

UPDATE V

Harrison's

PRINCIPLES OF INTERNAL MEDICINE

Petersdorf • Adams • Braunwald • Isselbacher • Martin • Wilson



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UPDATE V:

Harrison's

Principles of Internal Medicine

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UPDATE V

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**PRINCIPLES
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PREFACE

The editors of *Harrison's Principles of Internal Medicine*, encouraged by the positive response of physicians and medical students to the publication of the Updates, have decided to continue the Update series between the 10th and 11th editions of *Harrison's*. The purpose in publishing the Updates remains as it was when the series was first initiated: (1) to review certain clinical topics that could not be covered comprehensively in *Harrison's* and (2) to cover selected new and important medical advances that have become an integral part of medical knowledge since the preparation of the 10th edition.

One Update a year (V-VII) will be published between now and the 11th edition of *Harrison's*. Two of the volumes will have central themes: Update VI will focus on new treatment modalities and Update VII will focus on oncology. For Update V the editors have selected topics in the various clinical disciplines that in their judgment are timely and relevant. Brief explanatory summaries of each article in the table of contents provide insight into the selection process.

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THE ACQUIRED IMMUNE-DEFICIENCY SYNDROME

ALVIN E. FRIEDMAN-KIEN and JEFFREY B. GREENE

The unexpected appearance of opportunistic infections and an aggressive form of Kaposi's sarcoma among apparently healthy homosexual men and intravenous drug users in the latter half of 1980 heralded the recognition of a new clinical entity known as the *acquired immune-deficiency syndrome (AIDS)*. Its sudden occurrence was reminiscent of Legionnaires' disease and the toxic-shock syndrome, but its impact on public health has already exceeded these illnesses. The over 2000 reported cases exhibiting a greater than 50 percent mortality rate represent an as yet undefined fraction of the true number of cases of AIDS.

AIDS, as its name implies, represents a form of secondary immunologic disorder that results in profound depression of cell-mediated immunity. The unique feature of this illness is that the observed abnormalities of immune function are persistent.

The syndrome has become the subject of intensive worldwide clinical and scientific investigation. Its study promises to provide insights into the fundamental mechanisms of immune function, host-parasite relationships, and perhaps the understanding of neoplasia. The clinician is anxiously awaiting the development of diagnostic and therapeutic modalities for use in the ever-increasing numbers of patients afflicted with this life-threatening illness.

DISEASE DESCRIPTION

Experience with AIDS over the past 3 years has led to the recognition that this illness may present to the physician in different ways. At one end of this clinical spectrum is the asymptomatic

patient who demonstrates cutaneous anergy, lymphopenia, reversal of the T-helper/T-suppressor cell ratio, and depressed in vitro lymphoproliferative responses to various antigens and mitogens. At the distant end of the spectrum is the patient who presents with fulminant, disseminated Kaposi's sarcoma or with respiratory failure due to *Pneumocystis carinii* infection. Between these extremes are patients suffering from a vague persistent constitutional illness suggestive of a chronic viral disease, or a more characteristic set of symptoms involving the pulmonary, gastrointestinal, or central nervous systems. Other individuals may develop unexplained lymphadenopathy associated with constitutional symptoms. They do not necessarily go on to develop more serious complications of AIDS. It is probably inaccurate to label the less ill patients as "prodromal-AIDS" since many have not progressed from their vague constitutional illness to life-threatening infections or disseminated Kaposi's sarcoma. It is possible that their clinical picture, unaffected by secondary diseases, better depicts the true characteristics of AIDS. Still another group may seek medical attention because of the discovery of a mucocutaneous lesion of Kaposi's sarcoma in the absence of any systemic symptoms.

