# The Brain Drain

Forgot your own name? Join the club. It sounds nuts, but it’s not: Cognitive and Motor Complex-NEVER SAY DEMENTIA!-It is hitting more and more healthy HIVers. But early detection and treatment can stop the insanity.

February 1, 2001 By Bob Lederer

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Michael Depper is one of those smart, but not smart-alecky, New York City corporate lawyers. With a laser-sharp mind, the 46-year-old HIVer has been at the top of his profession as well as a mover and a shaker in the gay and AIDS communities for two decades. But last summer, Depper (not his real name) began losing his touch. “My memory had become really bad,” he says, “particularly around names, dates -- things I should just know. And although I’d always been well coordinated, I started dropping things and clicking the wrong item with my mouse.” He found himself blowing work deadlines and needing help handling major financial decisions such as taking out a second mortgage -- “though I did fine with my first.” At first, he says, he wrote it off as “just getting older” and the chronic depression that he had finally, after months of can’t-get-out-of-bed misery, controlled with a combo of antidepressant meds. He never suspected that the cause was more serious and linked to HIV.

In August he mentioned the symptoms to his HIV doc, who, Depper says, “just catalogued it as part of the depression.” When Depper went back to his psychiatrist, however, he got an immediate referral to the Neuropsychological Assessment Service (NAS) at Cornell University in New York City. After an eight-hour battery of tests -- such as repeating back an oral 16-item shopping list, putting the right peg in the right hole and assembling blocks to match a photo -- the diagnosis, according to NAS director Wilfred van Gorp, PhD, was clear: “Michael Depper was a textbook case of HIV-associated dementia: poor memory, psychomotor [mental and movement] slowing and -- especially given his law degree and illustrious career -- poor executive problem-solving skills.”

Depper puts it a little differently. “The elevator’s not going all the way up,” he says, laughing.

Van Gorp urged Depper to obtain extensive, expensive lab tests to clarify whether HIV was indeed the culprit by ruling out other potential causes.

Few diagnoses can undo veteran HIVers as quickly and completely as the much-dreaded dementia, and Depper was no exception. “My first reaction was shock,” Depper recalls. “I had watched the life slip away from several friends with dementia -- their need for assistance with daily life was devastating for everyone. I immediately fast-forwarded to the worst-case scenario --

having to get a legal power of attorney, complete my will, sign a living will and the inevitable downhill slide. It took me three weeks to get up the nerve to schedule the tests."

The mental mire Depper is stuck in is much less common among HIVers now than just five years ago. Since the introduction of HAART, rates of AIDS dementia complex -- dubbed HIV-associated Cognitive and Motor Complex (CMC) by neurologists -- have dropped by about half. Combo therapy suppresses HIV, which otherwise would travel from the bloodstream to the fluid bathing the brain, causing neurological symptoms. HAART also helps protect or restore immune function, preventing the bulk of frank (full-fledged) dementia that often accompanies plummeting CD4s for reasons that remain mysterious. As long-overdue CMC research yields new advances, clinicians finally have good tools for measuring and treating one of the most alarming AIDS ogres.

But HAART-heartened HIVers, beware: While rates of frank dementia are down, they are falling more slowly than rates of other opportunistic infections (OIs). Worse, the condition is actually increasing among one group of HIVers -- those who, like Depper, have CD4 counts above 400. "The worry is that whatever HAART we're putting patients on may not be adequately treating the virus' effect on the brain," says Susan Morgello, MD, director of the Mount Sinai School of Medicine's Manhattan HIV Brain Bank, a neurological study center that uses cell samples donated by PWAs. And one of the self-evident but cruel ironies of Lazarus syndrome is that the longer people live, the more time the virus -- even when undetectable in the blood -- has to migrate to, and flourish in, the central nervous system.

Equally troubling is the evidence that a milder condition -- Minor Cognitive and Motor Dysfunction (MCMD) -- is also on the rise. But because MCMD can show up as, say, difficulty recalling familiar names, forgetting appointments or trouble putting a key into a lock, some experts say the adjective minor doesn't quite cover it. "People get fired because they forget things, relationships go bad because a partner can't accept small behavior lapses," says Michael Wool, MD, associate clinical professor of medicine at UCLA, who has treated hundreds of patients with HIV-related neurological problems. Unfortunately, the symptoms are often overlooked, ignored or hidden. One study found that more than 70 percent of PWAs with fewer than 200 CD4 cells had MCMD that, according to Wool, "could only be teased out with neuropsychological testing." The brush-off Depper first gave his symptoms is typical. "Many PWAs in their 40s and 50s think they're just getting a little forgetful from advancing age," Wool says.

