abnormalities</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Cutaneous or mucous membrane abnormalities</td>
</tr>
</tbody>
</table>
In table III some laboratory findings are grouped together. There was slight leucopenia and marked lymphopenia in the peripheral blood: 65 per cent of the patients had an absolute lymphocyte count of less than $1.0 \times 10^9/l$. The absolute number of OKT4-positive lymphocytes and the ratio between OKT4-positive and OKT8-positive cells were below normal in all patients except one, who presented with a solitary Kaposi’s sarcoma. He was treated locally, but unfortunately he withdrew from follow-up after 3 months. In-vitro lymphocyte responses to phytohaemagglutinin antilymphocyte serum were disturbed in 34 cases (exceptions were the abovementioned patient with Kaposi’s sarcoma and another patient presenting with this disorder). The immunoglobulin levels were increased. Antibodies to HTLV-III were found in 100 per cent of our patients.

Infections and malignancies

Fig. 1 lists the opportunistic infections and malignancies diagnosed during life. Two types of malignancies considered part of the AIDS syndrome were seen: non-Hodgkin lymphoma (maxillary region) in 1 case and Kaposi’s sarcoma (cutaneous and/or intestinal localizations) in 12 cases. Of the 32 patients with opportunistic infections, 21 had Pneumocystis carinii pneumonia. In 5 cases there was a co-existing lung infection with cytomegalovirus and in one case a co-existing infection with Candida albicans. Opportunistic bowel infections were encountered 7 times, mostly due to Cryptosporidium spp. Central nervous system involvement was seen in 11 cases. In 7 patients a clinical picture of ‘progressive presenile dementia’ developed with severe cerebral atrophy on CT-scan. Ophthalmological examination revealed cotton wool spots and/or presumed CMV retinitis in 4 patients. Chronic perianal ulcerative herpes simplex lesions were found in 4 patients. Disseminated infection with the unusual human pathogen Mycobacterium avium intracellulare was seen in 5 cases, mostly found by culture of bone marrow, buffy coat and/or blood.

Apart from the opportunistic infections many other infections were seen. In most cases there was severe oropharyngeal candidiasis, sometimes relapsing despite treatment. Other infections seen were syphilis, Salmonella sepsis, shigellosis, giardiasis and amoebiasis, but no distinctive pattern of non-opportunistic infections appeared. Fig. 2 shows the number of opportunistic and non-opportunistic serious infections diagnosed during life in the 36 patients. A mean of two opportunistic infections and one non-opportunistic infection was found per patient. Only two patients, both presenting with Kaposi’s sarcoma, remained free from infections; one of them was lost for follow-up after 3 months of observation and the other has been observed now for 9 months. Almost all patients had evidence (serology and/or isolates) of past or present EBV, CMV and hepatitis B infections. Details about this will be reported elsewhere°°.

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**TABLE II: PRESENTING DISORDERS WHICH HAVE LED TO THE DIAGNOSIS OF AIDS IN 36 PATIENTS**

<table>
<thead>
<tr>
<th>Presenting disorder</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>15</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>10</td>
</tr>
<tr>
<td>Oesophagitis caused by Candida albicans</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonia caused by Candida albicans</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia caused by cytomegalovirus</td>
<td>1</td>
</tr>
<tr>
<td>Encephalitis caused by Toxoplasma gondii</td>
<td>1</td>
</tr>
<tr>
<td>Enteritis caused by Isospora belli</td>
<td>1</td>
</tr>
<tr>
<td>Enteritis caused by Cryptosporidum spp.</td>
<td>1</td>
</tr>
<tr>
<td>Meningitis caused by Cryptococcus neoformans</td>
<td>1</td>
</tr>
<tr>
<td>Septicaemia caused by Mycobacterium tuberculosis</td>
<td>1</td>
</tr>
</tbody>
</table>

