Published in final edited form as:
Neurol Clin. 2010 February ; 28(1): 253–275. doi:10.1016/j.ncl.2009.09.018.

Neurologic Presentations of AIDS

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Keywords

AIDS; HIV; brain; opportunistic infection; encephalitis

The human immunodeficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS) has infected an estimated 33 million individuals worldwide{1}. HIV is a member of the lentivirus genus, part of the Retroviridae (retrovirus) family{2}. HIV is associated with immunodeficiency, neoplasia and neurological disease.

The development of an identifiable neurological syndrome in an HIV infected person is the culmination of a chain of events, determined by properties of HIV itself, genetic characteristics of the host, and interactions with the environment (including treatment). HIV-associated neurological syndromes can be classified as primary HIV neurological disease (in which HIV is both necessary and sufficient to cause the illness), secondary or opportunistic neurological disease (in which HIV interacts with other pathogens, resulting in opportunistic infections ((OI)) and tumors), and treatment related neurological disease (such as immune reconstitution inflammatory syndrome or IRIS).

HIV is neuroinvasive (can enter the central nervous system ((CNS)), neurotrophic (can live in neural tissues), and neurovirulent (causes disease of the nervous system){2}. Presumed mechanisms of CNS invasion include the “Trojan horse” mechanism in which HIV-infected monocytes are admitted by the blood-brain barrier and mature into long-lived, persistently

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infected perivascular macrophages; infection of the choroid plexus; and direct infection of capillary endothelial cells, among others. HIV-infected cells include capillary endothelium, microglia, monocytes, macrophages, astrocytes, and choroid plexus {3}. Neurons and oligodendrocytes are rarely, if ever, infected (although this is still under discussion), and "indirect" mechanisms are postulated to account for most damage {4}. There is a burst of viral replication in primary infection, followed by an aggressive immune response that declines over time, and by a long period of subclinical infection, followed by recrudescence of disease, and death {2}. Persistent infection and inflammation results in blood-brain barrier breakdown, neuronal and axonal injury, neurotoxicity, and clinical symptoms; damage to the immune system, particularly cell-mediated immunity, results in vulnerability to OI.

In addition to its importance as a cause of neurological problems, HIV infection of the CNS constitutes a serious barrier to management and eradication of the virus. The CNS is incompletely permeable to antiretroviral drugs, resulting in subtherapeutic levels of many antiretrovirals {5}; it is part of a protected reservoir {6} (along with the gut and several other organs), where HIV can evade the immune system; and it provides an environment where HIV can replicate, mutate, and re-infect the circulation. HIV stimulates a persistent inflammatory response that may activate pathways leading to other neurodegenerative diseases {7}.

HIV-1-associated syndromes in primary infection

Acute HIV infection is the period from initial infection to complete seroconversion. During this time 40-90% of individuals describe physical symptoms, similar to influenza, or mononucleosis. The most common features include a short period of fever, lymphadenopathy, night sweats, headache, and/or rash {8,9}. Early CNS infection is usually asymptomatic, but cerebrospinal fluid (CSF) {10} and imaging studies {11} can detect abnormalities even during the "asymptomatic" period that presage later neurological events.

A minority of seroconverters will experience a neurologic event that brings them to medical attention, such as aseptic meningitis, Bell's palsy {12,13}, or inflammatory neuropathy. Individuals with symptomatic neurological disease tend to have higher CSF HIV levels than those without. Neurological symptoms may occur before an HIV diagnosis is suspected, e.g., before there are sufficient HIV antibodies to produce a positive HIV enzyme-linked immunosorbent antibody (ELISA, also called an HIV enzyme immunoassay). In such cases, a Western Blot or a polymerase chain reaction (PCR) test for HIV may lead to the diagnosis. Early diagnosis of acute HIV infection is important, as these individuals are at high risk to transmit the virus.

The most common neurologic syndrome associated with primary HIV infection is an acute aseptic (viral) meningitis or meningoencephalitis. The symptoms are similar to other viral meningitides, with fever, headache, stiff neck, and photophobia. Cerebrospinal fluid (CSF) shows a mild lymphocytic pleocytosis, normal or slightly elevated total protein, and normal glucose {14}. HIV may be detectable by antigen or PCR testing {15}. Most individuals will recover with supportive care. A few will have recurrent bouts.

Information on the management of HIV aseptic meningitis is limited to case reports. Initiating treatment with cART, or changing and intensifying the regimen to include more CNS-penetrating drugs, may suppress the symptoms {16}. Others have recurrent meningitis when they stop combined antiretroviral therapy (cART), e.g. during structured treatment interruptions {17}.

HIV Associated Neurocognitive Disorders (HAND)

The most common CNS manifestation of HIV is a chronic neurodegenerative condition characterized by cognitive, central motor and behavioral abnormalities. A variety of names (e.g. AIDS Dementia Complex, HIV Associated Dementia, HIV Associated Cognitive Motor Complex) have been applied to this syndrome. Recently, HIV Associated Neurocognitive Disorder (HAND) {18} has become a widely accepted nosology for classifying individuals with varying levels of HIV-associated neurocognitive deficits. HAND is stratified into 1) asymptomatic neurocognitive impairment (ANI) 2) minor neurocognitive disorder (MND) and 3) HIV Associated Dementia (HAD). ANI is characterized a subclinical decline in cognition. MND is characterized as mild decline in cognition in addition to mild everyday functioning impairment that affects the more difficult activities of daily living). HAD is characterized by significant decline in cognition along with a significant degree of functional impairment that affects routine activities{19}. There is no diagnostic marker or combination of markers for HAND. The diagnosis is made in HIV+ patients with cognitive impairment, after ruling out confounding conditions (CNS OI, neurosyphilis, substance abuse, delirium, toxic-metabolic disorders, psychiatric disease, age related dementias).

