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I HIV & THE BRAIN

A. The need for more research and boosting the brain

When the AIDS pandemic first appeared in North America, doctors were puzzled by the sight of previously healthy young men who had inexplicably developed one or more life-threatening infections. They quickly established that these infections flourished because their patients had severely weakened immune systems.

The cause of this apparent immune deficiency would remain mysterious until 1983, when researchers at the Institut Pasteur in Paris, France, would first isolate HIV from the lymph nodes of an affected patient.

In addition to the life-threatening infections and relentless weight loss that soon became the hallmark of AIDS, doctors also noticed that some of their patients had complex neurological problems that affected certain functions, such as:

- memory
- clear thinking
- concentration
- coordination of movement

In extreme cases, other problems occurred, including:

- speaking incoherently
- loss of control of reflexes
- severe muscle weakness

At first, researchers thought that some of these problems arose as consequences of the life-threatening infections that had spread to the brain. However, when these neurologic problems were seen in people who had HIV infection but not

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AIDS, researchers sought other culprits. Eventually researchers found that HIV, either directly or indirectly, was responsible for many of these problems.

How damage occurs

HIV does not appear to infect brain cells. However, this virus does infect cells of the immune system—such as T-cells, monocytes and macrophages—that can enter and leave the brain as well as other cells (such as microglia) that reside within the brain.

These cells of the immune system, particularly macrophages, do not quickly die once infected with HIV. Rather, they survive and rove around the brain and body, spewing HIV and HIV-related proteins as well as chemical signals that incite inflammation. Together, these products—HIV, viral proteins and inflammatory signals—cause brain cells to become dysfunctional and, in some cases, die.

ART to the rescue

In the time before potent combination therapy for HIV (commonly called ART or HAART) was available, the severe loss of intellectual functioning was called HIV-related dementia and its devastating impact on personality, behaviour and ultimately survival was greatly feared by HIV-positive people.

Beginning in 1996, ART became widely available in Canada and other high-income countries, and HIV-related dementia became and has remained relatively uncommon today.

Neuro-ART

There have been isolated reports of a severe decline in neurocognitive function among a small number of HIV-positive people who have been taking ART. In most of these cases, HIV is often well suppressed in blood samples but not in samples of the fluid that bathes the brain and spinal cord—cerebrospinal fluid, or CSF. In such cases, doctors may change a person's regimen to include more drugs that can enter the CSF and suppress HIV in that part of the body, often resulting in improved neurocognitive function.

Researchers are still trying to understand why there are sometimes differences in the amount of HIV produced in the brain and blood despite the use of effective ART. As yet, researchers have not reached a consensus about the best combination of anti-HIV drugs to ensure suppression of HIV in the brain, perhaps because results from clinical trials to explore this effect have produced somewhat confusing results.

Persistent, mild cognitive impairment

Although ART can greatly suppress production of HIV in the body and brain, it does not cure HIV infection. Also, ART is unable to completely suppress HIV-related inflammation. Some researchers fear that over many years exposure to chronic low-level inflammation has the potential to make many of the body's organ-systems more susceptible to age-related decline; one of those organs may be the brain. However, firm evidence for this remains elusive. Moreover, despite the use of ART, researchers have identified mild neurocognitive issues in some HIV-positive people. Long-term studies need to be done to find out if mild neurocognitive problems continue or are reversed over time with prolonged ART. Fortunately, mild neurocognitive impairment does not seem to affect people's ability to do routine tasks associated with self-care.

Stopping or reversing neuro-degeneration

In addition to crossword puzzles and numeracy games such as Soduku, some HIV-positive people have found so-called brain-training exercises very useful in improving their memory. These exercises appear to work by stimulating and improving parts of the brain involved in information processing and memory. Results from clinical trials in HIV-negative people suggest that brain-training exercises can improve memory, speech (by helping people to remember and use more words) and speed of thinking. Although large controlled clinical trials of brain-training exercises are lacking in HIV-positive people, some have found them useful.

