

THE NEUROLOGY OF AIDS

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AIDS, acquired immunodeficiency syndrome, is a cause of world wide medical, moral and social turmoil. Its impact upon the health of the world, and the political, ethical and moral issues connected with it, can well be compared to the disruption on global society caused by syphilis during its scourges in Europe in the Middle Ages. In the United States of America the "gay" or homosexual/bisexual population, particularly males, are notable for the devastation AIDS has caused among them. AIDS also affects large numbers of intravenous drug users, the recipients of blood transfusions and blood products, the newborn infants of affected mothers and a few heterosexuals, particularly the more promiscuous among the latter lot. The rate of incidence of AIDS is beginning to decline from very high levels among American homosexual or bisexual men but its incidence is rising in intravenous drug users and among the newborn.

Many of the issues about AIDS remain unknown or are the subject of heated debate. The precise origins of the disease are still unclear as are the ways in which AIDS virus effects and ultimately kills populations of human cells.

It is not clear how or precisely where AIDS might have originated. In the first three years after AIDS was originally recognized, the epidemic of the illness appeared to be doubling each nine or ten months. The etiology of the illness was not known until 1984 and no predictably reliable serologic test was available until 1985. The spread of virus was measured rapidly among active homosexual men, particularly in the American cities of New York and San Francisco. In a cohort of 6,875 homosexual men in San Francisco, a retrospective serologic testing of stored blood showed that 4% were AIDS positive in 1978, 24% in 1980 and 68% in 1984. How and when the disease entered the United States is an issue for debate. Recent evidence indicates that a 15-year old boy, perhaps a passive homosexual, died of an overwhelming chlamydial infection in St. Louis, Missouri in 1969. He was highly likely to have had AIDS. Based upon genomic similarities among certain retroviruses affecting monkey and AIDS virus (HIV-111), some have suggested that an African monkey retrovirus, normally endemic in Zaire, underwent mutation and was subsequently transmitted by monkey bite or by consumption of infected monkey meat to human beings. In a recently published and very popular American book, Randy Schiltz suggests that a promiscuous homosexual flight steward, called "Patient Zero" was responsible for transmitting the disease from Africa to many places in North America and around the world.

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Currently in the United States, there are approximately 60,000 cases of AIDS. AIDS has been responsible for 30,000 deaths. HIV-111 infections are believed to be present in 1-2 million people.

To put the issue in numeric context, the current United States situation may be stated as follows: AIDS affects approximately 4% of males and 3% of females in the total United States population. AIDS affects, overall, about 45% of homosexual American men, 35% of adult haemophiliacs in the United States, 20% of the entire population of Zambia, 17% of drug-using American prostitutes and 5% of non-drug-using American prostitutes.

Adult and pediatric cases of Aids in the United States are summarized in the tables below:

Table I
**REPORTED ADULT CASES OF AIDS, BY
PATIENT GROUP
UNITED STATES, 1981 TO
FEBRUARY 2, 1987
(N = 29,959)**

Homosexual/bisexual men	66%
Homosexual and IV drug user	8%
IV drug users	17%
Homophilia cases	1%
Heterosexual cases	4%
Transfusion recipients	2%
Undetermined from (HHS/PHS/CDC)	3%

Table II
**PEDIATRIC AIDS: DISTRIBUTION BY PATIENT
GROUP
FEBRUARY 2, 1987
(N = 437)**

Hemophilia/coagulation disorder	5%
Parent with AIDS or at increased risk for AIDS	80%
Transfusion with blood/blood products	12%
Undetermined from (HHS/PHS/CDC)	3%

The rise in AIDS among intravenous drug users has disproportionately effected Americans blacks and Hispanics. Most of the infants born with AIDS due to the presence of the disease, or at least the presence of the virus in an infected mother, are also black or Hispanic.

THE CAUSE OF AIDS

AIDS is caused by one or more members of the family of viruses called retroviruses. These viruses code their genetic information on viral RNA and are capable of encoding viral RNA onto viral DNA because of the presence of unique viral enzyme called reverse transcriptase. (The antiviral drug AZT, (3'-Azido-2',3' Dideoxythymidine, Zidovudine, Burroughs Wellcome interferes with this enzyme to impair reverse transcription). Viral DNA is then inserted into a host cell (T lymphocytes, mast cells and others) where the viral DNA attaches to the cellular genome to become reproduced. During replication, viral RNA is once again produced by the host cell and virus replicated. In the process the host cell is destroyed.

AIDS related viruses are now termed human immunodeficiency viruses (HIV). The illnesses that they may cause are as follows:

HIV I

T-cell leukemia, lymphoma, tropical spastic paraparesis (Caribbean, Tumaco [Columbia], Peru, Seychelles)

HIV II

T-cell lymphoma, AIDS

HIV III

AIDS

The ability of the HIV III virus to attack cells depends on the presence upon susceptible cells of a CD 4+ surface antigen (T4+ surface epitope). This receptor is present on T helper lymphocytes and on other cells. The development of AIDS infection after viral acquisition appears to require a latency of between five and seven years. Human immune responses to AIDS virus infection are of the following types: humoral immunity causes the production of antibodies, but these may not be protective against any consequence of the disease. Viral antigen is detected by Western blot techniques and by ELISA assays. These are the bases for diagnostic tests. Cellular immunity may play a role in combating certain aspects of HIV infections. Proliferation appears to occur with HIV challenge to human lymphocytes in vitro.

