Acquired immune deficiency syndrome: An overview

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Acquired immune deficiency syndrome is caused by human immunodeficiency virus (HIV), an RNA retrovirus. The T-helper cell, the primary target cell, is destroyed, thus leading to profound immune deficiency of the host and the subsequent clinical sequelae—infection, malignancy, and death. The virus is transmitted primarily by blood in the sharing of drug abuse paraphernalia and of blood and semen during sexual activity. High-risk behavior includes not only male homosexual or bisexual activity and intravenous drug use, but also multiple sex partners and prostitution. It is anticipated that heterosexual transmission of the virus will continue to increase. Efforts to prevent further HIV transmission throughout the population offer the best current hope for stopping or slowing the current progressive increase in the number of AIDS cases. Education of the populace, those with high-risk behavior, and especially health care personnel is essential.

Since the initial clinical reports of pneumocystis pneumonia in young men, the syndrome responsible for this infection has been the object of intensive research efforts and the subject of numerous papers, conferences, and reports in the scientific, medical, and lay press.¹ Acquired immune deficiency syndrome (AIDS) has become the best known of the retroviral infections of man. The Surgeon General² of the United States has prepared a report for the President and testified before Congress regarding AIDS. Most recently, a Presiden-

tial Commission on AIDS has begun meeting, not without some controversy, to address this syndrome and its ramifications. With so much activity, so many publications, and so much media coverage, it is a challenge for the clinician to sort out "the basics" in order to provide an understanding of this disease and some of the recognized issues related to it.

AIDS is a clinical pattern of disease, which is protean in its manifestations and which quantitatively is a small part of a larger whole. AIDS has been determined to be caused by an RNA retrovirus; now known as the human immunodeficiency virus (HIV), it formerly was known as human T-cell lymphotropic virus type III (HTLV III), lymphadenopathy-associated virus (LAV), or AIDS-associated retrovirus (ARV).³ The retroviruses use host cells' endogenous DNA for their replication and propagation. The viral infection initiated by HIV is primarily one of the immune system, although other cells, including macrophages, natural killer cells (NK cells), B-cell lymphocytes, and neuronal cells, can be targets for infection. The virus is tropic for T-lymphocytes of the specific type identified as T-helper cells. These are identified by a cell surface antigen reactive with a monoclonal antibody (OKT₄) and are called T₄ cells, and they serve a "helper" function in the immune system. Table 1 lists the T-helper cell functions. The CD₄ cell surface antigen expressed on T-helper cells (and others) appears to be the initial binding site for the HIV and provides access for cellular infection. T₄ cells are responsible for a number of essential immune system functions, especially new antigen recognition and lymphokine release. Subsequent to infection, these cells are depleted from the circulation, thus leading to profound immune deficiency. The loss of T₄ cells is manifested clinically by increased susceptibility to new infections, reactivation of infection, and malignancy.

TABLE 1. T-HELPER LYMPHOCYTE FUNCTIONS.

New antigen recognition	} Helper function
Interleukin-2 production	
Gamma-interferon production	
T-cell differentiation	
B-Cell activation	
Macrophage stimulation	
Immune modulation	

TABLE 2. CDC CLASSIFICATION SYSTEM FOR HIV INFECTIONS.⁴

Group	Signs/symptoms	Comments
I	Acute infection	May not have positive HIV serology
II	Asymptomatic infection	Healthy appearance, largest group
III	Persistent generalized lymphadenopathy	Abnormal lymphocyte count, abnormal T ₄ /T ₈ ratio
IV	Other disease	
A	Constitutional manifestations	
B	Neurologic manifestations	
C	Secondary infection	
D	Secondary carcinoma	
E	Other conditions	

Groups III, IV-A, and IV-B: AIDS-related complex

Groups IV-B, IV-C, IV-D, and IV-E: AIDS

HIV classification

The spectrum of HIV infections is broad and can be conceptually divided into four groups (Table 2).⁴ Group I persons become acutely infected with HIV, which must have gained access to the body by transmission of infected material through a break in normal protective barriers, that is, skin or mucous membranes. Clinical manifestations include fever, chills, lymphadenopathy, myalgias, or aseptic meningitis.⁵ The acute infection may be so mild as to go undetected or be attributed to the flu.

