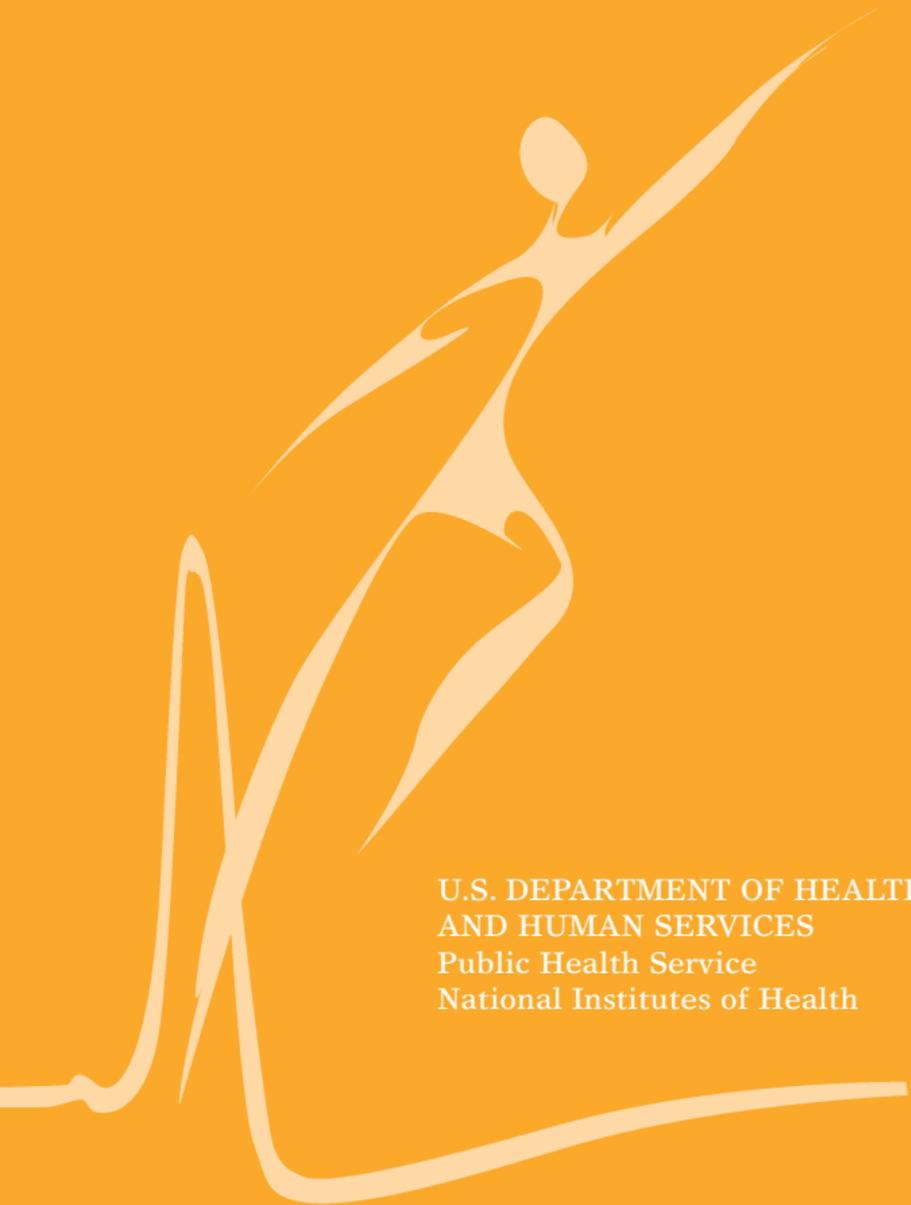


Neurological Complications of AIDS



U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health



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What is AIDS?

AIDS (acquired immune deficiency syndrome) is a condition that occurs in the most advanced stages of human immunodeficiency virus (HIV) infection. It may take many years for AIDS to develop following the initial HIV infection.

Although AIDS is primarily an immune system disorder, it also affects the nervous system and can lead to a wide range of severe neurological disorders.

How does AIDS affect the nervous system?

