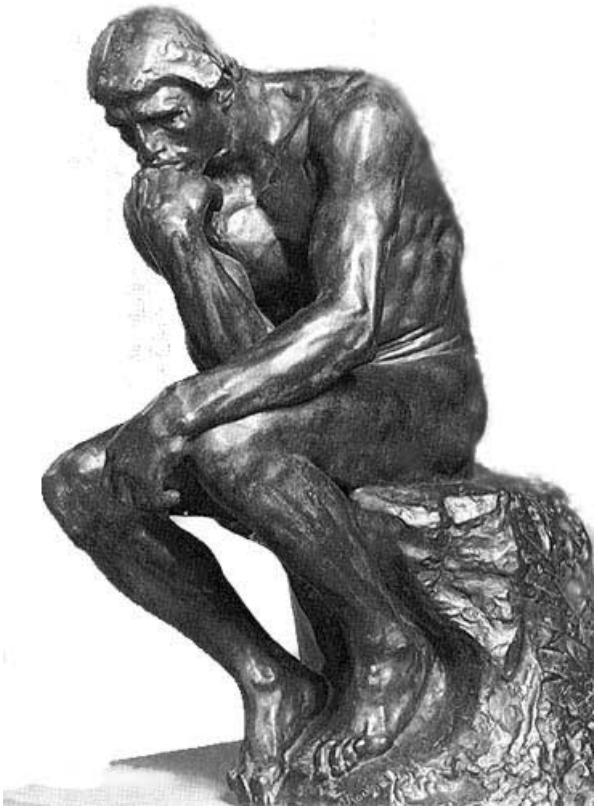

HIV-Associated Neurocognitive Disorder

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This is to acknowledge that Ellen Kitchell, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Kitchell will be discussing off-label uses in her presentation.

Biography:

Inspired by books like *And the Band Played On* and *Voices from the Epidemic*, Dr. Kitchell moved from the University of Iowa Carver College of Medicine to the University of Texas, Southwestern to complete internal medicine residency and infectious disease fellowship. She currently serves as an assistant professor in the Infectious Diseases department. Most of her time is spent in clinical practice caring for HIV-positive patients and in educational activities for rotating trainees at Parkland Hospital. She is Associate Medical Director of HIV Clinical Services at Amelia Court. Her research primarily focuses on improving quality of care for patients with HIV, including reducing inpatient readmissions and increasing rates of HIV testing in asymptomatic patients.

Purpose and overview:

To provide a basic understanding of the clinical diagnosis and management of HIV-associated neurocognitive disorders, including HIV-associated dementia and mild HIV-associated neurocognitive impairment. Epidemiology, risk factors, pathogenesis, typical clinical symptoms, physical examination, laboratory and imaging findings will be discussed. Studies regarding the use of antiretroviral therapy in general and specific antiretrovirals will be reviewed, as well as adjunctive treatments. Finally, the controversy regarding prevention of HIV-associated neurocognitive disorder through early initiation of antiretroviral therapy and future directions for research will be discussed.

Objectives:

1. To understand the importance of HIV testing in patients with cognitive impairment to evaluate for a potentially reversible cause of dementia

2. To recognize cognitive, behavioral and motor symptoms as well as physical examination findings typical of HIV-associated dementia and mild neurocognitive disorder

3. To order appropriate lab, imaging and adjunctive testing to assess patients with suspected HIV-associated neurocognitive disorder

4. To recognize the importance of antiretroviral therapy in treatment and prevention of HIV-associated dementia, but also to realize the limitations of these medications in treatment of milder forms of neurocognitive disorders

HIV-Associated Neurocognitive Disorder

Soon after its discovery, human immunodeficiency virus (HIV) was found to cause neurologic damage separate from its ability to allow opportunistic infections. The introduction of highly-active antiretroviral therapy (HAART) resulted in significant decreases in the morbidity and mortality associated with HIV-associated dementia. However, the prevalence of less severe HIV-associated neurocognitive impairment, which may be undiagnosed through routine clinical visits, has progressively increased over time. In the routine care of the general population of patients with HIV, the effects of antiretrovirals on prevention and treatment of neurocognitive disorders are not a major focus of attention; rather, clinicians evaluate timing of antiretroviral initiation and measure efficacy of medications primarily through serum CD4+ counts and HIV RNA levels.

HIV-associated neurocognitive disorder (HAND) can cause significant disability in patients living with HIV, placing burdens on caregivers and the health-care system. HIV predominantly impacts the subcortical central nervous system structures, and symptoms of HIV neurocognitive disorder typically involve slowing of thought, memory disturbances, difficulty with complex intellectual tasks, and changes in personality. HIV-associated dementia and milder neurocognitive impairment can be diagnosed through clinical interview, neuropsychological testing, neuroimaging, and analysis of cerebrospinal fluid if necessary.

Appropriate management of patients with HIV-associated neurocognitive disorder not currently taking antiviral medications is initiation of highly-active antiretroviral therapy, although which antiretrovirals are best in treating this disorder is controversial. Many adjunctive treatments have been tested for HAND, but none have been found to be effective so far. Whether early initiation of antiretroviral therapy in asymptomatic patients with high CD4+ counts would prevent HIV-associated neurocognitive disorder is also under investigation.

History

The first report of *Pneumocystis carinii* (PCP) in young homosexual men was published in 1981 (1). In 1982, after multiple other case series of patients presenting with Kaposi sarcoma and PCP, the Centers for Disease Control (CDC) defined the condition of acquired immune deficiency syndrome (AIDS). Shortly afterwards, cases of progressive encephalopathy without diagnosis of other opportunistic infections were identified. The term "AIDS dementia complex" was proposed in 1986 to describe patients with progressive cognitive and motor deficits, usually in patients with advanced AIDS (2).

In the 1990s, after the introduction of highly-active antiretroviral therapy (HAART), patients with HIV survived longer, and milder forms of cognitive impairment were recognized. In 2007, the American Academy of Neurology revised the diagnosis guidelines for "HIV-associated neurocogni-

tive disorder," including "asymptomatic neurocognitive impairment" (ANI), minor neurocognitive disorder (MND), extending to HIV-associated dementia (HAD) (3).

Epidemiology

During the late 1980s and early 1990s, HIV-associated dementia affected between 17-46% of patients (4,5). One autopsy study of patients who died of complications of AIDS showed that over 80% had evidence of central nervous system (CNS) injury attributable to HIV-1 regardless of whether the patient had clear symptoms of dementia prior to death (6). The introduction of effective HIV therapy led to a decrease in new cases of HIV-associated dementia, although those who survive with this disorder usually continue to have some degree of cognitive improvement. A small number of patients who are diagnosed very late in infection continue to present with HIV-associated dementia in current clinical practice.

