

MEMORY LOSS AND OTHER BRAIN PROBLEMS

What's the Problem, and How Do You Diagnose It?

There is a long list of mental and physical symptoms that can occur in HIV+ people when the central nervous system (which is composed of the brain and spinal cord) is affected by HIV, by opportunistic infections or cancers, by nutrient deficiencies, or by drug side effects. The effects of HIV disease on the central nervous system can result in changes in both cognition (thought, perception, and memory) and motor skills (movement). In some people, these symptoms can ultimately become quite severe, causing serious problems with memory, mental functioning, and ability to carry out life activities. In the worst cases, some people will develop serious personality or acting-out problems, serious difficulties with movement, extreme confusion and inability to communicate, and, ultimately, depression and withdrawal from life.

When symptoms reach this extreme, the term used is “frank dementia”, but the term that is preferred for the overall set of problems that results from central nervous system changes is “HIV-associated cognitive and motor complex” (CMC). Neurologists point out that many people may develop some set of such symptoms without the true mental impairment that the term “dementia” indicates. The inappropriate use of the term could result in people being stigmatized as mentally impaired when they are not.

During the HAART era, the occurrence of CMC has dropped by about half compared to the pre-HAART time, but has actually increased in one group, those who have CD4 counts above 400. This may be because although HAART usually raises CD4s and may help with HIV-associated cognitive changes in many ways (discussed below), it may also ultimately result in keeping people alive long enough for HIV to cause ever-increasing problems in the brain and spinal cord.

The incidence of a milder form of cognitive changes, called Minor Cognitive and Motor Dysfunction (MCMD) has also increased. In one study, researchers found that more than 70 percent of HIV+ people with CD4 counts below 200 had developed MCMD. This may often go undiagnosed because the symptoms may be relatively subtle, and may be overlooked or ignored as the person writes them off as a sign of aging or stress. Typically, people experiencing this may seem to have relatively minor mental lapses when they begin to forget appointments, have trouble remembering a long-known phone number, be unable to remember a familiar name, or have difficulty sliding a credit card through the slot at the grocery store or a key into a lock. Although these problems may seem relatively minor, some people may develop anxiety or depression or fearfulness related to their concerns about what they perceive as happening to their brains.

Scientists are not sure whether MCMD is just the first stage of CMC, or possibly a separate condition. They do know that not everyone with MCMD progresses. Many, usually those who start an effective HAART regimen, will remain stable, with no worsening of symptoms, and some return to normal. In those in whom the condition worsens, the rate of change among individuals is widely variable, but is usually very slow, with significant worsening often taking many months or even years. Memory problems are often the most obvious early symptom. In general, it is recall memory that is most affected at first, with less if any effect on recognition memory. There may also be a problem with attention or concentration, with the feeling being that it's more difficult to stay focused than in the past.

This may be accompanied by gradually increasing communication problems. The person may feel that s/he knows what s/he wants to say but can't get it across as clearly as in the past. Usually, with these types of problems, cuing will help. In other words, if you give the person a hint, s/he'll be able to remember what s/he couldn't retrieve entirely unassisted. Over time, there may be a general slowing of both thought and motor movements. People will talk more slowly, move more slowly, and respond to conversation more slowly. There may also be increasing problems with balance, subtle changes in vision, difficulties with normal eye-to-hand coordination, or gradually increasing weakness or loss of sensation in the arms and legs which can cause difficulties in walking. These are often accompanied by exaggerated reflexes and excessive muscle tension, particularly in the legs.

Diagnosis begins with neuropsychological testing, usually with the use of the HIV Dementia Scale. This set of verbal, paper and hand exercises is used to estimate the severity of cognitive changes. Most HIV neurology specialists recommend that all HIV+ people be given this dementia scale every six months. Because of the recent evidence that central nervous system changes may occur even in those with CD4 counts that are higher than was once thought likely,

this would include even those who otherwise appear to be in earlier disease stages. The initial results of the dementia scale can provide a baseline, and followup testing can show if there are any negative changes.

At any point that the scale indicates the beginning of cognitive changes, much more in-depth testing is recommended. In part, assessments are done to ascertain whether any changes are actually the result of CMC or MCMD, or possibly other problems that could cause similar symptoms, including drug side effects, infections or cancers, recreational drug use, depression, anxiety, and so on.

Some psychiatric disorders are known to increase in frequency in those with CMC. Mania may appear in HIV+ people with only mild cognitive impairment, and is seen in both early and later disease stages. Mania has also been observed shortly after AZT therapy is begun, even in those with no prior psychiatric history. There may also be a higher risk of depression in HIV+ people. Although findings from several studies had suggested that depression is not more prevalent in HIV+ people than in those who are uninfected, a large-scale meta-analysis of 10 studies has shown a twofold increased risk for depression among HIV+ people. Another study has shown an increased level of major depression among those on HAART. It is not clear which is the chicken and which is the egg here. It is possible that HIV+ people have an increased vulnerability to depression, but it's also possible that depression might lead to increased high-risk behavior that increases the likelihood of becoming infected with HIV. Depression may also be a consequence of antiretroviral treatment or HIV-induced brain injury.