**TABLE III: SOME LABORATORY FINDINGS IN 36 AIDS PATIENTS AT THE TIME OF DIAGNOSIS**

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Mean</th>
<th>Range</th>
<th>Normal values (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (mmol/l)</td>
<td>34</td>
<td>7.2</td>
<td>4.2 - 10.9</td>
<td>8.1 - 9.9</td>
</tr>
<tr>
<td>Leucocytes ($\times 10^9/l$)</td>
<td>35</td>
<td>4.8</td>
<td>2.1 - 12.2</td>
<td>4.0 - 11.0</td>
</tr>
<tr>
<td>Lymphocytes ($\times 10^9/l$)</td>
<td>34</td>
<td>0.9</td>
<td>0.2 - 2.9</td>
<td>1.0 - 3.5</td>
</tr>
<tr>
<td>Platelets ($\times 10^9/l$)</td>
<td>34</td>
<td>206</td>
<td>95 - 350</td>
<td>150 - 350</td>
</tr>
<tr>
<td>OKT4-positive cells ($\times 10^9/l$)</td>
<td>32</td>
<td>0.17</td>
<td>0.01 - 0.62</td>
<td>0.5 - 2.0</td>
</tr>
<tr>
<td>OKT8-positive cells ($\times 10^9/l$)</td>
<td>32</td>
<td>0.54</td>
<td>0.01 - 2.18</td>
<td>0.2 - 1.4</td>
</tr>
<tr>
<td>OKT4/OKT8 ratio</td>
<td>33</td>
<td>0.36</td>
<td>0.03 - 1.02</td>
<td>0.8 - 3.2</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>22</td>
<td>19.3</td>
<td>7.0 - 38.0</td>
<td>8.0 - 19.2</td>
</tr>
<tr>
<td>IgM (g/l)</td>
<td>22</td>
<td>3.8</td>
<td>0.8 - 18.3</td>
<td>0.8 - 3.6</td>
</tr>
<tr>
<td>IgA (g/l)</td>
<td>22</td>
<td>5.6</td>
<td>0.9 - 17.1</td>
<td>0.7 - 4.1</td>
</tr>
</tbody>
</table>
Fig. 1. Opportunistic infections and malignancies in AIDS. I. Findings during life since diagnosis in 36 patients.

Fig. 2. Number of opportunistic infections and of all infections since diagnosis in 36 AIDS patients.

AIDS in the Netherlands
AIDS in the Netherlands

Survival rate

- - - all AIDS patients
- - - patients with Kaposi’s sarcoma
- - - patients with opportunistic infections
- - - patients with both Kaposi’s sarcoma and opportunistic infections

Time (months)

Outcome

The prognosis of the disease is poor. So far, 26 of 36 patients have died. Fig. 3 shows the actuarial survival curve. Very remarkably, the patients with only Kaposi’s sarcoma are still alive (one of them lost for follow-up).

Table IV lists the causes of death in 26 patients. Pneumonia was the most important cause of death. Although infections with Pneumocystis carinii were frequently seen in those patients, that organism was

The sole infectious agent responsible for a fatal pneumonia in only one case. On the other hand, 5 of 7 severe lung infections caused by both Pneumocystis and CMV (CMV inclusion bodies seen in lung biopsy material and confirmed by culture) led to intractable respiratory failure.

Postmortem findings

In 21 of the 26 cases permission for a postmortem was obtained. Fig. 4 lists the opportunistic infections and malignancies which had not been detected during life but were found at postmortem. The importance of postmortem examination in AIDS cases is clearly illustrated. Numerous episodes of fever, wasting or localized symptoms of unknown origin, were explained by the postmortem findings. Organ involvement by Mycobacterium avium intracellulare, cytomegalovirus, Cryptococcus neoformans and Kaposi’s sarcoma was frequently found. Besides the clinical syndrome of progressive dementia due to an unknown agent in 7 patients, two additional cases of encephalitis due to an unknown agent were found at the postmortem.

