



AIDS and the Impact of Cognitive Impairment

Penelope Ziefert, PhD, Mark Leary, MD MS, MFCC, and Alicia A. Boccellari, PhD

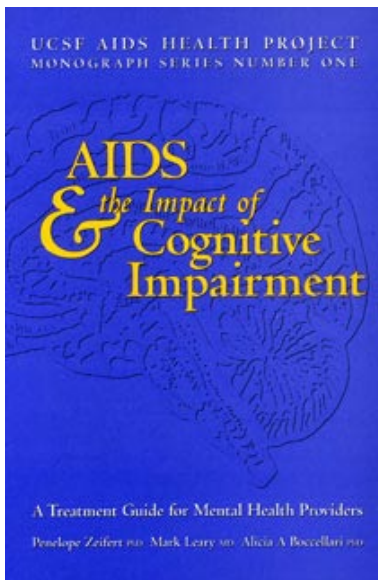
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Chapter 1: Causes of Cognitive Impairment

HIV-related cognitive changes are caused by a variety of conditions. The most common cause is direct infection of the brain by HIV, which may result in HIV-associated dementia. Other causes include opportunistic conditions such as toxoplasmosis and lymphoma; organic affective disorders such as mania and depression; and conditions that lead to transient impairment such as delirium and substance abuse. Some aspects of cognitive impairment are treatable if addressed quickly; others are untreatable and rapidly progressive. When cognitive impairment occurs among people with HIV disease, more than one disorder may be present, a situation that complicates assessment and treatment.



- HIV infects the brain by crossing the blood-brain barrier in “macrophages,” infection-fighting blood cells. It causes impairment by damaging the “myelin,” the “white matter” of the brain, a fatty substance that insulates the branches of neurons and facilitates electrochemical conduction of nerve impulses.

- Diagnosis of HIV-associated dementia requires fulfilling three criteria: a positive HIV antibody test confirming HIV infection; confirmation of disabling cognitive, motor, or behavioral symptoms that interfere with occupational or social functioning; and the exclusion of other potential causes of cognitive impairment, for example, toxoplasmosis, vitamin B12 deficiency, or substance abuse.

- It is the degree of impairment in activities of daily living and the resulting impact on independence that distinguishes HIV-associated dementia from HIV-associated minor cognitive/motor disorder. Among the functions affected by impairment are: concentration, memory, thinking, speech, emotional expression, social behavior, the ability to perform complex tasks, the ability to focus on specific stimuli, coordination and balance, and muscle strength.

HIV-associated dementia is the most prevalent of the HIV-related brain disorders and the condition that mental health providers find the most challenging. It is difficult to determine the presence and degree of cognitive impairment in people with dementia, and psychotherapy in this context is unfamiliar to many practitioners. In contrast to other brain disorders, HIV-associated dementia is caused by direct infection of the brain by HIV itself. It presents with disturbances in cognition, motor function, and behavior. In advanced stages, it profoundly affects an individual's ability to care for him or herself and to participate fully in treatment decisions.¹

Since its identification in 1983, HIV-associated dementia has been known as “AIDS

Direct Infection of the Brain by HIV

Summary

- Most HIV-related cognitive impairment is caused by direct infection of the brain. Two conditions result from infection: “HIV-associated minor cognitive/motor disorder” at the mild end of the impairment continuum, and “HIV-associated dementia” at the severe end. HIV-associated dementia is an AIDS-defining condition.

- Cognitive impairment occurs in 55 percent to 65 percent of people with AIDS. The most severe aspects of HIV-related cognitive impairment occur in the later stages of HIV infection as the immune system becomes more suppressed. Other co-factors include low weight, constitutional symptoms, and anemia (low hemoglobin values).

encephalopathy,” “subacute encephalitis,” “AIDS encephalitis,”² “AIDS dementia complex (ADC)”^{3,4} and most recently, “HIV-associated dementia complex” (HAD).⁵ The name changes have in part been attempts to describe the phenomenon more clearly. For example, subacute encephalitis reflected the belief that cognitive impairment was caused by acute inflammation of the brain that persisted for an extended period of time. As it became clearer that these symptoms were not caused by inflammation alone, researchers coined “AIDS Dementia Complex” to describe a constellation of symptoms affecting three areas—cognition, motor function, and behavior—that developed late in the course of HIV infection. In 1987, the Centers for Disease Control and Prevention (CDC) added AIDS dementia complex to its list of AIDS-defining disorders, thus acknowledging the importance of the syndrome and confirming its relationship to HIV disease.