There is research that has shown that HIV infection may be linked to the development of psychosis, a term used to describe those who have extreme distortions of reality, thought disorders, hallucinations, and delusions. Psychosis can be a manifestation of psychiatric conditions such as delirium, affective disorders, or schizophrenia, but it has also been seen to occur in people who do not have such conditions. Researchers have estimated that the prevalence of new-onset psychosis in HIV+ people may range from 0.5 to 15 percent (which is much higher than would be expected in the general population). Researchers have theorized that such new-onset psychosis may result from HIV-associated brain problems (encephalopathy).

There is also evidence that HIV infection may exacerbate psychiatric conditions, including major depression, bipolar disorder, and schizophrenia. In a study of people who had schizophrenia prior to their HIV diagnosis, it was found that there were more severe depressive episodes and reduced tolerance to psychopharmacologic medications (including benzodiazepines and neuroleptics) after HIV infection than before.

Certain antiretroviral drugs may also cause cognitive or motor symptoms. For those on HAART, it is always possible that mental problems may be arising from drug side effects. It will be very important to look at this possibility so that symptoms that are actually being caused by drugs are not diagnosed as stemming from central nervous system damage.

With certain symptoms, including problems with balance and walking, it is very important to rule out conditions like myelopathy (spinal cord degeneration) and peripheral neuropathy (nerve damage in the limbs, hands, and feet) that could also cause such problems. [For more information on these, see *Myelopathy* and *Neuropathy*.]

It is very important to do the physical exam and other tests needed to diagnose the possibility that certain infections or cancers are causing the problems. This may include the use of MRIs (magnetic resonance imaging), CT (computed tomography) scans, and PET (positron emission tomography) scans. With these brain images, it is possible to see brain lesions or other changes that could indicate certain infections or cancers. Blood tests are also done in order to look for evidence of certain infections that can cause mental changes, including cryptococcal meningitis or syphilis. A lumbar puncture (spinal tap) is also done to look for viruses and bacteria in the cerebrospinal fluid (CSF).

A measurement of HIV viral load in the CSF may also be done. Although experts have not always agreed on the usefulness of this test for assessing the presence or degree of CMC, new research indicates that early increases in CSF viral load may be predictive of a worsening condition. In a study of 139 HIV+ people, University of California at San Diego researchers performed medical, neuropsychological and laboratory evaluations, both at the beginning of the study and again at least 6 months later. Initially, 94 people were rated as *not* having any neuropsychological impairment. Out of this group, in those whose viral load was detectable, there was a 26 percent chance of impairment being diagnosed at the second evaluation. The problems seen included impaired attention, memory problems, and problems with learning and motor skills. In those whose viral loads had been undetectable (at 200 copies), there was only a six percent chance of diagnosis with impairment at the second evaluation. The researchers found that the initial CSF viral load was a better

predictor of future CMC problems than either the standard blood viral load or CD4 counts. Other studies have, however, found that elevated viral load in the blood is also tied to an increased incidence of CMC. In one study, it was shown that viral load over 3,000 and CD4s below 500 were predictive of CMC.

Another test used by some specialists is spectroscopy, a specialized MRI that shows the brain's chemical functioning. In some ways, the overall diagnosis is reached by excluding all the other possible causes of mental symptoms.

What are the Causes?

Memory problems and other cognitive changes, as well as movement problems, can have multiple possible causes in HIV disease, and in many people, there may be more than one factor contributing to the development of such problems. **HIV's effects on the brain are clearly a major cause of cognitive problems.** Although the virus does not actually infect neurons (brain and nerve cells), it lives in the fluid in the brain spaces. Scientists believe that it enters the brain in what has been described as a Trojan Horse approach, infecting a macrophage (a white blood cell) which then carries the virus through the blood-brain barrier. The macrophage then causes harm in two ways: by infecting brain support cells and by pumping out chemicals called neurotoxins that damage or destroy neurons, particularly in the cerebral cortex (the major thinking center of the brain). Researchers are not yet sure which neurotoxin(s) may be contributing to or causing the harm, or exactly how the process works. The neurotoxins that researchers have looked at as possible sources of central nervous system harm include quinolinic acid, platelet activating factor, and tumor necrosis factor (TNF).

Researchers have also theorized that there may be a loss of integrity of the blood-brain barrier which normally prevents the passage of many potentially brain-damaging things from the blood into the brain. This may allow both cellular and non-cellular inflammatory components of the immune system to enter the central nervous system. The end result is damage to neurons and non-neuronal support cells.

Damage to synapses may also contribute to brain problems. Synapses are, in essence, the connectors between neurons—the sites across which impulses are transmitted from one neuron to another, thus allowing appropriate nerve cell function. Synaptic damage has been found in those with mild HIV-associated cognitive changes, and the amount of this damage has been shown to correlate to neuropsychological functioning.