Scientists are in the dark about whether MCMD represents the early stage of CMC or an entirely separate condition. "Some individuals with MCMD return to normal -- usually after starting HAART -- or may stay stable for a long time," Morgello says. When the condition advances, it usually does so slowly over months or years, although the rate of progression and the particular symptoms vary greatly. "As you go down the immunologic slide, the incidence rises," Wool says. Memory lapses often pop up first, followed by difficulty communicating ideas and focusing attention. Problems with balance, walking and hand-to-eye coordination indicate that the condition has progressed. (These physical misfires may also be caused by two other HIV-related neurological disorders -- the spinal cord degeneration known as myelopathy [see "Hitting Below the Belt," POZ, February 2000], which can produce lower-body dysfunction up to paralysis; and the outlying-nervous-system

damage called peripheral neuropathy, which causes pain and numbness in the arms and legs.) In the stage of frank dementia, all these mental and motor maladies intensify even to the point of personality disorders such as bizarre behavior, extreme confusion or withdrawal -- the very dementia nightmare many HIVers' share. Because symptoms are so variable, practitioners often make a point of using the official CMC term, limiting the word dementia to the worst cases. This is especially important because, according to Justin McArthur, MPH, deputy director of neurology at Johns Hopkins University School of Medicine, "Dementia can be stigmatizing and even suggest mental impairment. But really we're dealing with a brain infection, or encephalitis, which principally impacts cognitive function."

Of course, only two letters separate dementia from demented, and many HIVers avoid diagnosis and treatment for fear that to do so is the first step on a road that ends at The Snake Pit. In fact, some HIVers labeled with the D word -- especially if their symptoms are advanced -- are talked down to by friends and family, and cut out of decisions about their own future. "I still want to do health advocacy, but I fear my strong opinions will be dismissed as the wailings of a nut," Depper says, explaining one reason he has chosen to speak to POZ about his diagnosis only under an alias. In past years, some HIVers with advanced dementia were so demoralized that they opted for suicide, but better treatments have made that a comparatively rare occurrence today.

As with other areas of AIDS science unrelated to antiretroviral drug development, HIV neurological research was minimal until a decade ago when activists began clamoring for change. Today the boosted budgets are paying off, with science finally shedding light on the mystery of how HIV -- which does not infect neurons (brain and nerve cells) -- causes CMC damage. "HIV resides in the fluid in brain spaces," Wool says, "and it enters the brain in a Trojan Horse manner" -- specifically by "hopping on a macrophage," a large white blood cell that carries it through the thick bag of the blood-brain barrier, in which the brain and spinal cord float. Once HIV-infected and activated, the macrophage not only pumps out neurotoxins -- chemicals that damage or destroy neurons in the cerebral cortex (the brain's thinking center) -- but infects brain support cells with HIV. Which type of neurotoxin is involved, and precisely how it poisons neurons, remains an urgent challenge for researchers (see "Feed Your Head" ).

Although damage is sometimes irreversible, treatment can prevent or reverse CMC progression, so early detection is key. All HIVers should take pains to track any glitches or hitches in thinking, moving or other functioning -- don't wait until "Help! I've fallen and I can't get up!" And it is equally important for doctors to take note (and notes), because neurological problems in HIVers can be caused by an almost-endless list of conditions -- some quite serious but almost all treatable, ranging from viral and bacterial infections such as CMV and toxoplasmosis to cancers or even side effects of AIDS or antidepressant medications. One oft-overlooked contributor is B-vitamin deficiency. Shortages of thiamine (B1), niacin (B3), pyridoxine (B6) and folic acid have been connected with cognitive problems. Most important of all, deficiency of B12 -- which protects the myelin covering of nerve cells -- is a well-known cause of dementia that scientists say is near-impossible to diagnose with existing tests. "I give B12 shots routinely to patients, even though I can't document that their levels are low," Wool says.

Unfortunately many of the non-HIV-caused conditions “can masquerade exactly” as CMC, says the Brain Bank’s Morgello. “HIV dementia is frequently misdiagnosed in both directions.” Wool says, “Rather than diligent diagnosis, the doctor may say, ’Oh, the person’s depressed,’ and prescribe antidepressants, when actually the HIV in their central nervous system is surging, and they just need their antiretrovirals adjusted.” Alternatively, they may be told it’s “just HIV” when in fact symptoms may stem from one or more of numerous other conditions. So at the first sign of trouble, HIVers should insist on a full workup.