For more detailed information on brain-training exercises, see this very interesting article in *The Positive Side* by Maggie Atkinson:

- http://positiveside.ca/e/V11I2/Mind_e.htm

Neurologist Bruce Brew (Sydney, Australia) and colleagues who have done extensive research on HIV's effect on the brain note that there are no data from large randomized, controlled clinical trials to assess different ways of maintaining or improving brain function in HIV-positive people. However, he suggests that based on research with HIV-negative people, there are steps that people with HIV can take that may be "helpful in minimizing the effects of aging as well as perhaps delaying the onset of

[neuro-degenerative conditions such as Alzheimer's disease]." These steps include:

- aerobic exercise
- getting tested for and treating, if necessary, pre-diabetes and diabetes
- effectively treating higher-than-normal blood pressure (hypertension)
- controlling abnormal cholesterol levels in the blood

Getting inside the brain

Brain studies are complex, in part because scientists do not fully understand how this impressive organ works. Also, for obvious reasons, scientists are not able to routinely remove brain tissue from people. So, instead, neurologic research sometimes involves using brain tissue from animals—with monkeys, rats and cats being particularly popular with neuroscientists. Other aspects of brain research involve sophisticated scans of the human brain, particularly magnetic resonance imaging (MRI). Still other studies probe the functioning of the brain by having volunteers undergo written, spoken and pictorial assessments. Some studies involve a spinal tap, where a small amount of the fluid that bathes the brain and spinal cord is removed for analysis. A minority of studies involves analysis of human brain samples collected at autopsy.

All of these different ways of trying to find out what is happening within the brain are complicated and time consuming and require skilled technicians and scientists to interpret the results. Brain research, like much bio-medical research, is expensive. This means that the imaging and other assessments mentioned in this report are not routinely used as part of health monitoring for the average person.

In an attempt to get around some of these obstacles, some researchers have tried to assess blood samples to see if this can provide some insight into the health of the brain.

In this issue of *TreatmentUpdate*, we explore several recent developments concerning HIV's impact on the brain and possible future avenues to reduce this impact.

REFERENCES:

1. Snider WD, Simpson DM, Nielsen S, et al. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Annals of Neurology*. 1983 Oct; 14(4):403-18.

2. Levy JA, Shimabukuro J, Hollander H, et al. Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms. *Lancet*. 1985 Sep 14;2(8455):586-8.

3. Vilmer E, Barré-Sinoussi F, Rouzioux C, et al. Isolation of new lymphotropic retrovirus from two siblings with haemophilia B, one with AIDS. *Lancet*. 1984 Apr 7;1(8380): 753-7.

4. Klatzmann D, Barré-Sinoussi F, Nugeyre MT, et al. Selective tropism of lymphadenopathy associated virus (LAV) for helper-inducer T lymphocytes. *Science*. 1984 Jul 6; 225(4657):59-63.

5. Wiley CA, Schrier RD, Nelson JA, et al. Cellular localization of human immunodeficiency virus infection within the brains of acquired immune deficiency syndrome patients. *Proceedings of the National Academy of Sciences USA*. 1986 Sep;83(18):7089-93.

6. Koenig S, Gendelman HE, Orenstein JM, et al. Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. *Science*. 1986 Sep 5;233(4768): 1089-93.

7. Carne CA, Tedder RS, Smith A, et al. Acute encephalopathy coincident with seroconversion for anti-HTLV-III. *Lancet*. 1985 Nov 30;2(8466):1206-8.

8. Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: cause and consequences. *Journal of Pathology*. 2008 Jan;214(2):231-41.

9. Gendelman HE, Zheng J, Coulter CL, et al. Suppression of inflammatory neurotoxins by highly active antiretroviral therapy in human immunodeficiency virus-associated dementia. *Journal of Infectious Diseases*. 1998 Oct;178(4): 1000-7.

10. Kadiu I, Gendelman HE. Human Immunodeficiency Virus type 1 Endocytic Trafficking Through Macrophage Bridging Conduits Facilitates Spread of Infection. *Journal of Neuroimmune Pharmacology*. 2011 Dec;6(4):658-75.

11. Kraft-Terry SD, Buch SJ, Fox HS, et al. A coat of many colors: neuroimmune crosstalk in human immunodeficiency virus infection. *Neuron*. 2009 Oct 15;64(1):133-45.