Immune response generally results in specific antibody development, usually within 3-6 weeks of infection.⁶ Recent evidence⁷ suggests that the latency period from the time of HIV infection to seroconversion may be as long as 14 months. The number of viral particles needed to cause infection is not known.

An asymptomatic phase follows acute infection. These group II individuals appear healthy but are capable of virus transmission and, thus, are infectious. This group is estimated by the Public Health Service⁸ to total 1-1.5 million persons, which makes it the largest group of HIV-infected individuals in the U.S. Some 20-30 percent of this group is expected to develop the complete syndrome of AIDS within 5 years of infection.⁸ The true proportion of infected persons who will develop AIDS remains unknown. The natural history of the asymptomatic phase remains undefined; there may be a latent phase of up to 5 years before the development of AIDS or AIDS-related complex (ARC).⁹

With the onset of generalized lymphadenopathy, infected individuals again become clinically symp-

tomatic (group III). They may have lymphopenia, thrombocytopenia, or an abnormal T-helper cell:T-suppressor cell ratio (T₄ T₈ ratio < 1.0), any of which indicates an abnormal immune state. Individuals may manifest fever, weight loss, or diarrhea (constitutional disease), or dementia, myelopathy, or neuropathy (neurologic disease), or both constitutional and neurologic symptoms. Group IV includes persons who have ARC or AIDS. The Centers for Disease Control's surveillance definition¹⁰ is presented in Table 3. Fully developed AIDS includes secondary opportunistic infections or carcinomas or both (Table 4). AIDS is a fatal illness; there have been no spontaneous recoveries from infection or cancer or restored immune systems.

Virus transmission

HIV is transmitted by infected material, primarily blood, blood products, or sex fluids (semen, vaginal/cervical secretions). Although HIV has been recovered from tears, saliva, urine, and cerebrospinal fluid, transmission of disease by these fluids has not been demonstrated.^{11,12} There is an isolated report¹³ that suggests transmission of the virus by breast milk.

The primary routes of infection transmission are via sexual intercourse in which body fluids are exchanged with an infected individual, sharing of intravenous drug paraphernalia, and perinatal maternal-fetal transmission. A report of HIV infection developing after only two sexual encounters has been published.¹⁴

Heterosexual transmission of HIV as manifested by AIDS still occurs in a minority of cases (approximately 7 percent in 1986). However, heterosexual infection incidence and prevalence data are lacking. Projections for 1991 indicate that heterosexuals will represent 9 percent of the total number of cases (projected to be 270,000 cumulative cases) by that year.⁸ The virus is not transmitted from person to person by insects, pets, or casual contact with infected persons.^{2,12}

The inoculum size or cofactors necessary for infection are unknown. In vitro virus production and cytopathic effects are augmented by immune stimulation of infected T-cells. Serologic evidence of cytomegalovirus infection is virtually 100 percent in men with AIDS or ARC; however, a cofactor role for a CMV in the HIV infection has not been defined.¹⁵

Risk behavior

Because of the large number of asymptomatic HIV-infected individuals who may or may not fit into the previously defined high-risk groups, it is preferable to think of HIV infection in relation to behavior that may be associated with virus transmission.

TABLE 3. 1987 REVISION OF CDC CASE DEFINITION FOR AIDS FOR SURVEILLANCE PURPOSES.¹⁰

For national reporting, a case of AIDS is defined as an illness characterized by one or more of the following "indicator" diseases, depending on the status of laboratory evidence of HIV infection, as shown below.

(I) Without laboratory evidence regarding HIV infection

If laboratory tests for HIV were not performed or gave inconclusive results and the patient had no other cause of immunodeficiency listed in section I.A, then any disease listed in Section I.B indicates AIDS if it was diagnosed by a definitive method.