Although HAND can affect any neuropsychological domain, the most commonly reported deficits are in attention/concentration, psychomotor speed, memory and learning, information processing, and executive function, while language and visuospatial abilities are relatively unaffected {20}. HAND has been characterized as a “subcortical dementia”{21}, in which deficits in working memory (e.g., “short-term” memory, the ability to remember information over a brief period of time) and executive function (e.g., planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions) tend to occur early on. Deficits in delayed recall are more typical of “cortical” dementias such as Alzheimer’s disease. Like other subcortical dementias, the pattern of episodic memory impairment in HAND is consistent with a mixed encoding and retrieval profile {22}, whereas that of Alzheimer’s Disease consists of rapid forgetting due to inability to encode novel information {23}.

HIV can have profound effects on the pyramidal and extrapyramidal motor systems. Milder manifestations of CNS motor impairment include ataxia, motor slowing, incoordination, and tremor. This may progress to disabling weakness, spasticity, extrapyramidal movement disorders, and paraparesis {24,25}. Behavioral effects of HAND include apathy, irritability, and psychomotor retardation {26-28}, which can be mistaken for depression. This is difficult to disentangle because of the high rate of major depression and dysthymia in the HIV population, {29}, and because many symptoms queried in depression screening instruments, such as loss of appetite, can be due to HIV. Some AIDS patients develop “manic” symptoms {30}. Again, this must be disentangled from a pre-existing bipolar disorder, or a reaction to drugs. So-called “secondary” or AIDS mania tends to occur in patients with poorly controlled disease, concurrent cognitive deficits, irritability, aggression, and talkativeness, and have hallucinations and paranoia {31}.

Historically, the onset of HAND was associated with low CD4+ counts{32}, other AIDS symptoms{33}, elevated CSF viral load {34}, and elevated CSF markers of immune activation (e.g. beta 2 microglobulin and neopterin) {35}. Much of this dates back to the 1980s when no effective treatment was available and only the most demented patients came to medical attention {36,37}. At that time, a diagnosis of HAD was considered to be a precursor of death {32}. These aggressive forms of HAND remain prevalent in Third World countries and among individuals with late diagnosis, or who have refused or failed cART. However, such presentations are uncommon in cART-treated individuals, who manifest a milder, more slowly progressing and less lethal “attenuated” form of HAND {38,39}.These mild presentations

typically occur in persons with partial immune reconstitution, higher CD4 + counts, and suppressed viral loads, and are less strongly associated with markers of immune activation {40,41} {42} {43}. Due to increased awareness of HAND it is also possible that it is identified at an earlier stage.

The traditional neuroimaging approach (in which a diagnosis is made through qualitative image examination) is useful in excluding structural or inflammatory processes, such as abscess, or tumor, that may mimic HAND, but is limited as a diagnostic marker. The HAND brain may appear grossly normal until advanced disease, when atrophy may be noted. White matter changes may appear, typically in the periventricular region. These must be differentiated from other diseases that affect myelin such as progressive multifocal leukoencephalopathy (PML), and unrelated processes such as leukoariosis. Currently, there are few ways to distinguish among these white matter abnormalities except for the pattern and distribution of the lesions, which are not definitive. Advanced, investigative neuroimaging techniques show promise as biomarkers of HAND {44}. Brain mapping indicates that there may be a unique pattern of atrophy in HAND that distinguishes it from other dementias. There are reports of ventricular enlargement, atrophy of the caudate, putamen, nucleus accumbens, and other subcortical regions that may characterize HAND {45,46} {47}. Another technique that may identify HAND and measure its progression or improvement, is magnetic resonance spectroscopy (MRS){44,45}. MRS is sensitive to the earliest signs of CNS infection. Lentz et al {48}, reported on subjects followed from early seroconversion and reported initial decline in n-acetylaspartate (NAA), a marker of neuronal viability, in the frontocortical gray matter. NAA levels were found to be decreased in the centrum semiovale white matter of chronically HIV-infected subjects, but not in early infection. This study is still ongoing so further follow up will be needed to map changes over time. Paul et al, {49} reported that impaired neuropsychological performance in HIV is associated with reduced NAA and increased myoinositol (MI, a marker of gliosis) in the basal ganglia and frontal white matter, but not with markers in the parietal region (Figure 1). Flurodeoxyglucose (FDG) positron emission tomography (PET) studies in HIV are few, but show early hypermetabolism in the basal ganglia {50}, followed by hypometabolism in late HAND {51}. This pattern is unlike Alzheimer's disease and other dementias.

Neurological and neuropsychological improvement of HAND after treatment with antiretrovirals was established with studies of zidovudine monotherapy in randomized placebo-controlled trials that demonstrated improved neuropsychological test scores versus placebo {52,53}. Current treatment of HIV is based on the use of cART, that includes two or more antiretroviral agents to suppress HIV, and increase CD4+ counts. The most common initial cART regimens consist of two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a "boosted" protease inhibitor (PI). Ritonavir (in small doses) is a PI most commonly used as a booster; it enhances other PI so they can be given in lower doses. No placebo–controlled trials of cART for HAND have been performed, because it would be unethical to refuse treatment to a symptomatic patient. Based on well-conducted (albeit, not randomized, double blinded, controlled) studies {54}, it appears that cART improves neuropsychological performance {55}. It also appears that cART has reduced the incidence of new cases of severe HAND (HAD), while apparently increasing the number and lifespan of individuals living with milder forms of HAND {38,56}.

The CNS penetration of the various components of a cART regimen may vary widely, and there is ongoing discussion regarding the importance of the CNS-penetrability of a cART regimen. Letendre et al., have proposed a CNS-Penetration Effectiveness (CPE) Rank {5} in which cART regimens are ranked by summing up various criteria associated with CNS effectiveness. In a large study, subjects whose regimens scored low on the CPE ranking had

higher CSF viral loads{5} In a related study, Marra et al.{57}, confirmed the association of low CPE scores with higher probability of detectable CSF viral load, and poorer neuropsychological performance. An independent group {58} confirmed that higher CPE scores were associated with greater improvements in neuropsychological performance.