Three recently-published cohort studies, including data from the multi-center CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research) cohort in the United States, the Aquitaine cohort from France, and a Swiss cohort, demonstrated the evolving prevalence of neurocognitive impairment in patients with HIV in the HAART era (7,8,9). Researchers performed neuropsychological testing on large groups of patients with HIV, regardless of whether patients reported cognitive symptoms. The studies were performed in clinically stable patients with high CD4+ counts and low HIV RNA viral loads. In these cohorts, 2-7% met diagnostic criteria for HIV-associated dementia, 12-31% had mild cognitive impairment, and 21-42% had abnormal results on cognitive testing despite no reported symptoms. Overall, 42-71% of patients were found to have some form of cognitive impairment as compared to age-based HIV-negative controls. As mild neurocognitive impairment is not something for which clinicians typically screen in general practice, these studies raise the concern of a hidden epidemic of cognitive disorder in otherwise stable patients. One autopsy study from the early HAART era showed actually an *increase* in the prevalence of pathologic changes of HIV encephalopathy in patients with HIV as compared to the pre-HAART era (10).

Risk Factors for HIV-Associated Neurocognitive Impairment

Low CD4+ count nadir (the lowest CD4+ count ever documented on a patient prior to starting HAART) has been identified by multiple cohorts as one of the most important risk factors for development of HIV-associated neurocognitive impairment (4, 11-12). CD4+ counts lower than 200 cells/μL are particularly associated with higher rates of neurocognitive disorder, especially with HIV-associated dementia. One recent observational study performed in patients identified to have been recently infected with HIV (seroconversion on average 11 months prior to study entry). Within 5 years of seroconversion, approximately 40% of patients with a baseline CD4+ count of less than 400 cells/μL had developed HIV-associated neurocognitive disorder, as compared to 10%

of those with higher baseline CD4+ count. Viral load of greater than 30,000 copies/mL was also independently associated with more rapid cognitive decline (13).

Genetic characteristics of various strains of HIV, particularly polymorphisms of the *Tat* protein that activates HIV transcription, have been postulated to affect the severity of HIV-associated neurocognitive disorder. However, data regarding the neurotoxicity of certain clades of HIV have been conflicting. Some studies have indicated that clade C HIV-1, the strain most prevalent worldwide, particularly in Sub-Saharan Africa, was associated with increased rates of HIV dementia, but others have shown no differences in prevalence or severity of neurocognitive impairment in patients with clade C HIV-1 infection as compared to other clades of virus (14, 15).

A number of non-HIV factors have also been associated with increased rates of neurocognitive impairment in cohort studies. Increasing age is strongly correlated with development of HIV-associated neurocognitive disorder, of particular concern as the cohort of HIV-positive patients in the United States grows older. Several studies have shown that, in patients with high CD4+ count and undetectable HIV viral load, increased traditional cardiovascular risk factors, such as diabetes, increased carotid intimal thickness, and central obesity, were associated with increased cognitive impairment as compared to HIV-positive peers without these risk factors (16,17). Hepatitis C co-infection has also been identified as a risk factor for HIV dementia in several studies (18), perhaps related to its neuro-inflammatory properties.

Drug and alcohol use can impair cognitive function and contributes additively to HIV-associated damage in the brain, especially in patients with a history of chronic methamphetamine, heroin, cocaine, or alcohol use (19). Current use of illicit substances and alcohol can cause confusional states and mood symptoms, which can confound the diagnosis of HIV-associated neurocognitive disorder. Chronic use of illicit drugs and alcohol can lead to damaged central nervous system structures, including the dopaminergic system, leading to difficulties with attention and executive function.

Finally, patients may have increased genetic susceptibility to HIV neurocognitive disorder. For example, patients with the ApoE4 genotype have increased rates of HIV-associated dementia, and patients with particular CCR-2 polymorphisms (a receptor involved in monocyte chemotaxis) have increased neuropsychological abnormalities (20, 21).

Pathogenesis

Despite the amount of literature about the pathogenesis of HIV in the central nervous system, the mechanism of HIV-associated neurocognitive dysfunction is not completely clear. Virus enters into the central nervous system very early after primary infection and establishes a productive infection. It is theorized that some neural damage results from direct effects of viral particles, but inflammation resulting from the immune response to HIV in the CNS likely causes most of the noted injury. Figure 1 demonstrates the most recent theories regarding HIV-associated neurotoxicity.

Within 1 to 2 weeks after primary infection with HIV, monocytes from the peripheral circulation appear to cross the blood-brain barrier carrying the virus, which is known as the "Trojan Horse" theory (22). Once in the central nervous system, macrophages start producing HIV-1 virions, which can serve as a "sanctuary site" from the systemic circulation. This is implicated as a protected reservoir of virus in patients with an undetectable viral load in the serum which is difficult to eradicate. Infected macrophages from the periphery activate microglia (the resident macrophages of the central nervous system), leading to chronic immune activation within the central nervous system (23). Neurons do not appear to be directly infected by HIV-1.

Two major models of HIV central nervous system pathogenesis exist: the direct and indirect models, which are not exclusive. The direct model states that viral proteins, particularly gp120 and *Tat*, can interact directly with neurons and astrocytes, causing cellular injury and death (24). The indirect, or "bystander," model, theorizes that damage is mediated by the inflammatory response against HIV infection. When activated by HIV, macrophages and microglia release inflammatory cytokines and by-products (such as quinolinic acid, arachadonic acid, and nitric oxide), that can cause neuronal damage. Chemokines and pro-inflammatory cytokines (such as tumor necrosis factor) promote further immune activation and recruitment, amplifying the potential for neurotoxicity (23). Multiple studies *in vitro* and in patients with HAND show increased cytokine production by macrophages and oxidative stress in the central nervous system are associated with increased HIV-associated neurodegeneration (25,26).

Astrocytes can be infected by HIV-1, but the infection is usually not a productive one, with restricted viral gene expression. Infected astrocytes can become targets for the inflammatory response, leading to increased cytokine production and impairment of the blood-brain barrier. As malfunctioning astrocytes are unable to reduce glutamate uptake, a neuroexcitative environment is propagated (27,28). In response to the excitotoxic environment and inflammatory cytokines, neuronal loss, decreased synaptic connections and lower dendritic density are observed (29). Viral proteins such as gp120 and *Tat* further accelerate neurotoxicity by activating CXCR-4 and CCR-5, chemokine receptors, and triggering cellular apoptotic pathways in neurons. Viral proteins also increase the amount of glutamate in the cellular environment by interfering with astrocyte function (30).

Pathology studies of brain tissue of patients with HIV dementia and HIV-associated neurocognitive disorder reveal brain atrophy, white matter pallor, microglial nodules, multinucleated giant cells (formed by fusion of infected and activated macrophages) and gliosis (31). Some neuronal loss is noted, but damage to dendrites and synapses is more prevalent. Viral particles are detected preferentially in the basal ganglia (especially the globus pallidus), hippocampus, subcortical regions and frontal cortices (32).

