# Current Review

# AIDS: acquired immunodeficiency syndrome

N.J. GILMORE, PH D, MD
R. BEAULIEU, MD
M. STEBEN, MD
M. LAVERDIÈRE, MD

**Acquired immunodeficiency syndrome, or AIDS, is a new illness that occurs in previously healthy individuals. It is characterized by immunodeficiency, opportunistic infections and unusual malignant diseases. Life-threatening single or multiple infections with viruses, mycobacteria, fungi or protozoa are common. A rare neoplasm, Kaposi's sarcoma, has developed in approximately one third of patients with AIDS. More than 800 cases of AIDS have been reported in North America, over 24 of them in Canada. The majority of patients are male homosexuals, although AIDS has also developed in abusers of intravenously administered drugs, Haitian immigrants, individuals with hemophilia, recipients of blood transfusions, prostitutes, and infants, spouses and partners of patients with AIDS. The cause of AIDS is unknown, but the features are consistent with an infectious process. Early diagnosis can be difficult owing to the nonspecific symptoms and signs of the infections and malignant diseases. Therefore, vigilance by physicians is of utmost importance.**

**Le syndrome d'immunodéficience acquise, ou SIDA, est une nouvelle maladie qui survient chez des individus antérieurement en bonne santé. Devenant immunodéficient, ceux-ci développent des infections opportunistes ou des néoplasies malignes inhabituelles. Qu'il s'agisse de virus, de mycobactéries, de champignons ou de protozoaires, l'issu de ces infections, simples ou multiples, est souvent fatale. Environ un tiers des patients porteurs du SIDA ont développé une néoplasie maligne rare appellée le sarcome de Kaposi. Il y a eu plus de 800 cas rapportés en Amérique du Nord, et 24 de ces cas l'ont été au Canada. La majorité des patients sont des homosexuels mâles. Cependant, de nombreux cas ont aussi été découverts au sein des toxicomanes utilisant des drogues intraveineuses, des immigrants haïtiens, des hémophiles, des receveurs de transfusion sanguine, des prostituées, et des enfants ainsi que des partenaires sexuels de patients porteurs de SIDA. La cause de cette affection n'est pas connue, mais tout laisse croire qu'elle serait de nature infectieuse. Un diagnostic précoce peut s'avérer difficile étant donné la nonspécificité des symptômes et des signes que peuvent produire ces infections et ces néoplasies malignes. Il en résulte que les médecins doivent être d'une vigilance particulière face à ce syndrome.**

Opportunistic infections, neoplasia and autoimmune phenomena are common expressions of immunodeficiency.[1] During the past 3 years a new immunodeficiency syndrome, characterized by infections, neoplasia and, less frequently, autoimmune phenomena, has appeared in North America.[2-14] Acquired immunodeficiency syndrome, or AIDS, is an illness of unknown cause that occurs inexplicably in previously healthy adults and infants.[6-8,10-14] The associated infections have been caused by *Pneumocystis*, *Candida*, *Aspergillus*, *Cryptococcus*, *Nocardia*, *Strongyloides*, *Toxoplasma*, mucormycetes, atypical mycobacteria, *Entamoeba*, cryptosporidia, cytomegalovirus and the viruses causing herpes simplex, genitalis and zoster. Malignant diseases have included generalized Kaposi's sarco-

Prepared on behalf of the Quebec AIDS Committee/Comité SIDA du Québec, whose members, in addition to the authors, include R. Morisset, MD (chmn), M. Bergeron, MD, J. Davies, MD, R. Duperval, MD, E. Goldberg, MD, S. Handzel, MD, J. Hoey, MD, T. Maroun, DEd, G. Martineau, MD, D. Phaneuf, MD, D. Portnoy, MD, J. Portnoy, MD, J. Robert, MD, G. Tarjan, MD, R. Thomas, MD and J. Yelle, MD.