There is also evidence from test-tube and animal research that several HIV proteins may contribute to brain problems. Included are glycoprotein 120 (gp120), HIV-1 negative factor (Nef), and transactivating protein (Tat).

In the end, it may be that many of these mechanisms combine to produce many of the brain changes and resulting symptoms seen in HIV+ people.

Nutrient deficiencies. Neurologists have long known that chronic infection in someone with vitamin deficiencies (which most HIV+ people are known to have) is strongly associated with neurological problems. The nutrient deficiencies created by the HIV disease process may well be the underlying cause of a significant percentage of CMC. It is critical that this cause of neurological dysfunction be addressed early on because although most of the dysfunction related to vitamin deficiencies can be reversed in early deficiency stages, there is definitely a time window, after which it may no longer be possible to reverse the damage.

There are several vitamins known to be essential for normal cognition. Included are vitamin B1 (thiamine), vitamin B3 (niacin), vitamin B-6 (pyridoxine), vitamin B12, and folic acid, one or more of which have been found to be deficient in a significant portion of people living with HIV, according to a number of published studies. Thus, supplementation with these may be an important component of treatment for neurological problems.

It is known that deficiency of B12, very common in HIV+ people, can cause a loss of the myelin covering around nerve cells, resulting in a slowing or stopping of nerve impulses. B-12 deficiency is a well-known cause of dementia. Justin C. McArthur, M.D., M.P.H., Deputy Director of Neurology at Johns Hopkins University School of Medicine, strongly recommends considering the possibility of B12 deficiency in anyone suspected of developing dementia, and notes that even without a measurable B12 deficiency, B12 nutraceuticals may help.

The textbook symptoms of a B-12-related dementia include confusion, memory defects, slow mental reactions, and depression. It also causes a slowing of brain wave patterns and a lowered level of cerebral oxygen use. Research has

shown that B-12 deficiency in HIV+ people is specifically tied to mental slowing and memory problems. There have been published case studies of improvements in dementia when injections of B12 are given.

Because researchers have shown that B-12 deficiency does not always cause the red blood cell changes that physicians look for as a sign of deficiency, diagnosis of this problem may not happen. In addition, because the standard blood test reflects only what's in the bloodstream and not what is in the body's cells, a reading that appears normal may not truly reflect the body's status. Even with these problems related to accurate testing (which almost certainly result in significant under-diagnosis of B-12 deficiency), many studies have shown that a large percentage of HIV+ people are B-12 deficient, even sometimes in relatively early disease stages. For many people, a simple trial of B-12 therapy may be the best way to see if it can help with memory problems.

It has been reported that people living with HIV have decreased levels of folate (folic acid) in their cerebrospinal fluid. Researchers have hypothesized that this folate deficiency could be the cause of significant neurological degeneration in many. Folate deficiencies are extremely common in North America, even in the non-infected. Such deficiencies are known to cause memory problems, poor concentration, apathy, and disorientation, all of which have been seen in many of those suffering from CMC.

It is also possible that folic acid and/or B-12 deficiency may cause harm by allowing levels of homocysteine to become elevated. Homocysteine is a damaging chemical, known to be tied to arterial damage, that has more recently also been shown to possibly make the brain more vulnerable to damage from certain toxins. So far, this has only been shown in animal studies but the evidence is strong enough to provide a warning that the chronic B-12 and folate deficiency found in so many HIV+ people might allow an elevation of homocysteine that could open the door to brain damage from the HIV-associated neurotoxins (discussed above).

HIV infection can cause gastrointestinal malabsorption syndromes, chronic diarrhea, and vomiting, all of which have been associated with a resulting deficiency in many nutrients, including thiamine. A thiamine deficiency has long been known to cause memory problems and even severe dementia. It was reported in *The Lancet* that a neuropathology characteristic of a thiamine deficiency-induced condition called Wernicke's encephalopathy has been seen in autopsies done of people who died from AIDS who were not alcoholics, the latter fact being important because alcoholism is the usual cause of this. The author of this report evaluated 39 patients at various stages of HIV disease and found thiamine deficiency in 9 people (23 percent). It is possible that many people living with HIV may be thiamine deficient and at risk for Wernicke's encephalopathy, a dangerous inflammatory brain condition which can cause hemorrhaging and lesions in several parts of the brain. It can cause cognitive dysfunction ranging from forgetfulness to psychosis, along with paralysis of the eye muscles, a lack of muscular coordination, double vision, and involuntary eye movements.

Another B vitamin deficiency that may be involved in the development of cognitive changes is niacin. Many things can cause a niacin deficiency, including chronic diarrhea, chronic infections, dietary deficits due to alcohol use, and cirrhosis of the liver. A niacin deficiency has long been known to be a potential cause of dementia. Because all HIV+ people are, of course, living with a chronic infection and many others have had, or currently have, one or more of the other niacin-deficiency inducers, it is possible that deficiencies of niacin may contribute to cognitive problems in many people.