(A) Causes of immunodeficiency that disqualify diseases as indicators of AIDS in the absence of laboratory evidence for HIV infection

- (1) High-dose or long-term systemic corticosteroid therapy or other immunosuppressive/cytotoxic therapy ≤ 3 months before the onset of the indicator disease
- (2) Any of the following diseases diagnosed ≤ 3 months after diagnosis of the indicator disease: Hodgkin's disease, non-Hodgkin's lymphoma (other than primary brain lymphoma), lymphocytic leukemia, multiple myeloma, any other cancer of lymphoreticular or histiocytic tissue, or angioimmunoblastic lymphadenopathy
- (3) A genetic (congenital) immunodeficiency syndrome or an acquired immunodeficiency syndrome atypical of HIV infection, such as one involving hypogammaglobulinemia

(B) Indicator diseases diagnosed definitively

- (1) Candidiasis of the esophagus, trachea, bronchi, or lungs
- (2) Cryptococcosis, extrapulmonary
- (3) Cryptosporidiosis with diarrhea persisting > 1 month
- (4) Cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes in a patient > 1 month of age
- (5) Herpes simplex virus infection causing a mucocutaneous ulcer that persists longer than 1 month, or bronchitis, pneumonitis, or esophagitis for any duration affecting a patient > 1 month of age
- (6) Kaposi's sarcoma affecting a patient < 60 years of age
- (7) Lymphoma of the brain (primary) affecting a patient < 60 years of age
- (8) Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia (LIP/PLH complex) or both affecting a child < 13 years of age
- (9) *Mycobacterium avium* complex or *M. Kansasii* disease, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- (10) *Pneumocystis carinii* pneumonia
- (11) Progressive multifocal leukoencephalopathy
- (12) Toxoplasmosis of the brain affecting a patient > 1 month of age

(II) With laboratory evidence for HIV infection

Regardless of the presence of other causes of immunodeficiency (Section I.A.), in the presence of laboratory evidence for HIV infection, any disease listed in sections I.B, II.A, or II.B indicates a diagnosis of AIDS.

(A) Indicator diseases diagnosed definitively

- (1) Bacterial infections, multiple or recurrent (any combinations of at least two within a 2-year period), of the following types affecting a child < 13 years of age: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media or superficial skin or mucosal abscesses), caused by *Hemophilus*, *Streptococcus* (including pneumococcus), or other pyogenic bacteria
- (2) Coccidioidomycosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)

- (3) HIV encephalopathy (also called "HIV dementia," "AIDS dementia," or "subacute encephalitis due to HIV")
- (4) Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- (5) Isosporiasis with diarrhea persisting longer than 1 month
- (6) Kaposi's sarcoma at any age
- (7) Lymphoma of the brain (primary) at any age
- (8) Other nonHodgkin's lymphoma of B-cell or unknown immunologic phenotype and the following histologic types:
 - (a) Small noncleaved lymphoma (either Burkitt's or nonBurkitt's type)
 - (b) Immunoblastic sarcoma (equivalent to any of the following, although not necessarily all in combination: immunoblastic lymphoma, large-cell lymphoma, or high-grade lymphoma)

Note: Lymphomas are not included here if they are of T-cell immunologic phenotype or if their histologic type is not described or is described as "lymphocytic," "lymphoblastic," "small cleaved," or "plasmacytoid lymphocytic."

- (9) Any mycobacterial disease caused by mycobacteria other than *M. tuberculosis*, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
 - (10) Disease caused by *M. tuberculosis*, extrapulmonary (involving at least one site outside the lungs, regardless of whether there is concurrent pulmonary involvement)
 - (11) *Salmonella* (nontyphoid) septicemia, recurrent
 - (12) HIV wasting syndrome (emaciation, "slim disease")
- (B) Indicator diseases diagnosed presumptively

Note: Given the seriousness of diseases indicative of AIDS, it is generally important to diagnose them definitively, especially when therapy that would be used may have serious side effects or when definitive diagnosis is needed for eligibility for antiretroviral therapy. Nonetheless, in some situations, a patient's condition will not permit the performance of definitive tests. In other situations, accepted clinical practice may be to diagnose presumptively based on the presence of characteristic clinical and laboratory abnormalities.

