



# HIV AND THE BRAIN

Liz Highleyman

**R**ight from the early years of the epidemic, researchers have recognized that HIV can affect the brain. Before effective antiretroviral therapy (ART), people with AIDS were susceptible to a variety of opportunistic infections of the brain, as well as HIV-related dementia.

With the advent of effective combination ART in the mid-1990s, the prevalence of both conditions declined dramatically in areas with widespread access to treatment. Less severe neurocognitive impairment, however, remains common. In fact, some research indicates that the frequency of HIV-related neurological impairment is rising as people with HIV live longer.

After some time out of the spotlight, neurocognitive problems have again become a pressing concern as the average age of the HIV positive population rises (nearly 25% are now over 50, according to the National Institute on Aging). Recent conferences and journal articles reveal an increased emphasis on the effects of HIV on the brain, part of a larger shift of focus from classic AIDS-related illnesses to long-term progressive conditions in an aging population that are related to HIV and its treatment in ways that are not yet fully understood.

In particular, there is a new appreciation of the detrimental effects of low-level HIV replication and HIV-related immune activation and inflammation, even while the CD4 cell count remains high. And researchers and people with HIV are increasingly questioning whether the virus somehow accelerates the aging process. (See “Aging and HIV: A Conversation with Dr. Malcolm John,” page 37, for more on getting older with HIV.)

This article discusses the spectrum of neurocognitive manifestations related to HIV/AIDS, looks at their natural history and possible causes, and reviews recent research, including studies presented at the 16<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) in Montréal in February 2009 and the 5<sup>th</sup> International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention in Cape Town the following July.

## SPECTRUM OF CONDITIONS

Neurocognitive impairment in people with HIV may involve cognition (thinking), motor control, and psychological state. Symptoms may include

any combination of the following:

- Poor concentration or attention
- Confusion or altered mental status
- Impaired short-term or long-term memory
- Decreased problem-solving or calculation ability
- Reduced ability to plan ahead
- Difficulty learning new things
- Changes in speech and language comprehension
- Vision changes
- Psychomotor slowing
- Impaired movement
- Decreased fine motor skills
- Poor coordination
- Changes in mood (e.g., apathy, depression)
- Personality changes
- Altered behavior

Specific neurological manifestations depend on which parts of the brain are affected. Impairment can range from so mild that it is not apparent without specialized testing, to so severe that it prevents independent living.

Before the advent of effective ART, individuals with advanced immunosuppression and low CD4 counts were susceptible to a host of opportunistic infections (OIs) that attack the brain, including cryptococcal meningitis, toxoplasmosis, and progressive multifocal leukoencephalopathy (PML), as well as primary central nervous system (CNS) lymphoma, an AIDS-related malignancy (see sidebar on page 19).

Though less common now, OIs still frequently occur in areas where access to ART is limited and among people who do not begin treatment until HIV disease has already progressed.

## ABBREVIATIONS USED FREQUENTLY IN THIS ARTICLE

ANI: asymptomatic neurocognitive impairment

CNS: central nervous system

CSF: cerebrospinal fluid

HAD: HIV-associated dementia

HAND: HIV-associated neurocognitive disorder

HNI: HIV-related neurocognitive impairment

IRIS: immune reconstitution inflammatory syndrome

MCI: mild cognitive impairment

MCMD: mild cognitive-motor disorder

MND: mild neurocognitive disorder

OI: opportunistic infection

Today, most neurocognitive impairment among HIV positive people is not due to opportunistic pathogens, but rather to the effects of HIV itself. As discussed below, neurological disorders are not the result of the virus attacking neurons directly, but instead result from changes in the brain's chemical environment triggered by HIV infection.

## HIV-ASSOCIATED DEMENTIA

People with HIV—especially those with severe immune suppression—can develop frank (clearly evident) HIV-associated dementia (HAD), formerly called AIDS dementia complex. HAD is characterized by significant cognitive impairment that affects activities of daily living (for example, taking medications properly, personal care, handling money, or preparing meals). The ability to perform learned complex tasks (e.g., buttoning a shirt) is particularly affected.

A diagnosis of HAD requires significant impairment in at least two separate “domains,” or areas of function. HAD is considered to be a

For information on psychiatric conditions and peripheral neuropathy, which are not discussed in this article, see the following articles in past issues of *BETA*:

“Conquering Anxiety,” Winter 2007

“Overcoming Depression,” Winter 2004

“Peripheral Neuropathy,” Winter 2002

subcortical form of dementia, meaning it is more likely to involve executive functions, such as attention, concentration, and processing speed. Cortical dementias, in contrast, are more likely to involve memory loss and deficits in higher-level cognitive functions controlled by the cerebral cortex, such as language comprehension and problem-solving. These categories overlap, however, and patients with HAD may experience the full range of symptoms.

People with HAD typically also develop some degree of motor impairment, including psychomotor slowing, poor coordination, tremors, or impaired fine motor skills (e.g., handwriting). Changes in personality, behavior, and mood are common as well, especially apathy, lack of motivation, or depression.

Individuals with a nadir (lowest-ever) CD4 cell count below 200 cells/mm<sup>3</sup> remain at higher risk for significant neurocognitive problems even if they subsequently achieve undetectable viral load and good CD4 cell recovery. This has led some researchers to conclude that HIV-related brain injury may in part be irreversible, thus underlining the importance of timely ART to prevent neurocognitive impairment from the outset.

### MILDER NEUROCOGNITIVE DISORDERS

In the ART era, HIV positive individuals with well-preserved immune function generally experience less severe cognitive impairment, known as HIV-related mild cognitive-motor disorder (MCMD). Overall, the neurocognitive manifestations of MCMD are similar in kind to those of HAD, but of lesser severity. As with HAD, there is no single prototypical pattern of impairment.

A newer classification scheme divides MCMD into asymptomatic neurocognitive impairment (ANI) and HIV-associated mild neurocognitive disorder (MND) or mild cognitive impairment (MCI). People with asymptomatic impairment score below average on standardized neuropsy-

chological tests, but do not have functional deficits apparent either to the individuals themselves or to their families, friends, and coworkers.

Symptoms in people with mild neurocognitive disorder can range from noticeable changes in concentration and short-term memory—sometimes described as “brain fog”—to increasing difficulty carrying out daily tasks.

It is not clear whether mild neurocognitive disorder is a precursor to HAD. Some individuals do experience this progression, but many others have stable mild-to-moderate impairment for years without significant worsening. Whereas neurocognitive disorders often appeared suddenly and progressed rapidly in the pre-ART era, today chronic, slowly progressing impairment is a more typical pattern.

The use of varying terminology can make it difficult to compare findings across studies. Because symptoms can wax and wane and there is no clear dividing line between mild and severe impairment, researchers often refer to the entire spectrum as HIV-associated neurocognitive disorder (HAND) or HIV-associated neurocognitive impairment (HNI).

### CHANGING EPIDEMIOLOGY

Prior to the widespread availability of combination ART, it was estimated that about 20% of people with HIV/AIDS developed dementia. About 90%—including many patients without evident impairment prior to death—showed some type of pathological brain changes on autopsy.

Today, the incidence (number of new cases) of HAD is dramatically lower—less than 1% in some studies. In the European CASCADE cohort, for example, the incidence rate of HAD fell from 6.49 per 1,000 person-years (PY) before 1997 to 0.66 per 1,000 PY by 2003–2006. However, HAD prevalence (total cases) may actually be higher because affected individuals are living longer.