In addition to cART there have been attempts to identify non-antiretroviral neuroprotective drugs to avert HAND. A review of clinical studies {59} have been performed on memantine (an N-methyl-D-aspartate antagonist drug), selegiline (a monoamine oxidase-B inhibitor), nimodipine (a calcium channel blocker), and non-approved drugs Peptide T, CPI-1189, and others. None of the drugs studied were effective. Studies of valproic acid (an anticonvulsant) and minocycline (an antibiotic) are in progress.

There are a few studies of psychostimulant drugs to palliate neuropsychiatric symptoms frequently seen in HAND. These included a randomized, placebo-controlled trial of methylphenidate for severe HIV associated fatigue {60}, and a single-blind, placebo-controlled, crossover-design study of methylphenidate for HIV-associated cognitive slowing {61}. Both showed significantly more improvement with methylphenidate than placebo.

HIV-Associated Vacuolar Myelopathy (HIV VM)

Vacuolar myelopathy is the most common spinal cord disease in AIDS, found in up to 30% of Autopsies in the pre-cART era {62}. It is under diagnosed {63} and must be differentiated from other causes of myelopathy such as infection with Human T-cell lymphotropic virus (HTLV) I or II; herpes simplex 1 or 2, varicella zoster, cytomegalovirus, enteroviruses, syphilis and tuberculosis, tumors, and nutritional deficiencies such as B12 {64}. In the past, HIV VM was more common in patients with opportunistic conditions{63}, but this association has not be reviewed in the cART era.

The clinical presentation of HIV VM is slowly progressive leg weakness, which may be asymmetric at first, spasticity, dorsal column (vibration, position) sensory loss, ataxic gait, and urinary frequency and urgency{65}. Erectile dysfunction is an early sign in men. Paresthesias in the legs are common but neuropathic pain rarely rises to the level seen with peripheral neuropathy. There is prominent hyperreflexia, and extensor plantar responses. In advanced cases, patients may become wheelchair-bound and doubly incontinent {65}.The diagnosis should be questioned if symptoms present in an acute fashion, the arms are affected, there is a sensory level, or if there is back pain.

The most important test is a spinal MRI, to rule out abscess or tumor. In many HIV VM cases, the MRI is normal. Some will have high signal hyperintense areas on T2 weighted imaging, primarily in the thoracic region and affecting the posterior columns, that do not enhance with contrast; these areas correlate to vacuolation on histopathology{66}. Cord atrophy has also been reported{67}. A lumbar puncture is important to exclude treatable infections or carcinomatous meningitis. Somatosensory evoked potentials are useful to disentangle cases in which both HIV VM and sensory neuropathy are present {68}.

The precise pathophysiology of HIV VM is unknown. The distribution of pathology, involving the posterior columns and pyramidal tracts, resembles B12 deficiency {69}. The relationship to productive HIV infection within the cord remains controversial {70-73}. Suspected mechanisms include defective methylation due to a deficiency of S-adenosylmethionine {74}, triggered by inflammatory products secreted by activated macrophages and microglia {75} {76}.

There is no specific treatment for HIV VM. A pilot, open label study of L-methionine to address the suspected abnormality of transmethylation mechanisms in HIV VM did not show benefit

{77}. There are case reports of improvement with cART{78-80}. However, axonal degeneration is a late feature of HIV VM {81}, and would not be expected to resolve. Patients with HIV VM benefit from physical and occupational therapy, baclofen, tizanidine, dantrolene, and intramuscular botulinum toxin to manage spasticity, pain management, and anticholinergic drugs to improve bladder function{65}.

HIV associated peripheral neuropathies

Many peripheral neuropathic syndromes have been reported in the context of HIV infection. Herein, we will confine our discussion to HIV-associated distal sensory neuropathy, neurotoxic nucleoside neuropathy, and inflammatory demyelinating neuropathy.

HIV associated distal peripheral sensory neuropathy (DSPN) (also called predominantly sensory neuropathy, or distal symmetrical peripheral neuropathy), is the most common neurological problem in AIDS {82}, with incidences ranging from 19-66%, depending upon the age, disease stage, and treatment history of the cohort {83}. The risk factors for HIV DSPN are older age, history of alcohol abuse, and advanced HIV disease (e.g., a low nadir CD4+ count and high plasma HIV viral load){84,85}, prior use of a neurotoxic antiretroviral drug (e.g., didanosine, stavudine, zalcitabine), and diabetes.

The most universally reported symptoms are paresthesias {86}, that virtually always begin in the feet, as this is a length-dependent neuropathy. Patients complain of burning, of numbness, of hot or cold sensations, and of episodic electric-shock like sensations. Some complain of a sensation that they are walking on sand, or glass. Many cannot bear to wear shoes. The symptoms ascend over time, as far as the thighs, and will also involve the hands in a glove-like fashion. Cramps and fasiculations may develop in the extremities. Most patients do not develop any motor weakness or muscle wasting until late in their course, and this is limited to the distal extremities {87}. The most common physical findings are decreased or absent ankle jerks, diminished vibratory sensation in the legs, and increased threshold to temperature and pinprick (alternatively, some patients develop hyperesthesia) {87}. Some patients will have all the physical findings of neuropathy but do not report pain. They usually have an asymptomatic neuropathy. Others will have hyper-reflexia proximally and hypo-reflexia distally, in which case a mixed myelopathy and neuropathy should be suspected.

The pathogenesis of HIV DSPN is unknown. Related viruses such as feline immunodeficiency virus (FIV) also cause neuropathy in cats {88}. FIV (and HIV-1) infects and activates macrophages{88} and CD8+lymphocytes {89} in the dorsal root ganglion, and these cells can release substances, such as tumor necrosis factor {88}, that are toxic to neurons and oligodendrocytes. The HIV protein gp120 is also neurotoxic, causing hyperesthesia, allodynia, and spinal gliosis{90}. The major neuropathologic features in HIV DSPN include a loss of unmyelinated axons in the distal regions of sensory nerves, followed by Wallerian degeneration of the distal myelinated fibers. Some degree of demyelination and remyelination and has also been reported{91}.