Over the past decade, these terms have been used interchangeably to indicate a generally accepted clinical picture of dementia.⁶ In 1991, the American Academy of Neurology developed nomenclature and operational definitions to detail criteria for diagnosing HIV-associated dementia. These criteria emphasize the range of cognitive and motor impairment embodied by dementia: “HIV-associated dementia” describes the severe end of the spectrum; and “HIV-associated minor cognitive/motor disorder” describes mild impairment that does not meet the threshold for dementia.⁵

Diagnosis of HIV-associated dementia requires fulfilling three criteria: a positive HIV antibody test confirming HIV infection; disabling cognitive, motor, or behavioral symptoms that interfere with occupational or social functioning; and the exclusion of other potential causes of cognitive impairment, for example, toxoplasmosis, lymphoma of the central nervous system (CNS), vitamin B12 deficiency, or substance abuse. Diagnostic evaluation of cognitive impairment itself may entail: laboratory and radiological procedures; neurological examination; neuropsychiatric evaluation, including mental status exam; and neuropsychological testing.

Dementia and The Trojan Horse

The mechanism by which HIV disrupts the functioning of the brain remains unknown. However, neuroscientists have several theories of HIV brain infection and

its subsequent damage based on autopsies of HIV-infected brain tissue. To understand these theories, it is important to appreciate the physiology of the brain.

Because of the brain’s overriding physiologic importance, it has evolved special defensive systems to protect it from invasion by bacteria, viruses, and other infectious agents. The most important of these systems is the “blood-brain barrier,” a tight network of cells that limits entry into the brain only to blood cells it recognizes as “self.” HIV appears to circumvent the blood-brain barrier by utilizing an ingenious “Trojan Horse” ploy.⁷ As it circulates in the blood, the virus is engulfed by macrophages, the body’s normal infection-fighting blood cells. Since the blood-brain barrier cannot distinguish HIV-infected macrophages, it recognizes them as “self” and allows them to enter the brain with HIV concealed inside.

Once in the brain, HIV is able to replicate within the macrophages and other similar immunologic cells called multinucleated giant cells. In individuals with HIV-associated dementia or lesser cognitive impairment, HIV presumably breaks out of its hiding places in the macrophages and multinucleated giant cells. It appears that HIV does not primarily infect the main cell elements of the brain—neurons and oligodendrocytes—to a significant degree. While autopsy studies of HIV dementia show some loss of brain cells, including neurons, this loss is insufficient to explain the severity of clinical symptoms observed in living clients. What appears more important is the commonly observed loss of myelin tissue, also called “white matter.” Myelin is a fatty substance that insulates the branches of neurons, facilitating the electrochemical conduction of brain impulses and the quickness with which a person thinks. In this way, HIV appears to disrupt brain functioning and leads to symptoms of cognitive and motor impairment.

Brain scans—magnetic resonance imaging (MRI) and computerized tomography (CT)—of many, but not all, people with HIV dementia or minor cognitive impairment show the loss of brain tissue. This loss of tissue, commonly called atrophy, is most prominent in the areas surrounding the brain’s ventricles, spaces normally filled with fluid; but it may also be seen in the cortex, the outer surfaces of the brain, especially in advanced disease. In addition, brain scans typically reveal abnormalities of the myelin, particu-

larly in the centrally-located area beneath the cortex (called the “subcortex”), particularly the basal ganglia (the centers controlling motor function) and the thalamus (an area that integrates the different functions required to perform complex tasks).

Chemical Sabotage of Nerve Cells

Studies have implicated several chemical substances as instruments of HIV-related nerve cell degeneration. At least two protein components of HIV damage the outer membranes covering nerve cells. The two proteins, gp120 (“glycoprotein 120,” a molecule that makes up a portion of the outer coat of the virus) and tat (short for “trans-activator,” a protein within the virus) change the permeability of nerve cell membranes. This may change the chemical balance inside nerve cells, disrupting their normal function and leading to cell damage or death. In one study, high levels of gp120 were found to be associated with abnormally elevated levels of calcium within nerve cells. This latter finding has prompted research into nimodipine, a drug that blocks the entry of calcium into cells, as a treatment for HIV-associated dementia.⁸

Other studies suggest that cytokines, chemicals produced by macrophages and glial brain cells in response to HIV infection, may themselves damage nerve cells. These naturally occurring substances—called interleukin-1, interleukin-6, neopterin, and tumor necrosis factor alpha—are part of the body’s normal immune response to infection and disease. However, HIV brain infection appears to subvert this response: cytokines actually have a toxic effect, presumably interfering with nerve cell conduction, causing clinical symptoms of HIV dementia and cognitive impairment. Other chemicals generated by the immune system in response to HIV brain infection, including beta2 microglobulin and quinolinic acid, have been associated with the disruption of brain cell functioning. For example, it appears that quinolinic acid interacts with a specialized chemical receptor in nerve cell membranes to cause dysfunction.