“Severe, life-shattering dementia is rare,” said HIV neurology expert Scott Letendre from the University of

California at San Diego (UCSD) in an overview presented at CROI. However, he added, a large number of people with HIV continue to experience mild or moderate neurological disorders.

Looking at this less severe form of impairment, several recent studies indicate that the overall rate of HIV-related neurocognitive problems is around 50%—about the same as during the pre-ART era. The proportion varies, however, according to demographic characteristics, degree of immune suppression, co-existing conditions, and other factors.

### CHARTER STUDY

At both CROI and the IAS conference, investigators with the large CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study presented findings on the epidemiology and natural history of HIV-related neurocognitive impairment.

Sponsored by the National Institutes of Health, CHARTER was designed to explore the changing presentation of HIV-related neurological complications in the ART era. The study is following 1,555 HIV positive patients enrolled between 2003 and 2007 at six sites (Baltimore, Galveston, New York City, St. Louis, San Diego, and Seattle). Participants have varying treatment histories and degrees of immune dysfunction and neurocognitive impairment; there were no neurological or psychiatric exclusion criteria.

About three-quarters of study participants are men, half are black, about 40% are white, and the average age at study entry was 43 years; about 25% are coinfecting with hepatitis C virus (HCV). Most are taking combination ART and the median CD4 count is relatively high (above 400 cells/mm<sup>3</sup>), but the average nadir level was below 200 cells/mm<sup>3</sup>, indicating a history of advanced immune suppression.

The CHARTER team reported in a poster at IAS that 52% of cohort participants overall had some degree of neurocognitive impairment relative to the general HIV negative population. This fell to 40% when considering only those patients with the fewest comorbidities

## Opportunistic Illnesses in the Brain

Most of the opportunistic pathogens that strike people with impaired immune function can infect the brain. Below is a description of several illnesses that primarily or frequently involve the central nervous system (CNS). Other opportunistic illnesses (OIs) less commonly linked to brain disease include histoplasmosis, coccidioidomycosis, aspergillosis, and human herpesvirus 6 (HHV-6).

In addition, many pathogens that are not traditionally classified as opportunistic and do not normally cause brain disease may do so in the setting of advanced immune suppression, including *Staphylococcus*, *Streptococcus*, *Salmonella*, herpes simplex virus, varicella zoster virus, *Treponema pallidum* (neurosyphilis), and *Plasmodium* (malaria).

**Cryptococcal meningitis (CM):** inflammation of the membranes surrounding the brain (meninges) caused by the yeast-like fungus *Cryptococcus neoformans*. Symptoms may include headache, fever, nausea, and confusion (stiff neck and sensitivity to light are less common compared with other forms of meningitis); altered mental state may result from increased pressure within the skull and altered glucose levels. CM usually occurs among people with advanced immunosuppression and is seldom seen in those on effective combination ART. Treatment involves potent initial therapy typically including the antifungal drug amphotericin B, followed by maintenance therapy with an antifungal such as fluconazole (Diflucan) until a patient achieves sustained immune recovery on ART ( $>200$  CD4 cells/mm<sup>3</sup>).

**Cytomegalovirus (CMV):** a herpesvirus that can infect the brain, but is more often associated with retinitis (inflammation of the retina in the eye) or gastroenteritis (irritation and inflammation of the stomach and intestines). Neurological symptoms may include confusion, lethargy, and fever. A very common pathogen, as many as 80% of U.S. adults are infected with CMV (often as children), but it usually does not cause illness unless immune function is severely compromised ( $<50$  CD4 cells/mm<sup>3</sup>). Standard therapy is ganciclovir (Cytovene) or valganciclovir (Valcyte); injections of the antiviral drugs cidofovir and foscarnet also may be used. Maintenance therapy can be stopped after sustained immune recovery on ART ( $>100$  cells/mm<sup>3</sup>). Immune reconstitution inflammatory syndrome (IRIS), a paradoxical worsening of symptoms as immune function improves, is a concern.

**Mycobacterium avium complex (MAC) and tuberculosis (TB):** disseminated *M. avium* and *M. tuberculosis* can spread from elsewhere in the body and infect the brain, causing meningitis or encephalitis (inflammation of the brain). Brain imaging findings are similar for the two diseases. CNS manifestations usually occur in people with advanced immune suppression. MAC prophylaxis with clarithromycin or azithromycin is recommended for patients with less than 50 CD4 cells/mm<sup>3</sup>. Treatment for both diseases requires prolonged combination antibiotic therapy; one frequently used drug, rifabutin, can interact with protease inhibitors. MAC maintenance therapy can be discontinued after sustained immune

recovery on ART ( $>100$  cells/mm<sup>3</sup>). IRIS is a concern with both diseases. For TB, recent studies show that delaying ART initiation until after TB treatment increases mortality.

**Primary CNS lymphoma:** lymphoma that originates in the brain, spinal cord, or eyes, rather than spreading from elsewhere in the body. Most HIV-related cases are B-cell non-Hodgkin lymphoma (NHL), though other types may also occur. Symptoms vary according to which parts of the brain are affected, and may include confusion, lethargy, personality changes, motor impairment, partial paralysis, and seizures. Brain imaging usually shows a single lesion; a brain biopsy may be done to distinguish it from other OIs. CNS lymphoma is strongly linked to Epstein-Barr virus (a type of herpesvirus) and usually occurs in people with advanced immunosuppression ( $<50$  cells/mm<sup>3</sup>). ART is a mainstay of treatment; incidence of CNS lymphoma has fallen and prognosis has improved since the introduction of effective combination therapy, though the disease is still often fatal. Specific treatment involves various regimens of radiation therapy and chemotherapy; surgery is not used.

**Progressive multifocal leukoencephalopathy (PML):** a life-threatening brain disease caused by the JC polyoma virus. The disease is characterized by demyelination, or loss of the insulation around neuron axons. It typically affects multiple localized (focal) areas, usually in the subcortical white matter. Symptoms vary depending on which parts of the brain are affected, and may include progressive motor impairment, weakness or paralysis, vision loss, and sometimes seizures and personality changes. Due to its localized nature, global neurocognitive impairment and dementia are unusual. JC polyoma virus infection is common, but usually only causes symptoms when immune function is compromised. There is no specific therapy for PML, and ART initiation or optimization is the mainstay of treatment; patients on suppressive therapy often achieve long-term PML remission. IRIS after starting ART is a concern, however. The incidence of PML has not declined as dramatically as that of most other OIs since the advent of combination ART, but most studies show survival has increased.

**Toxoplasmosis:** parasitic infection of the brain with the protozoa *Toxoplasma gondii*. Symptoms may include headache, fever, confusion, motor weakness, and seizures. Active disease usually occurs due to reactivation of existing cysts as immune function declines. The disease is rare in people with more than 200 CD4 cells/mm<sup>3</sup>, while those with less than 50 cells/mm<sup>3</sup> are at greatest risk. Initial infection occurs through consuming raw or partially cooked meat that contains *Toxoplasma* cysts, or through contaminated cat feces. Patients with advanced immune suppression should receive trimethoprim-sulfamethoxazole (TMP-SMX; Bactrim or Septra) as primary prophylaxis. Treatment involves a combination of drugs, usually including pyrimethamine, and perhaps also corticosteroids to manage immediate symptoms. Maintenance therapy is recommended, though evidence suggests it may be safely discontinued after sustained immune recovery on ART ( $>200$  CD4 cells/mm<sup>3</sup>). Here, too, IRIS is a potential concern.