12. Ellis RJ, Gamst AC, Capparelli E, et al. Cerebrospinal fluid HIV RNA originates from both local CNS and systemic sources. *Neurology*. 2000 Feb 22;54(4):927-36.

13. Lescure FX, Omland LH, Engsig FN, et al. Incidence and impact on mortality of severe neurocognitive disorders in persons with and without HIV infection: a Danish nationwide cohort study. *Clinical Infectious Diseases*. 2011 Jan 15; 52(2):235-43.

14. Grossman Z, Meier-Schellersheim M, Paul WE, et al. Pathogenesis of HIV infection: what the virus spares is as important as what it destroys. *Nature Medicine*. 2006 Mar; 12(3):289-95.

15. Bogoch II, Davis BT, Venna N. Reversible dementia in a patient with central nervous system escape of human immunodeficiency virus. *Journal of Infection*. 2011 Sep;63(3): 236-9.

16. Harezlak J, Buchthal S, Taylor M, et al. Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment. *AIDS*. 2011 Mar 13;25(5):625-33.

17. Wright E. Neurocognitive impairment and neuroCART. *Current Opinion in HIV/AIDS*. 2011 Jul;6(4):303-8.

18. Cysique LA, Waters EK, Brew BJ. Central Nervous System Antiretroviral Efficacy in HIV infection: A qualitative and quantitative review and implications for future research. *BMC Neurology*. 2011 Nov 22;11(1):148.

19. Cysique LA, Brew BJ. Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression. *Journal of Neurovirology*. 2011 Apr;17(2):176-83.

20. Knaepen K, Goekint M, Heyman EM, et al. Neuroplasticity—exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. *Sports Medicine*. 2010 Sep 1;40(9):765-801.

21. Griffin ÉW, Mullally S, Foley C, et al. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiology & Behavior*. 2011 Oct 24;104(5):934-41.

22. Igase M, Kohara K, Miki T, et al. The association between hypertension and dementia in the elderly. International *Journal of Hypertension*. 2012;2012:320648.

23. White WB, Wolfson L, Wakefield DB, et al. Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. *Circulation*. 2011 Nov 22;124(21):2312-9.

24. Seo SW, Lee JM, Im K, et al. Cardiovascular Risk Factors Cause Cortical Thinning in Cognitively Impaired Patients: Relationships among cardiovascular risk factors, white matter hyperintensities, and cortical atrophy. Alzheimer *Disease and Associated Disorders*. 2011 Sep 22. [Epub ahead of print]

25. Yaffe K, Lindquist K, Schwartz AV, et al. Advanced glycation end product level, diabetes, and accelerated cognitive aging. *Neurology*. 2011 Oct 4;77(14):1351-6.

26. Maarouf CL, Daugs ID, Kokjohn TA, et al. Alzheimer's disease and non-demented high pathology control nonagenarians: comparing and contrasting the biochemistry of cognitively successful aging. *PLoS One*. 2011;6(11): e27291.

27. Brew BJ, Crowe SM, Landay A, et al. Neurodegeneration and ageing in the HAART era. *Journal of Neuroimmune Pharmacology*. 2009 Jun;4(2):163-74.

28. Pulliam L, Rempel H, Sun B, et al. A peripheral monocyte interferon phenotype in HIV infection correlates with a decrease in magnetic resonance spectroscopy metabolite concentrations. *AIDS*. 2011 Sep 10;25(14):1721-6.

B. Exercise found to improve memory

Regular aerobic exercise—such as cycling, jogging, running, swimming and playing sports—has many benefits, including strengthening the cardiovascular system, maintaining a healthy weight and improving mood.

Experiments with mice have found that exercise improves their capacity to learn and remember information. Researchers have found that physically active HIV-negative older people are less likely to experience neuro-degeneration than people who are not physically active. This suggests that exercise may be a simple and useful strategy to help slow the loss of cognitive abilities as people age.

In younger HIV-negative adults, running and cycling have been found to enhance memory. Researchers are not certain how exercise has this effect, but evidence from experiments on animals suggests that the body is stimulated to release a chemical signal called BDNF (brain-derived neurotropic factor). BDNF helps brain cells thrive, supports their development and ability to make links with other brain cells, and plays an important role in strengthening memory. BDNF is produced mostly by the brain but also by the kidneys and, in men, the prostate gland.

