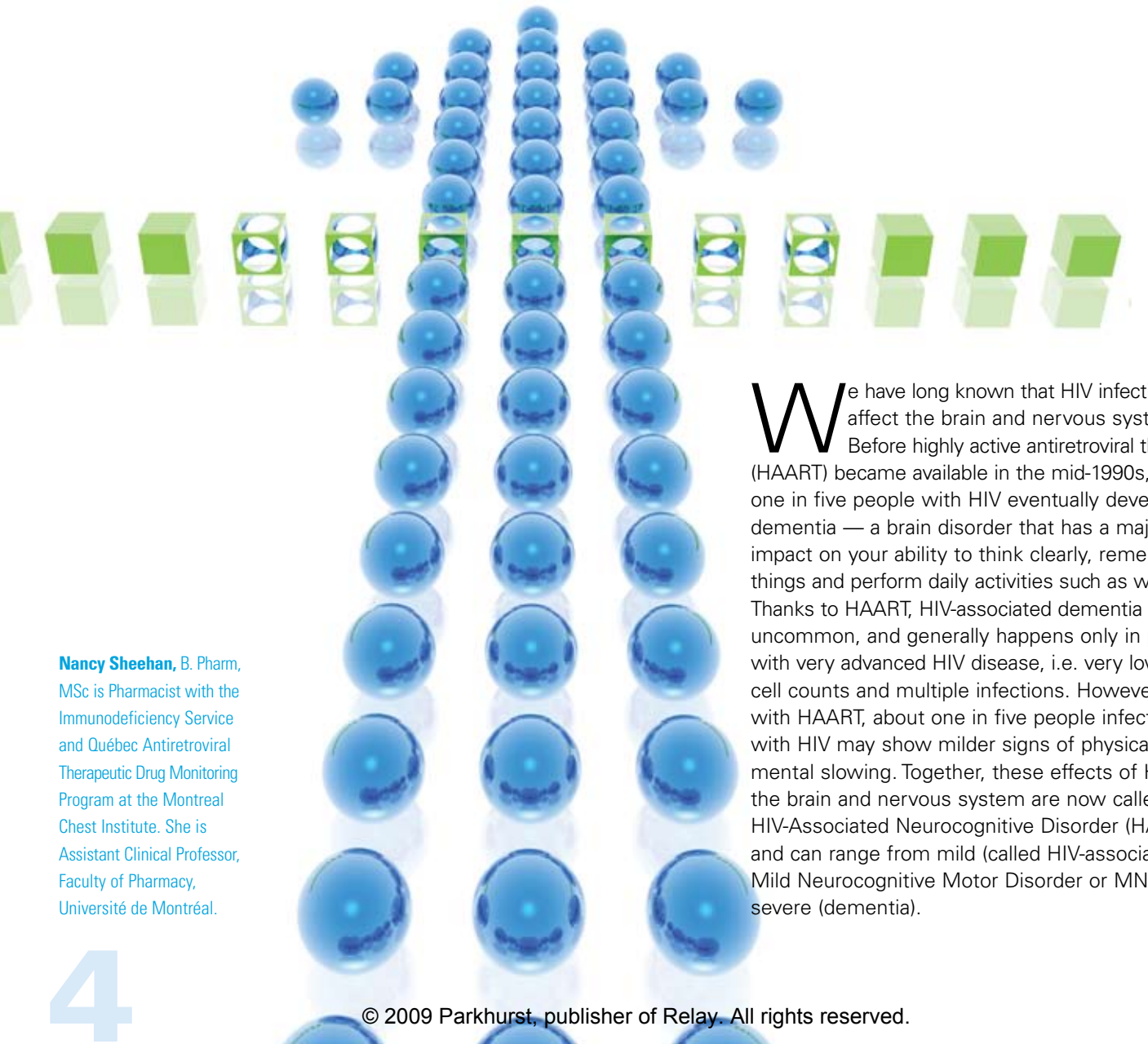
HIV, ARVs and the brain

Dementia is much less common than before HAART, but why do milder cognitive problems still occur?

by Nancy Sheehan, pharmacist and Dr. Marianne Harris



We have long known that HIV infection can affect the brain and nervous system. Before highly active antiretroviral therapy (HAART) became available in the mid-1990s, about one in five people with HIV eventually developed dementia — a brain disorder that has a major impact on your ability to think clearly, remember things and perform daily activities such as walking. Thanks to HAART, HIV-associated dementia is now uncommon, and generally happens only in people with very advanced HIV disease, i.e. very low CD4 cell counts and multiple infections. However, even with HAART, about one in five people infected with HIV may show milder signs of physical and mental slowing. Together, these effects of HIV on the brain and nervous system are now called HIV-Associated Neurocognitive Disorder (HAND) and can range from mild (called HIV-associated Mild Neurocognitive Motor Disorder or MND) to severe (dementia).

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How do I know if I have HAND?

Making a diagnosis of HAND isn't simple. First, the condition doesn't follow any standard or common course. In some people symptoms are mild and variable, while in others they get worse quickly. It's not clear whether the milder forms of HAND will always lead to dementia (**Table 1**), what factors might cause worsening disease, or how to predict how quickly this might happen. Also, many conditions cause similar problems and can be confused with HAND (**Table 2**). For example, some loss of memory and concentration can be part of the normal aging process. Also, many symptoms of HAND are the same as those of depression.