Common diagnostic clues to AIDS, even in the absence of seropositivity, include the following:

- * Unsuppressible fungal infections, particularly Candidiasis
- * Recurrent herpes zoster
- * Tuberculosis
- * Tertiary syphilis
- * Pneumocystis carinii pneumonia
- * Kaposi's sarcoma
- * Neurologic diseases

Group I	Acute infection
Group II	Asymptomatic infection
Group III	Persistent generalized lymphadenopathy
Group IV	Other disease
Subgroup A	Constitutional disease
Subgroup B	Neurologic disease
Subgroup C	Secondary infectious disease
Category C-1	Specified Secondary infectious diseases listed in the CDC surveillance definition for AIDS*
Category C-2	Other specified secondary infectious diseases
Subgroup D	Secondary cancers*
Subgroup E	Other conditions

* Includes those patients whose clinical presentations fulfill the definition of the acquired immunodeficiency syndrome (AIDS) USED BY Centers for Disease Control (CDC) for national reporting.

A complete outline of the neurological complications of HIV infections and AIDS-related illnesses is given below:

Table IV
NEUROLOGICAL COMPLICATIONS OF HIV INFECTION

INFECTIONS

A. Meningoencephalitis

1. Viral

- a. HIV
- b. Cytomegalovirus
- c. Herpes simplex 1
- d. Herpes simplex 2
- e. Herpes zoster
- f. Epstein-Barr virus
- g. Adenovirus?
- h. Measles?
- i. Others

2. Bacterial

- a. Treponema pallidum
- b. Listeria monocytogenes
- c. Mycobacterium tuberculosis
- d. E. coli
- e. Whipple's disease
- f. Others

3. Fungal

- a. Cryptococcus neoformans
- b. Aspergillus fumigatus
- c. Histoplasma capsulatum
- d. Coccidioides immitis
- e. Candida albicans
- f. Others

4. Parasitic
 - a. *Toxoplasma gondii*
 - b. *Taenia solium* (cysticercosis)
 - c. Others
- B. Leukoencephalopathy
 1. Viral
 - a. Papovavirus — Progressive multifocal leukoencephalopathy
 - b. HIV
 - c. Cytomegalovirus
 - d. Herpes zoster
- C. Brain Abscess
 1. Bacterial
 - a. Polymicrobial
 - b. *Mycobacterium tuberculosis*
 - c. *Nocardia asteroides*
 - d. Others
 2. Fungal
 - a. *Cryptococcus neoformans*
 - b. *Candida albicans*
 - c. Others
 3. Parasitic
 - a. Toxoplasmosis *gondii*
 - b. *Taenia solium* (cysticercosis)
 - c. Others
- D. Myelopathy
 1. Viral
 - a. HIV
 - b. Cytomegalovirus
 - c. Herpes simplex 2
 - d. Herpes zoster
 - e. Others
 2. Bacterial
 - a. *Treponema pallidum*
 3. Compressive myelopathy secondary to epidural abscess
 4. Parainfectious
- E. Neuropathy
 1. Viral
 - a. HIV
 - b. Cytomegalovirus
 - c. Others
 2. Bacterial
 - a. *Mycobacterium leprae*
 - b. *Treponema pallidum*
 - c. Others

- F. Myopathy
 1. Viral
 - a. HIV
 - b. Others

NEOPLASM

- A. Primary tumors
 1. Brain lymphoma
- B. Metastatic disease (including carcinomatous meningitis)
 1. Non-Hodgkin's lymphoma
 2. Hodgkin's lymphoma
 3. Kaposi's sarcoma
 4. Plasmacytoma
 5. Others

METABOLIC-NUTRITIONAL DISORDERS

- A. Drug side effects
 1. Drug-induced parkinsonism
 2. Neuroleptic malignant syndrome
- B. Electrolyte abnormalities (often associated with diarrhoea)
- C. Vitamin deficiency
 1. Folate
 2. Vitamin B₁₂
 3. Vitamin E
 4. Thiamine (Wernicke's encephalopathy)
- D. Central pontine myelinolysis

VASCULAR COMPLICATIONS

- A. Hemorrhage secondary to immune thrombocytopenia
 1. Subarachnoid hemorrhage
 2. Intracerebral hemorrhage
- B. Embolic stroke secondary to marantic endocarditis
- C. Parainfectious cerebral arteritis
 1. *Treponema pallidum*
 2. *Pseudomonas aeruginosa*
 3. Others
- D. Vascular complications secondary to *Aspergillus fumigatus*

Acute HIV Neurologic Disorders

Neurologic illness at the time of seroconversion with HIV virus is uncommon. In few individuals a flu-like encephalitic illness may occur, at times with fleeting skin rash. Accompanying this illness are fever, stiff neck, occasional focal cranial nerve abnormalities and lymphocytic pleocytosis in the cerebrospinal fluid. Rarely, severe encephalopathies with prolonged stupor, coma and seizures may occur. Peripheral nerve disorders and myelopathies at the time of seroconversions have been reported, but are extremely rare.