The diversity of clinical presentations of AIDS is mirrored by the wide range of infectious and noninfectious conditions that are associated with it. Review of the biologic agents that have been reported to cause life-threatening infections in the patients with AIDS gives some insights into the underlying immunologic defect of this disease (Table 1). Many of these infectious agents are ubiquitous and capable of causing mild or subclinical disease in healthy individuals. How-

TABLE 1

Biologic agents reported to cause infections in patients with the acquired immune-deficiency syndrome

<i>Parasitic</i>	<i>Fungal</i>	<i>Viral</i>	<i>Bacterial</i>
<i>Pneumocystis carinii</i>	<i>Candida albicans</i>	Cytomegalovirus	<i>Mycobacterium avium-intracellulare</i>
<i>Toxoplasma gondii</i>	<i>Cryptococcus neoformans</i>	Varicella-zoster	<i>M. tuberculosis</i>
<i>Cryptosporidium</i>	<i>Aspergillus</i> spp.	Herpes simplex	Other "atypical" <i>Mycobacterium</i> spp.
<i>Isospora belli</i>	<i>Histoplasma capsulatum</i>	Epstein-Barr	<i>Legionella</i> spp.
<i>Strongyloides stercoralis</i>		Papovavirus* (J-C virus)	<i>Salmonella</i> spp.
			<i>Nocardia</i> spp.

*Agent of progressive multifocal leukoencephalopathy.

ever, because these organisms are known to cause life-threatening infections, especially in the immunocompromised host, they are considered "opportunistic" pathogens. The profound immunosuppression seen in patients with AIDS

renders them particularly susceptible to severe infection by these agents (Table 2).

The neoplastic diseases that have been associated with AIDS are shown in Table 3. Prior to the AIDS epidemic, Kaposi's sarcoma, a rare

TABLE 2

Common infectious diseases complicating the acquired immune-deficiency syndrome

<i>Pathogen</i>	<i>Infection</i>
Protozoal	
<i>Pneumocystis carinii</i>	Pneumonia
<i>Toxoplasma gondii</i>	Necrotizing encephalitis
	Disseminated infection
<i>Cryptosporidium</i>	Enteritis
<i>Isospora belli</i>	
Fungal	
<i>Candida albicans</i>	Thrush
	Invasive esophagitis
	Disseminated Moniliasis
<i>Cryptococcus neoformans</i>	Meningitis
	Disseminated (lung, bone marrow, adrenal, renal, central nervous system)
Viral	
<i>Herpes simplex</i>	Extensive, persistent anogenital
	Visceral (pulmonary, gastrointestinal)
<i>Varicella zoster</i>	Severe, localized cutaneous
	Disseminated (cutaneous, visceral)
Human papilloma virus	Condylomata acuminata
J-C Papovavirus	Progressive multifocal leukoencephalopathy
Bacterial	
<i>Mycobacterium avium-intracellulare</i>	Disseminated infection
<i>M. tuberculosis</i>	Localized (pulmonary, cerebrospinal fluid)
	Miliary
<i>Legionella</i> spp.	Pneumonia

TABLE 3
Neoplastic disease associated with acquired immune-deficiency syndrome

Epidemic Kaposi's sarcoma
Undifferentiated lymphoma
Burkitt's-like lymphoma
Immunoblastic lymphoma
Cloacogenic carcinoma
Squamous cell carcinoma of the oral cavity

tumor predominantly seen in males, was known to occur in different populations. The classical form of Kaposi's sarcoma is a localized, indolent neoplasm, usually observed in elderly men of Mediterranean or eastern Ashkenazic Jewish European ancestry (Table 4). A more invasive localized variety of this tumor is seen in young black adults in equatorial Africa. In addition, a generalized, lymphadenopathic form is found in black African children. Kaposi's sarcoma has also been observed in the United States in iatrogenically immunosuppressed patients such as renal transplant recipients or patients who had received immunosuppressive therapy for other indications. A newly recognized epidemic form of Kaposi's sarcoma has been identified in association with or as a manifestation of AIDS. While this form is histologically identical to the others, it is a widely disseminated tumor with

unique clinical characteristics (see "Clinical Manifestations" below). In addition, diffuse undifferentiated lymphomas and Burkitt-type lymphomas have been reported in patients with AIDS. Further study is necessary to establish that these less frequently seen neoplasms are occurring in excess of their expected background incidence.

Certain nonneoplastic conditions appear to be associated with AIDS as well. Autoimmune-like thrombocytopenic purpura, qualitative platelet dysfunction, azoospermia associated with the presence of antispermatozoal antibodies, and an observed "cotton-wool" retinopathy are examples.