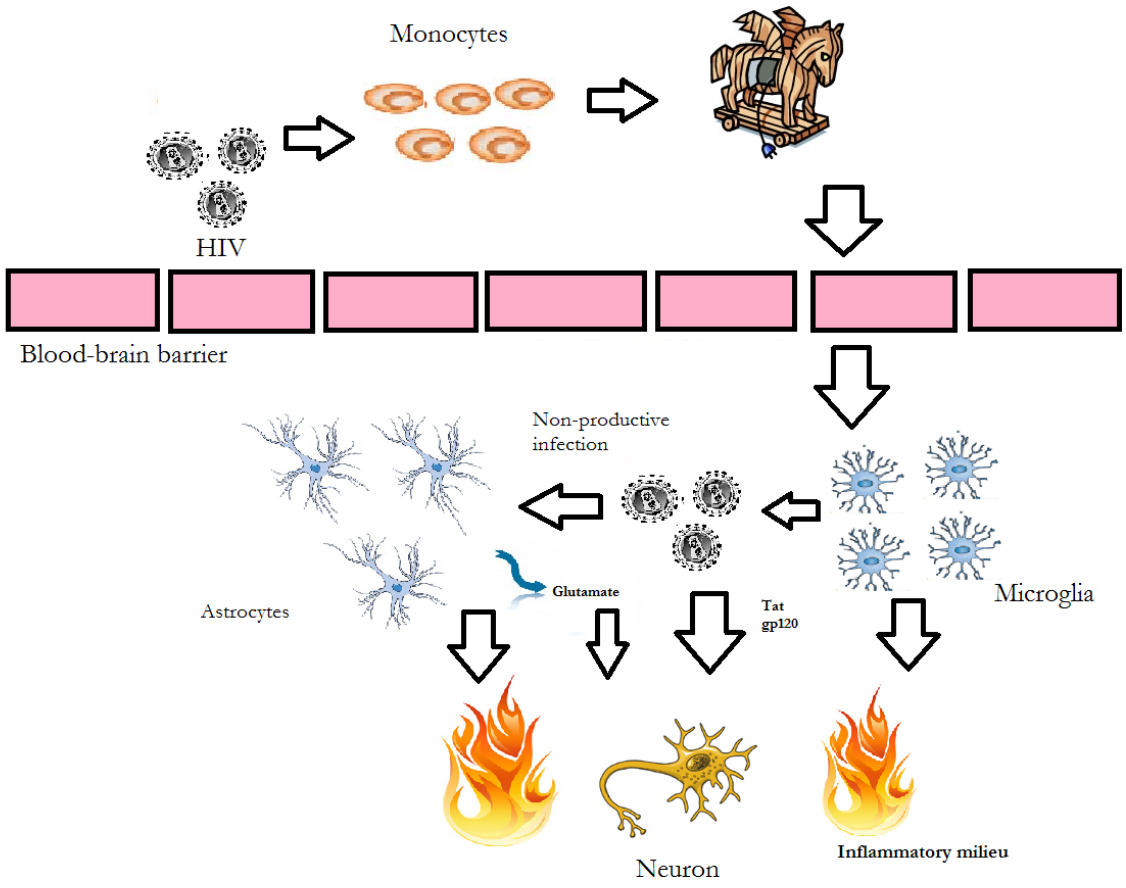

Figure 1. Model of proposed pathogenesis of HIV-1 in the central nervous system.

Clinical Presentation of HIV-Associated Neurocognitive Disorders

Patients with HIV-associated neurocognitive spectrum disorders can present with symptoms involving cognitive, behavioral, and/or motor function. As HIV primarily affects subcortical central nervous system structures, slowness of accessing thoughts and initiating processes is especially prominent, as are deficits in working memory and executive function.

Patients with mild neurocognitive impairment present with a gradual onset of symptoms over months to years. In the early stages, cognitive symptoms reported include slowed processing of information, impaired attention and concentration, and worsened short-term memory. Patients may have lower adherence to antiretroviral agents due to cognitive symptoms (33). Early behavioral symptoms may include apathy, social withdrawal, fatigue, loss of motivation, or disinhibition. Patients often develop symptoms mimicking major depressive disorder, including loss of interest in previously pleasurable activities. Motor symptoms in patients with mild impairment are typically minor, although patients may report change in handwriting, unsteady gait, or poor balance resulting in frequent falling.

The prognosis of patients with mild HIV-associated neurocognitive disorder is unclear; unlike Alzheimer's disease and many other dementias with an inexorable progression toward death, patients often present with a fluctuating, improving, or static course. The very low prevalence of HIV-associated dementia as measured recently indicates that HIV dementia is likely not an inevitability in patients with milder cognitive impairment.

In patients with HIV dementia, severe memory loss is noted, as well as word-finding problems, severe attention deficits and limited judgment. Patients have severe impairment in activities of daily living, and may progress to being bed-bound. Patients usually are extremely withdrawn and can develop mutism, but psychosis can also occur rarely. In addition, patients with HIV-associated dementia often develop motor symptoms, with severe motor slowing, incoordination, tremor, spasticity and paraplegia. The prognosis of patients with untreated HIV dementia is very poor, with death occurring from this disorder or other complications of advanced AIDS (median survival 5 months).

Criteria for HIV-Neurocognitive Disorder Spectrum Diagnoses

In 2007, the American Academy of Neurology updated their research case definitions for neurologic complications of HIV-1 infection (3). They described three diagnostic categories of cognitive disorder based on severity of impairment: asymptomatic neurocognitive disorder (ANI), HIV-associated mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). Part of the diagnostic criteria for these disorders is that they must not occur in the setting of delirium, and that other potential causes for cognitive impairment, including medical and psychiatric illness, are excluded. The diagnostic criteria strongly encourage formal neuropsychological testing; however, guidelines on diagnosing these disorders based on clinical interview alone are also suggested.

Asymptomatic neurocognitive disorder (ANI), used in research settings, describes patients with abnormal scores on neuropsychological tests but without any reported functional limitations. It is defined by performing at least one standard deviation below age- and education-adjusted standardized norms on neuropsychological testing. The testing must assess at least five cognitive domains, including: attention/working memory, language, abstraction/executive function, complex perceptual motor skills, memory, speed of information processing or sensory perception; and patients must score below the norm on at least two of these domains. Example neuropsychological tests for each of these domains are displayed in Table 1.

HIV-associated mild neurocognitive disorder (MND) describes patients with mild-to-moderate impairment of cognitive function, and with abnormal results on neuropsychological testing, at least one standard deviation below age- and education-adjusted norms. Patients or others close to the patient must report difficulties with work duties or housework due to cognitive or behavioral limitations.