Researchers at the University of Dublin, Ireland, conducted experiments with 47 young HIV-negative and healthy men who prior to the study did not engage in aerobic exercise. During the study the men engaged in intensive cycling (to exhaustion) lasting from three to up to 30 minutes— this is called acute exercise. In another part of the same study, the men engaged in regular, supervised, more moderate cycling, lasting between 30 and 60 minutes, three times weekly for five weeks (moderate exercise).

The researchers found that both acute and moderate exercise improved learning and memory in neurocognitive assessments. A shorter duration of moderate cycling for three weeks did not enhance memory and learning. The exercise-associated improvements in learning and memory were linked to increased levels of BDNF in the blood. Five weeks of moderate-intensity cycling were linked to improved cardiovascular fitness and lung capacity.

Other experiments with people suggest that regular exercise can increase the size of a part of the brain called the hippocampus. This growth in size is likely due to the formation of new brain cells. The Irish researchers suggest that it is not only the growth of new brain cells but the connections made between brain cells—forming a network—that are important and this may be why exercise takes weeks to exhibit its neurocognitive benefits. It is also possible that part of the reason for the improvement in learning and memory associated with exercise is that the flow of oxygen-rich blood to the brain improved because of exercise.

Although all of the work described in this report is based on experiments with HIV-negative animals and people, there is no reason why regular aerobic exercise should not benefit HIV-positive people. Until well-designed large studies are done with HIV-positive people to explore the neurologic impact of medium- and long-term aerobic exercise, HIV-positive people can discuss with their doctors what forms of aerobic exercise are suitable. At a minimum, exercise can help control weight and reduce cardiovascular risk.

REFERENCES:

1. Knaepen K, Goekint M, Heyman EM, et al. Neuroplasticity—exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. *Sports Medicine*. 2010 Sep 1;40(9):765-801.

2. Griffin ÉW, Mullally S, Foley C, et al. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiology & Behavior*. 2011 Oct 24;104(5):934-41.

C. Good news about HIV and the aging brain

Many studies of HIV's impact on the brain have been conducted since 1996 when ART became widely available in high-income countries. In these studies, researchers have enrolled HIV-positive people who had serious symptoms, such as AIDS, arising from a weakened immune system. It is therefore possible that such studies produced a skewed profile of the impact of HIV infection on the brain, perhaps portraying excessive damage.

To uncover what HIV does to the brain, it is important to study a wide variety of people, including people with HIV who have not had serious symptoms such as those seen in AIDS. Two studies have focused on HIV-positive people who have minimal symptoms of disease. One suggested that the rate of neurocognitive impairment in symptom-free HIV-positive people is not different from that of HIV-negative people. Another study suggested that mild neurocognitive impairment is relatively common among symptom-free people. As a result of these conflicting results, some neuroscientists argue that it is not certain whether HIV can cause deterioration in neurocognitive ability among "medically stable" people who are free from HIV-related symptoms.

Age or AIDS?

An additional concern faced when trying to assess neurocognitive impairment is the effect of aging. Some researchers suspect that the natural process of aging may intensify HIV's impact on the brain, and vice versa. Studies exploring this issue have produced mixed results.

In part, this mix of results arises from the confounding impact of co-morbidities in some older people, including depression, substance and alcohol abuse, cardiovascular disease and diabetes.

Researchers at King's College in London, UK, have conducted extensive neurocognitive assessments as well as MRI scans on 95 volunteers, some of whom were HIV positive. The researchers described the HIV-positive people as "medically stable." By this, they meant that not only were participants symptom free but that they were taking ART, had very low viral loads and relatively high CD4+ cell counts, and did not have a history of substance use or serious mental health issues.

The King's College team concluded that "HIV disease by itself does not significantly impair cognitive functions when patients are [free from symptoms of HIV disease and are medically stable]."

Study details

Researchers enrolled 95 gay and bisexual men. They were divided into the following four groups:

- HIV-positive men aged 20 to 40 years
- HIV-negative men aged 20 to 40 years
- HIV-positive men aged 50 to 75 years
- HIV-negative men aged 50 to 75 years

The health information gathered from each HIV-positive man was matched to that from an HIV-negative man of similar age and educational background.