University of Miami researchers have shown that B-6 deficiency is common in HIV+ people. Because B-6 is used in so many body processes, deficiency can cause decreased production of neurotransmitter chemicals (which could affect cognitive and motor processes), lack of coordination, confusion, nervousness, irritability, depression, anxiety, dizziness, inability to concentrate, and other symptoms.

Drug side effects. A number of drugs used by many HIV+ people may cause mental side effects. It is always possible that one or more antiretroviral drugs could be contributing to mental or physical changes. For example, symptoms caused by the NNRTI efavirenz (Sustiva) can include muddled or unfocused thinking, impaired ability to concentrate, short-term memory loss, feelings of paranoia and disorientation, drowsiness, altered moods (including euphoria, disorientation, anxiety, irritability, nervousness, and depression), insomnia, vivid dreams, and nightmares. Some people also experience dizziness, lightheadedness, unsteadiness, or a loss of balance. Although very rare, serious psychiatric disorders have occurred in some, including severe depression, suicide attempts, aggressive behavior, delusions, paranoia and psychosis-like symptoms. Patients with a prior history of psychiatric disorders appear to be at greater risk for these serious problems.

Other antiretrovirals may also cause mental symptoms. Indinavir (Crixivan®) and ddI (Videx®) can cause chronic feelings of anxiety, usually low-level but sometimes more severe, in some users, and the symptom normally remains until the problematic drug is discontinued. Videx® can also cause nervousness and sleeping difficulties, although these are not very common. Abacavir (Ziagen®) can also cause trouble sleeping, as well as dizziness, problems which may or may not disappear after a period of a few weeks on the drug. Depression can be caused by nevirapine (Viramune) and saquinavir (Fortovase®). AZT can cause confusion, agitation, insomnia, and psychiatric symptoms, including mania and depression. Luckily, with the lower doses of AZT used now (compared to the high ones used in the past) such symptoms are rare.

Other drugs used by many HIV+ people which may have psychiatric side effects include interferons (including alpha-interferon, used to treat hepatitis C) and corticosteroids (used in the treatment of some infections).

Because so many of these possible drug side effects may be similar to symptoms of CMC or MCMD, it will be very important for any diagnostic approach to include consideration of this possibility. If it appears likely that your antiretroviral combo is causing or contributing to mental problems, it will be very important to discuss with your physician possible ways to handle this, as well as the possibility of changing problematic drugs. [For additional discussion of approaches to handling mental problems caused by antiretrovirals, see *Depression, Anxiety, Insomnia, and Other Mental Problems.*]

Infections and cancers. The infections and malignancies that can cause cognitive and motor changes include cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), toxoplasmosis, herpes encephalitis, CMV diffuse micronodular encephalitis, CMV ventriculoencephalitis, CMV polyradiculopathy/myelitis, CMV mass lesions in the central nervous system, CMV mononeuropathy multiplex, neurosyphilis, central nervous system lymphoma, central nervous system tuberculosis, Kaposi's sarcoma, Bartonella henselae infection, candida infection, and others. Aggressive diagnosis to determine if any such infections or cancers could be contributing to problems is crucial.

Strokes. An often unconsidered cause of neurological problems in people living with HIV is a stroke. The rate of strokes in HIV+ people has been found to be much higher than in the population as a whole, especially for the age at which the stroke may occur. It is terribly important to consider this possibility since a failure to treat this properly could obviously be devastating and potentially fatal. A sudden onset of cognitive/motor problems should heighten suspicion for this as a cause. The classic warning symptoms of a stroke include sudden weakness or numbness of the face, arm or leg on one side of the body; sudden dimness or loss of vision, particularly in one eye; loss of speech, or trouble talking or understanding speech; sudden, severe headaches with no apparent cause; unexplained dizziness, unsteadiness or sudden falls, especially along with any of the previous symptoms. This may progress to paralysis and total inability to speak or move. It is important to know that not all of these symptoms may occur, and that in some cases there might be only minor problems like difficulty or hesitation in speaking and thinking.

Incidences of low blood sugar (hypoglycemia) can also contribute to mental/emotional changes. With more and more HIV+ people developing blood sugar problems and, in some cases, diabetes, hypoglycemia may be more common now. Initially, when the blood sugar drops too low, the brain is not getting the energy it needs, and the result can be irritability, emotional swings, irrationality, and confusion, along with a feeling of serious fatigue. This will be temporary, with these mental/emotional effects disappearing soon after the blood sugar returns to normal. However, many people suffering from hypoglycemia may at times experience a roller coaster effect as their blood sugar bounces from low to high to low again, with multiple episodes throughout the day. Thus, there may be people in whom the mental/emotional problems may recur several times in any given day. If the hypoglycemia has not been diagnosed, this could lead to a presumption that one or more of the other causes discussed here might be responsible for the symptoms.