- (1) Candidiasis of the esophagus
- (2) Cytomegalovirus retinitis with loss of vision
- (3) Kaposi's sarcoma
- (4) Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia (LIP/PLH complex) or both affecting a child < 13 years of age
- (5) Mycobacterial disease (acid-fast bacilli with species not identified by culture), disseminated (involving at least one site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- (6) *Pneumocystis carinii* pneumonia
- (7) Toxoplasmosis of the brain affecting a patient > 1 month of age

(III) With laboratory evidence against HIV infection

With laboratory test results negative for HIV infection, a diagnosis of AIDS for surveillance purposes is ruled out unless:

- (A) All of the other causes of immunodeficiency listed in section I.A are excluded, and
- (B) The patient has had either
 - (1) *Pneumocystis carinii* pneumonia diagnosed by a definitive method, or
 - (2) Any of the other diseases indicative of AIDS listed in section I.B diagnosed by a definitive method, and a T-helper/inducer (CD_4) lymphocyte count $< 400/\text{cu. mm.}$

TABLE 4. TYPES OF INFECTIONS AND CARCINOMAS IN AIDS PATIENTS—A PARTIAL LIST.

Viruses	Bacteria
Cytomegalovirus*	<i>Streptococcus pneumoniae</i>
Herpes simplex*	<i>Staphylococcus aureus</i>
Varicella zoster	<i>Clostridium perfringens</i>
Epstein-Barr	<i>Shigella</i>
Fungi	Uncommon causes of infection
<i>Candida</i> *	<i>Mycobacterium avium</i>
<i>Aspergillus</i> *	<i>Mycobacterium intracellulare</i> *
<i>Cryptococcus neoformans</i> *	<i>Mycobacterium tuberculosis</i> *
<i>Histoplasma capsulatum</i>	<i>Nocardia asteroides</i>
Parasites	<i>Legionella pneumophila</i>
<i>Pneumocystis carinii</i> *	<i>Salmonella</i>
<i>Toxoplasma gondii</i> *	<i>Listeria monocytogenes</i>
<i>Cryptosporidium</i> *	Cancer
<i>Strongyloides stercoralis</i> *	Kaposi's sarcoma
	Primary lymphoma of the brain
	NonHodgkin's lymphoma with positive HIV serology
	Squamous-cell carcinoma of the anus

*Fulfills surveillance definition of AIDS.

This includes male homosexual and bisexual activity (75 percent of AIDS cases occur in male homosexuals), intravenous drug use/abuse (17 percent of the first 10,000 AIDS cases), multiple sex partners, and prostitution. Healthy monogamous adults have virtually no risk of acquiring HIV as we now know it.² Transfusion-associated HIV infection has nearly disappeared because of voluntary deferment and antibody screening of all blood products. The estimated risk of unwitting HIV transmission varies from 1 in 34,000 to 1 in 391,000 transfusions.¹⁵

Geographic distribution

Cases of AIDS have been reported in all 50 states, U.S. territories as well as other North and South American countries, Europe, Australia, and Africa. The incidence and prevalence of infection in all locales remains largely unknown. The U.S. has the largest number of cases that fit the CDC surveillance definition—more than 40,000. Detailed and accurate reporting cannot be assured because of the psychosocial stigma associated with the diagnosis of AIDS. Since 1981, the majority of AIDS cases in the U.S. have been in persons from coastal urban areas. In certain parts of the country one type of behavior may predominate (for example, homosexual activity in San Francisco, intravenous drug use in New York City). However, the U.S. Public Health Service¹⁶ projects that by 1991, more than 80 percent of all AIDS cases will be reported from outside these urban areas.

