Neurological Consequences of HIV and AIDS

U.S. DEPARTMENT OF HEALTH
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What are HIV and AIDS?

HIV (human immunodeficiency virus) is the virus that causes AIDS (acquired immune deficiency syndrome). HIV attacks the immune system by destroying specific white blood cells called CD4 positive (CD4+) T cells that are vital to fighting off infection. The resulting shortage of these cells leaves people infected with HIV vulnerable to other infections and diseases, and additional complications.

AIDS is the final stage of HIV infection. A person infected with HIV is diagnosed with AIDS when he or she has a dangerously low number of CD4+ T cells as well as one or more "opportunistic" infections, such as some types of pneumonia or tuberculosis, that do not typically affect people with healthy immune systems.

Although HIV infection and AIDS primarily affect the immune system, they also disturb the nervous system and can lead to a wide range of severe neurological disorders, particularly if HIV goes untreated and progresses to AIDS. Many of the most severe neurological conditions can be prevented with antiretroviral therapy. However, even individuals who receive this treatment can develop less severe neurological and cognitive difficulties.

How do HIV/AIDS affect the nervous system?

HIV does not directly invade nerve cells (neurons) but puts their function at risk by infecting cells called glia that support and protect neurons. HIV also triggers inflammation that may damage the brain and spinal cord (central nervous system) and cause symptoms such as:

- confusion and forgetfulness
- inability to concentrate
- behavioral changes
- headaches
- mood disorders (anxiety disorder and depression)
- movement problems (loss of movement control) including a lack of coordination and difficulty walking.

Damage to the peripheral nerves can cause progressive weakness and loss of sensation in the arms and legs. Research has shown that HIV infection can cause shrinking of brain structures involved in learning and information processing.

Other nervous system complications that can occur as a result of HIV infection or the drugs used to treat it include:

- pain
- seizures
- strokes
- shingles
- difficulty swallowing
- fever

- vision loss
- coma, and
- problems with bladder control or sexual function.

These symptoms may be mild in the early stages of AIDS but can become increasingly severe.

In children, the disease can cause:

- developmental delays
- loss of previously achieved milestones
- brain lesions
- nerve pain
- smaller than normal skull size
- slow growth
- eye problems, and
- recurring infections.

Can neurological complications develop in individuals treated with antiretroviral therapy (ART)?

Even when HIV is well controlled with ART, many infected individuals still develop HIV-associated neurological and cognitive difficulties. This is because many drugs used to combat HIV cannot cross the protective layer called the blood-brain barrier and enter the brain, and even those that can may not completely control the virus in the brain. Antiretroviral drugs can also become toxic after long-term use and cause neurological side effects.

What are some of the neurological complications that are associated with HIV infection?

The nervous system may be affected directly by the HIV virus, by certain cancers and opportunistic infections that result from a weakened immune system, or by the toxic effects of medications used to treat infection. Other neurological complications may be influenced by, but are not directly caused by, the HIV virus.

HIV-Associated Neurocognitive Disorders (HAND) includes a spectrum from no symptoms to severe neurocognitive impairment. The more serious forms of HAND are also referred to as *AIDS dementia complex* (ADC) or *HIV-associated dementia* (HAD). ADC or HAD occurs primarily in people with more advanced HIV infection. Signs and symptoms include encephalitis (inflammation of the brain), behavioral changes, and a gradual decline in cognitive function, including trouble with concentration, memory, and attention. People with ADC also show progressive slowing of motor function and loss of dexterity and coordination. When left untreated, ADC can be fatal. However, death associated with ADC is rare when antiretroviral therapy is used. A person's risk for ADC or HAND increases if therapy fails to bring levels of the HIV virus down to undetectable levels.

Central nervous system (CNS) lymphomas are cancerous tumors that begin in the brain or result from a cancer that has spread to the brain 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. People with AIDS may develop one or more CNS lymphomas. The effects of these cancers are more serious in those with severely weakened immune systems.

Cryptococcal meningitis occurs in some individuals with untreated AIDS and in others whose immune systems have been seriously weakened by disease or drugs. It is caused by the fungus *Cryptococcus neoformans*, which is commonly found in soil and bird droppings. The fungus first invades the lungs and then spreads to the covering of the brain and spinal cord, called the meninges, where it causes inflammation (meningitis). Symptoms include fatigue, fever, headache, nausea, memory loss, confusion, drowsiness, and vomiting. If left untreated, affected individuals may lapse into a coma and die. HIV-positive individuals can be screened for a chemical marker of the fungal infection, which can be detected months before the onset of symptoms.

Cytomegalovirus infection (CMV) is one of several nervous system infections that can occur simultaneously with HIV infection and cause encephalitis. 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 also result in some paralysis, severe lower back pain, and loss of bladder function. CMV can also

cause pneumonia and gastrointestinal disease. CMV rarely affects HIV-positive individuals who are compliant with treatment since serious weakening of the immune system is required for CMV to emerge.