The virus does not appear to directly invade nerve cells but it jeopardizes their health and function. The resulting inflammation may damage the brain and spinal cord and cause symptoms such as confusion and forgetfulness, behavioral changes, severe headaches, progressive weakness, loss of sensation in the arms and legs, and stroke. Cognitive motor impairment or damage to the peripheral nerves is also common. Research has shown that the HIV infection can significantly alter the size of certain brain structures involved in learning and information processing.

Other nervous system complications that occur as a result of the disease or the drugs used to treat it include pain, seizures, shingles, spinal cord problems, lack of coordination, difficult or painful swallowing, anxiety disorder, depression, fever, vision loss, gait disorders, destruction of brain tissue, and coma. These symptoms may be mild in the early stages of AIDS but can become progressively severe.

In the United States, neurological complications are seen in more than 40 percent of adult patients with AIDS. They can occur at any age but tend to progress more rapidly in children. Nervous system complications in children may include developmental delays, loss of previously achieved milestones, brain lesions, nerve pain, smaller than normal skull size, slow growth, eye problems, and recurring bacterial infections.

What are some of the neurological complications that are associated with AIDS?

AIDS-related disorders of the nervous system may be caused directly by the HIV virus, by certain cancers and opportunistic infections (illnesses caused by bacteria, fungi, and other viruses that would not otherwise affect people with healthy immune systems), or by toxic effects of the drugs used to treat symptoms. Other neuro-AIDS disorders of unknown origin may be influenced by but are not caused directly by the virus.

AIDS dementia complex (ADC), or HIV-associated encephalopathy, occurs primarily in persons with more advanced HIV infection. Symptoms include encephalitis (inflammation of the brain), behavioral changes, and a gradual decline in cognitive function, including trouble with concentration, memory, and attention. Persons with ADC also show progressive slowing of motor function and loss of dexterity and coordination. When left untreated, ADC can be fatal.

Central nervous system (CNS) lymphomas are cancerous tumors that either begin in the brain or result from a cancer that has spread from another site in the body. CNS lymphomas are almost always associated with the Epstein-Barr virus (a common human virus in the herpes family). Symptoms include headache, seizures, vision problems, dizziness, speech disturbance, paralysis, and mental deterioration. AIDS patients may develop one or more CNS lymphomas. Prognosis is poor due to advanced and increasing immunodeficiency.

Cryptococcal meningitis is seen in about 10 percent of untreated AIDS patients and in other persons whose immune systems have been severely suppressed by disease or drugs. It is caused by the fungus *Cryptococcus neoformans*, which is commonly found in dirt and bird droppings. The fungus first invades the lungs and spreads to the covering of the brain and spinal cord, causing inflammation. Symptoms include fatigue, fever, headache, nausea, memory loss, confusion, drowsiness, and vomiting. If left untreated, patients

with cryptococcal meningitis may lapse into a coma and die.

Cytomegalovirus (CMV) infections can occur concurrently with other infections. Symptoms of CMV encephalitis include weakness in the arms and legs, problems with hearing and balance, altered mental states, dementia, peripheral neuropathy, coma, and retinal disease that may lead to blindness. CMV infection of the spinal cord and nerves can result in weakness in the lower limbs and some paralysis, severe lower back pain, and loss of bladder function. It can also cause pneumonia and gastrointestinal disease.

Herpes virus infections are often seen in AIDS patients. The *herpes zoster virus*, which causes chickenpox and shingles, can infect the brain and produce encephalitis and myelitis (inflammation of the spinal cord). It commonly produces shingles, which is an eruption of blisters and intense pain along an area of skin supplied by an infected nerve. In people exposed to herpes zoster, the virus can lay dormant in the nerve tissue for years until it is reactivated as shingles. This reactivation is common in persons with AIDS because of their weakened immune systems. Signs of shingles include painful blisters (like those seen in chickenpox), itching, tingling, and pain in the nerves.

AIDS patients may suffer from several different forms of *neuropathy*, or nerve pain, each strongly associated with a specific stage of active immunodeficiency disease. *Peripheral*

neuropathy describes damage to the peripheral nerves, the vast communications network that transmits information from the brain and spinal cord to every other part of the body. Peripheral nerves also send sensory information back to the brain and spinal cord. HIV damages the nerve fibers that help conduct signals and can cause several different forms of neuropathy. *Distal sensory polyneuropathy* causes either a numbing feeling or a mild to painful burning or tingling sensation that normally begins in the legs and feet. These sensations may be particularly strong at night and may spread to the hands. Affected persons have a heightened sensitivity to pain, touch, or other stimuli. Onset usually occurs in the later stages of the HIV infection and may affect the majority of advanced-stage HIV patients.