HIV-associated dementia (HAD) describes patients with significantly abnormal results on cognitive testing in multiple domains, especially in learning new information, speed of information processing and impaired concentration and attention. Patients must score at least two standard deviations or lower than age- and education-adjusted standardized norms for at least two measured cognitive domains on neuropsychological testing. In addition, patients must experience significant disability due to the cognitive impairments. HIV-associated dementia is considered an AIDS-defining diagnosis.

Diagnosis and Differential Diagnosis of HIV-Associated Neurocognitive Disorder

A prerequisite for diagnosis of HIV-associated neurocognitive disorder, of course, is laboratory confirmation of HIV infection through HIV ELISA/Western blot or polymerase chain reaction. As HIV-associated dementia is one of the few treatable causes of dementia, some clinicians recommend HIV testing in the diagnostic evaluation of patients with cognitive impairment, especially in those at high risk and under age 50 years.

History and Physical Examination

Several screening instruments for cognitive impairment and dementia are available for use in the clinical setting. The Mini-Mental State Examination (MMSE) can be used in patients with severe dementia, but patients with mild HIV-associated cognitive impairment often have normal scores. The MMSE is more sensitive at diagnosing cortical dementias (e.g. Alzheimer's disease) rather than subcortical disorders (e.g. HIV-associated impairment).

Developed to identify patients with HIV-associated neurocognitive disorders, the HIV Dementia Scale (HDS), tests four cognitive domains. It tests verbal memory recall (asking patients to recite

and recall words), psychomotor speed (writing the alphabet as fast as possible), visual construction (copying a cube) and response inhibition (antisaccadic eye movements) (34,35). For patients who are unable to read and write, the International HIV Dementia Scale was developed. This screening test consists of verbal memory registration and recall (giving 4 words to repeat and recall after several minutes), motor speed (tapping fingers as fast as possible), and psychomotor speed (performing a series of hand movements after demonstration by the observer as fast as possible) (36). However, both of these studies may not detect more minor forms of impairment.

The Montreal Cognitive Assessment (MOCA), although not yet tested in the HIV-neurocognitive setting, can detect milder forms of cognitive impairments and assesses several cognitive domains affected by subcortical processes such as HAND. The instrument includes a trail-making test (following the dots alternating from number to letter); a clock-drawing test that tests executive functioning and visuospatial skills; recognizing and naming animals; attention testing of repeating numbers forward and backward, as well as working memory (37).

In patients with suspected cognitive impairment as identified by the above screening tests, a clinical interview should be conducted to determine the type and severity of cognitive, behavioral and motor symptoms present. Baseline cognitive function should be assessed by asking about educational achievement and employment. For diagnosis of mild HIV-associated neurocognitive impairment (NCI), patients should report at least two of the following symptoms: impaired attention or concentration, mental slowing, impaired memory, slowed movements, impaired coordination, or behavioral changes such as emotional lability (38). Providers should ask patients about distractions limiting their ability to complete work projects, having to read the same passage in a book multiple times, or difficulty following the course of a conversation. Patients frequently report that it takes longer to complete tasks at work or home; in addition, patients feel difficulties becoming motivated to complete these tasks. Patients often report having to make lists to remember things and sometimes forgetting to take medications; however, procedural memory is usually preserved.

To be diagnosed with mild neurocognitive impairment, patients must report mild impact on activities of daily life, such as with work or taking care of the home, but should be able to perform basic self-care. For diagnosis of HIV-associated dementia, patients or caregivers will report similar symptoms with impaired attention and concentration, memory loss, mental slowing, as well as motor and behavioral changes, but the severity of the impairment is much worse. Patients may progress to the point of not being able to feed and bathe themselves.

Medical providers should inquire about symptoms of possible opportunistic infections and other neurologic disorders, such as fever, headache or focal neurologic symptoms (none of which are symptoms of HAND). A comprehensive medication history should be obtained, as well as information regarding drug and alcohol use. If patients have ongoing substance abuse with significant effect on everyday functioning, it is very difficult to evaluate whether HIV is also contributing to cognitive dysfunction. Providers should conduct a thorough evaluation for major depressive disorder and other psychiatric disorders, which can have similar symptoms to HAND. If

present, treatment of the underlying mood disorder can often improve cognitive function.

On physical examination, patients with HIV-associated neurocognitive disorder often have abnormal findings. Finger tapping speed is often decreased, and manual dexterity is often impaired. Increased tone as demonstrated by hyperreflexia or hypertonia, including a positive Babinski sign, is common. Patients with HIV-associated dementia may have significant difficulty ambulating, and may progress to paraplegia. Rarely, patients may have choreiform movements. Focal or lateralizing deficits such as isolated aphasia or hemiparesis are not seen in patients with HIV-associated neurocognitive disorders; if present, another diagnosis is suggested.

Laboratory and Imaging

Basic laboratory testing should be conducted on all patients with suspected HIV-associated neurocognitive disorder to evaluate for alternate etiologies of cognitive abnormalities, including studies of renal and hepatic function, thyroid function tests, and vitamin B12 stores. Toxicology testing should be considered to evaluate for active substance abuse. Syphilis testing, either serum RPR or VDRL, should be performed; if positive, spinal fluid analysis should be pursued.

In patients with mild neurocognitive symptoms and high CD4+ count (greater than 350-500 cells/μL), opportunistic infections are rare. However, patients with advanced AIDS are at risk for a number of infectious complications affecting the central nervous system that can present with cognitive impairment, including meningoencephalitides such as *Cryptococcus* and tuberculosis, mass lesions such as toxoplasmosis and CNS lymphoma, and demyelinating disorders such as progressive multifocal leukoencephalopathy (PML).

Magnetic resonance imaging (MRI) of the brain should be performed with contrast for diagnosis of HIV-associated neurocognitive disorders and to evaluate for other neurologic disorders. A typical appearance of HIV encephalopathy on MRI is global atrophy of gray matter with increased ventricular size. Especially-affected structures include the amygdala, the caudate nucleus in the basal ganglia, and the corpus callosum. The amount of atrophy correlates somewhat with degree of cognitive impairment, although volumetric measurements have not been standardized for routine clinical diagnosis of HAND outside of research settings (39).

Increased periventricular white matter signal with sparing of subcortical fibers on T2-weighted images is another common MRI appearance, although other disease processes can have a similar radiologic presentation, including progressive multifocal leukoencephalopathy and other viral encephalitides. In patients with advanced AIDS with these MRI findings, CSF should be sent for cryptococcal antigen, AFB stains, JC virus PCR, herpes simplex virus PCR, cytomegaloviral PCR and varicella zoster viral PCRs to exclude these conditions. Most patients with mild HIV-associated neurocognitive disorder have MRIs that are read as normal, or with nonspecific changes in subcortical structures.