Discussion

Shortly after its epidemic appearance in the USA, the new disease AIDS reached Europe, emerging
almost exclusively in urban areas. This article describes the findings in 36 of the 42 patients diagnosed by 31st January 1985 in The Netherlands. When compared with the US data, several differences can be noted: none of the AIDS patients was an intravenous drug user (17 per cent in the USA); so far we have found no haemophiliacs (1 per cent in the USA) and no female patients (7 per cent in the USA). All patients except one were homosexual or bisexual men with a moderately or highly active sexual life.

Two distinct features of the syndrome are the multiple simultaneous infections and the poor prognosis. Many deaths are due to intractable opportunistic infections, as clearly illustrated in our study by the fact that all patients with Kaposi's sarcoma without infections have so far survived. Theoretically, the poor prognosis might be improved by reconstitution of the impaired immune system. No patient has so far regained intact immune responses spontaneously, nor has any therapeutic regimen succeeded in restoring immunocompetence. All that can be done at the moment, therefore, is treatment of the infections and the malignancies.

Unfortunately, for many of these opportunistic infections no effective treatment is known, and for others therapy gives some clinical improvement, but seldom eradication of the micro-organism. Pneumocystis carinii, the most important cause of life-threatening pneumonia in AIDS patients, can be treated effectively with trimethoprim-sulphamethoxazole or pentamidine. Our results support this: although 21 patients experienced a pneumocystis infection, only 7 died from this cause. Moreover, in 6 of these 7 cases there was a co-existing lung infection (CMV in 5 cases, Candida albicans in 1). In our experience, supported by the literature, it is mandatory for successful treatment of pneumocystis pneumonia to start treatment as soon as possible, and especially before respiratory insufficiency becomes evident. The extremely high incidence of this potentially treatable infection in AIDS patients warrants a thorough search in each person at risk. Beside physical examination and chest X-ray this includes more sensitive techniques such as Gallium lung scintigraphy and determination of a gas diffusion parameter such as CO transfer capacity. If the results of all these examinations are normal, the likelihood that a patient has a pulmonary infection is negligible. If one or more of the results are abnormal, fibre-optic bronchoscopy with broncho-alveolar lavage and transbronchial biopsy must follow.
The biopsy and lavage specimens should be processed with appropriate stains or cultures for pneumocystis, mycobacteria, fungi, legionella, and such viruses as cytomegalovirus and herpes simplex; in addition, the specimens should be submitted to routine pathological and cytological analysis. Using this protocol, we found evidence of pneumocystis infection in 3 of our patients before there were any pulmonary symptoms and signs or chest X-ray abnormalities. Unfortunately, adverse reactions to co-trimoxazole occur in a large percentage of AIDS patients75,83,84 and a serious allergic reaction, prompting discontinuation of this drug, was found in one-third of our patients. Toxoplasmosis is another infection that can be treated effectively by drug therapy85. Life-long therapy is probably necessary86,87. In our 3 patients with postulated toxoplasma encephalitis, institution of pyrimethamine-sulphadiazine therapy caused prompt disappearance of clinical symptoms and CT-scan abnormalities.

A striking neurological syndrome, for which there is no treatment at present, is unexplained progressive dementia88. Many AIDS patients eventually develop this encephalopathy89, and so far it has been found in 7 of our patients. In 2 it was considered to be the direct cause of death, and in 5 others it contributed to death caused by fulminating bacterial pneumonia. Symptoms start with apathy, followed by progressive mental deterioration. The patient is apathetic, bedridden, assumes a foetal position and becomes unable to perform the activities of daily living. At last diminished consciousness, somnolence, and a comatose state develop. Pseudobulbar reflexes are found, but no focal neurological symptoms. The CT-scan reveals diffuse cerebral atrophy. Recently, HTLV-III virus has been found in brain cells of such patients, suggesting that the syndrome is the direct result of infection with this virus88.