(additional conditions that contribute to impairment), but rose to 85% among those with the most comorbidities.

Over four or more study visits, 29% of participants experienced a decline in neurocognitive function, 47% remained stable, and 17% improved.

Looking at extent of impairment, 21% were classified as having mild cognitive impairment, 29% had moderate impairment, and 2% had severe impairment. In more practical terms, presenter Igor Grant said that while about half of all participants had neurocognitive impairment, about 25% had deficits, revealed by testing, that patients and their families had not noticed.

### OTHER STUDIES

In the September 12, 2007, issue of *AIDS*, Kevin Robinson and co-investigators with the ALLRT (AIDS Clinical Trials Group Longitudinal Linked Randomized Trials) study—made up of 1,160 patients enrolled in several ACTG randomized clinical trials of ART—reported that 39% of study participants had evidence of at least mild neurocognitive impairment at baseline (26% had mild-to-moderate impairment when stricter criteria were used).

At the upper end of the range, Matteo Vassallo and colleagues reported at CROI that among 107 participants with an average CD4 count above 500 cells/mm<sup>3</sup> in the French Neuradapt cohort, 69% had HAND (11% with ANI, 10% with MCMD, 4% with HAD, and 44% with neuropsychological deficits that did not fall within these categories).

At the lower end, Fabrice Bonnet and colleagues reported that about 25% of 230 HIV positive participants (median age 46 years) in the French Aquitaine cohort—another group with well-controlled HIV disease—had mild neurocognitive disorder. Though low compared with other HIV studies, this rate is considerable higher than the 6% rate for the general French population aged 65 or older.

### GLOBAL PICTURE

HIV-related neurocognitive impairment is a concern on a global scale. As

more people in low-income countries gain access to ART, researchers have begun to see patterns that more closely resemble those in wealthy countries, with the rate of severe dementia declining and the frequency of mild cognitive impairment rising.

Robertson and colleagues with the International Neurological Study reported that nearly one-third of more than 800 participants in resource-limited countries in Africa, Asia, and South America had some form of HIV-associated neurological disease. The largest proportion, however, had peripheral neuropathy (nerve damage causing pain or tingling in the feet or hands), while just 6% had mild neurocognitive disorder and 1% had dementia.

Several other researchers have reported neurocognitive impairment rates more in line with those seen in the U.S. and Europe (for example, 57% in Nigeria, 47% in India, and 37% in China). Some studies, however, indicate that HAND rates may be lower in certain regions of the world, which some researchers suggest may be due to differences in predominant HIV subtypes.

### AGING AND ALZHEIMER'S DISEASE

Some recent research suggests that in addition to changes in overall prevalence of HAND, the pattern of neurocognitive impairment may be shifting as the HIV positive population ages.

A growing number of people with HIV appear to have neurocognitive manifestations more akin to those of Alzheimer's disease than classic HIV dementia. An analysis of 141 participants in two Australian cohorts, for example, found that along with an overall decrease in severity from the pre-ART to the ART era, patients were less likely to have subcortical symptoms such as poor attention, and more likely to experience impairment in complex cognitive functions such as learning.

Other researchers have shown that, compared with the general population, HIV positive individuals are more likely to have pathological changes in the

brain similar to those seen in people with Alzheimer's, notably the presence of excessive amyloid protein.

Several factors may put HIV positive people at increased risk for Alzheimer's disease. Studies of the general population indicate that metabolic abnormalities and inflammation increase the likelihood of developing this form of dementia. Many HIV positive people have metabolic risk factors such as elevated blood lipids (fats) or insulin resistance associated with chronic HIV infection or antiretroviral treatment.

Furthermore, a growing body of evidence suggests that chronic inflammation may underlie many of the non-AIDS-defining conditions—such as cardiovascular, liver, and kidney disease—that occur despite relatively high CD4 counts, and this likely also applies to neurological disease.

Chronic inflammation due to low-level residual virus, as well as immune reconstitution inflammatory syndrome (IRIS), may promote neurodegeneration. Some research suggests that HIV's neurotoxic effects may induce brain changes similar to those associated with Alzheimer's disease. The HIV Tat protein, for example, appears to inhibit amyloid breakdown.

Within the HIV negative population, Alzheimer's dementia usually develops after age 65 (though some people have early-onset disease). A growing proportion of people with HIV are over age 50, and recent research suggests that long-term HIV infection may essentially accelerate the aging process. One study presented at CROI found that some aspects of brain function in HIV positive people resemble those of HIV negative people about 15 years older.

If this is the case, people with HIV may develop Alzheimer's disease—or perhaps a novel condition with similar clinical symptoms and pathological findings—earlier than expected, and the processes underlying Alzheimer's and HIV-associated dementia may interact in ways that are not yet understood, possibly resulting in more severe neurocognitive impairment.

## NEUROCOGNITIVE RISK FACTORS

Many studies have looked at risk factors for neurocognitive impairment in people with HIV, producing a large body of conflicting data. It is clear that multiple factors contribute to neurological problems, but it is unclear how these interact with individual susceptibility, and it is not possible to reliably predict which individuals will or will not develop cognitive problems.

In addition to the factors discussed below, HIV-related neurocognitive impairment has also been linked—with varying degrees of consistency—to lower education level, psychiatric conditions such as depression, use of recreational drugs (including methamphetamine), and heavy alcohol consumption.

### IMMUNE SUPPRESSION

Immunosuppression is one of the strongest predictors of HAND, especially its more severe manifestations in untreated individuals. This applies not only to current CD4 cell count, but perhaps even more so to the CD4 nadir level.

Advanced immune suppression—below 200 cells/mm<sup>3</sup>—is a clear risk factor for brain OIs and HIV dementia, as demonstrated by the steep decline in their incidence after effective combination ART came into widespread use. The influence of CD4 count differences among people with relatively well-preserved immune function and the impact on milder neurocognitive impairment are less clear-cut.

In a study described in the October 2008 issue of *AIDS Research and Human Retroviruses*, ART-treated patients in Spain who had a nadir CD4 count of 200 cells/mm<sup>3</sup> or less had more neurocognitive impairment than treated or untreated participants with a higher CD4 nadir (73% vs 53%, respectively), and there was a trend toward greater impairment as CD4 nadir fell. This was a small study, and the overall differences did not reach statistical significance; there were, however, significant differences favor-

ing the higher CD4 nadir group on tests of specific cognitive abilities.

In the CHARTER study, participants who never had a CD4 count below 200 cells/mm<sup>3</sup> and who had undetectable plasma HIV RNA had about a 30% likelihood of neurocognitive impairment, compared with about 50% among patients with a CD4 nadir below 200 cells/mm<sup>3</sup> and detectable plasma viral load. A neuropathology study presented at CROI demonstrated a link between HIV-related brain pathology and nadir CD4 count.

In the ALLRT cohort, having a nadir CD4 count below 200 cells/mm<sup>3</sup> was associated with an increased prevalence of neurocognitive impairment, and patients with a current low CD4 count were more likely to have persistent impairment. But current immune status did not predict incident, or new-onset, neurological problems.