Neurosyphilis, the result of an insufficiently treated syphilis infection, seems more frequent and more rapidly progressive in people with HIV infection. It may cause slow degeneration of the nerve cells and nerve fibers that carry sensory information to the brain. Symptoms, which may not appear for some decades after the initial infection and vary from patient to patient, include weakness, diminished reflexes, unsteady gait, progressive degeneration of the joints, loss of coordination, episodes of intense pain and disturbed sensation, personality changes, dementia, deafness, visual impairment, and impaired response to light. The disease is more frequent in men than in women. Onset is common during mid-life.

Progressive multifocal leukoencephalopathy (PML) primarily affects individuals with suppressed immune systems (including nearly 5 percent of people with AIDS). PML is caused by the JC virus, which travels to the brain, infects multiple sites, and destroys the cells that make myelin — the fatty protective covering for many of the body's nerve and brain cells. Symptoms include various types of mental deterioration, vision loss, speech disturbances, ataxia (inability to coordinate movements), paralysis, brain lesions, and, ultimately, coma. Some patients may also have compromised memory and cognition, and seizures may occur. PML is relentlessly progressive and death usually occurs within 6 months of initial symptoms.

Psychological and neuropsychiatric disorders can occur in different phases of the HIV infection and AIDS and may take various and complex forms. Some illnesses, such as AIDS dementia complex, are caused directly by HIV infection of the brain, while other conditions may be triggered by the drugs used to combat the infection. Patients may experience anxiety disorder, depressive disorders, increased thoughts of suicide, paranoia, dementia, delirium, cognitive impairment, confusion, hallucinations, behavioral abnormalities, malaise, and acute mania.

Stroke brought on by cerebrovascular disease has been considered a somewhat rare complication of AIDS, although the association between AIDS and stroke may be much larger than previously thought. Researchers at the University of Maryland conducted the first

population-based study to quantify an AIDS-associated stroke risk and found that AIDS increases the chances of suffering a stroke by as much as tenfold. Researchers caution that additional studies are needed to confirm this association. Earlier studies have indicated that the HIV infection, other infections, or the body's immune system reaction to HIV may cause vascular abnormalities and/or make the blood vessels less responsive to changes in blood pressure, which could lead to rupture and hemorrhagic stroke.

Toxoplasma encephalitis, also called cerebral toxoplasmosis, occurs in about 10 percent of untreated AIDS patients. It is caused by the parasite *Toxoplasma gondii*, which is carried by cats, birds, and other animals and can be found in soil contaminated by cat feces and sometimes in raw or undercooked meat. Once the parasite invades the immune system, it remains there; however, the immune system in a healthy person can fight off the parasite, preventing disease. Symptoms include encephalitis, fever, severe headache that does not respond to treatment, weakness on one side of the body, seizures, lethargy, increased confusion, vision problems, dizziness, problems with speaking and walking, vomiting, and personality changes. Not all patients show signs of the infection.

Vacuolar myelopathy causes the protective myelin sheath to pull away from nerve cells of the spinal cord, forming small holes called vacuoles in nerve fibers. Symptoms include unsteadiness when walking and weak or stiff legs. Walking becomes more difficult

as the disease progresses and many patients eventually require a wheelchair. Some patients also develop AIDS dementia. Vacuolar myelopathy may affect up to 30 percent of untreated adults with AIDS and its incidence may be even higher in HIV-infected children.

How are these disorders diagnosed?

Based on the results of the patient's medical history and a general physical exam, the physician will conduct a thorough neurological exam to assess various functions: motor and sensory skills, nerve function, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior. The physician may order laboratory tests and one or more of the following procedures to help diagnose neurological complications of AIDS.*

Computer-assisted imaging can reveal signs of brain inflammation, tumors and CNS lymphomas, nerve damage, internal bleeding or hemorrhage, white matter irregularities, and other brain abnormalities. Several painless imaging procedures are used to help diagnose neurological complications of AIDS.

