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## I BRAIN-RELATED ISSUES

### A. HIV and the brain—then and now

In the late 1970s doctors in North America and Western Europe began to see cases of young adults (mostly men) who sought care because of a recent history of at least the following persistent symptoms:

- swollen lymph nodes
- prolonged fatigue
- night sweats
- swollen liver and/or spleen

What puzzled doctors is that these young adults had been previously healthy and there was no obvious reason for the onset of their symptoms.

Subsequently, over the course of months or several years, the doctors found that their patients would develop more symptoms, including the following:

- unintentional and persistent weight loss
- diarrhea
- recurring herpes infections

By 1981 doctors began to see more serious symptoms in these patients, such as life-threatening infections and cancers—and so the AIDS epidemic was first recognized.

These life-threatening infections and cancers arose because of extraordinarily weakened immune systems. Trying to diagnose, treat and save infected patients became the focus of doctors who were immersed in the epidemic.

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## The brain

As early as 1982, neurologists reported strange symptoms in some patients that underscored the involvement of the brain with this emerging syndrome. These symptoms were not caused by any of the typical life-threatening infections that signified AIDS and could include the development of one or more of the following:

- forgetfulness
- difficulty concentrating
- slowness of thought
- changes in personality
- difficulty maintaining balance
- poor control of and weakened leg muscles
- loss of interest in everyday activities

## The role of HIV

The underlying reasons for these problems involving the brain was later pinned on HIV. This virus does *not* infect key brain cells called neurons. However, HIV does infect cells of the immune system that travel to and sometimes reside in the brain, including T-cells, monocytes and macrophages.

Inside the brain, these infected cells of the immune system release HIV-associated proteins and chemical signals that incite inflammation. The result is that brain cells become dysfunctional and in some cases die.

HIV also infects accessory cells in the brain called astrocytes, which play a role supporting the health of neurons.

## HIV-related brain issues today

In high-income countries, the widespread availability of potent combination anti-HIV therapy (commonly called ART or HAART) has made cases of *severe* HIV-related brain injury—commonly called dementia—uncommon among people who are engaged in their care and treatment. Indeed researchers estimate that today only about 2% of HIV-positive people will develop dementia.

Instead of dementia, researchers are now finding milder forms of HIV-related brain injury. These milder cases, particularly if they are initially symptom free, are often subtle and discovered only through complex and time-consuming neuropsychological assessments.

Today, scientists who study the brain have divided HIV-related brain injury into three categories, as follows:

- **asymptomatic neurocognitive impairment** (symptom-free neurocognitive impairment) – In such cases, testing detects subtle or mild degradation or decline in memory and thinking processes not seen in people of the same age and who have similar levels of education. This decline is not sufficiently serious to affect a person’s ability to engage in everyday activities.
- **mild neurocognitive disorder** (MND) – Testing detects at least a modest decline in memory and thinking processes. This decline is below what would be seen in healthy people of the same age and educational level. In cases of MND, the ability to carry out everyday activities is affected.
- **HIV-related dementia** – Testing reveals a severe decline in clear thinking and memory and a moderate-to-severe decrease in the ability to carry out activities of everyday living.

All three categories now make up what researchers call HAND—HIV-associated neurological disorder. Overall, neuroscientists estimate that between 50% and 60% of HIV-positive people have some degree of HAND.

## An important note

Readers should note that everyone, regardless of HIV status, can have episodes of forgetfulness from time to time. However, cases of persistent problems with memory and thinking clearly need to be reported to doctors so that they can be investigated and their underlying causes can be revealed.

In this *TreatmentUpdate*, we review several key studies of emerging issues associated with HIV and the brain.

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## B. Strengthening the aging brain

Researchers in the U.S. have found that some ART users can sometimes develop problems with memory and thinking clearly. In cases where these problems persist and are of at least moderate intensity, researchers have found that activities of daily living can be affected, such as the following:

- financial management
- employment
- driving
- remembering medical appointments
- adherence – taking anti-HIV medicines every day exactly as directed

## Aging

Another issue that HIV-positive people and their care providers have to consider is the impact of aging on neurocognitive abilities. In this report we present some ideas from researchers who have reviewed the issues and studies about aging and HIV and the impact of both of these factors on brain health.

## Is it AIDS or age?

In one study of 161 people, researchers grouped people by different categories (over 50 years or under 50 years of age) and by HIV status (positive and negative). They found that as a group, older HIV-positive people had poorer assessments of neurocognitive function than younger HIV-positive people. Among HIV-negative people, a similar trend was found; that is, older people had poorer neurocognitive testing results than younger people.