Causes that may be unrelated to AIDS. Don't forget that cognitive or motor symptoms can develop that could appear to be CMC but are actually unrelated to HIV or any of its complications. It's always possible for an HIV-positive person to develop mental or physical problems in the same way that an HIV-negative person would. For example, people with depression, anxiety, panic attacks, manic depressive illness or any other serious mental illness may show some of the symptoms listed above, and effective resolution of those symptoms will require effective treatment for those problems.

These may, in some cases, be related to HIV infection, but they may also stem from other causes. Another possible cause of mental symptoms are side effects of many different drugs (not just antiretrovirals), including some antidepressants. With these or any of the other possible causes of mental or movement symptoms that are not (or may not be) related to HIV disease, proper diagnosis to establish all the causes will be required.

What are the possible treatments?

The first must for effective treatment of cognitive and motor changes is identification of all the possible contributing causes, to the greatest extent possible, followed by elimination of as many of these as possible.

Key Therapies

Antiretroviral therapy. It is clear that effective antiretroviral therapy reduces the incidence of cognitive and motor complex (CMC). However, it is less clear how this works. Are the drugs improving cognitive function by working directly in the central nervous system, or indirectly in the blood, thus preventing the infection of macrophages which then travel into the brain? More and more, researchers are coming to believe that suppressing HIV in the cerebrospinal fluid is very important. Since not all drugs penetrate the cerebrospinal fluid (CSF), they believe that any HAART combination should include one or two antiretrovirals that are known to penetrate the CSF, as long as these drugs are also effective in suppressing HIV in your blood. Included (in the approximate descending order of likely effectiveness, based on the opinion of some experts, although this order would be debated by some) are: efavirenz (Sustiva); nevirapine (Viramune); AZT (Retrovir®); d4T (Zerit®); 3TC (Epivir®); and indinavir (Crixivan®). Note that some physicians fear that the psychological side effects of efavirenz may confuse the assessment of how well this drug is working to counter CMC.

The one thing that all experts would agree on is that the first priority in choosing a HAART regimen for the treatment of CMC is to choose a combo that will effectively suppress viral load in the blood, and maintain the CD4 count. However, the viral load in the blood may not be the only test that should be used to assess the likelihood of effectiveness. Several studies have shown that HAART-takers with frank dementia, especially those with CD4s below 200, often have viral loads that are undetectable in the blood but quite elevated in the CSF. This might be because the drugs aren't getting into the central nervous system, or because the virus in the central nervous system has mutated into forms that are not susceptible to the drugs that are working in the blood.

For this reason, some experts believe that periodic CSF viral load tests should be done to monitor any HAART regimen's ability to suppress HIV in the central nervous system. Justin C. McArthur, M.D., M.P.H., Deputy Director of Neurology at Johns Hopkins University School of Medicine, recommends changing the HAART combo in anyone with dementia who has a persistently high CSF viral load and is not improving on their current combo. Other experts agree, and report that in those with elevated CSF viral loads, switching to HAART regimens that contain drugs that better penetrate the CNS will often result in symptom improvement.

It is important to remember that CNS problems are being seen in more and more HIV+ people with CD4s over 400. With many people delaying treatment until CD4s are lower than in the past, it will be important to watch for any possible development of cognitive and motor problems, regardless of CD4 levels. If any such problems develop, even in those with relatively high CD4s, it will be very important to consider treatment with HAART, especially in those with elevated CSF viral loads.

Crucial nutrients.

B vitamins. There are a number of B vitamins that may be very important in the treatment and prevention of cognitive and motor complex (CMC). At the top of this list are B-12 and folic acid. These two nutrients should always be given together since taking folic acid alone could prevent the blood cell changes that might otherwise indicate B-12 deficiency. Since B-12 deficiency, a known cause of memory and other cognitive problems, has been shown in many studies to be widespread in HIV disease—and researchers have noted that test results frequently do *not* accurately reflect deficiencies—supplementation with B-12 and folic acid would seem to be appropriate in anyone with CMC symptoms, or with blood signs of deficiency. As discussed above, Justin C. McArthur, M.D., M.P.H., Deputy Director of Neurology at Johns Hopkins University School of Medicine, strongly recommends considering the possibility of B-12 deficiency in anyone suspected of developing dementia, and notes that *even without a measurable B-12 deficiency, B-12 nutraceuticals may help.*

Doses of B-12 (1,000 mcg given daily via pills, or one to several times weekly through prescription nasal gel or injections) and folic acid (800 mcg daily via pills) may be useful in preventing or reversing memory problems and other cognitive changes, even when tests don't indicate obvious deficiencies. The injections or nasal gel forms of B-12 bypass absorption problems that may be present in many HIV+ people due to problems with the parietal cells that produce the intrinsic factor that is needed for absorption of B-12 consumed orally (in either foods or pills).