While autopsy studies suggest that HIV is present in the brains of more than 90 percent of people with AIDS at the time of death, a smaller percentage of people with AIDS appear to develop HIV-associated dementia or minor cognitive/motor disorder. Researchers offer several theories for this, including: different strains of HIV have different propen-

sities to disrupt brain functioning; genetic variations make some individuals more susceptible to the effects of HIV brain infection; and pre-existing conditions—for example, prior brain infection, trauma, or drug use—make some people more vulnerable.

Epidemiology and Natural History

The epidemiology and natural history of HIV-associated cognitive impairment have not yet been clearly defined. It is generally accepted that dementia occurs in conjunction with immunosuppression. Late in the course of HIV infection, a significant number of individuals have some degree of cognitive impairment, although it may not meet the criteria for HIV-associated dementia.⁹ A recent review of the literature estimates that the median prevalence of cognitive impairment among people with AIDS is 55 percent to 65 percent.^{7,10}

There is controversy about the extent to which cognitive impairment is present in people who are HIV-infected but not immune suppressed.¹¹ Some researchers have found subtle cognitive impairment among some asymptomatic HIV-infected people. Other researchers have found no differences in cognition between uninfected and asymptomatic people. Even those who support the view that cognitive impairment may occur early in the course of HIV infection acknowledge that the degree of impairment is subtle and not discernible in activities of daily living.¹² This controversy may in part be due to a lack of clarity regarding the term “asymptomatic.” There has been variation in the characteristics defining asymptomatic subjects, and this lack of standardization may have compromised the consistency of results across studies.

The progression of HIV-related cognitive impairment is also unclear. Originally the course was considered to be an invariable decline in function over time.⁴ “Dementia” was used to describe any degree of HIV-related cognitive symptomatology; terms clarifying the degree of impairment—mild and severe deficits, early and late stage—were used intermittently. Currently, however, progression is not considered orderly or predictable. HIV-associated minor cognitive/motor disorder and HIV-associated dementia may exist not just as poles on the continuum of HIV-related cognitive impairment, but also as separate entities,⁵ and people with HIV-associated minor cog-

nitive/motor disorder may remain functional throughout the course of illness.

The historical overinclusiveness and variability in diagnosis of dementia have led to a wide discrepancy in estimates of the prevalence of HIV-related cognitive impairment.¹¹ A review of neuropsychiatric studies estimates a prevalence of all HIV-related cognitive impairment at 33 percent to 87 percent among patients with symptomatic HIV disease, and a prevalence of HIV-associated dementia at 8 percent to 16 percent among people with AIDS.¹³ A large longitudinal study found that 15 percent of patients with AIDS in the United States developed HIV-associated dementia.¹⁴ The first extensive neuropsychiatric study in developing countries found a prevalence rate of HIV-associated dementia of 5.4 percent to 6.9 percent among symptomatic patients.¹⁵ Researchers conjecture that this is lower than the rate in industrialized countries because of a lack of medical intervention that may lead to an earlier death before progression to dementia.

A diagnosis of AIDS due either to an AIDS-defining illness or a T-helper cell count below 200 is generally considered a precondition to HIV-associated dementia. While absolute T-helper cell level correlates poorly with HIV-related cognitive impairment, the rate of T-helper cell decline is associated with poorer neuropsychological performance.¹⁶ Beta2 microglobulin, neopterin, and quinolinic acid levels may also be a better predictor of impaired neuropsychological functioning than absolute T-helper cell counts.^{17,18,19}

Co-factors for rapid development of HIV-associated dementia include anemia, low weight, and other constitutional symptoms. The single best predictor may be lower hemoglobin values.¹⁴ Some studies have found that lower education^{15,20} or prior head injury²¹ are co-factors for the expression of HIV-related cognitive impairment. This provides some support to the “threshold theory,” which proposes that individuals with a lower IQ, or a history of environmental deprivation, poor nutrition, or brain insults have less cognitive reserve or brain resiliency to compensate for brain impairment.²² These individuals may harbor an underlying structural or neurochemical vulnerability to subsequent brain insults such as HIV-related cognitive impairment.

Clinical Presentation

HIV-associated dementia is character-

ized by disabling cognitive impairment and is usually accompanied by motor and behavioral dysfunction. In some cases either motor or behavioral abnormalities may be missing, or one may predominate over the other. Regardless of the pattern, the essential feature in HIV-associated dementia is significant functional impairment in work and activities of daily life.

It is the degree of impairment in activities of daily living and the resulting impact on independence that distinguishes HIV-associated dementia from HIV-associated minor cognitive/motor disorder. The latter is characterized by mild cognitive impairment and interference with only the most complex or demanding of daily tasks.

For clinical purposes, it is useful to conceive of HIV-related cognitive impairment as a spectrum moving from mild deficits through severe dementia.⁷ However, as stated previously, it is unclear whether the two diagnoses, HIV-associated dementia and HIV-associated minor cognitive/motor disorder, actually exist as two distinct clinical entities or whether they are simply two points along the spectrum of a single disease entity. Regardless, it is important to note that progression through the continuum is not orderly and people may stabilize at different levels of impairment. (See Table 1: Spectrum of HIV-Related Neuropsychiatric Impairment, pages 12–13.)