A major drawback of this study is that it was cross-sectional in design. This is similar to a snapshot of people—it only gives information from one point in time and does not provide information about changes that happen over time. Such changes over time can be obtained from a study of a different design—a longitudinal study. However, such studies are expensive and can be cumbersome. Still it seems reasonable to conclude, based on the cross-sectional study, that age has an impact on the neurocognitive abilities of HIV-positive people. Bear in mind that the impact of age on the brain will vary considerably from one person to another.

## Cognitive reserve

Some U.S. researchers who study aging and the brain suggest that one factor that plays a role in the decline of the aging brain in some ART users is “cognitive reserve,” which they define as “the amount of damage that the brain can absorb and yet remain functioning”

They further suggest that “cognitive reserve may explain why individuals experience [different] rates of change in cognitive function such that cognitive reserve capacity may provide a buffer against cognitive decline.”

## Lessons from mice

The U.S. researchers underscore findings from experiments with mice that may serve as a broad guide for research on helping to improve brain health and cognitive reserve.

In summary, researchers have found that placing mice in an enriched environment with stimulating toys and social contact with other mice helps their brains to thrive. Specifically, researchers have found that the brains of these mice produced chemical signals that encourage brain cells to make and strengthen their connections to other brain cells. Furthermore, mice placed in an enriched environment are better at navigating mazes than mice that are placed in a less stimulating standard laboratory environment.

## Learning from drivers

In a study published in 2005, neuroscientists in London, UK, studied 35 healthy participants, 18 of whom drove taxis and 17 others who drove buses. These participants underwent extensive neuropsychological testing and had MRI (magnetic resonance imaging) scans of their brain taken and analysed.

The researchers noted that taxi drivers had to undergo between two and four years of training in order to effectively navigate London and learn about points of interest. In contrast, bus drivers only received about six weeks of training and drove fixed routes. Taxi drivers generally do not drive fixed routes.

Other neuroscientists have proposed that the taxi driver training program and work is somewhat analogous to the enriched environment previously described in the mouse experiments. Also, the

bus driving would stand in for the standard environment in the previous experiments with mice.

The UK researchers found that parts of the brains of taxi drivers were larger than those of bus drivers in their study.

Commenting on these experiments with mice and people, as well as other studies, neuroscientists have suggested that learning new information helps to stimulate and develop the brain, even in adults.

## Some factors that can decrease cognitive reserve

Researchers have noted that the following factors likely play a role in reducing a person’s cognitive reserve:

- anxiety, depression and other mood issues
- addiction and substance use
- shrinking social interaction – HIV infection carries stigma, which can cause some people to experience social isolation. At least one study has found that some older HIV-positive people have fragile social networks.
- co-morbidities – emerging research suggests that some of the issues associated with aging, such as elevated blood pressure, pre-diabetes and diabetes, abnormal cholesterol levels, kidney disease, cardiovascular disease and so on, can all indirectly or directly reduce cognitive reserve.
- Infections – emerging research suggests that hepatitis C virus co-infection and syphilis can also affect the brain’s cognitive abilities.

## A closer look at emotional and mental health

Anxiety and depression are relatively common among people with HIV. Ideally, doctors would screen their patients for these conditions and refer or discuss treatment options. If left untreated, emotional and mental health problems can reduce a person’s quality of life and overall health. Researchers have noted that people who experience depression and anxiety can inadvertently focus on past mistakes and other unhelpful negative thoughts. Neuroscientists have found that constantly reviewing and reliving unhelpful thoughts and experiences can “prevent other thoughts from emerging.” This process reduces a person’s ability to resolve

complex emotional issues. In studies with HIV-negative people, researchers have found that treating emotional and mental health issues “may help reverse or prevent” some neurocognitive problems. There is no reason the same beneficial effect of therapy should not occur in HIV-positive people experiencing emotional and mental distress. Untreated emotional and mental health issues likely contribute to increased inflammation within the brain and perhaps the entire body.

### **The benefit of HIV therapy**

Shortly after HIV spreads from the point of first contact (usually the wet tissues of the anus, penis and vagina) it reaches the body’s organs, including the brain. Therefore, starting ART as soon after diagnosis as possible is important not only for restricting the spread of the virus, but also for reducing the amount of HIV and HIV-infected cells in the body’s tissues and organs. HIV-infected cells release chemical signals and proteins that can cause brain cells to become dysfunctional.