Magnetic resonance spectroscopy (MRS), which uses MRI technology to evaluate patterns of metabolic activity in specific areas of the brain, has been used in research settings to evaluate for HIV-associated neurocognitive disorder, although it is not used typically in clinical settings. These studies evaluate areas of increased cell turnover and inflammation in the brain, indicated by increased levels of choline and myoinositol, and decreased levels of N-acetylaspartate (NAA), which is a marker of mature neurons (40). MRS has been found to be more sensitive for early cognitive impairment than MRI or single photon emission computed tomography (SPECT) (41). MRI-based arterial spin labeling (ARI) and positron emission tomography (PET) measuring regional cerebral blood flow patterns and cerebral metabolic rates of glucose uptake have also shown promise in research settings for early diagnosis of HAND.

Cerebrospinal fluid (CSF) HIV viral load testing used to be a popular method of diagnosing HIV-associated neurocognitive disorder, as an early study of AIDS patients demonstrated that higher CSF viral loads correlated with cognitive impairment (42). However, in patients with less advanced HIV, CSF HIV viral loads do not correlate with neurocognitive changes. Many patients with detectable HIV in the CSF have no neurocognitive impairment; alternately, 90% of patients on currently available HAART have undetectable CSF viral loads and can still develop HIV-associated neurocognitive disorder.

In current clinical practice, CSF HIV viral load is not typically used in the diagnosis of HIV-associated neurocognitive disorder. However, there have been several reported cases of "CNS escape" in which measurement of CSF HIV viral load is useful. In this entity, patients with undetectable viral load in the serum on long-term HAART have developed symptoms of neurocognitive disorder; on evaluation of the HIV in the CSF, the viral population was found to harbor resistance to the current antiretroviral regimen. Once the patient's HAART regimen was adjusted to better treat the resistant virus, the patient's cognitive status improved (43). Approximately 20 such cases have been reported in the clinical literature (44).

In clinical practice, patients with advanced AIDS (CD4+ count less than 200 cells/μL) must have lumbar puncture performed to exclude opportunistic infections such as *Cryptococcus*, *Histoplasma*, tuberculosis, and cytomegalovirus. In stable patients with high CD4+ counts, negative syphilis testing, and no concerning symptoms or signs of meningitis, the routine use of lumbar puncture for diagnosis of HIV-associated neurocognitive disorder is of limited benefit. Some clinicians do perform lumbar punctures on such patients to obtain HIV viral load and resistance testing. It should be noted that many patients with HIV, even if clinically stable and without another cause of meningitis, will have 5-10 lymphocytes per high-powered field on routine CSF analysis.

Neuropsychological Testing

When available, neuropsychological testing is very useful in supporting the clinical diagnosis of HIV-associated neurocognitive disorder. Examples of tests to measure certain cognitive domains are listed in Table 1. Neuropsychological tests should only be administered by trained personnel but are available in many clinical settings, including the UTSW psychology department.

Table 1. Example Neuropsychological Tests Measuring Cognitive Domains Affected in HAND (HIV-Associated Neurocognitive Disorder)

Cognitive Domain	Tests Measuring Cognitive Domain
Attention/working memory	Digit span (Weschler Adult Intelligence Scale-IV) Letter-number sequencing (WAIS-IV) Paced auditory serial addition test Woodcock-Johnson—III Cognitive Numbers Reversed, Memory for Words, Pair Cancellation and Auditory Working Memory subtests
Speech/language	Boston naming test Category fluency (animals) Letter fluency Controlled Oral Word Association Test
Executive functioning (abstraction/reasoning)	Stroop Color Naming Test Trailmaking Test Color Trails Wisconsin Card Sorting Test Delis-Kaplan Executive Function System Halstead Category Test
Motor-complex perceptual	Grooved Pegboard Test Purdue Pegboard Test Arendt Central Motor Test Battery Finger Tapping Test
Memory/learning skills	California Verbal Learning Test Rey Auditory Verbal Learning Test Story Memory Test Hopkins Verbal Learning Test Buschke Selective Reminding Test, Weschler Memory Scale-IV Logical Memory and Pair Associates tests Rey-Osterrieth Complex Figure
Speed of information processing	WAIS-IV Digit Symbol Coding and Symbol Search subsets Trailmaking Test Color Trails Digit Vigilance Test Stroop Color Naming

	Reaction Time Tests (Simple, Choice) Symbol Digit Modalities Test Figural Visual Scanning
Visuospatial skills	WMS-IV Visual Reproduction and Family Pictures Test Brief Visuospatial Memory Test Figure Memory Test Rey-Osterreith Complex Figure Test Bender Gestalt II Beery VMI 6th edition

References: 3, 45, 46

Neuropsychologic test results are normed by comparison to patients with similar age, education and sometimes other demographic variables. These results can be an objective measure of cognitive performance that can be followed over time, including evaluation for progression of disease and potential improvement in response to therapy. Neuropsychological tests can help differentiate between other confounding conditions, including pre-existing learning disabilities, depression and malingering. For example, depressive disorders can be distinguished from HIV-associated neurocognitive disorder by evaluating for impaired effort on testing. Patients with HAND typically respond well to cuing by the test administrator, with improved scores on memory testing, as compared to patients with depression.

Treatment

HIV-associated dementia is one of the few causes of dementia that can improve dramatically with treatment; namely, antiretroviral therapy. Early in the HIV epidemic, a randomized, controlled trial demonstrated significant improvement of neurocognitive function and functional status in patients with AIDS dementia complex treated with zidovudine monotherapy (the first approved antiretroviral medication for HIV) versus placebo (47).

As knowledge about the nature of HIV evolved, the need to combine antiretroviral medications from different drug classes, "highly-active antiretroviral therapy" (HAART), to treat all patients with HIV, was realized. As HIV replication is an error-prone process, the virus may quickly become resistant to single agents or medication classes if agents are used alone. When multiple agents are used in combination, the selection pressure on multiple genes reduces the likelihood that the virus will become resistant to all medications in the regimen. In a typical antiretroviral regimen prescribed in early 2013, three active antiretroviral agents are prescribed, which can suppress HIV replication to below detectable limits indefinitely.

In the HAART era, multiple studies have indicated the benefits of initiating combination antiretroviral therapy in treatment-naive patients with HIV-associated neurocognitive disorder. In one prospective study, the prevalence of neurocognitive impairment decreased from 80% at baseline to 21% after 15 months of therapy (48). Improvements were noted in multiple cognitive domains,

especially speed of mental processing. Neurocognitive impairment was correlated with lower plasma HIV viral load, a finding replicated in multiple studies (49-51).

The time course of improved cognitive changes in HAART-naïve patients with HIV-associated neurocognitive disorder initiating therapy is typically gradual improvement over the first several months of therapy. In a cohort of patients with HIV-associated neurocognitive disorder starting HAART, 13% of patients showed improvement at week 12, but improvement was more common at 24, 36 and up to 48 weeks after initiation (32% at 24 weeks, 40% at 36 weeks, and 33% at 48 weeks) (52).