HIV-associated minor cognitive/motor disorder reflects subtle cognitive impairment that causes only mild interference with work or activities of daily living (ADL). Although individuals with this disorder are able to continue functioning, for the most part, without interruption to normal routine, they are likely to notice and complain about decreased efficiency and difficulty concentrating and remembering. They may also complain of changes in motor function, such as sloppy handwriting. They are especially apt to experience difficulties when faced with novel or demanding circumstances, particularly in the workplace. Stressful situations are more likely than they had been to elicit irritability or emotional distress. Individuals with this level of cognitive impairment may naturally begin to compensate for deficits, for example, by making lists or by decreasing involvement in demanding activities.

When symptoms significantly interfere with work and social functioning, the diagnosis elevates to HIV-associated demen-

tia. This means that a person experiences at least moderate cognitive impairment and additional motor and behavioral abnormalities. At this point, clients have difficulty concentrating on complex information such as medication regimens. They have memory problems, tending to forget information after 20 to 30 minutes; this may not be immediately obvious as this type of memory loss is due to difficulty retrieving information, and thus cues or reminders will help recall. It may also be difficult to remember disparate information discretely; for example, separate conversations may become merged and remembered as one.

At this moderate stage, individuals may remark that they are slower in their thinking, and they may exhibit longer pauses between speech or decreased spontaneous speech. Their emotional expression may be limited and, when combined with slowness, may mimic depression. On the other hand, moderately impaired individuals tend to have preserved verbal skills and may talk at length, particularly about past experiences. Socially they may appear disinhibited; for example, they may make sexually inappropriate statements, and they may neglect grooming and personal hygiene to some degree. They may show a lack of reaction to events that would usually upset them, or a lack of awareness of deficits.

People with moderate dementia have significant difficulty planning and carrying out complex tasks (for example, cooking), so much so that others become alarmed enough to seek help. They also have difficulty paying attention to pertinent stimuli. As a result they may feel overwhelmed and confused in busy environments such as restaurants or grocery stores. They may also report instances of getting “turned around” and lost even in familiar neighborhoods. Finally, they may have gait, balance, and coordination problems, but these are mild and do not preclude ambulation. They may experience slowed motor speed, decreased muscle strength, and tremor.

Later-stage dementia is characterized by a notably sharp decline in functioning. Clients need 24-hour supervision and active assistance from caretakers to engage in the most basic activities of daily living. There is an obvious neglect of grooming and hygiene. Attention and concentration deficits interfere with the ability to read and even limit the ability to follow a conversation. Short-

term memory may be severely impaired, impeding the ability to remember conversations over even a short period of time. Clients may become disoriented. Their thinking becomes simplified. Spontaneous speech may diminish to the point of muteness.

Physically, later-stage dementia incorporates generalized weakness, with the legs affected more than the arms. Ataxia (balance problems) may require the use of canes or walkers, and eventually lead to wheelchair use or complete immobility. Clients may experience bowel and bladder incontinence. HIV-associated dementia complex may be complicated by organic mood disorders, either mania or depression. The risk of an episode of these disorders increases with immunosuppression and is greatest in individuals with moderate to severe cognitive impairment.^{25,26} (See Organic Affective Disorders, page 21, for descriptions and diagnostic criteria.)

A Note on Agitation

As clients develop HIV-related cognitive impairment, they may become more irritable and emotional in response to environmental demands. With moderate impairment, situations that are mildly stimulating (for example, being in a grocery store) may cause fear, anxiety, and agitation. Usually these feelings recede when people are placed in more familiar or structured situations. However with increasing HIV-associated dementia, clients may develop unease secondary to disorientation and confusion, and they may become agitated with fleeting delusions. Delusions tend to be simple and may concern care givers or medication. A common delusion in people with dementia is that other people are stealing from them.

Agitation presents as anxiety associated with significant motor restlessness, for example, pacing. It can be evident during depression, psychotic states, delirium, and substance-induced psychosis, as well as during dementing conditions.