### **Social interactions**

Some HIV-negative people can have hurtful and unpleasant attitudes toward people who are HIV positive. Repeated exposure to such behaviour can be stressful and can cause some HIV-positive people to disengage from the wider community and become socially isolated. This last point is important because meaningful social interaction is good for the brain.

It is important to strengthen and extend social networks as people age. Joining clubs, teams, book groups, gyms and other activities where social interaction takes place are ways that can incite the process for making new friends.

### **Higher-than-normal blood pressure (hypertension)**

Researchers have found that hypertension can affect cognition in HIV-negative people. Also, reducing hypertension has been found to improve cognition.

### **Sugar blues**

Brain cells need regular and relatively stable levels of the sugar glucose. These cells convert glucose into energy and use it to power their activities. Researchers have found that elevated levels of

blood sugar and the hormone insulin are linked to decreased cognitive functioning in some HIV-positive people. Treating these issues with changes to the diet, exercise and medicines can help normalize blood sugar levels and improve cognitive function.

### **Exercises for the mind**

All of the following interventions generally improve mood and, in some cases, make life more interesting and stimulate the brain:

- techniques to reduce the impact of stress—physical exercise, meditation, Tai Chi, yoga
- brain fitness exercises (we detail these later in this issue of *TreatmentUpdate*)
- learning a new language or skill
- playing games
- reading books
- taking a college course

### **Areas for future research**

Emerging research suggests that there are many possible ideas that could be studied in clinical trials with HIV-positive people for their potential on delaying the decline of the brain, such as the following:

- a Mediterranean diet
- supplements of probiotics
- regular intensive exercise
- certain antidepressants – The antidepressant lithium stimulates the brain to produce chemical signals that can improve brain health and may help to reduce HIV-related brain injury. However, people who use lithium require frequent monitoring to ensure that they do not develop side effects. Other antidepressants might also be worth studying for the same purpose.
- music designed to change brain waves to a state similar to that detected in people who are meditating. This type of music is called binaural beat therapy.

In this issue of *TreatmentUpdate*, we discuss other ideas that researchers are investigating to help the brains of HIV-positive people.

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## C. An intriguing shift in cognitive abilities

A team of researchers at the University of California at San Diego (UCSD) has been studying HIV-related brain issues for many years. In past studies the UCSD team has documented the presence of mild HIV neurocognitive impairment in some ART users. These studies were generally cross-sectional in nature; that is, they assessed participants at one point in time. Now the UCSD researchers have conducted a more meaningful study: They monitored neurocognitive changes in more than 300 HIV-positive people for at least four years. The researchers found that some participants who initially had mild, symptom-free brain injury were at significantly increased risk for subsequently developing symptoms of HIV-related neurocognitive impairment.

### Caution for readers

Some readers may understandably find these results distressing. However, later in this report, we explain the findings from the UCSD study and place them in context. Furthermore, it is important to note that not every HIV-positive person will develop neurocognitive impairment (caused by HIV) in the present era. Also in this issue of *TreatmentUpdate*, we present research findings about ways that scientists are exploring to try to remedy HIV-related brain injury. Readers should note that preliminary results from a Canadian study that is in progress suggest that it is possible to reverse the decline in neurocognitive functioning that can sometimes occur with HIV. However, before we discuss that study, we first deal with the San Diego research.

### Study details

Researchers analysed data collected from 347 HIV-positive participants who were part of a large observational study called the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER). The 347 participants underwent extensive assessment of neurocognitive functioning every six months, in addition to regular HIV and immunologic assessments. Also, researchers performed spinal taps (lumbar punctures) so as to get a sample of the fluid that surrounds the brain and spinal cord. This fluid is called CSF (cerebrospinal fluid).

On average participants were monitored for four years.

At the start of the study, the 347 participants were distributed as follows:

- symptom-free neurocognitive impairment – 121 people
- neurocognitively normal – 226 people

Researchers asked participants to rate their ability to carry out their daily activities. Among participants who were employed, researchers asked them about changes in their productivity, the accuracy and quality of their work and the effort required to produce such work. All of these assessments by participants were called self-reports.

Psychologists know that self-reports are not always accurate for at least the following reasons:

- denial
- loss of insight
- alteration of behaviour to avoid challenges

Mindful of these issues, the CHARTER team also developed its own assessments of daily functioning, called performance-based measures.