Common AIDS-related infections which are difficult to treat include those with the coccidial parasites Cryptosporidium spp. and Isospora belli89,90. Unlike the pattern in the immunocompetent, where the disease is usually self-limiting91-93, they cause severe malabsorption and devastating intractable diarrhoea in AIDS. In our patient with Isospora belli infection we successfully used the veterinary drug amprolium94. For cryptosporidiosis the therapeutic outlook at the moment is bleak89,90.

For several other opportunistic infections there is no specific treatment as yet. Of these, disseminated infection with Mycobacterium avium intracellulare must be mentioned separately. The organism has been isolated from blood and bone marrow in 10-30 per cent of patients, and has also been identified in lymph nodes, liver, spleen, soft tissues, lungs, sputum and urine95-97. The exact role of this organism in producing systemic or localized symptoms or pathology is still unclear. So far, no drug or drug combination has been documented to be clinically effective97. In-vitro studies usually show resistance to conventional antimycobacterial drugs. Excellent in-vitro activity against Mycobacterium avium intracellular isolates has been found with clofazimine, ansamycin and amikacin, but clinical results have not yet been published97. In our series disseminated Mycobacterium avium intracellularare was diagnosed during life in 5 patients, and in an additional 7 at postmortem examination. In one of our patients, similar to findings of others98,99, small bowel lesions resembling those of Whipple's disease, but due to Mycobacterium avium intracellular infection, were found. Apart from this case no clearcut disease pattern emerged.

Of the viral infections, especially cytomegalovirus takes a heavy toll. It causes considerable morbidity and mortality, particularly in terms of pneumonia, oesophagitis, retinochoroiditis and dissemination97,100. It may be a cause of adrenal insufficiency in AIDS patients101,102. It was cultured from the throat and urine of nearly all our patients. In our series, 5 of 8 patients with pulmonary CMV involvement developed fatal respiratory failure. In at least 2 patients ocular disorders were ascribed to CMV infection. As opposed to herpes simplex and herpes zoster infections, there is currently no effective therapy for disease caused by CMV97.

Although AIDS may be associated with a wide range of malignancies (including primary central nervous system lymphoma), disseminated Kaposi's sarcoma is by far the most common103. Together with pneumocystis pneumonia it led to recognition of the new syndrome3,4. Although AIDS-related Kaposi's sarcoma is histologically indistinguishable from more classic forms, it almost invariably takes a more rapidly progressive course, resembling that seen in iatrogenically immunosuppressed patients4,103-107. Patients present with skin lesions, but at that time there is often already co-existing lymph node and visceral (especially gastrointestinal tract) involvement4,103,106,107. Careful examination of the oral cavity is mandatory in AIDS patients, since in one out of 3 with Kaposi's sarcoma involvement of the hard palate is found103. In one of our patients hard palate involvement was the only evidence of Kaposi's sarcoma found during life.

In view of the distinctive characteristics of AIDS-related Kaposi's sarcoma, a new staging classification has been proposed107. However, the presence
of B symptoms (weight loss, fever, night sweats) and immunological status seem to be more important prognostic factors than the more traditional parameters of tumour size, employed in this system. In agreement with this is the fact that the full natural history of AIDS-related Kaposi's sarcoma is not known at the moment, since patients sooner or later die from opportunistic infections (occult infections presumably being the cause of B symptoms, and opportunistic infections being indicative of a worse immunological status than Kaposi's alone). Evidence of Kaposi's sarcoma was found in our series in 18 (50 per cent) patients. This reflects the high prevalence of this disorder in homosexual or bisexual men, as opposed to other risk groups.