- *Computed tomography* (also called a CT scan) uses x-rays and a computer to produce two-dimensional images of bone and tissue, including inflammation, certain

* See the NINDS publication, *Neurological Diagnostic Tests and Procedures*, for a comprehensive review of the diagnostic tests used in the treatment of AIDS patients: http://www.ninds.nih.gov/disorders/misc/diagnostic_tests.htm

brain tumors and cysts, brain damage from head injury, and other disorders. It provides more details than an x-ray alone.

- *Magnetic resonance imaging (MRI)* uses a computer, radio waves, and a powerful magnetic field to produce either a detailed three-dimensional picture or a two-dimensional “slice” of body structures, including tissues, organs, bones, and nerves. It does not use ionizing radiation (as does an x-ray) and gives physicians a better look at tissue located near bone.
- *Functional MRI (fMRI)* uses the blood’s magnetic properties to pinpoint areas of the brain that are active and to note how long they stay active. It can assess brain damage from head injury or degenerative disorders such as Alzheimer’s disease and can identify and monitor other neurological disorders, including AIDS dementia complex.
- *Magnetic resonance spectroscopy (MRS)* uses a strong magnetic field to study the biochemical composition and concentration of hydrogen-based molecules, some of which are very specific to nerve cells, in various brain regions. MRS is being used experimentally to identify brain lesions in people with AIDS.

Electromyography, or EMG, is used to diagnose nerve and muscle dysfunction (such as neuropathy and nerve fiber damage caused by the HIV virus) and spinal cord disease. It records spontaneous muscle activity and muscle activity driven by the peripheral nerves.

Biopsy is the removal and examination of tissue from the body. A brain biopsy, which involves the surgical removal of a small piece of the brain or tumor, is used to determine intracranial disorders and tumor type. Unlike most other biopsies, it requires hospitalization. Muscle or nerve biopsies can help diagnose neuromuscular problems, while a brain biopsy can help diagnose a tumor, inflammation, or other irregularity.

Cerebrospinal fluid analysis can detect any bleeding or brain hemorrhage, infections of the brain or spinal cord (such as neurosyphilis), and any harmful buildup of fluid. A sample of the fluid is removed by needle, under local anesthesia, and studied to detect any irregularities.

How are these disorders treated?

No single treatment can cure the neurological complications of AIDS. Some disorders require aggressive therapy while others are treated symptomatically.

Neuropathic pain is often difficult to control. Medicines range from analgesics sold over the counter to antiepileptic drugs, opiates, and some classes of antidepressants. Inflamed tissue can press on nerves, causing pain. Inflammatory and autoimmune conditions leading to neuropathy may be treated with

corticosteroids, and procedures such as plasmapheresis (or plasma exchange) can clear the blood of harmful substances that cause inflammation.

Treatment options for AIDS- and HIV-related neuropsychiatric or psychotic disorders include antidepressants and anticonvulsants. Psychostimulants may also improve depressive symptoms and combat lethargy. Antidementia drugs may relieve confusion and slow mental decline, and benzodiazepines may be prescribed to treat anxiety. Psychotherapy may also help some patients.

Aggressive antiretroviral therapy is used to treat AIDS dementia complex, vacuolar myopathy, progressive multifocal leukoencephalopathy, and cytomegalovirus encephalitis. HAART, or highly active antiretroviral therapy, combines at least three drugs to reduce the amount of virus circulating in the blood and may also delay the start of some infections.

Other neuro-AIDS treatment options include physical therapy and rehabilitation, radiation therapy and/or chemotherapy to kill or shrink cancerous brain tumors that may be caused by the HIV virus, antifungal or antimalarial drugs to combat certain bacterial infections associated with the disorder, and penicillin to treat neurosyphilis.

What research is being done?

Within the Federal government, the National Institute of Neurological Disorders and Stroke (NINDS), one part of the National Institutes of Health (NIH), supports research on the neurological consequences of AIDS. The NINDS works closely with its sister agency, the National Institute of Allergy and Infectious Diseases (NIAID), which has primary responsibility for research related to HIV and AIDS.