Here is the average profile of participants at the start of the study:

- age – 43 years
- gender – 82% men, 18% women
- years of education – 13
- having been diagnosed with substance use in the past – 70%
- having been diagnosed with major depression in the past – 50%
- CD4+ count – 440 cells/mm<sup>3</sup>
- currently taking ART – 70%
- proportion of participants with viral load in the blood less than 50 copies/ml – 43%
- proportion of participants with viral load in CSF less than 50 copies/ml – 68%
- estimated time living with HIV – 10 years
- proportion of participants with hepatitis C virus (HCV) co-infection – 24%

## Results—Overall

Using any of three metrics—self-reports, performance-based measures, or a combination of both—researchers found that having symptom-free neurocognitive impairment was significantly

associated with an increased risk for the future development of symptoms of such impairment.

## Results—Participants with low viral loads

When researchers restricted their analysis only to people whose viral load in the blood at the start of the study was less than 50 copies/ml, the increased risk for developing symptoms of neurocognitive impairment was still found and was statistically significant.

Researchers continued to focus on participants who had a low viral load (less than 50 copies/ml) and found that among this subset, self-reports did not achieve a statistically meaningful relationship in their ability to predict the decline of the brain. Perhaps this is because of reasons previously mentioned (see Study details).

## Several factors

Also, after the researchers took into account IQ levels, lowest-ever CD4+ count and years of education, having symptom-free neurocognitive impairment was still associated with an increased risk for developing symptoms of this problem.

## A closer look

According to the study team, the proportion of participants who eventually developed symptoms of impaired neurocognitive functions entered the study with the following neurocognitive status:

- symptom-free impairment at the start of the study – 50%
- normal neurocognitive functioning – 22%

In general, the researchers found that people who had symptom-free neurocognitive impairment at the start of the study were more likely to develop symptoms of such impairment. Some participants became somewhat disabled as a result of this worsening impairment.

Researchers found that, overall, participants whose neurocognitive functions declined during the course of the study tended to have the following profile:

- “were older, had less education, were more often female, were more likely to have [been diagnosed] with a substance use disorder [at some point in their life] had greater than [minimal] comorbidity...”

## Points to consider

1. The results from the present study show that some HIV-positive people who have initially symptom-free neurocognitive impairment have an increased risk—between two-and six-fold—for the subsequent development of symptoms of such impairment.
2. The results of the present study, while important, may not apply to all HIV-positive people for at least the following reasons:
  - a relatively small number of participants was analysed
  - the issue of disability (caused by neurocognitive impairment) was not fully explored by the study team. There was no information on whether or not symptoms of disability changed over time.
  - the parent study—CHARTER—focused on HIV-related neurologic disease. It is possible that because of this focus, it could have inadvertently attracted participants who were concerned about, and perhaps in some cases possibly prone to, neurocognitive issues. A larger, longer and more geographically diverse study is needed to confirm the findings reported. Such a study would be expensive, would require highly motivated participants and would likely take several years to complete.
3. Gender – in the present study women were nearly threefold more likely to develop symptoms of neurocognitive impairment. This may have occurred because women in the study had lower levels of education and were more vulnerable to substance use than men. Future studies need to take gender-related factors into account when assessing neurocognitive functions.

## What to do?

The study researchers, highly experienced in studying HIV-related brain issues, propose that people who have symptom-free neurocognitive impairment should receive more monitoring since they are at heightened risk for HIV-related disability.

The findings from the present study should be viewed as preliminary and intriguing. Furthermore, readers should note that while about 51% of people with initially symptom-free neurocognitive impairment declined, so did 22% of participants who were initially graded as neurocognitively normal.

## An external view

American neuroscientists Steven Albert, PhD, and Eileen Martin, PhD, who reviewed the study's findings made the following comment:

“Could it be that the development of cognitive impairment and associated disability is a feature of HIV infection more generally, despite [ART], viral suppression, and medical care?”

In the present study, the average age of participants who were initially assessed as being neurocognitively normal was 43 years, most were high school graduates and their IQs were in the normal range.

Based on this observation, the U.S. neuroscientists asked this troubling question:

“With longer follow-up, will most CHARTER participants who were initially diagnosed as cognitively normal also develop neurocognitive impairment and associated disability in their 40s and 50s?”

It is not clear how, if at all, the results from the present study apply to other groups of HIV-positive people, such as the following:

- people who have not used substances
- people who have never developed AIDS

In other parts of this issue of *TreatmentUpdate*, we report interventions that researchers are studying to reduce the risk of developing neurocognitive impairment or even reverse such impairment.