In summary, while immune recovery with effective ART reduces the likelihood of HAND, it is unfortunately not enough to completely cancel out the elevated risk of impairment due to a previous low CD4 count.

### OLDER AGE

Not surprisingly, increasing age is correlated with a higher likelihood of neurological impairment. As noted above, HIV-related brain problems and deficits related to Alzheimer's disease and other forms of dementia may interact in older patients (typically defined as age 50 or higher), potentially resulting in worse impairment.

A poster at CROI reported a high prevalence of neurocognitive impairment among HIV positive individuals aged 60 and older in the French Sigma study. Among the 37 participants included in a neurological analysis (Neurosigma), the median age was 67 years and the median CD4 count was about 500 cells/mm<sup>3</sup>, although the median CD4 nadir was much lower at just over 100 cells/mm<sup>3</sup>. All but one were on combination ART and had undetectable viral load.

Overall, half of the participants

showed evidence of impairment on neuropsychological tests. About one-third (30%) were classified as having severe impairment, including 11% with deficits affecting activities of daily living. The researchers concluded that despite sustained response to ART, neurocognitive disorders—especially of the subcortical type—occur more frequently in older HIV positive people compared with the general aging population, and that they tend to be underdiagnosed.

In another CROI presentation, Beau Ances and colleagues described findings from an analysis that used functional magnetic resonance imaging (MRI) to assess cerebral blood flow in 26 HIV positive patients (mean age 39 years, about 60% on ART, median current CD4 count 486 cells/mm<sup>3</sup>, median CD4 nadir 278 cells/mm<sup>3</sup>) and 25 HIV negative participants at rest and as they performed cognitive tasks.

Both HIV infection and older age were associated with reduced cerebral blood flow, an indicator of impaired neurological function. ART-treated HIV positive individuals aged 50 or older showed MRI patterns similar to those of HIV negative people 10 years older at rest, and 15–20 years older during mental activity. Untreated people with HIV had even greater functional impairment, but this was not correlated with age. The researchers suggested that these differences might reflect HIV-related systemic changes in inflammation, coagulation, and oxidative stress that persist despite ART.

### METABOLIC RISK FACTORS

The recognized link between metabolic abnormalities and Alzheimer's disease and other forms of dementia in the general population suggests that these same factors may contribute to HIV-related neurocognitive impairment.

In the January 1, 2006, *Journal of Acquired Immune Deficiency Syndromes*, Victor Valcour and colleagues reported a significant association between insulin resistance and impaired cognitive performance—both MCMD and HAD—among 145 participants in

the Hawaii Aging with HIV Cohort. “Metabolic dysfunction may contribute to the multifactorial pathogenesis of cognitive impairment in the era of HAART,” they concluded.

More recently, Allen McCutchan and colleagues presented findings from a metabolic substudy of CHARTER in a poster at CROI. In a cross-sectional analysis, the investigators looked at the link between laboratory markers and neuropsychological test performance among 145 HIV positive participants (average age 46 years) with available fasting blood samples.

Overall, 37% had some degree of neurocognitive impairment. In a multivariate analysis, impaired participants had a significantly larger waist circumference and were more likely to have type 2 diabetes (but not insulin resistance). Differences in blood cholesterol and triglyceride levels did not reach statistical significance. Based on these findings, the researchers concluded that “Weight reduction and [antiretroviral] drugs that are less likely to induce metabolic syndrome and diabetes might help to protect the brain.”

In various studies, rates of both metabolic abnormalities and neurological impairment were high, but this correlation does not necessarily imply that the former causes the latter. In the Sigma cohort, for example, about 70% had various metabolic risk factors, including diabetes (27%), high blood pressure (49%), and abnormal blood lipid levels (43%). But the association between neurocognitive impairment and metabolic problems was not statistically significant after controlling for potential confounding factors.

Further studies are needed to tease out the complex interrelationships among chronic HIV infection, antiretroviral drug toxicities, metabolic abnormalities, systemic inflammation, and serious non-AIDS-defining conditions, including neurocognitive disorders.

### HIV VIRAL FACTORS

Characteristics of the virus itself also appear to influence the development of

HIV-related neurocognitive impairment. Typically, HIV uses one of two coreceptors, CCR5 or CXCR4, along with the CD4 cell surface receptor to enter cells. In the brain, the primary targets of HIV—monocytes, macrophages, and microglia—lack the CD4 receptor.

Studies suggest that HIV variants that use the CCR5 coreceptor (so-called macrophage- or M-tropic strains) are more likely to cause neurological problems than those using the CXCR4 coreceptor (T-lymphocyte-tropic or T-tropic strains). Furthermore, “neurotropic” HIV variants that have evolved the ability to enter cells without CD4 receptors and preferentially target the types of monocytes and macrophages found in the brain appear to pose a particular risk.

As noted above, some researchers have proposed that observed differences in the prevalence of HIV-related neurocognitive impairment in various regions of the world may be due to differences in HIV-1 viral subtype.

Some studies have suggested that people with HIV subtype C (the predominant type in India and sub-Saharan Africa) are less likely to develop HAD. An animal study found that mice infected with HIV subtype B performed worse in a maze test than those infected with subtype C. Other research has implicated subtype D (found mainly in east and central Africa).

These differences may in part be attributable to genetic variations in the V3 loop of the HIV-1 envelope, which plays a key role in cell entry. Another potential contributor is variations in the HIV Tat protein, which triggers neurotoxicity. There is also some evidence that HIV may mutate and evolve faster in the brain than elsewhere in the body, leading to amplified immune activation and associated neurological damage.

### HEPATITIS COINFECTION

Due to overlapping transmission routes, a large proportion of people with HIV are coinfecting with hepatitis C virus (HCV) or hepatitis B virus (HBV).

Like HIV, HCV is known to enter

the brain, and it has been conclusively linked to neurocognitive impairment. As might be expected, coinfection with both HIV and HCV therefore further increases the risk of neurocognitive complications.

In the Neuradapt cohort, HIV/HCV coinfection was the sole independent risk factor for abnormal neuropsychological performance. This association remained even among patients with current or recent hepatitis C treatment. An Italian study found that concurrent HCV was associated with persistence of neurocognitive impairment during an average five years of follow-up. And in the CHARTER study, HCV coinfection was a significant predictor of worsening impairment over time, along with detectable HIV RNA in the cerebrospinal fluid (CSF).

Researchers studying a small cohort of patients at St. Mary’s Hospital in London reported at CROI, and at the British HIV Association conference shortly thereafter, that among ten individuals with established HIV infection, acute (within the prior six months) HCV infection was associated with CNS involvement, including increased immune activation and inflammation revealed by brain imaging and impaired performance on neurocognitive tests. HIV/HCV-coinfecting patients were significantly more likely to show impairment than were people infected with HIV alone, even though their average age was about ten years younger.

However, at the previous IAS conference in 2007, ALLRT investigators reported that differences in neurocognitive performance scores between HIV/HCV-coinfecting participants and those with HIV alone were not statistically significant.

The link between hepatitis B and neurocognitive disorders is more equivocal, as there is little research indicating that it is an important risk factor, either among HBV-monoinfecting individuals or those with HIV/HBV coinfection.

But one study presented at CROI suggested that HIV/HBV coinfection predicts greater likelihood of develop-

ing neurological problems. In an analysis of the French Aquitaine cohort, having HBV was one of the factors significantly associated with a higher risk of mild neurocognitive disorder, along with older age and advanced HIV disease.