The mechanism of action of highly active antiretroviral in treatment of neurocognitive disorder is not completely known. Highly active antiretroviral therapy does reduce HIV-1 RNA in the cerebrospinal fluid, which correlates with neurocognitive performance (53,54). It is theorized that decreasing the production of virus, both in the central nervous system as well as from macrophages traveling from the peripheral blood, leads to decreased inflammation and neuronal damage in the central nervous system. Several studies have shown CSF levels of inflammatory cytokines, including CCL-2, neopterin and neurofilament protein (NFL) decreased after initiating antiretroviral therapy in patients with HIV-associated dementia (55,56). Another study evaluated changes in cerebral metabolic disturbances in patients with HIV-associated neurocognitive disorder. Magnetic resonance spectroscopy demonstrated improved cerebral metabolite levels and ratios after HAART initiation (57).

While initiation of HAART is an effective treatment for HIV-associated dementia and milder forms of neurocognitive disorder for patients not initially taking antiretrovirals, unfortunately there are a number of stable patients already taking HAART who develop neurocognitive disorder while on therapy. This may occur despite having a suppressed peripheral HIV-1 RNA and excellent CD4+ count recovery, the typical indications of effective treatment of HIV infection (9,58).

The reasons for increasing rates of neurocognitive disorder in HIV-positive patients with excellent peripheral immune reconstitution are unclear. Some theorize that persistence of neurocognitive dysfunction despite HAART may be related to a "legacy effect," that current impairment is related to previous damage to the central nervous system in patients who have survived into the HAART era. Patients may start to develop symptomatic cognitive impairment related to cumulative co-morbidities in addition to HIV, including advancing age, previous substance abuse, and atherosclerotic changes. Another potential concern is continued viral replication in the central nervous system related to inadequate drug levels, despite apparent treatment success as measured by an undetectable serum viral load.

Appropriate Selection of Antiretrovirals for HIV-Associated Neurocognitive Disorder: Does the Penetration of Antiretrovirals into the Central Nervous System Matter?

While there is no question whether antiretrovirals in general are effective therapy for HIV-associated neurocognitive disorder, one of the greatest controversies in this field, and also in HIV medicine in general, is whether certain antiretroviral agents are better than others in treatment and prevention of central nervous system damage. When HIV medications are tested in clinical trials for licensing, their efficacy is measured solely through peripheral HIV viral load suppression in the serum and CD4+ cell increase. As clinicians approach patients initiating antiretroviral therapy, whether cognitively impaired or not, should the potential effects on neurocognitive performance inform our decisions?

Viewpoint: Yes, antiretrovirals that penetrate into the CNS are effective at treating neurocognitive disorder.

Some researchers claim that antiretrovirals that can cross the blood-brain barrier effectively would theoretically be more successful at treating and preventing HAND (59,60). The blood-brain barrier, composed of tight junctions of brain capillaries, prevents many compounds, including medications, from delivery into the brain. Medications that are more water-soluble or bind to proteins in the serum cross into the central nervous system less readily than lipophilic and non-protein bound molecules. Transporter systems such as efflux pumps, some of which are not fully understood, can also inhibit or enhance drug delivery to the central nervous system.

As some antiretrovirals enter the central nervous system more readily than others, there has been considerable interest in evaluating which antiretrovirals are able to penetrate the central nervous system as potentially improved treatments for HIV-associated neurocognitive disorder. One group has assigned a score to the availability of medications in the central nervous system, called the "cerebrospinal penetration-effectiveness" (61). The CPE score reflects the medication's size, lipophilicity, degree of protein binding, interaction with transporter systems, CSF pharmacokinetics and pharmacodynamics. Medications are either ranked as being low, moderate or high in cerebro-penetration efficacy (either by scores from 0-1 or 1-4). CPE indexes for each antiretroviral component of a patient's regimen are added for a complete score. Estimated CPE indexes for currently available antiretrovirals are listed in Table 2 (59,61,62).

Table 2. Estimated "Cerebral Penetration-Effectiveness" Index of Currently-Available Antiretrovirals.

Medication Class	Highest CNS Penetration-Effectiveness	High CPE	Average CPE	Below Average
Nucleoside reverse transcriptase inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	Efavirenz	Etravirine Rilpivirine	
Protease inhibitors	Indinavir/r	Darunavir/r Fosamprenavir/r Lopinavir/r	Atazanavir	Nelfinavir Saquinavir/r Tipranavir/r
Entry/Fusion Inhibitors		Maraviroc		Enfurvitide
Integrase inhibitors		Raltegravir		

*No data are yet available regarding elvitegravir/cobicistat

Several cohort studies have demonstrated that HIV CSF viral loads were lower with higher CPE-scoring regimens (more penetration into the central nervous system). In two large cohort studies, lower CPE-scoring regimens (less penetration into the central nervous system) were associated with higher CSF viral loads. A very low score was associated with an 88% increased risk of having a detectable CSF viral load (63,64). Another study in patients with AIDS and neurologic disorders, including HIV-associated dementia, showed a greater reduction of CSF HIV-1 RNA when three or more drugs penetrating the blood-brain barrier were used (65).

Some studies have shown that lower CSF RNA levels and high CPE regimens correlated with clinical improvement on neurocognitive testing. In one prospective cohort study of patients with HIV-associated neurocognitive disorder, use of a higher number of CSF-penetrating antiretrovirals was associated with a greater decrease in CSF viral load 15 months after HAART initiation and with greater neurocognitive improvement on testing (66). Another observational prospective trial of patients with mild-to-moderate HIV-associated neurocognitive disorder initiating HAART indicated that choice of a higher CPE-scoring antiretroviral regimen was associated with lower CSF viral load and improved performance on neuropsychological testing over time (67). Tozzi *et al.*, in a study of 185 patients with or at risk for HAND, found that patients taking regimens with higher CPE scores

performed better on neuropsychological studies 6 months after initiating HAART (68). The AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) cohort evaluated patients enrolled in 26 clinical trials starting various HAART regimens (not necessarily with HIV-associated cognitive disorder) who responded to antiretrovirals with a serum undetectable viral load. In patients whose antiretroviral regimens included more than 3 antiretrovirals, higher CPE scores were associated with better scores on neurocognitive testing; however, this was not observed in patients taking three or fewer antiretrovirals (69).

There is one small randomized, controlled trial comparing neurocognitive test results and imaging changes of treatment-naive patients starting different HAART regimens. The study was a sub-study of patients enrolled in a treatment efficacy trial, and patients did not report baseline symptoms of neurocognitive disorder. The regimens studied were: tenofovir-emtricitabine plus either efavirenz (estimated as a high-average CPE regimen), atazanavir/ritonavir (estimated as a low-average CPE regimen), or zidovudine and abacavir (high CPE regimen). Patients randomized to the tenofovir-emtricitabine-abacavir-zidovudine arm had improved scores on identification reaction time and executive function as compared to other HAART regimens. However, patients in the efavirenz-emtricitabine-tenofovir arm had the greatest improvement on magnetic resonance spectroscopy (70). However, no large randomized controlled trials have demonstrated that antiretroviral regimens with higher CNS penetration are more effective than those with low CNS penetration.