The main way to find signs of HAND is through mental status exams — these are special tests that identify problems with memory, abstract thinking, concentration, muscular coordination, walking, learning and mood. A complete mental status test must be done by a specialist (e.g. a neurologist or neuropsychologist) and takes several hours. People with the specialized training necessary to administer these tests are not available at all health centres. There are some shorter forms of mental status testing that can be used for screening, but most of these are impractical for use in a doctor's office due to limited time and lack of specific training.

Before deciding that a person has HAND, his or her doctor will need to rule out a number of other conditions. This may require brain scans (CT and/or MRI) to look for masses caused by infection or lymphoma, and/or a lumbar puncture (spinal tap) to check the cerebrospinal fluid for signs of infection.

Most doctors don't regularly screen for HAND so if you think you have symptoms, it's important to mention them to your doctor. He or she may do some tests to rule out other causes for your symptoms, and may refer you to a specialist for further evaluation.

HIV and the brain

The amount of HIV in the brain itself is thought to contribute to HAND. However, measuring the amount of HIV in the brain would require examining a piece of brain tissue — a hazardous operation. Instead, doctors measure the amount of HIV present in the fluid surrounding the brain and spinal cord, called the CSF. (We assume that the amount of HIV in the CSF reflects the amount in the brain tissue, but in fact this hasn't been definitely proven.) This test isn't done on a routine basis, because it requires a lumbar puncture, an uncomfortable procedure where complications, although rare, can be serious. What we know about HIV levels in the CSF comes from people participating in studies, or people with HIV who have had a lumbar puncture to assess another medical condition such as meningitis.

Studies done in the pre-HAART era showed that people with HIV-associated dementia had large amounts of HIV in their CSF. Furthermore, people without dementia who had higher viral loads in their CSF had worse results on mental status testing and were more likely to develop dementia later on. These relationships aren't always so clear in the HAART era.

Table 1

Indicators of HIV-associated dementia*

The indicators listed here are not in themselves diagnostic of dementia and can have a wide variety of causes. But they are important signs that should be mentioned to your doctor.

Cognition

Difficulties in processing, understanding and remembering information

memory loss • **speech problems** • **poor attention and concentration** • **poor judgment** • **trouble learning**

Behaviour

Difficulties in performing common tasks and activities of daily living

work • **home** • **social activities**

Motor coordination

Difficulties in controlling muscles and movements

incontinence • **trouble walking** • **dropping things** • **poor balance** • **stiffness**

Mood

Changes in emotional responses

depression • **personality changes** • **irritability** • **excitability (mania)** • **loss of interest** • **apathy** • **withdrawal**

* Previously called AIDS Dementia Complex or HIV encephalopathy

Antiretrovirals and the brain

It's generally been assumed that by suppressing HIV in the blood, HAART is also effectively suppressing it in the brain, leading to the lower rates of HIV-associated dementia seen over the last 10 years or so. However, we know that antiretroviral drugs (ARVs) that reach high enough levels to suppress HIV in the blood can be present in very low levels, or not at all, in the CSF. This is because of the blood-brain barrier, a tight network of blood vessels that protects the brain and spinal cord from most germs and toxins in the blood.

Some ARVs can penetrate the blood-brain barrier and are found in high levels in the CSF, while others don't penetrate as well. The effects of this possible lack of antiretroviral efficacy in the brain are currently not known.

The best evidence that ARVs can have a beneficial effect on the brain comes from the pre-HAART era, when high doses of AZT (1000-1200 mg daily), which crosses the blood-brain barrier well and is found in high levels in the CSF, were found to be an effective treatment for HIV-associated dementia.

With HAART regimens, there's evidence that combinations including two or more drugs that cross the blood-brain barrier are more effective in reducing the HIV viral load in the CSF. ARVs with the highest CSF penetration include zidovudine (Retrovir®), abacavir (Ziagen®), emtricitabine (Emtriva®, a component of Truvada®), delavirdine (Rescriptor®), nevirapine (Viramune®), indinavir (Crixivan®), lopinavir/ritonavir (Kaletra®), fosamprenavir (Telzir®)/ritonavir, darunavir (Prezista®)/ritonavir, raltegravir (Isentress®), and maraviroc (Celsentri®).

Researchers are now studying whether ARVs with high CSF penetration have an impact on HAND, an area complicated by the difficulties in assessing HAND mentioned earlier. Of the studies conducted to date, some, but not all, have shown mental functioning to stabilize or even improve after a number of months on HAART regimens that penetrate into the CSF. Longer and larger studies are still needed to know whether this type of HAART regimen may have clinical benefit in the management and/or prevention of HAND.

Table 2

Some conditions that can resemble dementia or HAND

- aging
- fatigue, insomnia, stress or anxiety
- depression
- drug side effects
- substance abuse or intoxication
- infections of the brain (encephalitis or toxoplasmosis) or spinal cord (meningitis)
- brain lymphoma
- stroke
- chronic pain
- head trauma
- problems with eyesight or hearing

What can you do to prevent cognitive decline?

- Stick to your ARV regimen
- Control conditions such as diabetes, high blood pressure and high cholesterol that affect circulation and may have an impact on cognitive function
- Ask your doctor about cognitive exercises that can help prevent or limit decline in function
- Avoid head injuries and drugs of abuse

Cognitive support

We're still a few years away from fully understanding the connections between HIV, viral loads in the blood and brain, and mental functioning. And it will always be difficult to pinpoint a particular cause of cognitive difficulties as so many factors can play into them. It's important to remember that symptoms of mental functioning problems are difficult for your doctor to recognize unless you bring them up. If you notice important changes, talk about them.