In most cases, an electromyogram (EMG) and nerve conduction studies (NCS) are not necessary to diagnose HIV DSPN {92}. If an electrodiagnostic study is performed, it will demonstrate findings similar to other degenerative, predominantly axonal neuropathies, such as reduced or absent action potentials. A few patients have apparently normal studies. They most likely have a small-fiber neuropathy, and quantitative sensory testing may be helpful if there is a reason to document the clinical diagnosis. It is important to search for processes that can mimic or exacerbate HIV DSPN, including syphilis, diabetes, B12 or folate deficiency, thyroid disease, hepatitis C virus, and any neurotoxic medication.

Treatment of DSPN itself is generally frustrating. Studies of nerve growth factor {93} and the experimental drug prosaptide {94} were unproductive. Randomized, controlled clinical trials of drugs to control neuropathic pain showed positive results for lamotrigine {95}, for an experimental a high-concentration capsaicin dermal patch {96}, cannabinoids {97,98} and gabapentin {99}. Treatments that were ineffective included amitriptyline {100,101}, mexilitene,{100}, memantine {102}, Peptide T {103}, and acupuncture {101}.

Nucleoside neuropathy in HIV+ patients (also called antiretroviral toxic neuropathy, or neurotoxic neuropathy), has classically been associated with three NRTI drugs: didanosine (ddI), zalcitabine (ddC), and stavudine (d4T). These drugs were used extensively early in the epidemic, and they are still used in resource-limited settings. Other risk factors include another, prior neuropathy, diabetes, alcoholism, poor nutrition, using higher doses of the offending nucleoside, and use of more than one nucleoside {86,104}. The clinical and electrophysiological features of neurotoxic neuropathy are very similar to HIV DSPN {105}, but usually begin within six months of starting the offending drug, with a peak around 3 months {106}. It has been proposed that mitochondrial toxicity {107}, competitive inhibition of human mitochondrial DNA polymerase-gamma {108}, downregulation of gene expression for brain derived neurotrophic factor in the dorsal root ganglion{109}, and specific host genetic polymorphisms {110} may predispose to nucleoside neuropathy. The only specific treatment is to remove the offending drug; if this is impossible, it should be maintained at the lowest dose. Many patients take up to three weeks after the drug is discontinued to see any improvement{111}; reduction in symptoms usually occurs by six weeks, but some may take up to six months.

Inflammatory Demyelinating Polyneuropathies (IDP)—The true prevalence of this complication is unknown, but it appears to be relatively rare. There are two major types of HIV inflammatory demyelinating polyneuropathies (HIV IDP). Acute IDP is similar to Guillain-Barre syndrome, and often occurs during or near primary infection {112}. Patients develop the rapid onset of ascending weakness, areflexia, autonomic instability, and some (usually minor) sensory symptoms{113}, but bowel and bladder function is spared. The disease can progress to involve the muscles of respiration. Unlike non-HIV Guillain Barre, there is usually a mild lymphocytic pleocytosis. Since the advent of cART, a few cases have occurred during immune reconstitution {114}.Electrophysiological studies show patchy distribution of abnormalities, including slow or absent nerve conduction, and abnormal F-waves{115}. Treatment consists of supportive care, intravenous gamma globulin, plasma exchange, and possibly cART {116-118}, and is based on case reports and extrapolation from the non-HIV literature {119}.

A chronic IDP (CIDP) may occur in late infection and is often associated with a CD4+ count of under 50 cells/mm^3 {120}. Unlike acute HIV IDP, this syndrome progresses slowly and may have a relapsing and remitting nature. It must be differentiated from neuropathies caused by CMV and related viruses. Treatment of HIV CIDP is similar to that of non-HIV related CIDP, with the exception for the need to control HIV infection, and is based on case reports on HIV patients and the non-HIV literature.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the CNS {121}. It is caused by the *John Cunningham virus* (JCV), a polyoma virus found world-wide, with a seroprevalence of 70-90% {122,123}. Previously a rare disease, PML became a frequent (up to 5%) complication of AIDS in the 1980s {124}, although the incidence has declined with cART {125}. Recently, PML has received occurred in association with the treatments for multiple sclerosis and rheumatological disorders {126}.

Most cases of AIDS PML occur during severe immunosuppression (under 100 CD4+cells/mm^3) although exceptions occur in about 11% of cases {124}. Most present with the subacute onset of altered mental status, accompanied by focal symptoms referable to the location of the one or more PML lesions, such as hemiparesis, hemianopsia, ataxia, vertigo, speech disorders, and seizures {125}. Patients usually do not have headaches, fevers, nausea, vomiting, or papilledema.

A definitive diagnosis is established by biopsy or autopsy. However, a diagnosis of probable PML can be made with a supportive clinical history along with correlative radiological and laboratory findings. The most common neuroimaging findings {127} are one or more space-occupying white matter lesions that are non-enhancing, hyperintense on T2 and hypointense on T1, and spare the cortical U-fibers. Having said that, some cases do enhance, a feature associated with a better prognosis {128}. There is no definitive MRI marker of PML. Cerebrospinal fluid examination (CSF) is invaluable in ruling out other infections, but otherwise is nonspecific, with mild pleocytosis, elevated total protein, and normal glucose. A positive JCV PCR is considered diagnostic in a case with typical clinical and imaging features; however, the sensitivity and specificity of this test is under discussion, as JCV has been detected in the CSF of immune suppressed persons without PML {129} and may not be detected in cART-treated patients with tissue-diagnosed PML or those with low JCV viral loads {130}. In a severe case such as shown in Figure 2 gross examination at autopsy may show multifocal areas of tan-gay discoloration and softening. The gray-white junction is a favored site. The larger lesions may be necrotizing at the center with loss of both myelin and axons and replacement by confluent lipid-laden macrophages. At the periphery there are scattered virally infected oligodendroglial cells with enlarged nuclei that contain deep amphophilic (purple) viral inclusions. PML lesions also contain grossly enlarged, pleomorphic “pseudoneoplastic” astrocytes. If necessary the diagnosis can be confirmed with immunohistochemistry or *in situ* hybridization for JCV.