Viewpoint: Using highly active antiretroviral therapy options that are effective at suppressing peripheral viral load and tolerable to patients is more important than CPE score.

In clinical practice, the antiretrovirals noted as the "highest CNS penetration effectiveness" are rarely used. These medications are associated with a number of long- and short-term toxicities, including metabolic syndrome, peripheral neuropathy, headaches, nausea/vomiting/diarrhea, bone marrow abnormalities, hepatotoxicity and nephrolithiasis. In terms of ability to suppress peripheral HIV-1 RNA to undetectable levels, all of these options have been proven inferior to more modern regimens. In addition, the pill burden of regimens including these options can make adherence difficult (particularly in cognitively-impaired patients).

In contrast to the above studies supporting high CPE-scoring regimens, there are a number of other cohort studies that showed no effect of CPE score on the incidence of neurocognitive disorder. Several cross-sectional studies of patients with high CD4+ cell counts on stable HAART showed no impact of CPE score on prevalence of neurocognitive impairment (8,71,72).

The early trials of HAART in neurocognitive disorder reported in the treatment section used HAART regimens with variable levels of CPE penetration, noting global improvement regardless of the regimen utilized (48-51). In one prospective study of patients initiating or changing HAART, CSF viral load decreased and neuropsychological scores improved regardless of the CPE score of the selected regimen (73). Another study of patients with mild neurocognitive disorder found no

difference in results of prospective neuropsychological testing in patients prescribed multiple CSF-penetrating agents as compared to a lower CPE-scoring regimen (74).

One randomized, controlled trial of HAART-naive patients comparing antiretroviral regimens performed serial neurocognitive testing on enrolled patients in the different treatment arms. The regimens studied were efavirenz/lamivudine/zidovudine; atazanavir/emtricitabine/didanosine; and efavirenz/emtricitabine/tenofovir. Significant improvement in neurocognitive testing and clinical symptoms was noted in all three groups, with no significant differences between the regimens (75) despite expected differences in CPE score.

Viewpoint: Antiretrovirals that enter into the central nervous system more readily are more likely to cause damage to the central nervous system.

A competing concern is that antiretrovirals that effectively penetrate into the central nervous system could more effectively cause neurotoxicity. One cohort study of patients with advanced HIV either initiating or changing HAART showed that patients with baseline neurocognitive impairment who were treated with antiretrovirals with higher CPE rank scores were more likely to suppress CSF HIV RNA; however, neurocognitive performance actually *worsened* over the 52 weeks of the study as compared to patients prescribed lower CPE-scoring regimens (76). Another study (**S**trategies for the **M**anagement of **A**nti-**R**etroviral **T**herapy, or SMART) examined patients with high nadir CD4+ count undergoing a structured treatment interruption. Patients who discontinued antiretrovirals showed a small neurocognitive *improvement* as compared to those who continued HAART (77). (Other results from SMART indicate increased global morbidity and mortality from discontinuation of HAART, and treatment interruptions are *not* recommended at this time by the vast majority of clinicians).

Some basic science studies support this concern regarding neurotoxicity of HAART. One article examined the *in vitro* toxicity of antiretrovirals on neurons, evaluating effects on dendritic beading and pruning, signs of neuronal injury. Toxicity of some antiretrovirals, including abacavir and nevirapine, was noted in concentrations that are regularly observed in the cerebrospinal fluid of patients in clinical practice (78). Another study showed increased cerebral metabolite disturbance on magnetic resonance spectroscopy in the frontal lobes of patients taking didanosine or stavudine as compared with HIV-positive controls receiving other regimens (79). These medications (as well as zidovudine) have been associated with mitochondrial toxicity, which may account for the injury pattern observed.

Limitations of Current Studies

A number of concerns with the above studies limit our understanding of antiretroviral selection in patients with HIV-associated neurocognitive disorder. There are no randomized, controlled trials comparing use of different antiretroviral regimens in patients with baseline HIV-associated neurocognitive disorder (the randomized trials reported above evaluated cognitive performance in

asymptomatic patients as part of a sub-study of drug efficacy). The remaining trials are cohort and cross-sectional studies of small populations which varied in terms of baseline impairment, educational status and immune status. The neuropsychological batteries used in the trials varied between studies, and some of these tests have not been normed for minority or non-English speaking populations.

The CPE scoring system is also continually being updated as new data regarding pharmacokinetics and pharmacodynamics within the central nervous system become available. Previous iterations of the CPE score focused on the cerebrospinal fluid concentration, which is more easily measured, rather than the parenchymal activity of the medication, the more important consideration. More recent modifications of the CPE score have also taken into account the possible neurotoxicity of antiretrovirals. For example, efavirenz has been associated with increased rates of cognitive disorder in some clinical studies and is not recommended in treatment of patients with HAND (80, *personal communication,* S. Letendre). Medications such as darunavir, raltegravir and maraviroc appear to have non-toxic, therapeutic concentrations in the central nervous system in most patients and may be better selections for treatment of HAND. While it is very likely that certain antiretrovirals are superior to others in treatment and prevention of HIV-associated neurocognitive disorder, further randomized, controlled trials are needed to establish more firm evidence for particular regimens.

Adjunctive Agents

As highly active antiretroviral therapy is not completely effective in treating HIV-associated neurocognitive disorder, multiple other agents have been studied as potential adjuncts to HAART. One strategy is to target the pathogenic processes underlying inflammation and neural destruction, while other medications focus on treating the behavioral symptoms of HIV-associated neurocognitive disorder.

A number of antioxidant medications, which inhibit the inflammatory effects of oxidative stress and cell damage, have been studied in randomized, controlled trials of patients with HIV-associated cognitive disorder. Unfortunately, there was no benefit of OPC-14117, thioctic acid, CPI-1189, vitamin C and E, curcumin, or green-tea derived epigallocatechin on performance on neurocognitive testing as compared to placebo (81-83). Another anti-inflammatory agent, lexipafant, a platelet-activating factor antagonist, was studied in a randomized, controlled trial of patients with HIV-associated neurocognitive disorder. A trend toward improvement was noted in verbal recall in patients treated with lexipafant as compared to placebo (84).

A recent *in vitro* study has again raised the interest in another antioxidant compound in treatment for HIV-associated neurocognitive disorder. Epicatechin, a compound found in cocoa and green tea leaves, was found to increase brain-derived neurotrophic factor (a growth factor that supports growth, differentiation and survival of neurons) counter to the neurotoxic effects of HIV proteins *Tat* and gp120. As it is a small molecule, epicatechin is hypothesized to cross the blood-brain barrier

more readily than previously-studied antioxidants; clinical trials further examining this compound are planned (85).