Merging and Cueing: The Case of Roberta

Roberta, a 38-year-old White woman, was hospitalized with her second episode of *Pneumocystis carinii* pneumonia (PCP) and placed in a skilled nursing facility while she recovered. She had a T-helper cell count of 36. Early in her hospitalization, she was referred to a neuropsychologist—Dr. Janis Hauer—for assessment of

References

1. Boccellari A, Zeifert P. Management of neurobehavioral impairment in HIV-1 infection. In Zegans L, Coates TJ, eds. *Psychiatric Manifestations of HIV Disease*. Psychiatric Clinics of North America, Vol. 17(1). Philadelphia: WB Saunders, 1994: 183–204.
2. Snider WD, Simpson DM, Nielsen S, et al. Neurological complications of acquired immune deficiency syndrome: Analysis of 50 patients. *Annals of Neurology*. 1983; 14(4): 413–418.
3. Navia BA, Cho ES, Petito CK, et al. The AIDS dementia complex: II. Neuropathology. *Annals of Neurology*. 1986a; 19(6): 525–535.
4. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Annals of Neurology*. 1986b; 19(6): 517–524.
5. Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. *Neurology*. 1991; 41(6): 778–785.
6. Brew B. HIV-1 related neurological disease. *Journal of Acquired Immune Deficiency Syndromes*. 1993; 6(Suppl. 1): S10–S15.
7. Price RW, Brew BJ. The AIDS dementia complex. *Journal of Infectious Diseases*. 1988; 158(5): 1079–1083.
8. Dreyer EB, Kaiser PR, Offermann JT, et al. HIV-1 coat protein neurotoxicity prevented by calcium channel antagonist. *Science*. 1990; 248(4953): 364–367.

depression, having talked continuously about the recent death of her husband.

On interview at her bedside, Roberta presented as verbal and animated, focusing on her life with her husband and her husband's death, at times becoming tearful about the loss. She denied vegetative symptoms although reported feeling depressed at times. She was alert, "oriented times three," that is, she knew the date, who she was, and where she was. She refused neuropsychological testing, however, stating politely but firmly, "I don't want to spend whatever time I have left doing that."

Asked about her adaptation to the hospital where she would remain for another two weeks, Roberta stated initially that there were no problems since she had been moved from a 20-bed ward to her current semi-private room. She explained that the staff on the open ward had been brusque and uncaring, but that the new nursing staff was much better. This perception was notable, because the same doctors and staff served both areas. Roberta then admitted that there was one orderly she disliked, whom she described as "rough" in bathing her. In addition, she stated that this orderly had removed some candy, a gift from a friend. Roberta tearfully expressed concern that the orderly would retaliate against her for reporting this, but stated that she felt she had to do so because other clients on the unit were sicker and more vulnerable than she.

There was no evidence on interview or by staff report that suggested Roberta might be cognitively impaired, although her immune system was significantly suppressed. Dr. Hauer immediately discussed Roberta's complaint with the attending physician, but the client's description of a brusque and uncaring staff was troublesome, not at all fitting with the psychologist's experience of this staff. Roberta's report suggested symptoms of cognitive impairment, specifically of mental slowing, a propensity to become overwhelmed in a stimulating environment, a lack of awareness of cognitive deficits and, thus, the perception of the etiology as external. The world seemed confusing, noisy, and moving too quickly. A logical way of thinking about this situation was for Roberta to perceive people as curtly rushing her.

When Dr. Hauer returned to Roberta's room, the client was welcoming. She said that she remembered Dr. Hauer, but not her name or position. Dr. Hauer noticed what was

obviously a candy box on a table, covered by some papers. In response to a comment about the candy, Roberta became animated, stating it had been brought by a friend, and she generously offered Dr. Hauer a piece. Almost immediately she looked stricken, stating, "I told you the orderly took them. . . . Oh no, why would I want to get him in trouble?!"

This case demonstrates two aspects of HIV-associated dementia: "misremembering" by merging of information, and the use of cueing to facilitate recall. Roberta experienced the orderly as rough, and she was later unable to locate her candy. She may then have thought that the orderly took it, and confirmed her own suspicions by remembering her feelings about the brusque treatment. When attention was called to the candy, this cued her memory.

Although Dr. Hauer was unable to conduct formal testing, Roberta's behavior and impaired memory suggested a diagnosis of possible HIV-associated dementia. Review of Roberta's medical condition, including blood tests, brain MRI, and current medications, excluded other causes of her behavioral symptoms. Further examination for depression did not reveal significant symptomatology. Dr. Hauer informed hospital staff of Roberta's diagnosis, and they structured her environment to reduce demands placed upon her. For example, they explained procedures before conducting them, confirming that she understood what was to take place. They kept clutter in her room to a minimum. They created a "memory book" so that she could record important information, events, and appointments.

Opportunistic Diseases

Summary

- Four HIV-related opportunistic conditions commonly cause cognitive impairment: toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and lymphoma.
- Toxoplasmosis, a parasitic infection, may affect different parts of the brain and therefore cause different symptoms, ranging from motor weakness and sensory loss to seizures. Common presenting symptoms of toxoplasmosis include fever and constant headache. While the toxoplasma organism cannot be eliminated, toxoplasmosis symptoms can be controlled through drug treatment.
- Cryptococcal meningitis, a fungal infection, typically presents with fever and

9. Atkinson JH, Grant I. Natural history of neuropsychiatric manifestation of HIV disease. In Zegans L, Coates TJ, eds. *Psychiatric Manifestations of HIV Disease*. Psychiatric Clinics of North America, Vol. 17(1). Philadelphia: WB Saunders, 1994: 17–34.