Instead of waiting for problems to develop, it would be better to take these vitamins preventively in hopes of heading off any contribution they might make to CMC. This may be particularly important because research done in non-HIV+ people has shown a definite time window for getting the best results from B-12 supplementation. In the elderly, it has been shown that treatment with B-12 that is given shortly after development of deficiency-related symptoms like memory loss or other cognitive changes will often fully reverse the problems. However, the same level of supplementation given later may not, and as the time interval between initial appearance of symptoms and initiation of B-12 supplementation lengthens, the likelihood of symptom reversal decreases. Thus, you may lose the chance to fully reverse B-12-deficiency-caused mental problems if you wait too long to supplement. This would make preventive use of B-12, given as part of a total approach to HIV from early disease stages on, a preferable approach. Most of the folate deficiency-related neurological problems are reversible with proper treatment, but not always all of them. As with B-12, the best approach is to provide plenty of folic acid as part of your long-term daily supplementation program in order to prevent the problem rather than trying to fix it later.

Supplementation with thiamine will prevent further deterioration in memory problems related to thiamine deficiency but, unfortunately, cannot usually reverse defects already present that were caused by the deficiency. This makes it particularly urgent to not wait to do such supplementation, but rather make thiamine one part of a long-term preventive plan. Thiamine is contained in multiple vitamin/mineral nutraceuticals, and in B complex nutraceuticals. Taking one or both of these with each meal would normally provide sufficient amounts to prevent problems.

However, for those with malabsorption, chronic diarrhea, vomiting, or problems with alcohol, all of which greatly increase the likelihood of thiamine deficiency, supplementation with an additional thiamine product may be useful. Because water-soluble forms of thiamine (the standard form in most nutraceuticals) are somewhat poorly absorbed, it may be best to use a fat-soluble form such as thiamine tetrahydro-furfuryl disulfide. One such product is Ecological Formulas/Cardiovascular Research's **Allithiamine**. An appropriate dose would be one capsule, twice daily, with meals. The only limitation on this would be for those suffering from serious fat malabsorption. For them, water-soluble forms of thiamine may be preferable. [For a discussion of approaches to diagnosing and treating fat malabsorption, see *Diarrhea*.]

Supplementation with niacin and B-6 can help reverse the cognitive symptoms that could otherwise result from deficiencies of these nutrients. Both niacin and B-6 are contained in multiple vitamin/mineral nutraceuticals, and in B complex nutraceuticals. Taking one or both of these with each meal would normally provide sufficient amounts of these nutrients to prevent problems.

Taking healthy quantities of all the B vitamins throughout all your years of living with HIV may be the best possible way to help ensure that deficiencies of these nutrients never contribute to cognitive and motor problems. Again, since B vitamins are contained in both multiple vitamin/mineral nutraceuticals and in B complex nutraceuticals, daily supplementation with one or both of these, taken with meals, should provide much of the desired protection, although the problems related to oral intake of B-12 make it best to supplement B-12 via nasal gel or injections.

Allithiamine 50mg x 60	1 daily
B-6/P-5-P 50mg x 100	1-3 daily
Folic Acid 800mcg	1 daily
Methylcobalamin 1,000mcg x 100	1+ daily

Antioxidants. Antioxidant nutrients—including especially vitamins C and E, N-acetyl-cysteine, alpha-lipoic acid, carotenoids, bioflavonoids, and selenium—can help to reduce the oxidative stress that is common in HIV disease, and thus potentially lower the body's production of the cytokines (like tumor necrosis factor) that may contribute to brain

damage in HIV disease and, in general, reduce the oxidative stress that may be contributing to cognitive and motor problems. One of the major goals of antioxidant therapy is to reduce the level of neurotoxins that may be involved in causing the brain damage that results in CMC.

Tissues of the central nervous system are known to be particularly vulnerable to oxidative stress because of their high rate of oxygen consumption and high mitochondrial density. The mitochondria produce lots of free radicals during normal oxidative metabolism and, especially without sufficient antioxidant protection, the mitochondria may be damaged.

It is believed that this sort of oxidative stress damage may be partially responsible for a number of neurodegenerative diseases. In animal studies, alpha-lipoic acid has been shown to improve memory, apparently by reversing the damage that had been induced by oxidative stress so this antioxidant may be particularly useful. Although no research has been done to look at the possible usefulness of alpha-lipoic acid for cognitive and motor problems in HIV+ people, it has been shown to reverse damage to nerve tissue in those with neuropathy so it is certainly an interesting possibility.

Appropriate antioxidant doses for countering oxidative stress might be vitamin E (800 to 2,000 IU daily), vitamin C (2,000 to 6,000 mg daily, spread across three meals), carotenoid complex (1 capsule with each meal), selenium (400 to 600 mcg daily, total from all sources, including your multiple), coenzyme Q-10 (100 to 500 mg daily), N-acetyl-cysteine (1500mg to 2500mg daily), bioflavonoids (1 capsule with each meal), and alpha-lipoic acid (200 to 400 mg, three times daily). For further information on antioxidants, please see NYBC's *Basic Nutrient Protocols* and *Counteracting Inflammation* in the introduction.