Several treatment regimens have been tried in AIDS-related Kaposi's sarcoma. The most extensively evaluated single agent cytotoxic drugs have been vinblastine and the podophyllotoxin VP-16. For the former drug the reported complete response rate is 5 per cent (complete and partial response rate 37 per cent); for VP-16 it is 38 per cent (complete and partial response rate 79 per cent). Total response rates of about 40 per cent have been found with recombinant alpha interferon. There is no agreement on optimal interferon dosage yet, high dosage often being limited by intolerable subjective symptoms (malaise, fever, headaches). Combination chemotherapy with doxorubicin, bleomycin and vinblastine (DBV) has been abandoned in view of a high rate of opportunistic infections (50 per cent) and the possibility of aggravating immune suppression. At New York University Medical Center a trial with concurrent therapy with VP-16 and recombinant alpha-2 interferon is now in progress, but results have not yet been reported. At our centre we use a modified, similar protocol. So far, 3 patients have been treated with VP-16 alone, with one partial response and 2 not responding. The responder stopped therapy after 3 courses because of side effects (malaise, alopecia), and Kaposi's sarcoma soon became progressive again. Half a year later he died from an opportunistic infection. Another patient was treated concurrently with VP-16 and recombinant alpha-2 interferon and showed a partial response. He, too, died from an opportunistic infection. The patient with the single presenting lesion who was lost for follow-up, was treated locally (excision and postoperative radiotherapy).

AIDS is the most dramatic expression of infection with a newly discovered retrovirus, called LAV/HTLV-III. At present it is estimated that about 7 per cent of those infected by the virus will develop AIDS but, considering the long incubation period, this may be an underestimation. The disease poses a serious threat to persons at risk and has already been the cause of immense human suffering. Our efforts should focus on providing appropriate care and finding effective therapies (anti-HTLV-III drugs, immunomodulation?) for those affected, and on protection (screening of blood donors, development of a vaccine) of those at risk, but not yet infected.

Acknowledgements – The authors are indebted to all the physicians and nurses who took care of the patients described here.

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Neth J Med 28 (1985)
NOTE TO AUTHORS — VANCOUVER STYLE

Most medical journals agreed to accept articles prepared in accordance with the Vancouver style, and will introduce this system from January 1980 on. Consequently, the Editors of The Netherlands Journal of Medicine decided to adapt the Instructions to Authors accordingly.

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Authors should retain a complete copy of the manuscript, as the Editors do not accept responsibility for loss of papers submitted. Submission of a paper is held to imply that it does not contain material reported or published elsewhere, except as an abstract of 600 words or less.

Manuscripts should be written in English. All papers are published in English. The entire paper (including figures and tables) should be submitted in triplicate, typewritten (double-spaced) on one side of the paper (A4 format) and with margins of about 4 cm. Generally, the paper should be organized as follows: separate title page, summary, introduction, methods, results, discussion, acknowledgements, references, figure legends, and tables.

The title page should carry the title of the paper, the names of the authors, and the department or institute and the town where the work was performed. A short running title should also be supplied.

The summary should summarize the important information in the paper and not exceed 200 words.

No abbreviations without definition should be used in the text except those listed below. Mention the statistical method employed. Use a capital initial letter for proprietary names of substances and materials. At first mention of a chemical substance, use the correct chemical designation as well as the generic name.

Number footnotes to the texts as follows: (1), and type them at the foot of the page where they belong. Refer to footnotes in the title and the tables with the following symbols and in this order: *, **, ***; 1, §.

To indicate references in the text, use superior numbers: 1,2,3. Journal citations in the reference list should be typed double-spaced on a separate page and numbered consecutively in the order in which they appear in the text. The complete title should be given. Names of journals should be abbreviated according to Index Medicus, US National Library of Medicine. Examples:

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Books

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Enclose figures (three copies of unmounted photographs with good contrast printed on glossy white paper, width preferably 78 or 164 mm) in a separate envelope. Note on the back (with a soft pencil) the number of the figure and the name of the first author, and clearly indicate which is the top side. Lettering in drawings and diagrams should be large enough to be legible after reduction to column width. Double-space legends consecutively on a separate sheet. Legends should be concise and clearly explain the figures without reference to the text.

Tables should be typed double-spaced on separate sheets. Quotation-marks and vertical lines should not be used. Tables should be numbered with Roman numerals and should have a brief heading. The use of SI units is allowed.

A maximum of seventy-five reprints will on request be supplied to the first (or senior) author free of charge. Additional reprints can be ordered when proofs are returned.

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