Reprint requests to: Dr. N.J. Gilmore, Division of clinical immunology, Royal Victoria Hospital, 687 Pine Ave. W, Montreal, PQ H3A 1A1

Currently AIDS is not a reportable disease. However, it is being carefully monitored by the bureau of epidemiology, Laboratory Centre for Disease Control (LCDC), Department of National Health and Welfare. It is therefore recommended that all suspected or confirmed cases be reported to the LCDC (613-996-4041) or, when provincial regulations apply, to local health authorities. AIDS has recently been added to the list of notifiable diseases in British Columbia. Physicians in British Columbia wishing to report cases or obtain additional information should contact Dr. R.G. Mathias (604-874-2331). In Ontario, physicians should contact Dr. R. Andreychuk (416-963-2238). Our committee is coordinating information on and reported cases of AIDS. Similar committees may be formed in other provinces; until then our committee members can provide any additional information (514-489-6877).

ma, Burkitt's lymphoma, undifferentiated non-Hodgkin's lymphoma, cloacogenic carcinoma and carcinoma of the tongue in young nonsmokers.[15] Autoimmune thrombocytopenia or hemolysis, sometimes accompanied by rheumatologic syndromes, have occurred, but infrequently.[14]

AIDS has been confined to certain population groups: homosexual or bisexual men (75% of cases), abusers of intravenously administered drugs (13%), Haitian immigrants to North America (6%), individuals with hemophilia (less than 1%), and a heterogeneous group of individuals (less than 5%), who include prostitutes, recipients of blood transfusions, and infants, spouses or partners of individuals with AIDS.[2,15] During the past 3 years there has been an exponential increase in the number of cases reported, and at the time of writing over 800 cases have been reported in the United States and 24 in Canada.[15,16] The recent discovery of defective cell-mediated immunity in many asymptomatic and apparently healthy individuals with hemophilia[16-18] and homosexuals[13,19,20] suggests that AIDS may be widespread but not always overwhelming.

Morbidity and mortality are high among persons with AIDS: in approximately 70% of patients an opportunistic or life-threatening infection will develop, and more than 60% of those with *Pneumocystis* pneumonia will die. The 2-year survival rate has been reported to be less than 30%.[15] Those who survive will always have an immunodeficiency and be susceptible to repeated infection or malignant disease.

## Clinical manifestations of AIDS

The clinical manifestations of AIDS are protean, reflecting the diversity and varied presentation of the infections and malignant diseases that can occur in immunocompromised adults.[2-13] Multiple or concomitant infections, or both, and malignant disorders are common. The initial presenting symptoms and signs, which are often nonspecific, include fever, night sweats, extreme or persistent fatigue or malaise, unexplained weight loss, persistent diarrhea, oropharyngeal or esophageal thrush, new and persistent cough or dyspnea, various skin and mucous membrane lesions and unexplained adenopathy. Because these complaints are seemingly nonspecific, they are often not recognized as signals of profound impairment of immunity. Laboratory investigations are often unrevealing, especially in the absence of involvement of a specific organ system. Lymphopenia, polyclonal hypergammaglobulinemia, with or without increased serum concentrations of IgA, and anergy may be noted during testing with common microbial antigens that elicit cell-mediated immune responses.[7,8,10,13] Autoantibodies and changes in the titres of antibodies to infectious agents are usually absent.[6-13] Therefore, sophisticated laboratory testing is often needed to show evidence of impaired immunity.