The foregoing discussion has stressed the diversity of the clinical manifestations of AIDS. Consideration of diagnosis requires a high index of suspicion and familiarity with the epidemiologic risk factors. Clinicians in every field must be prepared for the possibility of having to diagnose this illness.

EPIDEMIOLOGY

Through the reporting of patients by clinicians in New York and California in the early part of 1981, the U.S. Centers for Disease Control

TABLE 4
Clinical variants of Kaposi's sarcoma

Type	Population	Clinical characteristics	Usual course
Classical	Elderly Jewish and Italian individuals; Male/Female = 10-15:1 Iatrogenically immunosuppressed	Localized nodular; lower extremities predominantly involved	Indolent, 10-15 years duration Rarely with late visceral involvement
Localized "florid" aggressive	African Adults; Male/Female = 17:1	Localized; invasive of muscle and bone	Slowly progressive, but fatal over 5-8 years Late visceral involvement
Lymphadenopathic	African children age 2-15 years; Male/Female = 3:1	Extensive and generalized lymph node and visceral involvement Rare cutaneous lesions	Rapid, fatal course within 3 years
"Epidemic" disseminated	Acquired immunodeficiency syndrome Iatrogenically immunosuppressed	Mucocutaneous lesions as well as widespread nodal and visceral involvement Males predominantly	Progressive, becomes fulminant, fatal in 2-3 years In patients on immunosuppressive drugs—occasionally tumor regresses after cessation of immunosuppressive therapy

TABLE 5

Neoplasms or infections used as criteria for the diagnosis of acquired immune-deficiency syndrome (AIDS) for surveillance purposes by the Centers for Disease Control

Epidemic Kaposi's sarcoma (in males under 60 years of age)
Lymphoma (central nervous system)
<i>Pneumocystis carinii</i> pneumonia
<i>Mycobacterium avium-intracellulare</i> (disseminated)
Cryptosporidial enteritis
Cryptococcal meningitis
<i>Candida albicans</i> (esophagitis)
Toxoplasmosis (encephalitis, pneumonia)
<i>Strongyloides stercoralis</i> (hyperinfection)
Aspergillosis (central nervous system or disseminated)
Progressive multifocal leukoencephalopathy
Cytomegalovirus (pneumonitis, colitis, encephalitis)
Herpes simplex (anogenital, persisting for greater than 1 month; esophagitis; pneumonitis)

(CDC) became aware of the AIDS epidemic. Since that time this agency has remained the most comprehensive source of epidemiologic information regarding this disease. For the purpose of surveillance, the CDC have formulated an operational definition of AIDS: The finding of any one of a number of infectious diseases or Kaposi's sarcoma, that is "moderately indicative of an underlying cellular immunodeficiency" in a patient where no cause of that immune defect can be found. The diseases that are currently being accepted as being suggestive of the underlying cellular immunodeficiency are shown in Table 5. By September of 1983, over 2600 cases of AIDS fulfilling this definition had been reported. Forty-six states had reported cases, with the largest numbers contributed by New York (43 percent of the total), followed by California and Florida. In addition to cases in the United States, more than 20 countries have reported cases of AIDS. While little epidemiologic data are available from Haiti, this country seems to have a very significant geographic cluster of cases, especially in the vicinity of Port-au-Prince.

In the United States, 93 percent of the reported cases have been in males with a mean age of approximately 37 years (range: 20 to 64 years). Several epidemiologic groups are now recognized as being at risk, including homosexual or bisexual males, intravenous drug users, and Haitians who have recently immigrated to North America. Men of homosexual or bisexual orientation account for 71 percent of the total number

of reported cases of AIDS. Male and female intravenous drug users and recent Haitian immigrants represent 17 and 5 percent of the cases, respectively. All primary racial groups have been represented among the reported patients without any apparent predilection.

Of the 175 cases of AIDS in females, 52 percent occurred in known parenteral drug users and 10 percent in Haitian immigrants. It is interesting to note that among these, only 7 cases of epidemic Kaposi's sarcoma have been reported, all parenteral drug abusers.