There is no specific treatment for PML with or without AIDS. Multiple agents have been tried without success including topotecan {131}, cytarabine {132,133}, and cidofovir {134}. However, cART has improved the course of AIDS PML, decreasing the mortality rate, improving the neuroimaging features, improving survival, and decreasing CSF JCV viral load {135,136} {125}. Patients who survive AIDS PML are likely to have serious residual neurocognitive deficits. Levine et al (2008) reported that eight patients with past PML differed as a group from AIDS patients without history of CNS-OI with regards to information processing and motor functioning{137}. Further, while the PML group was less severely impaired overall than those with history of AIDS and toxoplasmosis, their deficits in information processing and motor functioning were the most severe of all groups examined.

Cytomegalovirus (CMV)

Cytomegalovirus (CMV), a member of the Herpesvirus family, can infect the brain, spinal cord, meninges, retina, the dorsal root ganglion of peripheral nerves, and many visceral organs {138}. Approximately 60% of the population show evidence of exposure to CMV {139} but the prevalence is higher in homosexual men {140}. Cytomegalovirus (CMV) establishes a life-long, latent infection without clinical disease in immunocompetent individuals after initial infection, and may remain latent for years, or reactivate under conditions such as HIV or other immunodeficient states. CMV and HIV are known to transactivate each other *in vitro* {141}.

Typically, CMV of the nervous system presents in individuals with CD4+ counts under 50 CD4+ cells/mm^3, CMV viremia, and one or more systemic site(s) of infection {138}. Neurological CMV disease can present as encephalitis, ventriculitis, myelitis, radiculoganglionitis and peripheral polyneuropathy, or various combinations thereof {138,

142}. Presenting signs and symptoms are extremely variable depending upon the area affected; CMV encephalitis and ventriculitis may present with fever, lethargy, confusion, or coma, seizures, and cranial nerve palsies, ataxia and hemiparesis, or even coma; some patients present with dementia, which may or may not be due to a concurrent HIV encephalitis {143,144}. CMV infection of the spinal cord may cause either a transverse myelitis or a myeloradiculitis characterized by flaccid paraparesis associated with back pain, incontinence, areflexia, paresthesias and sensory loss, and ascending weakness{145,146}.

The CSF CMV PCR is considered the gold standard for identifying and quantifying CNS CMV and for following the response to therapy {147}. The literature also refers to a CSF profile that consists of a polymorphonuclear pleocytosis, {148}, but this is not a consistent finding{145}.

Unlike HIV, CMV can directly infect astrocytes, neurons, oligodendroglia, endothelial, ependyma, and meningeal cells {149,150}, and can directly kill, neural cells, e.g., by inducing apoptosis {151,152}. The most common pathological finding is a microglial nodule encephalitis, but other findings include ventriculoencephalitis (a focal or diffuse destruction of the ependymal lining and necrosis of periventricular tissue); focal necrosis; and isolated cytomegalic cells{153}.(Figure.3)

Randomized, placebo-controlled trial data regarding treatment of CNS CMV is lacking. Based on data extrapolated from case reports and clinical trials of other organ systems, it is recommended that treatment be initiated immediately with intravenous ganciclovir, at an induction dose of 5mg/kg twice daily{54}. Intravenous foscarnet 90 mg/kg twice a day, can be used in lieu of ganciclovir{54} but has greater renal toxicity. Cidofovir can be used if these regimens fail {54}. Based on information extrapolated from other CMV infections, patients should continue chronic suppressive therapy, until CD4+ cell counts rise above 100 cells/mm^3 {154}. Patients who have not started cART should do so, and those with suboptimal cART should have that adjusted {155}.

Cryptococcal meningitis (CM)

Cryptococcus neoformans is an encapsulated yeast found throughout the world. It is spread through inhalation of spores, which can be found in dust and bird droppings. The initial infection is usually a self-limited pneumonitis. In most individuals the immune system clears the disease, but some the organism remains in a latent state within granulomas {156}, from which it can disseminate to multiple organs, particularly in immunosuppressed patients. In AIDS, the most common presentation is a subacute meningoencephalitis, usually in a patient with under 100 CD4+ cells/mm^3. Cryptococcus has an affinity for the CNS, possibly related to its consumption of catecholamines {157}.

Common presenting symptoms of CM include malaise, headache, and fever. As the disease progresses, patients may develop seizures and signs of increased intracranial pressure (nausea, vomiting, visual loss, diplopia, coma){156}. A diagnosis of CM can be made by visualizing the yeast in CSF, using India ink; or by detecting cryptococcal antigen in the CSF using the latex agglutination test {54}. If lumbar puncture is contraindicated, a presumptive diagnosis can be made with a serum antigen test. AIDS patients may not have a CSF cellular pleocytosis, abnormal protein, or low CSF glucose{158}. Neuroimaging may be normal, but abnormalities such as masses (cryptococcomas), dilated perivascular spaces, or pseudocysts, are associated with higher blood and CSF antigen titers {159}.

Immediate treatment is essential to prevent loss of brain and loss of life, as this is a lethal disease and even with optimal treatment, the mortality rate is still 15% {160}. The recommended initial standard treatment is amphotericin B, at a dose of 0.7 mg/kg daily, combined with flucytosine, at a dose of 100 mg/kg daily in four divided doses, for at least 2

weeks for those with normal renal function {155}. Primary treatment with fluconazole has failed {161}. In addition to antifungal therapy and cART, it is important to manage increased intracranial pressure, as this may lead to permanent neurologic deficits, blindness, and death {162}. The CSF can be removed by repeated lumbar puncture, or a lumbar drain or shunt may be necessary{54}. After at least a 2-week period of successful induction therapy, defined as significant clinical improvement and a negative repeat CSF culture, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole 400 mg daily {155}. This should continue for at least eight weeks. Discontinuation of secondary prophylaxis can be considered in patients with sterile CSF, clinical improvement, and an increase in CD4 + cell count to at least 200 cells/mm^3.