## HIV IN THE BRAIN

How HIV causes neurocognitive impairment is not fully understood, but likely involves multiple processes such as inflammatory damage to brain cells and blood vessels, vascular dysfunction related to metabolic abnormalities, and acceleration of age-related neurodegeneration.

HIV enters the brain soon after initial infection—typically within the first several days—but does not cause significant damage right away. The virus is able to cross the blood-brain barrier, which protects the central nervous system from toxins and other harmful agents, by hiding in immune cells known as monocytes.

Lipopolysaccharide in the blood from bacteria released when HIV damages the gut lining appears to make the blood-brain barrier more permeable (“leakier”), letting in more virus. In a vicious cycle, once inside the brain, HIV triggers an inflammatory response that further disrupts the barrier.

HIV in the brain does not infect neurons, the key cells responsible for transmission of electrical impulses that control the body. A small amount of HIV may enter support cells known as astrocytes and oligodendrocytes, but it does not replicate and produce new virus (these cells may act as a viral reservoir, however).

Instead, the primary target is specialized brain macrophages called microglia, and other cells of the monocyte line (a type of immune cell produced in bone marrow). Once inside these long-lived cells, HIV may remain in a prolonged latent state.

Rather than directly killing brain cells—as it does with CD4 T-cells elsewhere in the body—HIV exerts its detrimental neurological effects by

setting off a cascade of inflammatory changes. Immune cells activated to fight the virus produce various cytokines (chemical messengers)—such as interferon-alpha and tumor necrosis factor-alpha—that in turn activate astrocytes and attract more immune cells to the battlefield.

These chemicals also trigger the release and inhibit the removal of glutamate, an excitatory neurotransmitter that can overstimulate and thereby injure neurons. This proinflammatory cascade disrupts cellular communication channels and promotes damaging oxidative stress.

Furthermore, HIV Tat and gp120 proteins released when the virus replicates appear to have direct neurotoxic effects. One study in mice showed that gp120 also inhibits neurogenesis, or proliferation of new neurons to repair injury.

Examined on autopsy, brains of people with HIV show inflammatory changes, excessive accumulation of astrocytes (known as astrocytosis or gliosis), demyelination (loss of the protective insulation surrounding neuron axons), and build-up of amyloid precursor proteins. Studies have revealed atrophy or abnormalities in various brain regions and structures, including the basal ganglia, hippocampus, and corpus callosum.

Ian Everall and colleagues with the National NeuroAIDS Tissue Consortium looked at autopsy results from nearly 600 HIV patients who had died since 1999, soon after the advent of combination ART. While only about 18% of examined brains showed typical HIV-related brain pathology, most exhibited some other type of abnormality, and only 22% were normal. Interestingly, however, HIV brain pathology did not correlate with the presence of HAND.

Turning to brain imaging in living patients, MRI scans of participants in the CHARTER study showed that neurocognitive impairment was associated with atrophy or loss of gray matter (comprised of neuron cell bodies) and

abnormal white matter (largely made up of myelin-covered neuron axons). Using magnetic resonance spectroscopy, Bradford Navia and colleagues with the HIV Neuroimaging Consortium found evidence of inflammation in people with HIV and loss of neurons in people with HAND.

While there is some loss or death of neurons in the brains of people with HIV-related neurological disorders, a more typical finding is damaged neurons with their dendrites “cut off” so they can no longer receive neural impulses (known as synaptic pruning). The fact that some neurons are injured rather than dead may explain why partial reversal of impairment may occur after starting ART.

The end result of this assault on the brain is the spectrum of cognitive, motor, and psychological manifestations that characterize HAND. The extent of this inflammatory response does not appear to be closely correlated with the amount of HIV in the brain. Thus, even among individuals receiving suppressive ART, low-level residual virus may be enough to maintain this neurotoxic environment and its associated impairment.

## DIAGNOSTIC CHALLENGES

HIV-related neurocognitive impairment can be difficult to diagnose because its symptoms—such as poor attention, memory lapses, and mood changes—overlap with those of many other conditions (see sidebar on page 24).

## PHYSICAL FINDINGS

Brain-related OIs and malignancies are often marked by physical rather than cognitive symptoms. Encephalopathy—a general term for physiological brain disease (while encephalitis more specifically refers to brain inflammation)—may cause headaches, seizures, tremors, problems with coordination or balance, and vision or speech disturbances.

Meningitis (inflammation of the membranes covering the brain and spinal cord) typically causes symptoms including headaches, altered mental

status, and, most characteristically, stiff neck.

Sudden onset or rapid progression of such symptoms should prompt a thorough examination, especially for HIV positive people with advanced immune suppression. While brain OIs are less common in the ART era, they still occur—even in wealthy countries—among people who do not know they have HIV and do not access care until later stages of disease.

A lumbar puncture (spinal tap) may be done to obtain a sample of the cerebrospinal fluid surrounding the brain and spinal cord to test for pathogenic organisms, or a brain biopsy may be performed to extract a sample of tissue to examine under a microscope.

Neuroimaging methods, including computed tomography, MRI, and radiography (X-rays), may reveal characteristic physical features associated with specific OIs. The location and number of lesions—single or multiple, symmetric or asymmetric, affecting gray or white matter—can suggest specific causes.

Diagnosing neurocognitive impairment can be more difficult, since HIV-related cognitive disorders—even

frank dementia—have not been linked to specific, consistent brain imaging findings in most studies (though, as described above, some brain changes can be seen using imaging methods, and characteristic alterations are apparent on autopsy).

### NEUROPSYCHOLOGICAL TESTING

Early signs of HIV-related neurocognitive impairment may be so subtle that affected individuals and their families and friends are not aware of them. A wide range of standardized neuropsychological tests are used to identify subclinical deficits in specific functional domains.

These may include tests of psychomotor speed (e.g., finger-tapping test), hand-eye coordination, fine motor control (e.g., grooved pegboard test), ability to register and recall memories, attention and concentration (e.g., trail-making test, color-naming test), problem-solving ability, language abilities (both verbal fluency and comprehension), and visual acuity. There are also numerous tests, such as the Beck Depression Inventory, designed to diagnose psychiatric conditions and

assess mood or personality changes.

Cognitive deterioration that happens very slowly over a long period may escape notice until it reaches advanced stages. Symptom checklists, diaries, and functional inventories (e.g., which tasks of daily living a person can perform) may be compared over time to reveal such changes. When evaluating neurocognitive symptoms, it is important to keep in mind what is “normal” for a particular individual.

Researchers have designed tools to specifically diagnose and classify HIV-related neurocognitive impairment—such as the International HIV Dementia Scale developed by Ned Sacktor and colleagues—but investigators continue to use a wide variety of instruments, making comparisons across studies difficult.

Experts do not favor running every HIV positive person through a full battery of neuropsychological tests to identify the most subtle deficits. But Letendre recommends that clinicians ask their patients about neurocognitive impairment—including difficulties carrying out activities of daily living—if patients do not bring up the subject.

While specialized neurocognitive testing is typically administered by a psychologist, neurologist Greg Pauxtis emphasizes that HIV care providers can do basic cognitive screening using a brief office test such as the Mini-Mental State Examination or Short Test of Mental Status.

### DIFFERENTIATING DEMENTIA

It can be particularly challenging to distinguish HIV-related impairment from Alzheimer’s disease and other forms of dementia, especially in older individuals who may have features of both.