## Immunologic defects in AIDS

The immune system protects the body from infections, neoplasia and, by suppressing autoimmune phenomena, self-destruction.[1] It has four compartments: B (bone-marrow-derived) lymphocytes, which produce antibodies; T (thymus-derived) lymphocytes (helper and suppressor cells), which kill unwanted cells and regulate immune function; phagocytic cells (neutrophils and monocytes/macrophages); and the complement system. Immune defects in AIDS appear to be restricted to the T-cell compartment.[6-8,10-14] T-cell defects include lymphopenia, abnormal numbers of immunoregulatory T cells (decreased numbers of helper cells and increased numbers of suppressor cells) in the blood, diminished cytotoxicity, and anergy to microbial antigens.[6-8,10-14]

## The gay lymphadenopathy syndrome

In some homosexuals a syndrome of generalized adenopathy, fever, night sweats, extreme malaise, weight loss and, in some cases, diarrhea has developed.[21] Biopsy of nodes usually shows florid hyperplasia. Individuals with the gay lymphadenopathy or lymph node syndrome have T-cell defects similar to those in persons with AIDS,[13,19,20] but usually no other laboratory abnormalities. In some of these individuals the syndrome has progressed to classic AIDS, with infection or malignant disease developing,[21] which suggests that it may be a prodrome or a milder form of AIDS. In general, though, the outcome in patients with this syndrome has not been defined.

## Immunologic defects in asymptomatic homosexual men and individuals with hemophilia

T-cell abnormalities have also been noted in apparently healthy homosexual men.[13,19,20] Kornfeld and associates[20] noted that over 75% of asymptomatic homosexual men had abnormal numbers of regulatory T cells in their blood, a proportion similar to those reported for AIDS and the gay lymphadenopathy syndrome. However, these abnormalities are not restricted to healthy homosexual men. Whereas individuals with hemophilia represent a small proportion of patients with AIDS, a significant proportion of apparently healthy adults with hemophilia A have been shown to have abnormal numbers of T cells in the blood and to have anergy.[16-18] Thus, asymptomatic immune defects appear to be widespread in at least two of the populations at risk of AIDS. If these abnormalities are due to the same process that results in AIDS, then two conclusions are evident: AIDS is a very widespread disease, and its clinical spectrum is broad. Therefore, in many individuals AIDS may be subclinical, manifested by asymptomatic laboratory abnormalities; in some it becomes symptomatic, with adenopathy, fever, malaise and weight loss but without infection or malignant disease; and in a few there may be profound immunodeficiency accompanied by life-threatening infection and malignant disease. AIDS is so new that data on how long such abnormalities persist and on what proportion of patients become symptomatic or acquire infections or cancer are not available.

## Infection due to AIDS

Infection due to AIDS is frequent and may be the presenting complaint. Multiple infections are common, and sexually transmitted diseases (e.g., syphilis, gonorrhea and

hepatitis) may also be present.[5-11] The lungs, gastrointestinal tract and central nervous system are the most frequent sites of infection. *Pneumocystis carinii* pneumonia is the most common infection, and its mortality is 47%.[15] Cytomegalovirus infection is also frequent and often occurs with *Pneumocystis* pneumonia.[9] Mycobacterial infection, invasive fungal infection (e.g., aspergillosis or cryptococcosis), protozoal infection (e.g., toxoplasmosis), and fungal and parasitic infections of the central nervous system have also been reported in AIDS. Aggressive investigation, including a biopsy of the brain, may be needed to establish a diagnosis and is justified in view of the poor prognosis of such infections. Infections of the gastrointestinal tract are common, as is oropharyngeal and esophageal candidiasis.[2-13] Severe, often ulcerating, herpetic infections of the mouth and rectum have occurred,[8] and amebic and cryptosporidial enterocolitis is very common.[15] These parasitic infections and unexplained diarrheal syndromes may precede more virulent infections by many months.

### Malignant disease due to AIDS

Perhaps the most fascinating manifestation of AIDS is Kaposi's sarcoma, which has developed in 37% of individuals with AIDS.[15] It is a fulminant disease, unlike that encountered in elderly Jewish or Italian men. It may present as isolated nodules, multiple lesions, an invasive disease or an aggressive generalized disease characterized by diffuse multiple lesions and generalized adenopathy.[22] Although Kaposi's sarcoma associated with AIDS may present as isolated lesions it usually progresses fulminantly to generalized disease.[5,9,10,13,15] Kaposi's sarcoma in patients with AIDS has not responded to therapy that is effective for patients without AIDS and for those living in Africa, where a generalized form of Kaposi's sarcoma is prevalent. The initial lesions may be nondescript and restricted to mucous membranes. Recognition of these lesions requires great vigilance by physicians. As a result, meticulous examination of skin and mucous membranes is mandatory, and biopsy of new or unexplained lesions is often necessary.