AIDS in Africa is being studied intensely because of the implications for the U.S. and other countries. Sexual transmission is the major mode of disease spread in Africa. However, the serologic positive reactivity for HIV is 1.1:1 for men and

women, respectively, and heterosexual transmission appears to be predominant.^{17,18} Prevalence of HIV infection in prostitutes may be as high as 66-80 percent in some areas.^{15,18} Spread of the AIDS epidemic to East Africa by heterosexual transmission is of great concern. The implications of the large number of asymptomatic HIV-infected individuals in the U.S. and the demonstration of heterosexual transmission in Africa and the U.S. are profound—both in the potential for increasing further the prevalence of HIV infection and in the cost in human suffering and lives.

Serologic diagnosis of HIV infection

The serologic assessment for viral specific antibodies in the diagnosis of HIV infection has provided a tool for safeguarding the blood supply and identifying those at risk of AIDS/ARC and those at risk of transmitting the infection. At the same time, testing has created turmoil regarding civil liberties, confidentiality, and societal protection.

There are several techniques for testing for HIV. The enzyme linked immunosorbent assay (ELISA) is frequently used for screening. It is a very sensitive test and does not exclude true positives, thus its utility in screening blood products. Its overall sensitivity and specificity rates range from 95 to 99 percent.^{12,15} Enzyme immunoassay (EIA) has a sensitivity of 99 percent or greater and a specificity of 99 percent.¹⁶ Reactive screening tests should be followed by a more definitive assessment, such as a Western blot analysis, which identifies antibodies specific to HIV proteins. Tests are reactive with a number of viral proteins, but they are considered to be confirmatory if antibodies to proteins identified as (1) P24 and P41, (2) P24 and P55, or (3) P41 can be

seen.¹⁵ New methods of testing¹⁹ remain an active area of research.

HIV therapy

There is no specific curative antiviral therapy for HIV infection. Azidothymidine (Zidovudine) has been shown to prolong survival and improve symptoms in those with ARC and AIDS, but it remains only a palliative treatment in a bleak disease.^{20,21}

Specific therapies for documented infections include antifungal and antibacterial agents, the use of which is dependent upon accurate identification of the offending organism. A review²² of infections in AIDS patients has been published recently. New or previously unrecognized infections are reported frequently. Treatment of Kaposi's sarcoma and non-Hodgkin's lymphoma, HIV-related malignancies, remains disappointing and an area of active research.²³ The interferons have shown activity in Kaposi's sarcoma (50-60 percent overall response rates), and occasional complete remissions have been seen. These responses have not led to improved survival, however. Multiagent chemotherapy with alkylating agents, *Vinca* alkaloids, and antineoplastic antibiotics has been tried with variable success at remission induction. The use of cytotoxic drug therapy in AIDS patients engenders the risk of further immunosuppression secondary to drug-induced lymphopenia, neutropenia, or disruption of anatomic barriers. A recent report²⁴ of complete remissions in AIDS patients with non-Hodgkin's lymphoma is encouraging.

For other manifestations of AIDS, particularly HIV-induced neurologic disease,²⁵ specific therapeutic interventions are lacking.

Vaccines for disease prevention are being pursued actively in the laboratory and soon are to undergo human testing.^{21, 26} The first trial for a phase one investigation is open. Time estimates of the availability of a reliable vaccine vary from 1 to 10 years. Meanwhile, they remain theoretical and investigational.

Conclusion

Prevention of disease transmission provides the best hope for controlling HIV infection. Therefore, identification of those at risk because of behavior and instruction in risks and methods of stopping transmission are necessary. Education about HIV infection is needed in all segments of our society, especially among health care workers.

Clinicians must be able to identify those at risk by taking good sex activity histories and by developing skills for eliciting histories of drug use/abuse. They must have a thorough knowledge of the clinical manifestations of HIV infection to provide

the best care for their patients.

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