Diagnosis begins with the type of neuropsychological testing Depper had. First is the HIV Dementia Scale, a battery of verbal, paper and hand exercises, the results of which measure CMC’s severity and whether therapy is working (see "Could You Have HAD?," POZ, December 1999). Ideally HIVers should all have this exam every six months to provide a baseline from which to monitor any deterioration down the line. Anyone who screens positive should get more in-depth psychological tests to help determine whether the symptoms are caused by depression, anxiety, recreational drug use, medication side effects or actual dementia. If the results indicate a problem, a complete set of physical diagnostic exams is vital in order to detect possible biological causes. This often requires taking brain images via MRIs (magnetic resonance imaging), CT (computer tomographic) scans and PET (positron emission tomography) scans, to detect lesions or other malformations that signal infections or cancers. Blood tests can show evidence of cryptococcal meningitis or syphilis. And a lumbar puncture (spinal tap) -- which, Wool says, ”in skilled hands is virtually painless" -- can detect other viruses and bacteria in the cerebrospinal fluid (CSF).

Scientists are now debating the use of two new lab tests in detecting the presence and degree of CMC: an HIV viral load measure of the CSF (Wool calls this test “the gold standard” for diagnosis, though other experts remain skeptical) and a specialized MRI called spectroscopy, a noninvasive scan of the brain’s chemical functioning. Both can measure the severity of dementia, and early rises in CSF viral load can predict later deterioration. In the end, diagnosing CMC involves carefully excluding all the so-called usual suspects, so it pays to find a doc with HIV and neurological smarts.

Meanwhile, great strides have been made by using antiretrovirals to attack the virus head-on. Shortly after AZT was introduced in 1987, CMC rates began declining, presumably because the drug was crossing the blood-brain barrier and suppressing the virus in the CSF. It was later found that very high doses (1,000 to 2,000 mg daily) could often reverse severe cases of CMC. But long-term use of that dosage produced unmanageable side effects. Later nukes offered little benefit, so in the early 1990s dementia rates inched upward again. Fortunately, with the advent of HAART, there are now several effective options for CMC. Still, mixing and matching is a guessing game. “It’s well understood today that the CSF is a big sanctuary for the virus where certain drugs don’t go,” Wool says. Many practitioners suggest including in your combo at least one, preferably two, antiretrovirals that penetrate the CSF -- so long as they do their primary job of suppressing HIV in your blood. Wool’s list of most-to-least recommended goes as follows: efavirenz (Sustiva), although some docs fear that the drug’s psychological side effects may muddy the CMC picture; nevirapine (Viramune); AZT (Retrovir); d4T (Zerit); 3TC (Epivir); and indinavir (Crixivan).

But other experts disagree. “We’re fooling ourselves if we think it’s possible to prioritize,” says David Simpson, MD, director of the Neuro-AIDS Research Program at Mt. Sinai. “Though many of us believe that including CSF-penetrating drugs improves dementia, it’s not been proven.” Adds the Brain Bank’s Morgello, “The $64,000 question is, are these drugs improving cognitive function by working directly in the central nervous system or indirectly in the bloodstream?” While each theory has its advocates, it bears repeating that all experts would agree with Simpson that in choosing a HAART regimen to treat CMC, “the first priority is to control viral load in the blood and maintain the CD4 count” -- just like for other HIVers.

Several studies have shown that HAART-takers with frank dementia, especially those with under 200 CD4s, often have viral loads undetectable in the blood but sky-high in the CSF. “Either the drugs aren’t getting into the central nervous system, or the virus in that compartment has mutated,” Wool says. This leads McArthur to propose periodic CSF viral load tests to monitor a regimen’s CMC effectiveness. “If a person with dementia is not improving on HAART and has persistently high CSF viral load,” he says, “I’d change their regimen.”

With the right combo, HAART can definitely defang dementia. “I’ve had a dozen patients with cognitive disorders who switched to a better-penetrating cocktail and their symptoms turned around,” Wool says. “Who knows how many people with HIV are needlessly in psychiatric institutions because their CSF viral loads haven’t been checked?” In the end, early detection and treatment make all the difference. “As people with HIV are living longer and neurologic complications are more subtle,” he says, “we have to make doctors and PWAs aware: Education is the best detector.”

For PWA Michael Depper, whose viral load has risen from 1,000 to 20,000 in the past six months, the writing is on the wall, and it reads: HAART. As if with one voice, each of his practitioners has echoed van Gorp’s advice: “From a strictly cognitive standpoint, he has to be on those meds. They’re his lifeline.” Depper, who has never had an OI and has a CD4 count of 425, knows the score -- and doesn’t much like it. “I’ve always resisted taking any HIV meds because I’ve watched too many friends die of AIDS-drug toxicity,” he says. “But I realize I have to start antiretrovirals” -- he pauses for a long moment -- “unless I learn of another promising treatment.” And while dementia still limits his ability to practice law, he’s grateful for a clear diagnosis and hopeful about his future. “Finally, there’s light at the end of the tunnel,” he says. “I’ve learned you can never take a lax attitude toward the virus. It’s really true that knowledge is power.”

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