Initial reports have shown an association between the histocompatibility antigen HLA-DR5 and the development of Kaposi's sarcoma both in patients with AIDS and in elderly men without AIDS,[10] which suggests a genetic susceptibility to this disease. However, additional studies are needed to determine if HLA typing will be useful in assessing the risk or the prognosis of this disease.

Lymphoproliferative diseases, such as immunoblastic lymphadenopathy, Burkitt's lymphoma and non-Hodgkin's lymphoma,[2,15] also occur in association with AIDS. Epidermal cancers of the mouth or rectum have also been reported in persons with AIDS.[2,3] The diagnosis of these rare malignant diseases in individuals at risk of AIDS is considered evidence of AIDS.

### Autoimmune disease due to AIDS

Recently autoimmune thrombocytopenia was reported in eight homosexual men, some of whom had evidence of systemic lupus erythematosus, rheumatoid arthritis or autoimmune hemolysis.[14] Autoantibodies appear to be uncommon in patients with AIDS.

### Pathogenesis of AIDS

The cause of AIDS is a mystery. Many of its features suggest an infectious origin, but proof is lacking. The circumstantial evidence includes the distinctive groups at risk, the recent appearance of AIDS, the exponential increase in the number of reported cases, the clustering of cases in certain cities, the close contact between some patients and the possible spread by blood products.[2,16-18,23] The loss of immunity in AIDS is also compatible with an infectious origin. Transient immunosuppression follows many viral infections, such as measles, mumps and mononucleosis due to the Epstein–Barr virus or the cytomegalovirus.[24] Cytomegalovirus is being examined as a cause of AIDS since cytomegalovirus infections are common in homosexual men[2] and since florid infections are often associated with AIDS.[2,9,12]

A specific transmissible agent has not been identified. In view of the possibility that AIDS is a transmissible disease, the LCDC in Ottawa has recommended that suitable precautions be taken to avoid exposure to potentially infectious materials from individuals with AIDS.[16] However, there is no evidence that AIDS has been transmitted to health care personnel.

Many factors have been implicated in the pathogenesis of AIDS: the use of certain drugs, such as nitrites, which are repeatedly inhaled by many homosexual men,[2,10,15,19,20,25] and antimicrobial agents;[2] repeated infections, including sexually transmitted diseases; sexual practices and promiscuity; and exposure to blood products by individuals with hemophilia and abusers of parenterally administered drugs.[16-18] Although these factors may contribute to the loss of immunity their pathogenetic role has been questioned owing to the increasing occurrence of AIDS that is not associated with these factors.[23] Common to many of the individuals with AIDS is prolonged or repeated exposure to potentially antigenic materials, possibly producing an "overload" of the immune system.[21] Among these materials are blood products (in individuals with hemophilia), contaminated drugs or apparatus used in the illicit administration of drugs (in drug addicts) and infectious agents (in homosexual men).

### Diagnosis of AIDS

Since AIDS is an acquired immunodeficiency disease of unknown cause, its diagnosis is only valid when potential causes of immunodeficiency are absent. These include age greater than 60 years, pre-existing malignant disease, protein–energy malnutrition, treatment with corticosteroids, immunosuppressive drugs or radiation, and recent viral infections, such as measles, mumps or mononucleosis.[24] An opportunistic infection or an unusual neoplasia such as Kaposi's sarcoma can be considered evidence of immunodeficiency when confirmation of the immunodeficiency by sophisticated laboratory testing is not readily available. Autoimmune phenomena in individuals at risk of AIDS who show evidence of profound immunodeficiency is also consistent with AIDS. Laboratory evidence of immunodeficiency in the absence of infection, malignant dis-

ease or autoimmune phenomena is not diagnostic of AIDS, even though such abnormalities may represent a prodrome or a milder form of AIDS.