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## D. Exercise and the brain

Researchers at the University of California at San Diego (UCSD) surveyed more than 300 HIV-positive people about their overall health, behaviours and activity, including exercise habits. Additionally, participants underwent complex assessments of their brain health. The researchers found that participants who reported that they



exercised had about 50% less neurocognitive impairment than participants who reported *not* exercising. Future clinical trials with supervised exercise are needed to help doctors determine the amount of exercise needed to prevent or reverse the decline of the brain among HIV-positive people.

## Study details

Researchers recruited 335 HIV-positive adults for this study.

The average profile of participants was as follows:

- age – between 20 and 79 years
- gender – 76% men, 24% women
- education – up to one year of college
- taking ART – 82%
- received a diagnosis of AIDS in the past – 65%
- duration of HIV infection – from one month to 28 years

In their survey, researchers stated that exercise was “any activity in which the heart beats rapidly” and gave participants the following examples:

- running
- jogging
- lifting heavy weights
- aerobics
- hockey
- football
- soccer
- squash
- basketball
- cross-country skiing
- judo (and similar sports)
- roller-blading/skating
- vigorous swimming
- vigorous long-distance cycling

Participants also underwent neurocognitive assessments.

Researchers assessed participants’ health and their use of substances and checked for the presence of mood disorders. In some cases, researchers also accessed medical records to check lab test results and for the presence of other conditions.

People who had issues unrelated to HIV that could affect neurocognitive assessments were not included in this study. According to the researchers, such issues included the following:

- seizures
- head trauma

- learning disabilities
- psychotic disorders
- current substance use

## Results

According to researchers, participants who reported engaging in exercise had the following:

“Significantly more formal education, [were less likely to have been diagnosed with AIDS], higher current CD4+ counts, [were less likely to be depressed] and [had better overall physical health].”

## Results—Cognitive impairment

Overall, more participants who did not exercise in the past three days were significantly likely to have neurocognitive impairment (31%) compared to people who did exercise (16%).

## Further comparisons

It seems obvious that some of the study’s findings could have been affected by factors that were not measured or that were not adjusted for in the researchers’ comparisons and calculations. For instance, it is possible that people who have more years of education could be expected to exercise more regularly and this could have inadvertently biased researchers’ interpretations of their findings.

To try to overcome such potential biases (or confounding factors), the researchers created complex algorithms that took into account some of these issues. Also, they analysed a sub-group of participants: 83 people who exercised and 83 people who did not. In this sub-group of 166 people, participants had similar levels of education, gender, ethnicity and age. The analysis of this subgroup confirmed that participants who reported no exercise had the following:

- lower CD4+ cell counts
- higher rates of depression at the time of the survey
- greater risk for AIDS in the past

Furthermore, in the subgroup analysis, a lack of exercise remained a significant predictor for reduced neurocognitive functioning even when researchers took into account several potential confounding factors.

## Bear in mind

The UCSD study is cross-sectional in design, which means it is akin to a snapshot in time. Such studies are good at finding associations but can never prove cause and effect. That is, such studies cannot prove that not engaging in regular vigorous exercise will lead to a greater risk of neurocognitive decline. Such conclusions can only be drawn from well-designed and expensive prospective studies that monitor participants over time and compare different interventions (exercise vs. no exercise).

However, the present study's findings do support clinical trials of exercise to assess its impact on brain health among HIV-positive people.

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## E. Good for the brain—advice from neuroscientists

According to Mark Mattson, PhD, chief of the Laboratory of Neurosciences at the National Institute on Aging in Bethesda, Maryland, research on animals and with HIV-negative people has found that regular exercise can do the following:

- improve mood
- lessen anxiety
- improve cognitive performance
- make people less susceptible to depression

Dr. Mattson adds that exercise can have these effects by doing the following:

- stimulating cells in the brain to build new connections and strengthen existing connections

- stimulate the production of new cells in some parts of the brain
- release the protein BDNF (brain-derived neurotrophic factor), which has been linked to improvements in memory. BDNF has also been linked to the formation of new brain cells

According to one of Canada's leading neuroscientists, University of Toronto professor Sean Rourke, PhD, there are many things that are good for the brain. The easiest way to remember these, he says, is with this phrase:

“Anything that's good for the heart is good for the brain.”