10. Heaton RK, Grant I, Butters N, et al. The HNRC 500 - Neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society*. 1995; 1(3): 231–251.

11. Grant I, Heaton RK. Human immunodeficiency virus-type 1 (HIV-1) and the brain. *Journal of Consulting and Clinical Psychology*. 1990; 58(1): 22–30.

12. Maj M, Satz P, Janssen R, et al. WHO Neuropsychiatric AIDS Study, cross-sectional phase II: Neuropsychological and neurological findings. *Archives of General Psychiatry*. 1994; 51(1): 51–61.

13. Levy RM, Bredesen DE. Controversies in HIV-related central nervous system disease: Neuropsychological aspects of HIV-1 infection. In Volberding P, Jacobsen M, eds. *AIDS Clinical Review 1989*. New York: Marcel Dekker, Inc., 1989.

14. McArthur JC, Hoover DR, Bacellar H, et al. Dementia in AIDS patients: Incidence and risk factors. *Neurology*. 1993; 43(11): 2245–2252.

15. Maj M, Janssen R, Fabrizio S, et al. WHO Neuropsychiatric AIDS Study, cross-sectional phase I: Study design and psychiatric findings. *Archives of General Psychiatry*. 1994; 51(1): 39–49.

16. Bornstein RA, Nasrallah HA, Para MF, et al. Rate of CD4 decline and neuropsychological performance in HIV infection. *Archives of Neurology*. 1991; 48(7): 704–707.

severe headache. Mental status changes range from mild behavioral and personality changes to severe memory loss and confusion. Antifungal drugs can clear infection.

- Progressive multifocal leukoencephalopathy (PML) is a neuropsychiatric disease caused by infection by the JC virus. Soon after infection, clients require major assistance with tasks of daily living and often become bed-bound. Death usually results within several months. There are encouraging reports of a small number of clients who stabilize in response to experimental treatments.

- Other infections of the brain that cause impairment include: herpes, cytomegalovirus, CNS tuberculosis, and neurosyphilis.

- Lymphoma, a cancer originating in the lymphatic system, can invade the brain and cause cognitive impairment, behavioral and personality changes, and neurologic deficits. Radiation therapy is the most effective form of treatment for brain lymphoma.

Common HIV-related opportunistic infections and cancers of the central nervous system are a significant cause of cognitive impairment and, like other opportunistic infections, manifest when the immune system is significantly weakened. The nature of the particular tumor or pathogenic agent—parasite, virus, or fungus—as well as the location of the brain lesion it causes, will determine the pattern of symptoms in an individual client. This section describes the clinical manifestations of the main opportunistic infections and tumors that affect the brain, emphasizing the behavioral and cognitive abnormalities they can cause.²⁷

Toxoplasmosis

Toxoplasma gondii, a parasite that is able to live within human cells, causes the most common HIV-related opportunistic infection of the brain. Toxoplasmosis (or “toxo” as it is colloquially called), the clinical disease that the organism produces, causes a number of neurologic symptoms, for example, muscle weakness, incoordination, and seizures, as well as transient mental status changes and sustained cognitive impairment. The organism is ubiquitous; studies suggest that 50 percent of people in the United States have been exposed to toxoplasma, but the parasite seldom causes clinically evident disease unless a person is immunologically compromised. Toxoplasmosis is the AIDS-defining diagnosis for approximately

5 percent of people with AIDS in the United States. HIV-infected immigrants from countries where exposure to *Toxoplasma gondii* is higher—for example, Haiti and France—have a higher incidence of toxoplasmosis.²⁸

When the toxoplasma organism becomes active, it typically causes multiple infectious masses in different parts of the brain. This accounts for its varying clinical presentations; depending on the part of the brain that is infected, symptoms may include motor weakness, sensory loss, and focal seizures, that is, those limited to specific muscle groups. Common presenting symptoms of toxoplasmosis include fever and constant headache. Subtle changes in mental status—including confusion, memory loss, and ill-defined personality or behavior change—may predate presenting symptoms by weeks. Diagnosis of toxoplasmosis is accomplished in three ways. Blood tests for antibodies to the organism document exposure, MRI of the brain reveals the characteristic pattern of multiple mass lesions, and analysis of cerebrospinal fluid (CSF) obtained by lumbar puncture (“spinal tap”) rules out other infectious causes of symptoms.

Antibiotic therapy with sulfadiazine and pyrimethamine is effective in treating acute toxoplasmosis. However, since the organism is never eliminated, suppressive therapy with these antibiotics is necessary for the duration of the client’s life to prevent active infection.