The groups at risk of AIDS include homosexual or bisexual men, drug addicts, Haitian immigrants to North America, individuals with hemophilia or other recipients of blood transfusions, prostitutes, and the spouses, partners and offspring of these groups.[2,15,16,23,26] Symptomatic individuals suspected of having an immunodeficiency who belong to these groups should undergo aggressive investigation to ensure that their symptoms are not due to opportunistic infection or malignant disease. AIDS may be exceedingly difficult to recognize, but failure to recognize it or to start treatment promptly can be catastrophic. Since the immunodeficiency appears to persist in patients with AIDS despite treatment of the infection or the malignant disease, continued close observation is mandatory.

The gay lymphadenopathy syndrome represents a vexing clinical problem since generalized adenopathy and a variety of constitutional symptoms may be the presenting manifestations of many diseases. There is no specific diagnostic test for this syndrome, so extensive investigation is usually needed.[21] Although the value of lymph node biopsy has not been clearly defined it may be useful in eliminating other possible causes of the adenopathy. On the basis of the experience in the United States, a small proportion of individuals with the gay lymphadenopathy syndrome can be expected to acquire infection or malignant disease.[21] Since no investigation can define the risk of these complications, thorough evaluation and periodic re-evaluation, as well as immediate intervention whenever there is clinical deterioration, are indicated.

The available evidence suggests that asymptomatic individuals who belong to the groups in which AIDS has developed are in fact at a low risk. Although there are T-cell defects in some asymptomatic individuals their significance is unknown. Tests of cell-mediated immunity have not been validated as predictors of the development of AIDS or of the extent, activity or prognosis of the disease. Therefore, until such information is known, extensive immunologic investigation should be reserved for symptomatic individuals when evidence of immunodeficiency may be of value in establishing a diagnosis. Evaluation of asymptomatic individuals requires clinical assessment, including meticulous examination of the skin, lymph nodes, lungs and gastrointestinal tract, for evidence of opportunistic infection or malignant disease. Subsequent laboratory investigations should be dictated by the results of the clinical examination.