In addition, adding to the antioxidants the other nutrients that may help counter mitochondrial toxicity is important. Included would be a broad spectrum of B vitamins, and the amino acid carnitine. Appropriate dosing to obtain the B vitamins would be a B complex formula (1 capsule with each meal) or a potent multivitamin/mineral formula that includes the whole B complex (as directed, with meals).

Carnitine is available in two forms: L-carnitine and L-acetyl-carnitine. There are both over-the-counter and prescription forms of L-carnitine. *Unfortunately, the plain L-carnitine has not been shown to improve cognitive function as has the acetyl-L-carnitine in European Alzheimers trials. Doses of the acetylcarnitine range from 1,000 to 3000 mg or more per day.* For a review of **Antioxidants** please see *The Introduction* and *NYBC's Core Nutrient Protocols* and *Counteracting Inflammation*.

Botanicals . Botanicals used for improvement of mental acuity fall in a variety of classes including nervines (see Mental Disorders section), those (such as ginkgo) that act directly on mental processes, and those that increase energy and endurance in general (see Fatigue section). The botanicals discussed below are those specifically related to mental processes. While some studies have reported beneficial effects when used in healthy individuals, others suggest that a greater effect is seen in those with impaired mental function.

Bacopa (*Bacopa monniera*): The primary herb used in Ayurvedic medicine to enhance mental acuity. Clinical studies have reported on its ability to enhance learning ability in children. Mechanisms of action have reported that it demonstrably effects GABA levels, either through increased GABA synthesis or through an inhibition of GABA metabolism. (Recall that GABA, or **gamma-aminobutyric acid**, is an amino acid found in the central nervous system that is associated with the transmission of nerve impulses.) In addition to its ability to increase learning and cognitive functions, it also has anticonvulsant, anxiolytic, and sedative activity.

Ginkgo-D MMS Pro (*Ginkgo biloba*) is the most widely studied pharmaceutical grade extract. Ginkgo is one of the most widely researched plants in the Western world, primarily for its effect in promoting mental acuity and slowing the progression of Alzheimer's disease. Numerous clinical studies report on its efficacy for use in both healthy and elderly, cognitively impaired individuals. A number of mechanisms of action have been postulated including its ability to increase cerebral blood flow and strong antioxidant activity. A number of studies suggest that it is as effective as comparable approved conventional medications. Ginkgo is also used to promote peripheral blood flow, specifically for the treatment

of intermittent claudication (inadequate circulation in the legs, often leading to clotting), increase blood flow to the genitalia, and reestablish blood flow to the brain after a stroke.

Caution: Ginkgo elicits a blood thinning activity. Therefore, if using ginkgo and abnormal bleeding occurs, discontinue use and consult with a qualified health care professional. Those with bleeding disorders or using blood-thinning medications, should not use ginkgo unless otherwise directed by a qualified health care professional.

There are also a number of other compounds for memory loss and other cognitive disorders:

Neuro Plus: A formula designed to maintain and support nerve and neurological functioning. Contains DMAE and a number of botanicals including Gotu Kola, Korean ginseng and *Ginkgo biloba*.

Phosphatidyl serine: A form of the amino acid L-serine that in large doses appears to have a powerful effect in reducing dementia and improving concentration and memory in aging populations and people with Alzheimer's. In smaller amounts many anecdotally report that it improves mental function.

NYBC Nutraceuticals for Memory Enhancement:

Acetylcarnitine 500mg x 100	3-6/d (1-2B, 1-2L, 1-2D)
Bacopa monnieri 20% 100mg x 90	3/d (1B, 1L, 1D)
Ginkgo-D 60mg x 90	2-4/d (1-2B, 1-2D)
Neuro Plus x 60	2-3 daily between meals
Phosphatidyl serine 100 mg x 120	3/d (1B, 1L, 1D)

Addressing antiretroviral drug side effects. As discussed above, it is always possible that one or more antiretroviral drugs could be contributing to mental or physical changes. If this appears to be a possibility it will be very important to discuss with your physician possible ways to handle this, as well as the possibility of changing problematic drugs. There is one important caveat to this. Although it would be appropriate to look for possible substitutions for any medication that appears likely to be contributing to mental or movement problems, there may not always be available substitutes. This may be a particular problem for people who are very treatment experienced with HAART meds. They may have become resistant to many previously used drugs, and might well be on the only combo currently available to them. If the combo is otherwise working well and providing the anti-HIV benefits needed, it may be necessary to stay with those meds. Remember that in terms of preventing HIV-associated damage to the brain, the most important thing is an effective antiretroviral combo so discontinuing meds (because of mental problems that they seem to be causing) and allowing the viral load to rise could mean exchanging one problem for another very serious problem. [For additional discussion of approaches to handling mental problems caused by antiretrovirals, see *Depression, Anxiety, Insomnia, and Other Mental Problems*.]