Cryptococcal Meningitis

Cryptococcus neoformans is the yeast-like fungus that causes cryptococcal meningitis, an infection of the outer covering of the brain (the meninges) seen in 5 percent to 10 percent of people with AIDS.²⁹ “Crypto,” as it is commonly known, is the most common fungal infection of the brain in people with HIV disease. It typically presents with fever and severe headache, although initial symptoms may be more subtle with mild headache, nausea, and ill-defined malaise. Mental status changes may range from mild behavioral or personality changes to severe memory loss and confusion similar to that seen in HIV-associated dementia.

To accurately diagnose cryptococcal brain disease, clients must undergo lumbar puncture and CSF analysis. Several tests detect the presence of the fungus in the spinal fluid. Brain imaging with MRI or CT is generally not useful except to rule out other conditions, since *cryptococcus* rarely causes

17. Boccellari A, Dilley JW, Chambers DB, et al. Immune function and neuropsychological performance in HIV-1 infected homosexual men. *Journal of Acquired Immune Deficiency Syndromes*. 1993; 6(6): 592–601.

18. Boccellari A, Shore M, Strood M. Neuropsychologic assessment in HIV-related disorders. In Cohen PT, Sande MA, Volberding PA, eds. *The AIDS Knowledge Base*. Boston: Little, Brown & Company, 1994: 5–32.

19. Boccellari AA. Neuropsychology of HIV infection: A clinician-researcher perspective. Address to the 99th Annual Convention of the American Psychological Association, San Francisco, August 1991.

20. Satz P, Morgenstern H, Miller EN, et al. Low education as a possible risk factor for cognitive abnormalities in HIV-1: Findings from the Multicenter AIDS Cohort Study (MACS). *Journal of Acquired Immune Deficiency Syndromes*. 1993; 6(5): 503–511.

21. Marder K, Stern Y, Malouf R, et al. Neurologic and neuropsychological manifestations of human immunodeficiency virus infection in intravenous drug users without acquired immunodeficiency syndrome: Relationship to head injury. *Archives of Neurology*. 1992; 49(11): 1169–1175.

22. Satz P. Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*. 1993; 7(3): 273–295.

23. Boccellari AA, Dilley JW. Management and residential placement problems of patients with HIV-related cognitive impairment. *Hospital and Community Psychiatry*. 1992; 43(1): 32–37.

the mass lesions that would become apparent through these scans. Effective treatment requires intravenous amphotericin B for six weeks. Following successful treatment, ongoing suppressive anti-fungal therapy with fluconazole should prevent relapse.

PML and Other Infections

Progressive multifocal leukoencephalopathy (PML) is a devastating neuropsychiatric disease caused by infection of the white matter of the brain with the JC virus. Approximately 2 percent of people with AIDS develop this condition, which can at times be difficult to differentiate from HIV-associated dementia.³⁰

Following JC infection, PML develops quickly causing extensive damage to the myelin covering the nerves responsible for carrying motor signals to the muscles. Although the course of PML may be variable, with periods of decline alternating with periods of relative stability, usually clients require major assistance with tasks of daily living and often become bedbound. Death usually results within several months, although there are encouraging reports of a small number of clients who stabilize in response to experimental treatment with very high dose zidovudine (ZDV; AZT) or with cytosine arabinoside administered into the cerebral-spinal fluid.

PML typically causes marked focal neurological symptoms, including hemiparesis (one-sided weakness), partial loss of vision, or impaired walking. It usually results in cognitive impairment with memory loss and visual-spatial dysfunction, and behavioral and personality changes as the illness progresses. In the presence of PML, MRI scan usually shows multiple abnormalities in the white matter areas of the brain. Single white matter lesions and JC infection of other parts of the brain occur occasionally.

Definitive diagnosis of PML is difficult to make without a brain biopsy. Instead, PML is most frequently diagnosed on the basis not only of cognitive impairment but also of marked focal neurological symptoms, which are not present in HIV-associated dementia. MRI scans are necessary to rule out other opportunistic conditions and confirm the pathologic changes in the white matter.

Although not as common as toxoplasmosis, cryptococcal meningitis, and PML, there are other infectious agents that invade the brain and cause cogni-

tive impairment and neurological symptoms in clients with AIDS. These include:

- Herpes simplex I and II: the viruses that cause oral, anal, and genital ulcers;
- Herpes zoster: the virus that causes “shingles”;
- Cytomegalovirus (CMV): the virus that infects the retina, causing blindness;
- Mycobacterium tuberculosis: the same organism responsible for pulmonary tuberculosis, often presenting with cranial nerve weakness;
- Treponema pallidum: the cause of syphilis, which can remain latent in the body for years before causing symptoms of dementia and neurological impairment in its late stages.