Herpes zoster virus, which causes chickenpox and shingles, often infects individuals with AIDS. The virus can lead to encephalitis and myelitis (spinal cord inflammation). In people exposed to herpes zoster, the virus can lie dormant in the nerve tissue for years until it is reactivated as shingles. This reactivation is common in people with AIDS because of their weakened immune systems. Signs of shingles include painful blisters (like those seen in chickenpox), itching, tingling, and nerve pain (neuropathy). The varicella vaccine, which is given to prevent chickenpox in those who have not yet had it, can also stop the herpes zoster virus from infecting people whose HIV is well controlled with antiretroviral therapy. However, individuals with AIDS cannot be vaccinated because their immune systems are too weak.

Neuropathy often occurs in people with HIV infection or AIDS. Different forms of neuropathy are associated with a specific stage of the 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 through the spinal cord. HIV damages the nerve fibers that help conduct these 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 are more sensitive to pain, touch, or other sensations. Onset usually occurs in the later stages of the infection and may affect most people with advanced HIV.

Neurosyphilis, the result of an untreated syphilis infection, is more common and progresses more rapidly in HIV-positive individuals compared to those who are HIV negative. 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 decades after the initial infection and vary among individuals, can include weakness, diminished reflexes, walking difficulties, loss of coordination, episodes of intense pain and disturbed sensation, personality changes, dementia, deafness, and vision problems. The disease is more frequent in men than in women. Onset typically occurs during middle age.

Progressive multifocal leukoencephalopathy (PML) mainly affects individuals with weakened immune systems, including some people with AIDS. PML occurs when the JC virus travels to the brain 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, loss of motor coordination (ataxia), paralysis,

brain lesions, and, ultimately, coma. Some people experience problems with memory and cognition as well as seizures. PML worsens rapidly and death usually occurs within 6 months after the first symptoms appear. However, strengthening the immune system with antiretroviral treatment now allows more than half of those with HIV-associated PML to survive.

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. Individuals may experience anxiety disorder, depressive disorders, thoughts of suicide, paranoia, dementia, delirium, cognitive impairment, confusion, hallucinations, behavioral abnormalities, malaise, and acute mania.

Toxoplasma encephalitis, also called cerebral toxoplasmosis, occurs in some untreated individuals with AIDS. It is caused by the parasite *Toxoplasma gondii*, which is carried by cats, birds, and other animals and can be found in soil or water contaminated by cat feces and sometimes in raw or undercooked meat or shellfish. Once the parasite invades a host it remains there. Healthy people may carry the parasite, but their immune systems are able to prevent the parasite from causing illness. 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.

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 people eventually require a wheelchair. Some individuals also develop AIDS dementia complex.

How are these disorders diagnosed?

Based on an individual's medical history and findings from a general physical exam, a 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. (See the NINDS publication, *Neurological Diagnostic Tests and Procedures*, for a comprehensive review of the tests used in diagnosing neurological and other disorders: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Neurological-Diagnostic-Tests-and-Procedures-Fact.)

Brain imaging can reveal signs of brain inflammation, tumors and CNS lymphomas, nerve damage, bleeding, white matter

irregularities, and other 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 to show inflammation, certain brain tumors and cysts, brain damage from head injury, and other abnormalities. It provides more details than an x-ray alone.
- *Magnetic resonance imaging* (MRI) uses computer-generated 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 the ionizing radiation that an x-ray does and provides a better look at tissue located near bone.
- *Functional MRI* (fMRI) uses the blood's magnetic properties to map 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 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 can show decreases in chemicals related to nerve cells and increases in chemicals related to inflammation in patients with HAND.

Electromyography, or EMG, is used to diagnose nerve and muscle dysfunction, including spinal cord disease, nerve fiber damage, and other nerve problems caused by the HIV virus. It records spontaneous muscle activity and muscle activity driven by the peripheral nerves.

Biopsy is the removal of tissue from the body for examination. A brain biopsy, which involves the surgical removal of a small piece of the brain or tumor, is used to diagnose a tumor, inflammation, or another brain irregularity. Unlike most other biopsies, it requires hospitalization and carries its own risks. Muscle or nerve biopsies can help diagnose neuromuscular problems.

Cerebrospinal fluid analysis can detect bleeding in the brain, infections of the brain or spinal cord such as neurosyphilis, and any harmful buildup of fluid. It can also be used to sample viruses that may be affecting the brain. 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 HIV/AIDS. Some disorders require aggressive therapy while others are treated as symptoms arise.

Neuropathic pain—chronic pain caused by damage to the nervous system—is often difficult to control. Medicines range from over-the-counter pain killers to anticonvulsant drugs, opiates, and some classes of antidepressants.