Several NINDS-funded projects are studying the role of virally infected brain macrophages (cells that normally work to protect against infection) in causing disease in the central nervous system of adult macaques. The focus of these projects includes gene analyses and the study of key neuroimmune regulatory molecules that are turned on in the brain during the course of viral infection at levels that have been shown to be toxic.

Several animal-based models of HIV (including mouse, rat, and simian models) are used by scientists to study disease mechanisms and the course of AIDS, and NINDS grantees are working to develop new models of HIV. Several projects rely on a mouse model of severe combined immunodeficiency (a group of inherited disorders that are characterized by a lack of or severe defect in cells responsible for protecting the immune system). This model allows researchers to transplant developing human brain tissue from culture into the brains of the mice to monitor and assess neurologic damage caused by HIV infection.

Other studies use mice bred to carry symptoms of HIV, and NINDS grantees are using these animals to see if the brain can function as a sanctuary for HIV-infected cells that can migrate to and infect peripheral lymph tissue.

The NINDS also supports research into the mechanisms of neurological illnesses related to immunodeficiency in AIDS patients. Several different investigators are studying the JC virus, which can reproduce in the brains of immunosuppressed patients and cause PML, and one study identified a novel receptor for the JC virus. Other studies of infectious agents include an investigation of the interaction of the fungal agent *Cryptococcus* with the blood vessels of the brain, and an analysis of neurosyphilis in people with AIDS. Scientists are also studying the effect of neurotoxic proteins and antiviral therapies directly on nerve cells as the cause for distal sensory peripheral neuropathy.

Several researchers are studying AIDS dementia and cognitive changes in HIV. NINDS-sponsored scientists are using fMRI and MRS to assess brain function and any behavioral deficits in HIV-affected individuals. Investigators hope to better understand how progressive neuronal cell death contributes to cognitive dysfunction and AIDS dementia. The National NeuroAIDS Tissue Consortium, a project supported jointly by the NINDS and its sister agency, the National Institute of Mental Health, is collecting tissues from people with AIDS who have suffered from dementia and other neurological

complications of HIV infection for distribution to researchers around the world.

The Neurological AIDS Research Consortium was established by the NINDS in 1993 to design and conduct clinical trials on HIV-associated neurologic disease. To date, the Consortium has supported studies of neurological function in advanced AIDS and the treatment of HIV-associated peripheral neuropathy, PML, and CMV infection. Consortium researchers are studying the drug selegiline as an add-on to antiretroviral therapy for HIV dementia, as well as the natural history of neurological disease in advanced HIV. Clinical studies have included a double-blind controlled study of prosaptide for the treatment of HIV-associated peripheral neuropathy, and trials of acetyl-L-carnitine and erythropoietin as treatments for toxic neuropathy in HIV infection.

Where can I get more information?

For additional information about AIDS and its neurological complications, please contact the following organizations:

National Institute of Allergy and Infectious Diseases (NIAID)

National Institutes of Health, DHHS
6610 Rockledge Drive, MSC 6612
Bethesda, MD 20892-6612
(301) 496-8190
www.niaid.nih.gov

National Institute of Mental Health (NIMH)

National Institutes of Health, DHHS
6001 Executive Boulevard
Room 8184, MSC 9663
Bethesda, Maryland 20892-9663
(301) 443-4513
(800) 615-6464
www.nimh.nih.gov

American Foundation for AIDS Research

120 Wall Street
13th Floor
New York City, New York 10005-3902
(212) 806-1600
www.amfar.org

Elizabeth Glaser Pediatric AIDS Foundation

1140 Connecticut Avenue, NW
Suite 200
Washington, DC 20036
(202)-296-9165
(888) 499-4673
www.pedaids.org

National Association of People with AIDS

8401 Colesville Road

Suite 750

Silver Spring, Maryland 20910

(240) 247-0880

www.napwa.org

Neurological AIDS Research Consortium

Washington University School of Medicine

660 South Euclid Avenue

Campus Box 8111

St. Louis, Missouri 63110

(314) 362-9733

http://neuro.wustl.edu/patientcare/

clinicalservices/narc/

Additional information about neurological disorders and research supported by the NINDS is available by contacting the Institute's Brain Resources and Information Network at:

BRAIN

P.O. Box 5801

Bethesda, Maryland 20824

(301) 496-5751

www.ninds.nih.gov





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