Other compounds studied *in vitro* showed promising results in neuroprotection and suppression of HIV replication but failed to show benefit in clinical trials. Minocycline, a tetracycline antibiotic, showed inhibition of microglial activation and HIV replication in *in vitro* studies; however, a recent randomized controlled trial in patients with HAND showed no efficacy in improving neuropsychological functioning (86). Selegiline, a MAO-B (monoamine oxidase B) inhibitor used primarily in treatment of patients with Parkinson's disease, is thought to reduce oxidative stress and have neuroprotective properties. Two pilot studies indicated that selegiline may improve cognitive functioning in patients with HAND (87,88); however, several larger studies have shown no significant effect on results of neuropsychological testing (89). Memantine, an NMDA antagonist approved for Alzheimer's disease, was shown in several *in vitro* studies to have neuroprotective effects against *Tat* and gp120-induced toxicity (90,91); however, two clinical trials showed no efficacy at improving neuropsychological functioning (92,93).

Valproic acid has been shown to inhibit neuronal loss by stimulating neurogenesis and reducing neurotoxicity of HIV-infected macrophages. One small study demonstrated a trend toward cognitive improvement clinically and significant improvement in MRS brain metabolic profile (94); however, another observational study of patients taking valproate for six or more months showed decreased neurocognitive performance over time in HIV-positive patients taking this medication (95). Lithium, which is used for bipolar depression, has been found to protect neurons against *Tat*-induced cell death. Lithium was shown in one small, open-label clinical trial to improve neurocognitive impairment (96). In another small study, no cognitive performance changes were noted, but neuroimaging, including magnetic resonance spectroscopy and functional MRI, showed decreased glutamate-glutamine peaks and changes in brain activation patterns, suggestive of improvement (97).

Psychostimulants, such as methylphenidate and dextroamphetamine, can stimulate the dopaminergic system, which is impaired in patients with HAND. In a randomized trial, methylphenidate improved cognitive function over the short-term (98), but this may be more related to the treatment of underlying major depression or attention-hyperactivity disorder. In addition, these agents have the potential for dependence, especially in those with a history of substance abuse.

Use of selective serotonin reuptake inhibitors (SSRIs) is very common in clinical practice to treat the vegetative symptoms of HIV-associated neurocognitive disorder, including sleep disturbances, depressed mood, and psychomotor retardation, although no clinical studies have been conducted regarding this practice. Interestingly, one cross-sectional study found lower rates of detectable HIV RNA in the CSF in patients taking SSRIs, although the mechanism of this is unknown (99). Some practitioners have started using cholinesterase medications such as donepezil, rivastigmine, and

galantamine for mild to moderate neurocognitive impairment; however, these medications have not been studied in HIV patients and are not FDA-approved for this indication.

Prevention of HIV Neurocognitive Disorder: Early Initiation of HAART? And if so, how early?

In early 2013, when to initiate highly-active antiretroviral therapy (HAART) in asymptomatic patients with high CD4+ counts is controversial. Randomized controlled studies have demonstrated an improvement in mortality and decreased opportunistic infections in patients who start antiretroviral therapy before the CD4+ count decreases below 350 cells/μL (100). In patients with CD4+ cell counts that are higher than 350 cells/μL, however, there are no randomized controlled trials to inform clinical practice. A number of cohort studies showing improved mortality and reduced co-morbidities in patients initiating antiretrovirals with baseline CD4+ count greater than 500 cells/μL have influenced the practice of starting antiretrovirals earlier (101). Another motivation for starting HAART early comes from the prevention literature, as starting antiretrovirals for the seropositive partner in a serodiscordant relationship can markedly reduce transmission (102).

Based on cohort studies and prevention data, in 2012 the guidelines for the national Department of Health and Human Services (DHHS) and International AIDS Society (IAS-USA) switched to recommending antiretroviral therapy for *all* patients, regardless of CD4+ count (103,104). However, concerns about long-term toxicity of HIV medications, risks of non-adherence and treatment exhaustion in patients, as well as the high costs (estimated at least $10,000 per patient per year) of this intervention raise concerns in some practitioners given the lack of randomized data.

As the risk of neurocognitive disorder increases as the nadir CD4+ falls, it is suggested that very early initiation of HAART may prevent HIV-associated neurocognitive changes (105). One animal model examined the hypothesis of starting antiretrovirals shortly after primary infection. After experimental infection with simian immunodeficiency virus (SIV), half of the monkeys were started on nelfinavir and tenofovir, and half were not started on HAART. In the group who started early antiretroviral therapy, a significant decrease in CSF viral load was noted. Brainstem evoked auditory potentials, which are slowed in untreated SIV infection, remained stable in monkeys treated with antiretrovirals as compared to placebo (106).

The prevalence of neurocognitive impairment in HIV-positive patients with very high CD4+ count (greater than 500 cells/μL) is unknown. Several early studies of asymptomatic patients with HIV (although this was not reported according to CD4+ count) showed that patients with asymptomatic HIV do have mild neurocognitive deficits as compared to HIV-negative controls, although whether HAART would affect the incidence of this disorder is not known at this time (107,108).

The ongoing Strategic Timing of Antiretroviral Therapy (START) randomized, clinical trial, of which the University of Texas, Southwestern is a participant site, is addressing the survival and

disease progression benefits of early versus deferred HAART. Patients who have a baseline CD4+ count greater than 500 cells/μL are randomized to either immediate therapy versus deferring treatment until the CD4+ decreases below 350 cells/μL. A neurology sub-study is underway to evaluate whether early ART improves neurocognitive performance or prevents neurocognitive decline as compared with deferred treatment. A secondary endpoint of this study will evaluate the effect of CPE score on patients' neurocognitive performance.

Conclusion

Highly-active antiretroviral therapy (HAART) has led to miraculous improvements of patients with HIV-associated dementia, drastically reducing the incidence and prevalence of this disorder. However, the increasing rate of milder forms of neurocognitive impairment in the aging cohort of HIV-positive patients with excellent serum virologic and immunologic response to HAART is concerning.

The best antiretroviral medications for treatment and prevention of neurocognitive disorder are unknown. The cerebral penetration effectiveness score is a rough estimate, but more information is needed regarding optimal medication concentrations that affect the pathogenesis of HIV in the brain parenchyma rather than causing neurotoxicity. Effective adjunctive therapies that address the underlying inflammatory process of HIV in the central nervous system also are needed. Upcoming randomized, controlled trials examining effects on neurocognitive performance by initiation of varied HIV regimens will be very useful in future antiretroviral selection for patients with HIV-associated neurocognitive disorder.

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