With treatment, most HIV+ individuals will survive CM. Long-term outcomes in neurocognitive functioning have only recently been examined. In an exploratory study, Levine et. al., examined neurocognitive functioning in a cohort of fifteen individuals with history of AIDS and CM, compared to 61 individuals with AIDS, but without history of CNS disease. Those with a history of CM continued to demonstrate deficits in verbal fluency and motor functioning relative to HIV infected controls without CM.

Toxoplasmosis encephalitis (TE)—*Toxoplasma gondii* is a ubiquitous intracellular protozoan pathogen of both humans and animals. From 15% to 85% of the world's adult human population is infected with *Toxoplasma gondii* depending on geographical location. The definitive host is the cat, but the parasite can be carried by all mammals. Infection can be acquired transplacentally, or by ingesting contaminated water, undercooked meat, soil, or cat feces. Once in the gut, the parasite disseminates to the brain, muscles, and eyes, and invades cells, where it forms intracellular cysts. Most primary infections are asymptomatic or there may be flu-like symptoms. The parasite may remain latent for years; cases of AIDS-associated *Toxoplasmosis* encephalitis (TE) almost always result from reactivation, usually when the CD4 + count has declined below 200 cells/mm^3; higher risk is present when the CD4+ is under 50 cells/mm^3 {155,163}.

Fever, headache, focal neurological deficit, cognitive dysfunction, seizures, and altered mental status are the most common presenting symptoms of TE {164,165}. Because these are highly inflammatory and necrotic lesions with mass effect, elevated intracranial pressure is often a serious problem. The typical neuroimaging presentation includes multiple (in seventy percent of cases), contrast-enhancing lesions, frequently surrounded by edema {166}. Most lesions are supratentorial, and located at the gray-white matter junction or in the basal ganglia. MRI typically shows several T2 weighted hyperintense lesions with enhancement on postcontrast T1 images{166}. Some lesions are hemmorhagic.{167}. The most important differential diagnosis in AIDS patients is primary central nervous system lymphoma (PCNSL). Some investigators advocate the use of thallium-201 brain single-photon emission CT {168} or positron emission tomography{169} (PET) to differentiate between PCNSL (which has a high rate of uptake) and TE (which does not). However, most physicians still require a tissue diagnosis before treating a patient for PCNSL because of the lack of specificity of these techniques. Cerebrospinal fluid (CSF) frequently is not sampled in TE, because the mass lesions may make lumbar puncture unsafe. It is useful in excluding other pathogens. Almost all AIDS patients with TE are have toxoplasma immunoglobulin G (IgG) antibodies in blood. While a definitive diagnosis requires brain biopsy, a response to empiric toxoplasmosis treatment is also considered to be diagnostic {54}; failure to respond is an indication for biopsy {155}. The response to anti-parasitic therapy may be confounded, however, if corticosteroids are required to reduce brain inflammation, intracranial pressure, and prevent herniation.

The treatment of choice for toxoplasmosis encephalitis is a combination of pyrimethamine (200 mg oral loading dose followed by 50 mg by mouth per day, plus sulfadiazine 1 gram by

mouth, four times a day (to treat the parasite) and leucovorin (folinic acid) 10 mg by mouth per day, to reduce toxicity caused by pyrimethamine {54,155}. An alternative regimen is pyrimethamine 200 mg by mouth loading dose followed by 50 mg by mouth per day, plus clindamycin 600 mg by mouth four times a day plus leucovorin 10 mg per day. Acute therapy should be continued for at least six weeks, provided that the patient is improving, and longer in cases with extensive disease. Secondary prophylaxis should be continued until the lesions are resolved, symptoms have improved, cART has raised the CD4+ cell count to at least 200 cells/mm^3, and viral load is suppressed{170}.

Persistent neuropsychological deficits are evident in many survivors of TE. Examining the long term neurocognitive outcomes of individuals who survived AIDS CNS-OIs, Levine et al (2008) found that those with past TE performed worse on all but one neuropsychological domain than those with history of other AIDS CNS OI, including PML and CM {137}.

Primary CNS LYMPHOMA (PCNSL) in AIDS

Primary CNS lymphoma (PCNSL) arises in and is confined to, the CNS. It is second most common mass lesion in AIDS. The major risk factor is a CD4+ count under 100 cells/mm^3. These tumors are promoted by immunosuppression, chronic antigenic stimulation, and cytokine overproduction. In the setting of immunosuppression, PCNSL is almost always associated with Epstein-Barr Virus (EBV) {171}, a ubiquitous herpes virus with a seroprevalence of 90%. Most EBV infections are asymptomatic, or present as acute mononucleosis. The EBV can remain latent in B cells, and can immortalize the cell. In AIDS, immune surveillance fails and the immortalized EBV-infected B cells are no longer held in check {172}. Thus the risk of PCNSL is greatly increased. Prior to cART, PCNSL occurred in 5% of those with neurological symptoms {173,174}. The use of cART has resulted in lower incidence of PCNSL and improved survival {175,176}.

The presenting symptoms of PCNSL include lethargy, confusion, impaired memory, headache, seizures, or focal weakness. Many patients develop cranial neuropathies and/or ocular involvement. Increased intracranial pressure and herniation can result in papilledema, and coma if untreated.