Professor Rourke recommends that people seek help from their healthcare providers to deal with issues that can significantly affect heart and brain health, such as the following:

- smoking tobacco
- overall cardiovascular health
- moderate alcohol intake (too much is not healthy)
- sleep that does not leave people feeling refreshed
- pre-diabetes and diabetes
- higher-than-normal blood pressure
- stress, anxiety or depression

A significant body of research and a recent study published in the *Journal of the American Heart Association* backs up Rourke's phrase about the connection between the brain and the heart. In that study of more than 17,000 Americans, researchers found that people with intermediate or good cardiovascular health were at substantially reduced risk of cognitive impairment.

The American Heart Association has a new measure of cardiovascular health called “Life's Simple 7.” This is based on a mix of behaviours and assessments that can be improved over time to help increase a person's cardiovascular health. The key points of “Life's Simple 7” are as follows:

Behaviours:

- not smoking or quitting smoking
- eating a healthy diet
- physical activity
- body mass index (BMI)

Biological factors:

- blood pressure
- total cholesterol
- fasting blood sugar (glucose)

By working with a care team to deal with these issues, heart and brain health can be improved.

### Back to basics

The focus of care for HIV-positive people has historically revolved around assessments of the immune system and the response to anti-HIV therapy. However, as HIV-positive people live longer thanks to ART, looking after overall health becomes important. That's where family doctors, nurses and, in some cases, pharmacists play a key role. Their wisdom, experience, advice and referrals to specialists are a vital part of maintaining and/or improving overall health.

For more information about improving cardiovascular health, see *HIV and cardiovascular disease* [<http://www.catie.ca/en/fact-sheets/other-health-conditions/hiv-and-cardiovascular-disease>].

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## F. About brain fitness

Experiments with animals and people have found that as they age the brain slowly degrades. Specifically, the perception of senses, memory and thinking abilities are all affected. However, experiments have also found that the brain retains the ability to learn and to store information throughout life. In response to stimulation, the brain can undergo very subtle changes in shape and size. Researchers who study the brain (neuroscientists) refer to these changes as neuroplasticity.

Researchers in the U.S. with the company Posit Science (San Francisco, California) have developed exercises to stimulate the brain. These exercises specifically challenge the brain, causing it to improve its ability to capture, sort and retrieve information. The approaches used by Posit Science (and other companies that have developed well-designed brain-training exercises) have been tested in clinical trials with mostly HIV-negative people. Overall, these studies have found that significant improvements were detected in the following assessments among people 60 years of age or older:

- faster processing of information
- improvement in memory
- increased ability to focus
- improved ability to do everyday tasks
- reduced risk for developing depression
- reduced risk for cognitive decline

Researchers who study the impact of brain fitness have found that the overall health of participants seemed to improve, resulting in a small decrease (about US \$300) in healthcare costs. Furthermore, the benefits of brain training seem to persist for up to five years after the initial sessions.

### Different populations

Until recently, limited studies have been done with HIV-positive people and brain fitness exercises. Such studies have found improvements in HIV-positive people when brain training was done.

### Resources

- A Mind of her Own [<http://www.catie.ca/en/positiveside/winter-2009/mind-her-own>] – *Positive Side*

- Pilot study of brain training [<http://www.catie.ca/en/catieneews/2012-11-06/pilot-study-brain-training-exercises-promising-limited-results>] – *CATIE News*
- Studying memory provides clues about helping the brain [<http://www.catie.ca/en/catieneews/2011-02-17/studying-memory-provides-clues-helping-brain>] – *CATIE News*

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## G. Canadian research on brain rehabilitation

Researchers in Toronto and Calgary, led by University of Toronto neuroscience professor Sean Rourke, PhD, have been studying how HIV affects the brain and ways to improve the health of this vital organ. Their interim findings suggest that brain fitness exercises can help the brains of some HIV-positive people.

### Study details

Researchers recruited 50 HIV-positive volunteers from major hospitals and clinics in Toronto. Volunteers did not have histories of significant substance use, impaired hearing or psychosis. Volunteers with a history of depression were allowed into the study.

Once in the study, participants had their neurocognitive functions assessed, then underwent

a 10-week brain fitness program (more about that below) and on completion of the program had their neurocognitive functions assessed again.

The computer-based brain fitness program, developed by Posit Science, includes six exercises, each 15 minutes in length. These exercises help to challenge the brain, specifically aiming to increase the speed and accuracy at which this organ processes information. According to Professor Rourke, these exercises “build on each other so you get more challenging ones as you become more successful.”

Prior to starting the brain training exercises, all participants received a one-hour tutorial about how to do the exercises.

As part of the study, participants were asked to do the following:

- about 30 to 45 minutes of brain fitness exercises each day, for five days each week, for eight consecutive weeks

So far 17 participants have completed the study and we focus on their results below.