AIDS Dementia (chronic HIV Encephalopathy)

A progressive dementia, beginning with memory loss and mental slowing and progressing to severe confusion, disorientation and behavioral disruption is extremely common in AIDS patients. It appears to begin in many individuals long before AIDS is clinically diagnosed and, as demonstrated by neuropsychologic testing and neuroimaging procedures, AIDS dementia may occur with AIDS related complex (ARC, Class II illness). At autopsy, 90% of AIDS patients have gross

and histologic evidence of persistent and progressive AIDS-related disease.

HIV Myelopathy

This complication occurs in between 10-20% of persons with AIDS. It may be subacute or rapidly developing. It results in paraplegia, spastic weakness, impairment of bowel and bladder and most frequently effects the thoracic spinal cord. Lesions within the substance of cord are both inflammatory and demyelinating. Dysfunction depends upon the severity of the disorder but this manifestation of AIDS is not reversible.

Progressive Multifocal Leukoencephalopathy

This is the only known viral disease of brain which causes demyelination. It is related to chronic and persistent infection of oligodendroglial cells with JC virus (a papovavirus, related to SV 40 virus). PML is a fatal illness presenting with rapid dementia, visual disturbance, hemiparesis and rapidly evolving coma. Rarely will patients with this illness respond to the administration of cytosine arabinoside (ARA C).

Table V
**CLINICAL MANIFESTATIONS OF THE AIDS
 DEMENTIA-COMPLEX**

EARLY SYMPTOMS

- A. Cognitive
 1. Impaired concentration (lose track of conversation)
 2. Memory loss (names, historical details, appointments)
 3. Mental slowing ("not as quick", less verbal)
- B. Behavioral
 1. Apathy, withdrawal, "depression"
 2. Agitation, confusion, hallucinations
- C. Motor
 1. Unsteady gait, leg weakness
 2. Loss of coordination, impaired handwriting
 3. Tremor

EARLY SIGNS

- A. Mental status examination
 1. "Normal" bedside examination
 2. Organic psychosis
 3. Psychomotor slowing
 4. Impaired serial 7's or recent memory tasks
- B. Neurological examination
 1. Abnormal reflexes (snout, hyperreflexia)
 2. Impaired eye movements
 3. Impaired rapid extremity movements
 4. Gait ataxia (impaired tandem gait, rapid turns)
 5. Leg weakness
 6. Tremor ("postural")

LATE

- A. Mental status
 1. Distractibility, circumlocution
 2. Disinhibition, unawareness of illness
 3. Global dementia
 4. Psychomotor slowing; verbal responses delayed, near or absolute mutism
 5. Organic psychosis
- B. Neurological signs
 1. Ataxia
 2. Weakness; legs >> arms
 3. Pyramidal tract signs; spasticity, hyperreflexia
 4. Urinary and fecal incontinence

Cerebral Lymphomas

These are rare tumors in the general population but effect up to 5% of individuals with AIDS. The lymphoma may be related to the oncogenic properties of HIV.

Neuromuscular Disorders

These occur in between 15-50% of individuals with AIDS. The most common neuromuscular disorders are disorders of the peripheral nervous system. Among the complications are Guillian-Barre syndrome, chronic inflammatory demyelinating neuropathy, mononeuritis multiplex, sensory ataxic neuropathy due to ganglioneuritis, inflammatory neuropathies and autonomic neurology. The latter is rare. The most common neuropathy is a painful axonal neuropathy affecting distal nerves and beginning with painful paresthesias in the feet. Thirty percent of individuals with AIDS can be shown on clinical grounds to have this complication. A cauda equina syndrome which is painful and rapidly progressive has been shown to be associated with cytomegalovirus infection of the lumbosacral meninges in nerve roots.

Inflammatory myopathies have occurred as well in AIDS patients and resemble polymyositis. More rare forms of myopathy, including single fiber atrophy, rod myopathies and nemaline myopathy, have also been reported in AIDS.

Complications of treatment in AIDS

Iatrogenic complications occur in AIDS as well. In addition to the toxicity of AZT, the use of other agents in intrathecal therapy have been associated with encephalopathies, spinal cord disturbances and diseases of peripheral nerve.

The Effect of AIDS on Clinical Practice in the Neurosciences

There is no certainty about the ultimate number of AIDS cases which might develop in the next several years. If, however, current trends continue, by 1991 the following prevalence figures appear reasonable:

AIDS cases	270,000	Cryptococcosis	30,000
Dementia	150,000	CNS lymphoma	10,000
CNS toxoplasmosis	60,000	HIV infection	1-2 million

To put this in perspective, if the current trends continue, by 1991 the number of biopsies performed for diagnosis of intracranial mass lesions in AIDS will exceed the number of biopsies performed for diagnosis of primary brain tumors (currently 20,000 per annum).

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