The usual neuroimaging findings on CT or MRI are one or sometimes multiple, contrast-enhancing lesions surrounded by edema, with mass effect. On MRI, they are hyperintense on T1 imaging and often show a periventricular distribution These lesions typically have a high uptake of radioactive tracers on thallium 201 SPECT {168} or fluorodeoxyglucose PET {169}, as opposed to TE. If it is safe to perform a lumbar puncture, the CSF may be helpful. EBV can be detected and quantified by PCR in the CSF{177} and plasma {178} of these patients, and may be a biomarker of PCNSL. However, diagnosis ultimately depends on a tissue diagnosis.

AIDS PCNSL are almost always high-grade, diffuse B-cell lymphomas, often of immunoblastic subtype. Compared with similar tumors seen in immunocompetent individuals, they are more likely to be multifocal and necrotic. Biopsy can be problematic{179}, especially a needle biopsy, because of the small sample, the possibility of extensive necrosis of the tumor, and the angiocentric nature. Administration of corticosteroids to reduce cerebral edema prior to biopsy can result in lysis of most neoplastic lymphocytes, resulting in a non-diagnostic biopsy{179}.

The tumor is treated with cranial irradiation (usual adult dose is fractionated 4000-5000 cGy), and by instituting or optimizing cART. Chemotherapy, if used, typically includes methotrexate, and there are also some positive results using antiviral therapies (e.g., ganciclovir) that decrease EBV viral load {180}, but there are no large controlled trials that establish optimal therapy.

Unfortunately, many treatments for AIDS PCNSL can result in residual cognitive impairment, particularly when both whole brain radiation and methotrexate-based chemotherapy are used {181}. The literature on this topic almost exclusively involves non-HIV cases. Harder et al. {182} reported on the neurocognitive status and quality of life among 19 non-HIV patients treated for PCNSL. All patients were in remission after combined whole-brain radiation and methotrexate-based chemotherapy. Neurocognitive and quality of life scores were compared to demographically-matched controls who had systemic malignancies and had undergone chemotherapy or non-brain radiotherapy. The authors found neurocognitive impairment in twelve patients with PCNSL, with four showing severe cognitive deficits. Only two control subjects were cognitively impaired according to their criteria. Only 42% of the PCNSL patients returned to work, as compared to 81% of controls.

Immune reconstitution inflammatory syndrome (IRIS)

The immune reconstitution inflammatory syndromes (IRIS) is a serious problem complicating the treatment of AIDS{183}. It refers to a group of syndromes characterized by paradoxical clinical worsening that usually occurs within the first four to eight weeks after starting cART {155}. The reconstituted immune system generates an inflammatory response, resulting in either a worsening of a known, underlying infection, or the unmasking of a subclinical, indolent infection. This exaggerated “dysregulated” inflammatory response is characterized by massive infiltration of CD8+ cells. Neuroimaging features include development of, or increase in, contrast enhancement, and unusual patterns of contrast enhancement {184}. Intracranial pressure may rise {185}, requiring the use of corticosteroids. Among the most common CNS infections reported to be involved in IRIS are HIV encephalitis {186-188}, TE {187,189}, CM {185}, and PML {184} {155}. Risk factors for IRIS include taking cART for the first time, active or subclinical OI, CD4+ counts under 50 cells/mm^3, high CD8+ cells, anemia, and a rapid decline in HIV viral load {190,191}. There are relatively few biopsy or autopsy studies of IRIS, in part because most patients survive the syndrome. Some studies have reported both active lesions containing the pathogen (HIV-associated multinucleated giant cells, JCV, Toxoplasma parasites, etc.), and “sterile” lesions with inflammatory infiltrates. The treatment of CNS IRIS with corticosteroids has been advocated and remains controversial, as there are no formal studies, but should be considered if increased intracranial pressure is present.

The continuing evolution of the HIV epidemic has spurred an intense interest into a hitherto neglected area of medicine, neuroinfectious diseases and their consequences. This work has broad applications for the study of CNS tumors, dementias, neuropathies, and CNS disease in other immunosuppressed individuals.

Acknowledgments

This work was supported by Grants No. NS38841, U01MH083500, and R03DA026099, from the National Institutes of Health

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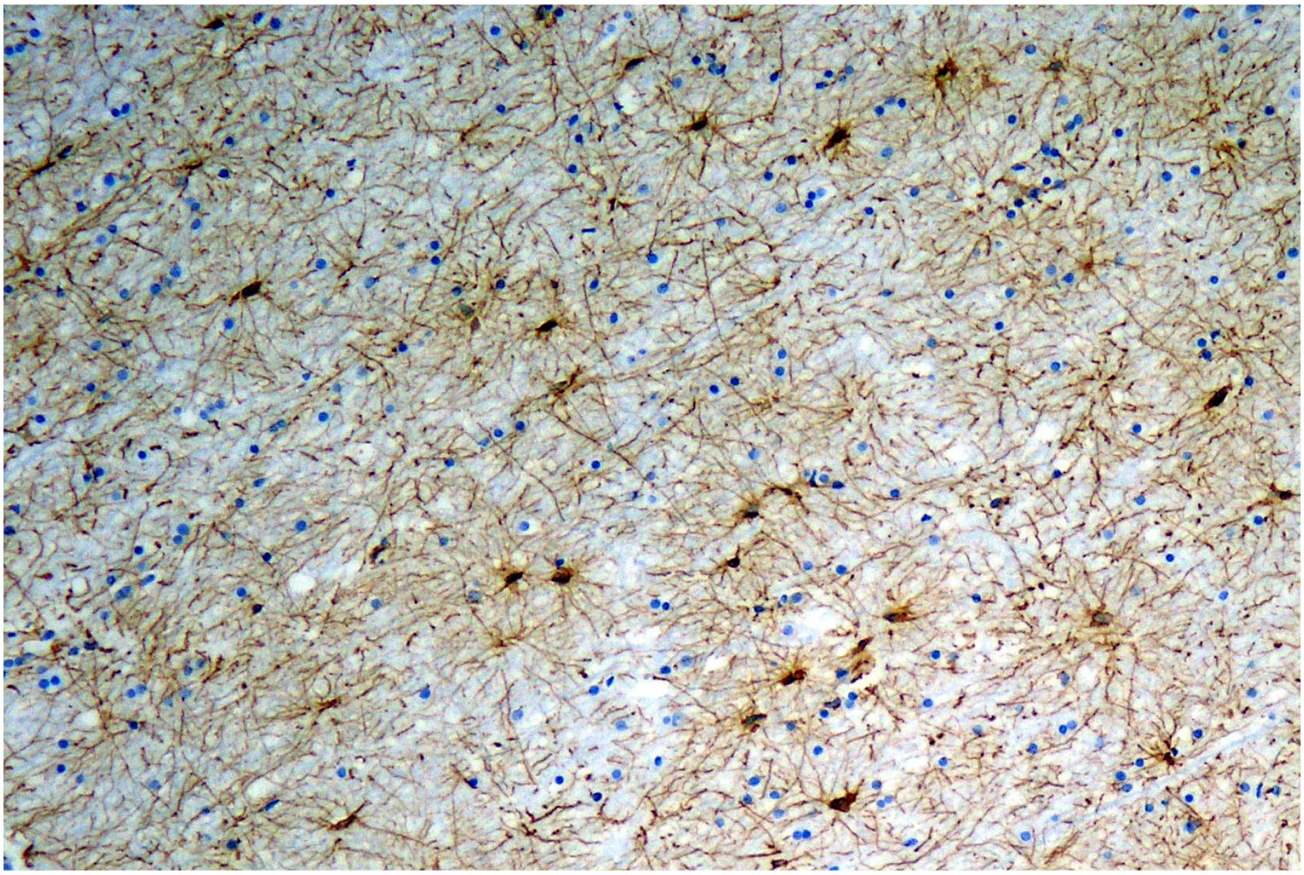