The average profile of these 17 participants was as follows:

- age – 55 years
- gender – all males
- years of education – 16
- proportion that was unemployed or retired – 77%
- years since HIV diagnosis – 19
- taking ART – 16 participants
- proportion of ART users with a viral load less than 50 copies/ml – 100%
- adherent to ART within the past four days – 13 participants
- proportion with a history of having a CD4+ count less than 200 cells – 87%

### Results

Researchers reviewed the neurocognitive assessments of the 17 participants who completed the study and placed 15 of them into the following three categories of HIV-associated neurocognitive disorders (HAND):

- neurocognitively normal – five people
- mild neurocognitive disorder – six people
- HIV-associated dementia – four people

Two of the 17 participants who were symptom-free were excluded from this initial analysis.

### **Results—After brain fitness exercises**

After regular engagement of brain fitness exercises over eight weeks, researchers found that improvements in symptoms of cognitive problems occurred in all groups, though the most significant changes appeared in participants who entered the study with a mild degree of neurocognitive impairment.

Here are the overall trends in each group:

- Among participants who were neurocognitively normal, there was a small and non-significant increase in neurocognitive functioning.
- Among participants with mild neurocognitive disorder, overall neurocognitive scores rose sharply approaching scores seen in people who were neurocognitively normal. These changes were statistically significant, that is, not likely due to chance alone.
- Among participants with dementia, neurocognitive scores increased sharply but did not reach those seen in neurocognitively normal people.

### **In perspective**

This Canadian study achieved several important results, as follows:

- It is the first Canadian study to “evaluate and demonstrate the potential benefits of brain fitness exercises for neurocognitive impairment in HIV, over and above the contribution of ART,” states lead investigator Sean Rourke, PhD, and colleagues.
- Although the present study is relatively small, several areas of improvement were documented, including different aspects of memory (working memory, verbal learning memory and visual memory). Furthermore, it provides the rationale for a larger study.
- According to Professor Rourke, an important finding was that the burden of cognitive symptoms experienced by participants fell between 30% and 50%. This was significant because it gave people renewed hope and self-confidence about viewing and coping with their condition. This is important because it means that people feel that they can re-engage

with and participate in society. In turn, this re-engagement with the outside world will likely improve participants’ outlook on life and their sense of mental and emotional well-being.

- The researchers note that their results so far suggest that HIV-positive people who have been diagnosed with mild neurocognitive disorders “may benefit more from brain fitness [exercises] than those with HIV-associated dementia.”

### **Bear in mind**

The results of the Canadian study should be treated as interim but extremely promising. Only results from some participants are currently available, but there will be more data in the future. The Canadian study paves the way for more complex, larger and longer studies that seek to understand ways of improving brain health for HIV-positive people.

### **Moving forward**

Professor Rourke is planning to conduct a larger study comparing the impact of the following interventions with HIV-positive people:

- brain fitness exercises
- mindfulness-based cognitive therapy
- psycho-educational tools – sudoku, crossword puzzles, etc

Rourke would also like to explore the role of exercise on neurocognitive functioning. As mentioned earlier in this issue of *TreatmentUpdate*, exercise can have many health benefits, particularly on the brain. One of Rourke’s ideas is about the timing of exercise. His theory is that engaging in physical exercise for several weeks improves the flow of blood throughout the brain (and body) and also stimulates the brain to produce the brain-derived neurotrophic factor (BDNF). This protein is associated with improvements in memory in some studies. After this period of physical exercise, participants can then begin brain fitness exercises. Rourke theorizes that this combination of exercise and brain fitness training could have a greater, more beneficial impact on neurocognitive functioning than either intervention alone.

Rourke would also like to conduct a study of magnetic resonance imaging (MRI) of the brain to assess the impact exercise might have on changes to blood vessels within this organ. This

would better help researchers understand the impact of both physical and brain fitness exercises on the brain.

Rourke states that it is likely that a combination of interventions—such as physical exercise and brain fitness training—will be needed to help maintain and improve brain health in HIV-positive people. He also notes that understanding the lived experiences of HIV-positive people as they find strategies to successfully deal with neurocognitive impairment can help guide scientists in devising ways to help heal the brain.

## Acknowledgement

We thank Professor Sean Rourke for his helpful discussion, research assistance and expert review.