Classic HAD typically produces more subcortical symptoms such as psychomotor slowing and diminished attention, while Alzheimers’s often produces more cortical manifestations such as memory loss and language deficits.

Alzheimer’s disease is also characterized by distinctive pathological features, including amyloid or senile

When evaluating HIV-related neurocognitive disorders, it is important to consider other conditions that may cause similar symptoms, and to recognize that more than one such condition may be present at the same time. Potential causes of neurocognitive symptoms include, but are not limited to:

- Psychiatric conditions (e.g., schizophrenia)
- Mood or affective disorders (e.g., depression, bipolar disorder)
- Post-traumatic stress disorder
- Substance use or withdrawal
- Use of psychoactive medications (e.g., opiates for pain relief)
- Drug-related toxicities (e.g., neuropsychiatric side effects of efavirenz [Sustiva])
- Non-opportunistic brain infections (e.g., neurosyphilis, herpes zoster)
- Brain malignancies (e.g., glioblastoma, CNS lymphoma)
- Benign brain tumors or masses
- Endocrine (hormone) imbalances
- Stroke or transient ischemic attack (interruption of brain blood supply)
- Traumatic head injury

plaques and neurofibrillary tangles. As noted above, these features are increasingly observed in people with HIV.

Finally, HIV-related neurocognitive disorders—unlike Alzheimer's—are often reversible to some extent with effective ART, though residual impairment may persist long-term.

### HIV STATUS

Markers of HIV disease progression provide useful but limited information. As discussed previously, HIV-related neurological disorders are associated with low CD4 cell count, particularly a low nadir level. But a relatively high CD4 count is no guarantee against neurocognitive impairment.

Immune status can, however, provide diagnostic clues. For example, since people with high CD4 counts seldom develop OIs, neurocognitive or motor symptoms or unusual brain imaging findings in these individuals are more likely to suggest other causes, such as a stroke or a malignant or benign brain tumor.

The association between HAND and HIV viral load in the blood plasma and CSF is subject to debate, due to conflicting study findings spanning more than two decades.

Considerable observational and controlled trial evidence has linked plasma HIV suppression and improved neurocognitive performance. Furthermore, in a recent analysis of patients in the Thai SEARCH 001 study, published in the March 17, 2009, issue of *Neurology*, Valcour and colleagues found that while plasma HIV RNA levels did not predict HAD, detectable HIV DNA in peripheral monocytes—an indicator of latent reservoir virus—was associated with poorer cognitive performance.

In the pre-ART era, high CSF viral load was associated with more severe neurological disorders. Among people receiving suppressive therapy, however, the relationship between CSF HIV RNA level and mild-to-moderate impairment is less clear, and CSF viral load is not a reliable diagnostic tool. Furthermore, HIV levels in the CSF

do not necessarily correlate with the amount of virus in brain tissues.

As described below, participants in the CHARTER cohort who had detectable CSF viral load using an ultrasensitive test had both a higher likelihood of neurological impairment and worsening impairment over time. A recent small British study likewise found that detectable HIV RNA in the CNS was associated with neurological deficits among ART-treated patients, despite suppression of viral replication in the plasma.

Other researchers, however, have observed no association between plasma or CSF viral load and prevalence or degree of neurocognitive impairment.

### ROLE OF ART

Most experts consider ART the key to preventing and managing HIV-related neurocognitive problems, and epidemiological studies clearly demonstrate declines in brain OIs and severe neurological disorders since the advent of effective combination therapy.

In general, ART reduces HIV RNA in both blood plasma and CSF, but the effect may be more pronounced in one compartment or the other. Furthermore, as discussed below, different drugs vary in their ability to reach virus in the brain. Researchers have not conclusively determined whether antiretroviral drugs must cross the blood-brain barrier in order to protect the brain from HIV-related damage, or whether suppressing viral replication in the blood is adequate.

Numerous studies have looked at the effects of antiretroviral drugs on CSF viral load, while others have gone a step further to assess their influence on brain pathology and neurocognitive performance. As with many aspects of HIV-related neurological disease, this research has yielded mixed results.

Studies showing a beneficial effect date back to the early years of the ART era. In 2001, for example, investigators with the HIV Epidemiological Research Study (HERS) reported that HIV positive women with advanced immune sup-

pression who started combination ART demonstrated improved neurocognitive performance. Women who were on ART the longest demonstrated the greatest improvement, while untreated women continued to decline. Neurocognitive improvement was strongly associated with the magnitude of CD4 cell gains.

More recently, McCutchan reported that in an observational study of more than 400 advanced AIDS patients who experienced good immune recovery after starting combination ART, 27% showed evidence of impairment on neuropsychological tests. This was significantly lower than the expected rate in untreated patients, but still twice that of HIV negative individuals of a similar age.

In the majority of studies that show neurocognitive improvement on ART, advances have been linked to plasma HIV RNA suppression. A team at San Francisco General Hospital, however, found that even patients who had detectable plasma viral load due to failing therapy could experience decreases in CSF viral load, as well as reduced immune activation and inflammation in the CNS.

Swedish investigators found that HIV patients with and without dementia who started ART showed decreased CSF levels of neurofilament protein, a substance associated with neurodegenerative disorders including HAD and Alzheimer's disease; after one year on therapy, 75% had attained normal levels. "HAART seems to halt the neurodegenerative process(es) caused by HIV-1," they concluded.

In a study published in the June 19, 2009, issue of *AIDS*, Maria Marcondes of Scripps Research Institute and colleagues compared rhesus monkeys newly infected with SIV (a simian virus similar to HIV) that received either no treatment or early (shortly after resolution of acute infection) antiretroviral therapy using tenofovir (Viread) and nelfinavir (Viracept), two drugs with minimal CNS penetration.

Treated monkeys experienced a significant drop in brain viral load,

reduced inflammatory response, and improved motor performance. The researchers concluded that “even with agents that show poor penetration into the central nervous system, early antiretroviral treatment prevented characteristic neurophysiological and locomotor alterations arising after infection.” They cautioned, however, that this might not be the case with later ART started *after* brain damage has become established.

On the other hand, some researchers have not seen similar effects, especially among patients with less advanced HIV disease and milder neurocognitive impairment. In 2004, Lucette Cysique and colleagues reported that the overall prevalence of neuropsychological impairment was essentially the same before and after the introduction of combination ART (41% vs 39%, respectively).

The pattern of impairment shifted, however, with improvement in simple attention, verbal fluency, and visuoconstruction (a test of visual/spatial ability), but deterioration in learning efficiency and complex attention. Based on the worsening in some domains, the investigators concluded that the observed deficits did not reflect only leftover past damage, but new injury as well.

An Italian study published in 2006, which looked at 165 patients with relatively well-controlled HIV disease on stable ART regimens (half with baseline neuropsychological impairment, half without), found that use of ART—including drugs with good CSF penetration—was not associated with improved neurocognitive performance.

More recently, a study from Argentina looked at 260 HIV patients (158 on ART with viral load below 1,000 copies/mL and 102 treatment-naïve) with a CD4 count above 350 cells/mm<sup>3</sup>; the mean age was 38 years. While younger participants performed better on the International HIV Dementia Scale, scores did not differ significantly between patients on and off combination ART.