Treating infections and cancers. If any of the infections or cancers that are discussed above as possible contributors to cognitive and motor changes are diagnosed, it will be crucially important to seek aggressive treatment for any or all of these. There are effective treatments for most of these, and with such treatment, there will usually be resolution of (or at least improvement in) the majority of mental or movement problems associated with these conditions.

Treating strokes. If a stroke occurs or is suspected, it will be crucial to get medical care immediately. When appropriate treatments are used within a short period after the stroke occurs, it is often possible to greatly limit damage to the brain, and thus prevent many of the worst problems that a stroke can cause. Never hesitate to seek emergency medical care, and never forget that the rate of strokes in HIV+ people has been found to be much higher than in the population as a whole, especially for the age at which the stroke may occur. Remember that sudden onset of cognitive/motor problems

should heighten suspicion that a stroke might be the cause. If you develop even minor symptoms that might be related to a stroke, including any difficulty or hesitation in speaking and thinking, report to a hospital immediately.

Preventing hypoglycemia (low blood sugar) and the mental/emotional changes that can result from that. If it appears that recurrent low blood sugar may be causing short-term symptoms like irritability, emotional swings, irrationality, and/or confusion, it will be very important to work on stabilizing the blood sugar in order to prevent this. [For information on approaches to preventing hypoglycemia, see *Blood Sugar Problems, Insulin Resistance, and Diabetes.*]

Helpful changes in the way others interact with people with cognitive problems. It is very important that any person experiencing cognitive/motor symptoms be treated with respect, understanding, and loving care. Don't be condescending when you talk to someone with such problems. Don't treat him or her like a child. Talk slowly and make sure that what you're saying is getting through. Give the person sufficient time to listen, understand, and respond. Providing structure in certain ways may also help. For example, put a large daily calendar in an obvious place and always remember to tear off the page so that it is on the current date. Note appointments or other plans on the calendar. Create a large chart that shows the time when each medication must be taken. Put up a poster-size board that lists the times of the person's favorite TV shows, with a large clock right next to it. The fact that a person is experiencing certain cognitive/motor symptoms should not result in their being written off, and deemed incapable of making decisions. Always remember that some or all of their symptoms may be reversible with proper treatment, and help the person gain access to all the treatments that might help. Even in cases where the cognitive/motor symptoms have progressed to disabling symptoms that are not reversible despite the best possible treatments, the person should be treated with respect, cared for with tolerance and understanding, and allowed to maintain dignity at all times.

Experimental Approaches

While the therapies listed above are for now the best approaches to preventing or treating mental and motor symptoms, there are also experimental approaches that may turn out to be useful, especially when the key treatments discussed above are all in place. Some of these therapies apparently block the toxins pumped out by HIV-infected immune cells that are believed to cause the death of neurons. Others may protect the neurons from the damage done by the toxins, or improve cognitive function in other ways.

Lexipasant. This experimental drug is believed to block a neurotoxin called platelet activating factor which participates in the inflammation process in the brain. In a small study of people diagnosed with CMC, there was a trend toward cognitive improvement in those given lexipasant. A larger trial is ongoing.

Memantine (Axura). This drug, approved in Germany to treat Parkinson's disease and dementia in the elderly (and soon to be approved in the U.S.), is thought to work by blocking the neurotoxin quinolinic acid. It is believed that in HIV disease there is abnormal metabolism of certain compounds in the brain. In this case, it appears that the amino acid tryptophan is diverted from its normal role in creating neurotransmitters to the production of the toxin quinolinic acid. Memantine appears to block this neurotoxin. There is an ongoing federal trial looking at the usefulness of memantine for people with CMC. Until the drug is approved, it will be available through NYBC. Appropriate dosing is to start with one 10mg tablet and build up slowly to three to four per day if necessary.

Peptide T. This drug, originally studied as an antiretroviral, has been shown to prevent neuron death by blocking gp120, a potent HIV toxin. It is a chain of 8 amino acids. It has also been shown to reduce tumor necrosis factor-alpha which is an inflammatory cytokine. Results of a federal trial published in 1998 showed that HIV+ people with CMC who took Peptide T for six months had overall cognitive improvement, while overall deterioration was more common among the placebo group. There is still a great deal of controversy over whether it works. Some anecdotal reports suggest it can be helpful. It may be something to try, if you can afford it, and see whether it works for you.

Selegiline (L-deprenyl). This drug, approved for Parkinson's disease, has antioxidant effects. It has been studied for treatment of MCMD and CMC in two small studies, both of which showed symptomatic improvement in those given the drug three times weekly. A larger federal trial is ongoing.

Experimental Therapies for Memory Enhancement

Memantine 10mg x 50 (Dr. Rx required)	10-40mg daily
PeptideT 90mg x 9ml	Dose uncertain: 3 - 6 mg. One squirt in each nostril three times a day would be 6 mg (each squirt is a milligram) making it a 14-day supply. Half that dose would make it a 28-day supply.