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## H. Menopause and HIV—their impact on cognition

As women age, their bodies undergo complex changes that affect many aspects of their health. Menopause is one such change, driven by altered hormonal levels. The ovaries produce estrogens, estradiol and estrone, and at around age 35 they begin to shrink. On average, by the age of 50, the production of estrogen has significantly decreased while the production of other hormones, LH and FSH, are on the rise. As women approach menopause, changing hormone levels can cause symptoms such as the following:

- hot flashes
- night sweats
- irregular periods with changes in bleeding
- vaginal dryness

Some women have reported the following symptoms as they transition through menopause:

- mood swings
- depression
- difficulty concentrating
- poor memory
- sexual dysfunction

The intensity and duration of these symptoms associated with the body's entry to menopause can vary considerably from one woman to another.

## Research on menopause

Scientists across the U.S. have been studying the intersection of menopause in women with HIV and in women at high risk for this infection. In particular, research teams have focused on the impact of menopause on neurocognitive functioning and mental and emotional health. They found that HIV-positive women undergoing menopause who had symptoms of anxiety were more likely to perform poorly on assessments of neurocognitive functions. The negative effect of anxiety was greater than that of HIV in this study. The researchers encourage doctors caring for HIV-positive women to screen them for anxiety and, if present, to treat it.

## Study details

Researchers in the following cities enrolled women with HIV and women at heightened risk for this infection:

- Bronx
- Brooklyn
- Chicago
- Los Angeles
- San Francisco
- Washington, DC

For this study the researchers focused on the following women:

- 708 who were HIV positive
- 278 who were HIV negative

Women underwent surveys, interviews, neurocognitive assessments, physical exams and blood tests. This report will focus on the outcomes in HIV-positive women.

At the time of the study (between April 2007 and April 2008) the average profile of the HIV-positive women was as follows:

- age – 44 years
- annual income of US\$12,000 or less – 48%
- tested positive for hepatitis C virus antibodies – 32%
- a history of using crack, cocaine or heroin – 50%
- currently used crack, cocaine or heroin – 11%
- engaged in what the researchers called heavy alcohol use – 15%
- currently smoked tobacco – 44%
- lowest-ever CD4+ count – 233 cells/mm<sup>3</sup>
- CD4+ count greater than 500 cells/mm<sup>3</sup> – 43%
- 95% or greater levels of adherence to ART – 48%
- HIV viral load less than 50 copies/ml – 51%

### Results—Stages of menopause

The distribution of women in the different stages of menopause was as follows:

- 56% were in premenopause
- 15% were in early perimenopause
- 5% were in late perimenopause
- 24% were postmenopausal

Here are the proportions of women with different symptoms associated with menopause:

- depression – 35%
- anxiety – 9%
- sleep disturbances – 29%
- hot flashes and/or night sweats – 18%

When researchers analysed the symptoms of menopause and linked these symptoms to stages of menopause, they found the following:

- Women with early perimenopause were significantly more likely to report symptoms of depression and anxiety than premenopausal women.
- Postmenopausal women were more likely to report problems concerning sleep than premenopausal women.

### Results—Neurocognitive assessments

Researchers found that HIV-positive women who had what they described as “elevated anxiety symptoms” performed poorly on several different

assessments of neurocognitive functioning compared to other HIV-positive women without symptoms of anxiety. These differences were statistically significant, that is, not likely due to chance alone. The negative effect of anxiety was greater than that of depression among HIV-positive women.

Furthermore, among HIV-positive women, researchers found that the impact of anxiety on assessments of neurocognitive functioning was “generally” greater than the impact of HIV.

### Digging deeper

Researchers sought to identify specific anxiety-related feelings that were linked to poorer neurocognitive functioning. They found that the following emotions were mentioned by women:

- “feeling tense/nervous”
- experiencing greater feelings of “fearfulness for no reason”

### Bear in mind

The present study was cross-sectional in nature. This type of study is analogous to a snapshot taken at one point in time. Cross-sectional studies are sometimes done as a first step to explore a research question. The results can sometimes provide the justification needed for a larger, longer and more expensive study. However, cross-sectional studies cannot provide definitive conclusions about health conditions. For instance, in the present study, researchers assumed that symptoms of anxiety and depression led to decreased neurocognitive functioning. However, it is possible that in some women, problems with neurocognitive functioning could have occurred before the onset of anxiety and depression.

The U.S. researchers now have a long-term study underway to better understand why some HIV-positive women develop neurocognitive problems and the impact of menopause on these issues.

They also encourage doctors caring for HIV-positive women to screen them for anxiety and, if present, to offer treatment.

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### Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

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#### *A Practical Guide to HIV Drug Side Effects*

The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

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