A number of other populations are now being suspected of being at risk for AIDS. One such group is patients with hemophilia; 15 cases with severe opportunistic infections have been reported. All of these 15 cases had been transfused with the lyophilized clotting-factor concentrate. A recent study has found low T-helper/T-suppressor lymphocyte ratios in apparently healthy hemophiliacs who had received lyophilized factor VIII concentrate. AIDS has not been diagnosed in hemophiliacs treated only with cryoprecipitate. These observations have been thought to support a theory that there is transmission of an AIDS agent during administration of lyophilized factor VIII but not cryoprecipitate because the former substance is prepared from a much larger commercial donor pool. However, immunosuppression by factor concentrates themselves offers an alternate explanation for this observation.

There have been about 20 cases of AIDS in

patients with no known risk factors who had received blood products up to 3 years before the onset of their disease. In each case blood-product donors with unexplained lymphadenopathy or a nonspecific constitutional illness could be identified. In one instance a blood-product donor was found to have AIDS fulfilling the CDC criteria. Thus, while the possibility of transmission of AIDS via transfusion of blood products is raised by the recognition of this small number of cases, a direct causal relationship has not been established. Over 30 million units of blood were transfused in the United States between 1979 and 1982. It would seem that the risk of developing AIDS in the face of blood transfusion is quite low.

There have been 21 infants or young children reported to the CDC with AIDS-like illnesses. All of these patients have had evidence of depressed cell-mediated immunity. Some of these children were born to mothers with AIDS or to mothers who were at risk for AIDS because of their Haitian origin or history of parenteral drug use. These cases of AIDS-like illnesses in children could be explained by exposure to an AIDS agent prenatally, during parturition, or after birth through intimate household contact (such as breast-feeding). The difficulty in evaluating these children, however, is that it is often impossible to exclude the many congenital causes of immunodeficiency. Therefore, these cases have not been included in the CDC figures.

In addition, eight female sexual partners of AIDS patients who had been parenteral drug users have had immunologic changes similar to those seen in AIDS. One of these women later developed AIDS. Thus female sex partners of AIDS patients may also be at risk.

Of the more than 2600 cases reported to the CDC during the past 3 years, approximately 6 percent cannot be placed into any of the defined epidemiological risk groups. This figure has not changed significantly during the epidemic, suggesting that AIDS remains relatively confined to the recognized risk groups. Some investigators have used this information to suggest that certain susceptibility factors common to the at-risk populations may be a prerequisite for the development of AIDS. The concept of susceptibility factors is consonant with the interesting observation that the mean age for AIDS is 37 years. Rela-

tively few cases of AIDS have been reported in homosexual men aged 18 to 23 years, implying that factors other than the level of sexual activity may be important.

After the recognition that men of homosexual orientation were at risk for AIDS, case-control studies were performed to attempt to identify specific risk factors. The major differences between the AIDS cases and their controls identified sexual activity with numerous partners and the use of various recreational drugs, especially amyl and butyl nitrite, as risk factors. Specific sexual practices, including analingus and passive rectal intercourse, were also more frequently reported among the cases. Recently, however, a greater percentage of homosexual patients are reporting fewer numbers of sexual partners.

Much less attention has been given to the epidemiologic study of other groups at risk, such as Haitians or intravenous drug users. There are some striking differences in the clinical aspects of the illness in these groups compared to homosexual men. An intriguing example is the relative paucity of cases of Kaposi's sarcoma in the non-homosexual groups. Ninety-five percent of all cases of epidemic Kaposi's sarcoma have been in homosexual or bisexual men. While 48.5 percent of homosexual or bisexual men with AIDS have the epidemic form of Kaposi's sarcoma, only 2 percent of the Haitians and 5.3 percent of the parenteral drug-using AIDS patients demonstrate this complication. No cases of Kaposi's sarcoma in hemophiliacs with AIDS have been reported. The reasons for these differences remain obscure. Other observed differences in the clinical manifestations of AIDS among the various groups at risk concern the infectious complications of the disease. The incidence of tuberculosis, or of toxoplasmosis in Haitians with AIDS, for example, exceeds that of the other defined risk groups. This may reflect a greater likelihood of premorbid exposure to these pathogens.