Overall, the most frequent find-

ing is that ART restores neurocognitive function—especially in patients most severely impaired when starting treatment—but not to the level of HIV negative people. Many studies, however, did not distinguish between regimens with more or less CNS penetration. Does persistent impairment reflect irreversible brain damage, or does it indicate that the drugs are not getting where they need to go?

## DRUG PENETRATION

If HIV in the brain causes an “inflammatory cascade” that disrupts normal function, it makes sense to ask whether antiretroviral drugs that cross the blood-brain barrier are particularly beneficial in preventing or improving HIV-related neurocognitive impairment.

## RANKING CNS PENETRATION

Antiretroviral drugs differ in their capacity to penetrate the brain, due to variations in several pharmacological properties. This may help explain why HIV can evolve into distinct strains within the CNS, even showing different drug-resistance patterns compared with plasma virus.

Researchers have developed a scoring system, known as the CNS penetration effectiveness (CPE) index, to rank the ability of antiretroviral drugs to enter the brain (see sidebar on page 27). CPE scores have been used in several studies looking at the comparative efficacy of agents with good versus poor penetration.

Rankings of CNS penetration are subject to disagreement, however, as drug levels in the brain can be difficult to determine. CSF levels are not necessarily a good indicator of drug levels in brain tissue, and different measuring methods can produce varying results. Efavirenz (Sustiva, also part of the Atripla coformulation), for example, has an intermediate CPE score, but some recent research suggests it actually penetrates the brain quite well.

Some drugs float more or less freely in the blood while others bind to proteins. Compared with nucleoside/

nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) bind more readily with proteins, which impairs their ability to cross the blood-brain barrier. But boosting with ritonavir (Norvir) may raise drug concentrations enough to enable significant penetration.

Low molecular weight also favors better brain penetration. As a class, PIs have a higher weight than NNRTIs, which in turn are “heavier” than NRTIs. Drugs that are lipophilic, meaning they dissolve in or combine with lipids, also tend to have better penetration, a property that favors NRTIs over PIs and NNRTIs. Some drugs are subject to the action of molecular “pumps” that expel drug molecules from cells.

Tenofovir (also part of the Truvada and Atripla combination pills) does not cross the blood-brain barrier in significant amounts. According to Letendre, this factor should be considered in the ongoing debate about the relative benefits and risks of tenofovir versus abacavir (Ziagen, also in the Epzicom and Trizivir coformulations), which penetrates the brain relatively well.

There are less data on the most recently approved drug classes. One recent study indicated that boosted darunavir (Prezista), the newest PI, reaches high CSF levels. Letendre holds that integrase inhibitors are unlikely to cross the blood-brain barrier in appreciable amounts, though pharmacokinetic studies suggest they do so to some degree. The CCR5 antagonists maraviroc (Selzentry) and vicriviroc appear to penetrate the CNS, and the M-tropic HIV strains that predominate in the brain should be susceptible to CCR5 blocking.

## PENETRATION AND PERFORMANCE

Does CNS penetration matter with regard to neurocognitive impairment? Constructing regimens that contain at least one drug that penetrates the brain has been emphasized to greater or lesser degrees as ideas about therapy have evolved. Some studies indicate

## CNS Penetration Effectiveness

The CNS Penetration Effectiveness (CPE) scale was developed to rank the ability of antiretroviral drugs to cross the blood-brain barrier. (Due to insufficient data, the chart below does not include the most recently approved drugs.)

Drug Class	0: Low Penetration	0.5: Intermediate Penetration	1: Higher Penetration
Nucleoside/nucleotide reverse transcriptase inhibitors	ddC (zalcitabine; Hivid [discontinued]) ddl (didanosine; Videx) tenofovir (Viread)	d4T (stavudine; Zerit) 3TC (lamivudine; Epivir) emtricitabine (Emtriva)	AZT (zidovudine; Retrovir) abacavir (Ziagen)
Non-nucleoside reverse transcriptase inhibitors		efavirenz (Sustiva)	nevirapine (Viramune) delavirdine (Rescriptor)
Protease inhibitors	nelfinavir (Viracept) ritonavir (Norvir) saquinavir (Invirase, boosted or unboosted) tipranavir/ritonavir (Aptivus)	unboosted amprenavir (Agenerase [discontinued]) unboosted fosamprenavir (Lexiva) atazanavir (Reyataz, boosted or unboosted) unboosted indinavir (Crixivan)	amprenavir/ritonavir fosamprenavir/ritonavir indinavir/ritonavir lopinavir/ritonavir (Kaletra)
Entry inhibitors	enfuvirtide (T-20; Fuzeon)		

that drugs that enter the brain can improve neurocognitive function, whereas others suggest that regimens that produce full plasma HIV RNA suppression protect the brain equally well.

Good penetration is clearly associated with reduced levels of HIV in the CSF, as demonstrated by Letendre and colleagues' work with the CHARTER cohort. In the January 2008 *Archives of Neurology*, they reported that ART regimens with a total CPE score less than 2 (determined by adding the individual scores for each drug) were associated with an 88% increase in the odds of detectable CSF virus, leading them to conclude that "Poorer penetration of [antiretroviral] drugs into the CNS appears to allow continued HIV replication in the CNS."

As to whether this correlates with improved performance, a smaller analysis published in 2004 indicated that among 31 patients with baseline cognitive impairment, using a regimen containing more CSF-penetrating drugs led to a significantly greater reduction in CSF viral load, and CSF virological suppression was in turn linked to greater improvement in neuropsychological test performance.

At CROI, CHARTER investigators reported that among 300 cohort participants with both plasma and CSF

viral load below 50 copies/mL, 41% of patients with "undetectable" CSF viral load were found to have low-level CSF HIV RNA (between 2.5 and 50 copies/mL) using an ultrasensitive test. Individuals who had detectable HIV RNA in CSF but not in plasma had significantly worse neurocognitive performance than those who had undetectable HIV in both blood and CSF, and also compared with those who had detectable virus in both compartments.

The CHARTER analysis also showed that regimens containing NNRTIs—which have intermediate-to-good CNS penetration—were associated with improved neurocognitive performance, as was being treatment-naive when starting the study. And, as the NeuroAIDS Tissue Consortium team reported at the 2008 CROI, an autopsy study of brains from 374 patients revealed that HIV-related brain pathology was about half as likely among people who had taken NNRTIs compared with PIs or no ART.

In the September 1, 2009, *Journal of Acquired Immune Deficiency Syndromes*, Valerio Tozzi and colleagues reported that higher CPE scores were associated with improved neurocognitive performance in various domains. However, an alternative method that involved simply counting the number of drugs in a regi-

men thought to have good CNS penetration did not predict improvement.

Two studies published this past summer came to opposite conclusions regarding the association between brain-penetrating ART and neurocognitive function.

Cysique and the UCSD team evaluated cognitive changes in 37 individuals with baseline mild-to-moderate neurocognitive impairment after they started combination ART. As reported in the August 4, 2009, issue of *Neurology*, cognitive improvement began soon after starting treatment, with 14% demonstrating better neuropsychological test performance by week 12. More patients improved with longer time on ART, reaching 32% at week 24, and 41% at week 36; by week 48, however, the improvement rate had slipped to 33%. Over the same period, only one person experienced worsening test performance.