Figure 1.
Marked gliosis of the white matter is a common finding in HIV+ patients at autopsy and may underlie changes seen premortem by magnetic resonance spectroscopy (MRS). Immunoperoxidase stain (brown) for the astrocytic marker, glial fibrillary acidic protein (GFAP).

Figure 2.
This coronal section through the formalin-fixed brain of an HIV+ person who succumbed to progressive multifocal leukoencephalopathy (PML) shows the characteristic multifocal areas of white matter discoloration.

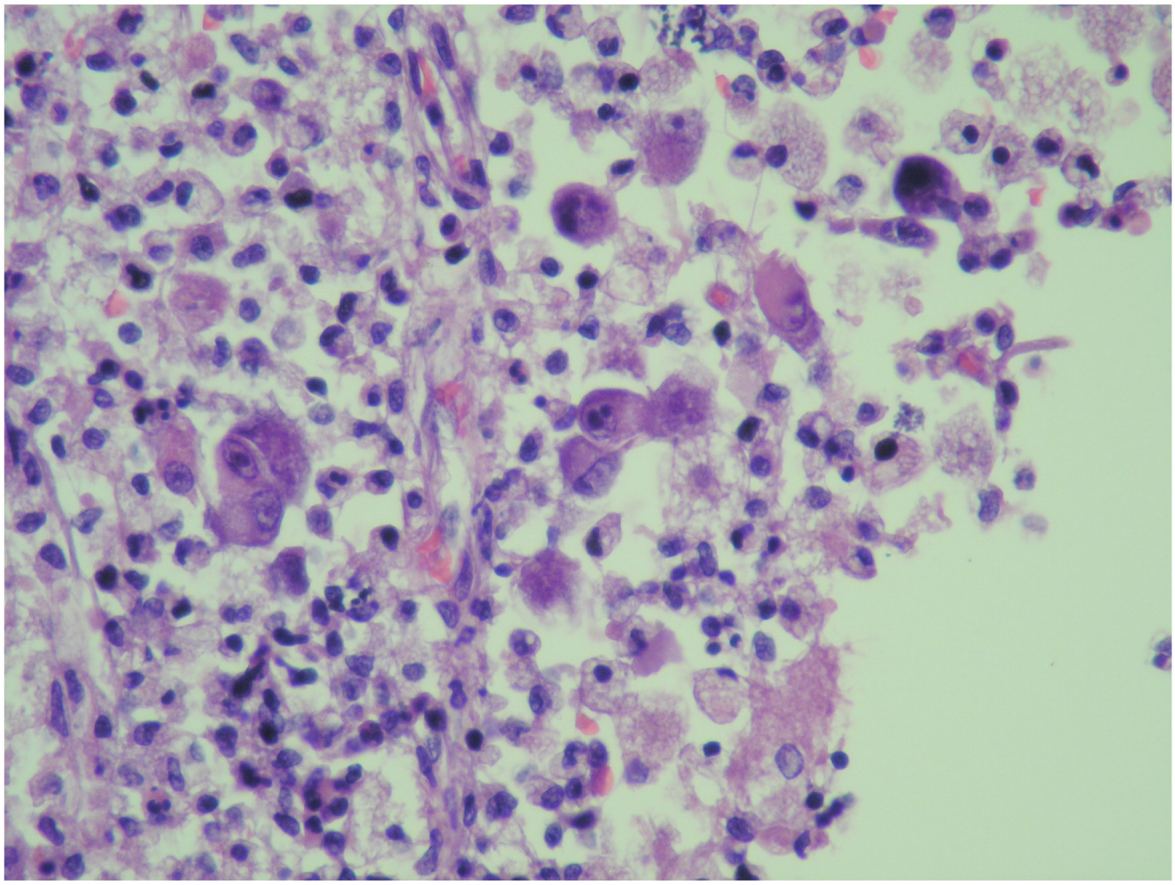

Figure 3.
Cytomegalovirus (CMV) infection of cells may result in the morphological changes shown here ie, cytomegaly and both intranuclear and intracytoplasmic viral inclusions. Immunohistochemistry for CMV (not shown) may detect additional infected cells that appear normal. Hematoxylin and Eosin stain.