New cases of AIDS are being reported to the CDC at a rate of three to four cases daily. The number of cases reported thus far has doubled every 6 months. As of September 1983, about 40 percent of the total number of reported cases have died. The mortality rate in patients with opportunistic infections is more than twice that of those with Kaposi's sarcoma alone. The

2-year survival of this illness may be less than 10 percent.

Clusters of cases with direct or indirect sexual contact support the belief that AIDS may be caused by a transmissible agent with similar biologic behavior to hepatitis B virus. Even if the disease is, in fact, transmissible, there is no information regarding the period of communicability, secondary attack rates (the incidence of the disease among contacts), or the precise routes of transmission. However, many nonsexual household contacts and health care personnel caring for cases do not appear to be at increased risk for AIDS. While there remain many unanswered questions regarding the epidemiology of this new syndrome, it does not appear that casual contact with patients represents a significant public health problem.

CLINICAL MANIFESTATIONS

The symptoms and signs in the patient with AIDS may be nonspecific and are often due to the infectious or neoplastic complications rather than to the disease itself. Nonetheless, physicians who have gained extensive experience with this complex illness have come to recognize a number of clinical manifestations that prove useful in the evaluation of putative patients.

Symptoms may be constitutional or may be organ system specific. The AIDS patient has often been aware of ill-health for several months and has usually sought medical attention at an earlier time. The predominant symptoms are marked malaise and pronounced fatigue that interfere with day-to-day activities. The patient often abandons his or her usual physical activity and requires excessive sleep. Patients frequently complain of anorexia and diminished libido. Low-grade fevers and night sweats are common symptoms, as is a moderate weight loss (of approximately 10 to 15 lb over a period of several months). Migratory myalgias and arthralgias that often respond to aspirin are also common.

Medical histories among the homosexual AIDS patients are remarkable for a variety of sexually transmitted diseases, including syphilis, gonorrhea, herpes progenitalis, condylomata acuminata, hepatitis A and B, amebiasis, giardiasis, and lymphogranuloma venereum. Accordingly, many patients have been repeatedly

treated under medical supervision with a variety of antimicrobial agents. Moreover, patients may have used self-prescribed antibiotics as infection prophylaxis for sexual activity.

Organ-specific complaints are common and should be sought in the medical history. Persistent lymphadenopathy is frequently recognized by the patient. The lymph node swellings are noted to wax and wane and the nodes are occasionally tender. The adenopathy is often generalized but most often is reported to occur in the posterior cervical, submandibular, or axillary regions.

Skin rashes and generalized pruritus that are new to the patient are also common, as are painful cheilosis, glossitis, and stomatitis. Some patients may report a change in their patterns of preexisting genital herpes infections, with unusually severe, protracted, or more frequently recurring episodes. The occurrence of shingles (herpes zoster) has been observed at an apparently increased rate as well.

Commonly, symptoms associated with opportunistic infections can fall into one or more complexes as indicated in Table 6. Recognition of the significance of these symptom complexes will help the physician direct a diagnostic plan and initiate early therapy.

The pulmonary symptom complex is encountered most often, reflecting the relative frequency of *P. carinii* pneumonia. High fever (102°F or higher), dyspnea on exertion, a non-productive cough, and vague, nonpleuritic chest discomfort are usually reported. In approximately two-thirds of these patients, respiratory symptoms are of an insidious onset and have been present for 2 to 12 weeks prior to initial evaluation. In contrast, other patients may present with a rapidly progressive pulmonary disease over a period of several days.

Patients with AIDS may present with, or eventually develop, involvement of the central nervous system or an opportunistic infection. Some of these patients will report the occurrence of aphasia, paresis, seizures, or sensory disturbances suggestive of a focal neurologic process. Others develop symptoms consistent with chronic meningitis, such as headache, photophobia, nuchal rigidity, or ocular myalgia. Still others may develop subtle symptoms of memory loss and an inability to concentrate, which may