Neurocognitive improvement was associated with use of drugs with higher CNS penetration scores (CPE > 2) and more severe impairment at baseline. Unlike prior research, however, this study did not show a link between improvement and lower CSF viral load or being treatment-naive. "[T]o minimize impact of HAND on productivity and life quality, drug regimens with the estimated CNS pen-

eration...should be selected when possible based on treatment and toxicity histories and drug resistance testing,” the researchers concluded.

In contrast, as reported in the July 17, 2009, issue of *AIDS*, Christina Marra and coinvestigators with study ACTG 736 actually found a negative correlation between use of CNS-penetrating therapy and neurocognitive performance.

In this longitudinal analysis of 79 patients with advanced HIV disease who were either starting first-line ART or switching therapy, using a regimen with a higher CPE score ( $\geq 2$ ) did not improve overall performance on a battery of neuropsychological tests, even though it increased the likelihood of CSF viral load suppression. In some functional domains, in fact,

test performance actually declined. Searching for an explanation for these unexpected results, the investigators suggested that drugs with good CSF penetration might cause more toxicities in the brain.

Whether or not they are required to improve neurocognitive function, drugs that cross the blood-brain barrier may still be needed to reach latent “reservoir” virus in the brain if HIV eradication is ever to be achieved. More immediately, HIV hiding in the CNS can escape and “reseed” the blood if ART is interrupted.

### CLINICAL IMPLICATIONS

Given these conflicting results, some researchers have suggested that suppressing HIV in the plasma may be

adequate for people with relatively well-preserved immune function and mild cognitive impairment, while brain-penetrating drugs may be necessary for those with more advanced HIV disease and more severe neurocognitive disorders.

“As a general rule, NNRTIs are well penetrating into the CNS, most PIs are poor penetrators, and NRTIs are somewhere in between,” Grant summarized at a CROI 2009 press briefing. “There is a modest association between patients on better-penetrating drugs being less likely to have detectable CSF viral load and cognitive impairment. The effects are there, but they’re not gigantic.”

Letendre noted that although observational studies support treating HAND with better-penetrating ART, data from controlled trials are lacking. Such studies are in the works, however, including neurological substudies in the large treatment strategy trials conducted by INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) and NEAT (Network on European AIDS Treatment).

“If a patient has neurological symptoms, it’s reasonable to switch to more neuro-penetrating drugs,” Letendre concluded. “Should all patients be put on neuro-penetrating drugs at the outset? No, that is just one of many factors to consider in individual cases.”

### CONCLUSION

In summary, while effective antiretroviral treatment and subsequent immune recovery dramatically reduce the occurrence of brain OIs and severe HIV-related dementia, mild-to-moderate neurocognitive and motor impairment remains a concern in the ART era.

Many people with HIV show signs of impairment on neuropsychological tests that are not apparent even to the affected individual. The clinical relevance of asymptomatic HAND is unclear, as it is not known whether impairment will remain stable as long as

## NON-ANTIRETROVIRAL THERAPIES

Suppression of viral load in the plasma and CNS may be necessary to reduce neurocognitive impairment, but it is not sufficient to halt inflammatory responses or completely undo the damage caused by HIV’s assault on the brain.

Experimental therapies may prevent or repair neurological damage by a variety of mechanisms:

- Agents that block the neurotoxic effects of HIV Tat and gp120 proteins (e.g., valproic acid, lithium)
- Agents that inhibit pro-inflammatory cytokines (e.g., kinase inhibitor CEP-1347, TNF-alpha antagonist CPI-1189, platelet-activating factor antagonist lexipafant)
- Monoclonal antibodies against pro-inflammatory cytokines
- Agents that inhibit excitotoxins such as glutamate and quinolinic acid (e.g., NMDA receptor antagonist memantine [Namenda])
- Antibiotics with neuroprotective effects (e.g., minocycline, ceftriaxone)
- Monoamine oxidase inhibitors (e.g., selegiline)
- Antioxidants to counteract oxidative stress (e.g., N-acetylcysteine, OPC-14117, green tea compound EGCG)
- Agents to improve cerebral vascular function (e.g., calcium channel blocker nimodipine, thioctic acid)
- Growth factors to stimulate cell repair
- Stem cells or neural progenitor cells to repair or replace damaged CNS tissue

Numerous therapies studied as potential treatments for neurological dysfunction in people with Alzheimer’s or Parkinson’s disease, as well as for individuals who have suffered strokes—areas of increasing urgency as the general population ages—may also help people with HIV-related impairment. And agents that fight inflammation may interrupt a host of disease processes, including HIV-related neurological damage.

a person stays on effective ART, or will inexorably progress as the person ages, perhaps combining with Alzheimer's disease or other age-related disorders.

ART generally improves neurocognitive performance, and it is important for people with memory difficulties or other cognitive problems to receive the support and assistance they need to achieve good adherence to therapy.

But ART is not enough to completely cancel out existing neurological damage, and the risk of impairment remains significant among people with previous advanced immune suppression (i.e., low nadir CD4 count).

"It is possible that low nadir CD4 represents a 'legacy' event whose neurologic consequences persist once triggered," according to the CHARTER investigators. Likewise, the ALLRT researchers concluded that "The association of previous advanced immunosuppression with prevalent and sustained impairment suggests that there is a non-reversible component of neural injury that tracks with a history of disease progression."

In contrast, according to Letendre, CHARTER participants on effective ART with undetectable plasma viral load whose CD4 counts had never dropped below 200 cells/mm<sup>3</sup> demonstrated significantly better cognitive performance than those who started ART with more advanced HIV disease.

Tozzi and colleagues found that severity of neurocognitive impairment at the time of ART initiation appeared to be the strongest predictor of persistent neuropsychological deficits despite long-term therapy. "HAART improves neurocognitive functioning but, in our experience, the greater is the impairment, the lower is the probability of its full reversal," Tozzi said.

Furthermore, since HIV-related brain injury is due not to direct infection of neurons, but rather to the toxic effects of viral proteins and the inflammatory cascade and oxidative stress

triggered by the virus, even a small amount of residual HIV may be enough to maintain a neurotoxic environment.

Nevertheless, as Ronald Cohen and Assawin Gongvatana pointed out in an editorial accompanying Cysique's *Neurology* article, the results of that study "indicate that HIV-associated cognitive impairment is treatable and may not reflect permanent structural damage to the brain, such as is presumed to occur in brain disorders like Alzheimer disease."

Taken together, recent research on neurocognitive disorders in people with HIV underline the potential hazards of treatment interruption and add to the growing body of evidence supporting earlier initiation of ART, before significant immune dysfunction occurs.

Since HIV enters the brain within days after infection, however—well before most people are even aware they have the virus—it may be practically impossible to start treatment early enough to prevent all neurological damage.

As such, there is a great need to develop other types of neuroprotective therapies, including agents that block the neurotoxic effects of HIV proteins, drugs that inhibit proinflammatory cytokines that trigger neuron injury, antioxidants that neutralize free radicals causing oxidative stress, and growth factors and stem cells to help repair or replace damaged brain tissue (see sidebar on page 28). Therapies to manage co-existing risk factors such as metabolic abnormalities and hepatitis C coinfection may also play a role.

Given the multiple factors and processes that play a role in HIV-related neurocognitive disorders, it is likely that a combination of different types of therapies may be needed to fully reverse established impairment.

**Liz Highleyman** ([liz@black-rose.com](mailto:liz@black-rose.com)) is a freelance medical writer based in San Francisco.

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