Brain (CNS) Lymphoma

Lymphoma, a cancer originating in the lymphatic system, is a common complication of AIDS. In approximately 7 percent of AIDS patients, lymphoma invades the brain causing clinical symptoms, including cognitive impairment, behavioral and personality changes, and neurologic deficits.³¹

Some clients with brain lymphoma may appear similar to those with HIV-associated dementia, but the presence of significant focal neurologic symptoms, for example, one-sided weakness, often differentiates the two conditions. CT or MRI scans are critical to the diagnosis of CNS lymphoma, although at times a brain biopsy may be necessary to confirm the cancer and distinguish the case from toxoplasmosis. Radiation therapy is the most effective form of treatment for brain lymphoma and it has been shown to prolong life in patients with AIDS by shrinking tumor size; even with treatment, however, life expectancy is only six months after diagnosis.

PML and Progressive Disability: The Case of Derek

Derek was a 26-year-old gay man, reportedly seronegative, brought to the hospital emergency room by his lover Jerry. Jerry was alarmed about Derek’s increasing confusion and memory loss, which had emerged over the prior two months. Derek had appeared to be healthy, working as a paralegal until three months earlier when he had decided to quit because of low energy and difficulty concentrating. Jerry noticed a gradual increase in social withdrawal.

When Derek did get up and walk around,

24. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *British Journal of Psychiatry*. 1982; 140: 566–572.

25. Lyketsos CG, Hanson AL, Fishman M, et al. Manic syndrome early and late in the course of HIV. *American Journal of Psychiatry*. 1993; 150(2): 326–327.

26. Boccellari AA. The neurobehavioral consequences of HIV-1: A clinician's/researcher's perspective. Paper presented at the American Psychological Association, Division 40, San Francisco, August 1991.

27. McGuire D, So YT. Intracranial disorders. In Cohen PT, Sande MA, Volberding PA, eds. *The AIDS Knowledge Base*. Boston: Little, Brown & Company, 1994: 5.7.1–5.7.13.

28. Israelski DM, Danemann BR, Remington JS. Toxoplasmic encephalitis in patients with AIDS. In Sande MA, Volberding PA, eds. *The Medical Management of AIDS*. Philadelphia: W.B. Saunders, 1990: 241–266.

29. Dismukes WE. Cryptococcal meningitis inpatients with AIDS. *Journal of Infectious Diseases*. 1988; 157(4): 624–628.

30. Berger JR, Kaszovitz B, Post MJ, et al. Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection: A review of the literature with a report of sixteen cases. *Annals of Internal Medicine*. 1987; 107(1): 78–87.

31. So YT, Choucair A, Davis RL, et al. Primary central nervous system lymphoma in acquired immunodeficiency syndrome: A clinical and pathological study. *Annals of Neurology*. 1986; 20(5): 566–572.

32. Cummings JL, Benson DF. *Dementia: A Clinical Approach*. Boston: Butterworth-Heinemann, 1992.

his movements were notably slower and more deliberate. He would occasionally stumble and hold on to furniture for support. In recent weeks, Derek began having trouble remembering what day it was or following simple instructions; he also acted strangely, for example, he would put dirty dishes in the refrigerator, not the dishwasher. His speaking ability was reduced, and he answered most questions simply “yes” or “no.”

Upon presentation at the hospital emergency room, Derek underwent a brief medical evaluation, which found no obvious cause for his symptoms. He appeared physically healthy, but because he continued to show dramatic changes in mental status and ability to care for himself, he was admitted to the inpatient psychiatry unit for a full evaluation under the care of Louise Goldwyn, MD. Antibody testing was positive, and a T-helper cell count of 20 indicated profound immune suppression and a diagnosis of AIDS. MRI brain scan showed shrinkage of brain tissue (atrophy) and demyelinating lesions of the white matter consistent with a diagnosis of PML. Neurological examination showed significant muscle weakness and incoordination. Nursing staff reported episodic bladder incontinence.

Dr. Goldwyn initiated treatment with ZDV in an attempt to slow PML progression. Nursing staff planned a routine of care

that emphasized consistency and simplicity. They placed large signs on the ward with arrows indicating directions to Derek's room and the bathroom. This planning allowed Derek to accept the nursing assistance even when he did not seem to understand what was happening to him.

Dr. Goldwyn and John Farmer, Derek's social worker, held a series of meetings with Jerry and Derek's extended family of origin. They discussed PML and the likelihood that Derek would soon become even more disabled. After several meetings, it was decided that Derek would live at his parents' home with in-home nursing care. Shortly thereafter, however, Derek's rapidly progressing disability required his transfer to a hospital unit that specialized in the care of patients with HIV-associated cognitive impairment. In the course of these meetings, it became clear that Jerry was also in considerable distress, and Mr. Farmer referred him to a weekly support group for partners and family members of people with dementia.

In the weeks before transfer to the specialized dementia care unit, Derek continued to lose both strength and cognitive ability. He required increasing assistance from nursing staff with basic functioning. By the time of his transfer, he was bed-bound and mute. He died shortly after the transfer. ■