## References


1. COOPER MD, BUCKLEY RH: Developmental immunology and the immunodeficiency diseases. *JAMA* 1982; 248: 2658–2669
2. Centers for Disease Control Task Force on Kaposi's Sarcoma and Opportunistic Infections: Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infections. *N Engl J Med* 1982; 306: 248–252
3. COOPER HS, PATCHEFSKY AS, MARKS G: Cloacogenic carcinoma of the anorectum in homosexual men: an observation of four cases. *Dis Colon Rectum* 1979; 29: 557–558
4. LEACH RD, ELLIS H: Carcinoma of the rectum in male homosexuals. *J R Soc Med* 1981; 74: 490–491
5. HYMES KB, CHEUNG T, GREENE JB, PROSE NS, MARCUS A, BALLARD H, WILLIAM DC, LAUBENSTEIN LJ: Kaposi's sarcoma in homosexual men — a report of eight cases. *Lancet* 1981; 2: 598–600
6. GOTTLIEB MS, SCHROFT R, SCHANKER HM, WEISMAN JD, PENG FT, WOLF RA, SAXON A: *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med* 1981; 305: 1425–1431
7. MASUR H and 10 others: An outbreak of community-acquired *Pneumocystis carinii* pneumonia. Initial manifestation of cellular immune dysfunction. Ibid: 1431–1438
8. SIEGAL FP and 13 others: Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. Ibid: 1439–1444
9. URMACHER C, MYSKOWSKI P, OCHOA M, KRIS M, SAFAI B: Outbreak of Kaposi's sarcoma with cytomegalovirus infection in young homosexual men. *Am J Med* 1982; 72: 569–575
10. FRIEDMAN-KIEN AE, LAUBENSTEIN LJ, RUBINSTEIN P, BUIMOVICI-KLEIN E, MARMOR M, STAHL R, SPIGLAND I, KWANG KS, ZOLLA-PAZNER S: Disseminated Kaposi's sarcoma in homosexual men. *Ann Intern Med* 1982; 96: 693–700
11. MILDVAN D, MATHUR U, ENLOW RW, ROMAIN PL, WINCHESTER RJ, COLP C, SINGMAN H, ADELSBERG BR, SPIGLAND I: Opportunistic infections and immune deficiency in homosexual men. Ibid: 700–704
12. FOLLANSBEE SE, BUSCH DF, WOFSY CB, COLEMAN DL, GULLET J, AURIGEMMA GP, ROSS T, HADLEY WK, DREW WL: An outbreak of *Pneumocystis carinii* pneumonia in homosexual men. Ibid: 705–713
13. STAHL RE, FRIEDMAN-KIEN A, DUBIN R, MARMOR M, ZOLLA-PAZNER S: Immunologic abnormalities in homosexual men. Relationship to Kaposi's sarcoma. *Am J Med* 1982; 73: 171–178
14. MORRIS L, DISTENFELD A, AMOROSI E, KARPATKIN S: Autoimmune thrombocytopenic purpura in homosexual men. *Ann Intern Med* 1982; 96: 714–717
15. Update on acquired immune deficiency syndrome (AIDS) — United States. *Morb Mortal Wkly Rep* 1982; 31: 507–514
16. Decreased cell-mediated immunity in a symptomatic hemophiliac and the immunologic status of asymptomatic hemophilia patients — Quebec. *Can Dis Wkly Rep* 1982; 8-50: 249–250
17. LEDERMAN MM, RATNOFF OD, SCILLIAN JJ, JONES PK, SCHACTER B: Impaired cell-mediated immunity in patients with classic hemophilia. *N Engl J Med* 1983; 308: 79–83
18. MENITOVE JE and 10 others: T-lymphocyte subpopulations in patients with classic hemophilia treated with cryoprecipitate and lyophilized concentrates. *N Engl J Med* 1983; 308: 83–86
19. GOEDERT JJ, NEULAND CY, WALLEN WC, GREENE MH, MANN DL, MURRAY C, STRONG DM, FRAUMENI JF JR, BLATTNER WA: Amyl nitrite may alter T lymphocytes in homosexual men. *Lancet* 1982; 1: 412–416
20. KORNFELD H, VANDE STOUWE RA, LANGE M, REDDY MM, GRIECO MH: T-lymphocyte subpopulations in homosexual men. *N Engl J Med* 1982; 307: 729–731
21. Centers for Disease Control: Persistent, generalized lymphadenopathy among homosexual males. *Morb Mortal Wkly Rep* 1982; 31: 249–251
22. SAFAI B, GOOD RA: Kaposi's sarcoma: a review and recent developments. *CA* 1981; 31: 2–12
23. HAVERKOS HW, CURRAN JW: The current outbreak of Kaposi's sarcoma and opportunistic infections. *CA* 1982; 32: 330–339
24. REINHERZ EL, O'BRIEN C, ROSENTHAL P, SCHLOSSMAN SF: The cellular basis for viral-induced immunodeficiency: analysis by monoclonal antibodies. *J Immunol* 1980; 125: 1269–1274
25. MARMOR M, FRIEDMAN-KIEN AE, LAUBENSTEIN L, BYRUM RD, WILLIAM DC, D'ONOFRIO S, DUBIN N: Risk factors for Kaposi's sarcoma in homosexual men. *Lancet* 1982; 1: 1083–1087
26. MASUR and 17 others: Opportunistic infection in previously healthy women. Initial manifestations of a community-acquired cellular immunodeficiency. *Ann Intern Med* 1982; 97: 533–539