Inflamed tissue caused by autoimmune or other conditions can press on nerves, causing pain. Such illnesses may be treated with corticosteroids or procedures such as plasma exchange, formally known as plasmapheresis, that 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 depression and reduce fatigue. Drugs such as cholinesterase inhibitors, which can temporarily improve or stabilize memory and thinking skills in people with dementia, may relieve confusion and slow mental decline. Benzodiazepines may be prescribed to treat anxiety. Psychotherapy may also help some individuals.

Aggressive antiretroviral therapy is used to treat AIDS dementia complex or HAND, vacuolar myopathy, progressive multifocal leukoencephalopathy, and cytomegalovirus encephalitis. Combined antiretroviral therapy (cART) uses at least three drugs to reduce the amount of virus circulating in the blood and may also delay the start of some infections. The goal is to use those agents that have good penetration into the brain.

Other treatments may include physical therapy and rehabilitation, radiation therapy and/or chemotherapy to shrink cancerous brain tumors that may be related to HIV, 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), a component of the National Institutes of Health (NIH), supports research on the neurological consequences of HIV and AIDS. NINDS works closely with its sister agencies, the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Mental Health (NIMH), to fund research related to HIV and AIDS. The Office of AIDS Research (OAR) coordinates AIDS research across NIH.

NINDS conducts research into how the weakened immune systems of individuals with AIDS lead to neurological illnesses. NINDS investigators are studying the JC virus, which can reproduce in the brains of people with impaired immune systems and cause progressive multifocal leukoencephalopathy (PML). In one small NINDS study, the anti-cancer drug pembrolizumab showed promise in slowing or stopping the progression of PML. Additional research is needed to confirm results, which could lead to new investigations that help revolutionize treatment for similar chronic infections in immune compromised individuals.

Many NINDS-funded projects are investigating how the HIV virus damages the brain and the reason for continued neurological injury even in individuals whose illness is well-controlled with combined antiretroviral therapy (cART). Some of this research focuses on the contributions of immune cells in the brain called microglia that are sent into overdrive by HIV infection and may be harmful to neurons as a result.

Other experiments are attempting to determine how the HIV virus damages the blood-brain barrier and are investigating new formulations of cART as well as drug delivery methods that are better able to cross into the brain.

Many individuals whose infection is successfully suppressed with cART experience a reactivation of the virus upon stopping treatment. Researchers are studying how a reservoir of inactive HIV is maintained in the brain. This research is a first step toward developing a means to render the virus permanently dormant or even to rid the brain of all traces of the virus.

Several researchers are studying AIDS dementia complex and cognitive dysfunction in HIV to better understand how the death of neurons contributes to these conditions. Investigators are also studying inflammatory mechanisms associated with HIV-1 dementia and how early proteins produced by HIV-1 alter cellular signaling mechanisms in a manner that contributes to the loss of cognitive functions in infected individuals. Other researchers hope to identify HIV mutant strains that will help develop vaccines that may have the potential to prevent HIV-1 brain infection and HIV-associated neurocognitive disorders with HIV-associated dementia.

Aging is consistently identified as a risk factor for HIV-associated cognitive impairment. Older adults infected with HIV are more likely to develop these neurocognitive disorders than their younger counterparts. Scientists are examining how the HIV virus accelerates brain aging and how natural aging affects the development and symptoms of HAND.

Several studies are aimed at understanding the role of genetics in HAND. Other researchers hope to identify how genetic differences in the HIV virus modify its impact on the brain.

Researchers are also investigating how HIV affects not only the brain but also the peripheral nervous system, where it causes peripheral neuropathy. Some of these studies focus on determining how HIV causes that condition, while others aim to develop new treatments for neuropathic pain or examine how brain activity differs in HIV-positive individuals with and without pain.

The National NeuroAIDS Tissue Consortium, a project supported jointly by NINDS and NIMH, is collecting tissue from people with AIDS who have suffered from dementia and other neurological complications. The Consortium also gathers brain tissue from such individuals after death. The samples are then distributed to researchers around the world for use in their research. (For more information, see https://nntc.org).

Where can I get more information?

For more information about neurological disorders and research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
301-496-5751
800-352-9424
www.ninds.nih.gov

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

amfAR, the Foundation for AIDS Research
120 Wall Street, 13th Floor
New York City, NY 10005-3908
212-806-1600
www.amfar.org

AIDSInfo (AIDS Information Service)
P.O. Box 4780
Rockville, MD 20849-6303
301-315-2816
800- 448-0440
TTY: 888-480-3739
https://aidsinfo.nih.gov

Elizabeth Glaser Pediatric AIDS Foundation
1140 Connecticut Avenue, NW, Suite 200
Washington, DC 20036
202-296-9165
888-499-4673
www.pedaids.org

National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health, DHHS
6610 Rockledge Drive, MSC 6612
Bethesda, MD 20892-6612
301-496-5717
www.niaid.nih.gov

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

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