Researchers did not enroll anyone who had any of the following diagnoses:

- AIDS-related infections that affected the brain
- hepatitis B or C viruses
- neurologic disorders
- a history of harmful substance use (including alcohol)
- any chronic cardiac, liver or kidney problems that could affect neurocognitive abilities
- moderate-to-severe psychiatric disorders

Researchers conducted extensive neurocognitive assessments, and blood tests were done to screen for many infections and conditions that could have an impact on neurocognitive assessments, such as

diabetes, untreated thyroid disease and so on. High-resolution MRI scans were also done.

Results—HIV and age

People with HIV infection did not have impaired neurocognitive function compared to HIV-negative people. HIV infection did not heighten age-related decline in neurocognitive function.

The researchers found that, in general, older people compared to younger people had some neurocognitive impairment, particularly affecting memory. This was considered a normal consequence of aging by the researchers.

Results—MRI scans

High-resolution scans detected changes in some regions of the brains of older participants. Again, these were considered a normal consequence of the aging process.

HIV-positive people had slightly reduced gray matter in one part of the brain, the frontal gyrus.

Making sense of the findings

The London researchers found that "in general, there was no significant [neurocognitive] impairment in our stable HIV-1 patient group." Furthermore, they stated that their findings "suggest that stable HIV-1 [symptom-free] participants with long-term suppression of viral load and CD4+ counts above 200 cells do not necessarily show cognitive decline."

The London team also states that previous studies that found neurocognitive impairment in HIV-positive people may not have taken into account factors such as alcohol and substance use, psychiatric conditions and other medical conditions.

According to the study team, in the present study participants had relatively high IQs and were in "good medical and psychiatric health." The researchers suggest that it is possible that that these factors may have played a role in protecting the men from neurocognitive degeneration.

Long-term studies are needed in order to learn what happens to such stable men as they age with HIV. Also, future studies need to include a broader range of HIV-positive people, including women.

If the results from the London study are confirmed, then dealing with co-morbidities that affect cognition (such as alcohol and substance use, metabolic problems such as diabetes and co-infections such as hepatitis C virus) may become more important to help reduce their impact on the brain.

REFERENCES:

1. Thompson PM, Dutton RA, Hayashi KM, et al. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. *Proceedings of the National Academy of Sciences USA*. 2005 Oct 25;102(43):15647-52.

2. Harezlak J, Buchthal S, Taylor M, et al. Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment. *AIDS*. 2011 Mar 13;25(5):625-33.

3. Towgood KJ, Pitkanen M, Kulasegaram R, et al. Mapping the brain in younger and older asymptomatic HIV-1 men: Frontal volume changes in the absence of other cortical or diffusion tensor abnormalities. *Cortex*. 2011; *in press*.

D. The immune system, HIV and shrinking brains

In the previous report, researchers in London, UK, found very little changes in the brains of medically stable HIV-positive men compared with those of HIV-negative men of similar age and educational background. However, the London team used a sensitive and high-resolution MRI scanner that found that parts of the brains of some HIV-positive men were smaller than those of HIV-negative men. The London team did not, as part of their study, further investigate possible reasons for this difference. However, an American team of researchers has conducted a study to begin the process of possibly explaining similar differences found in some HIV-positive American men.

Preliminary findings from the American study in the journal *Cerebral Cortex* suggested that there is a link between the proportion of HIV-infected cells circulating in the blood and decreased size of certain parts of the brain. If their findings are confirmed by future studies, this may have implications for when in the course of HIV infection therapy should begin. Also, research may be needed to develop drugs that can protect brain cells from the toxic effect of HIV's proteins and inflammatory signals released by HIV-infected cells. Before delving into the details about the American study, we review some background information and remind readers that due to limitations in the design of this study, its findings should be treated as preliminary.

Brain cells and HIV

HIV does not infect brain cells (neurons). However, it does infect monocytes, cells of the immune system, which, in their mature form are

called macrophages. Monocytes/macrophages (m/m) can be found throughout the body; indeed these cells travel all over the body, including the brain. Some cells that are closely related to macrophages, called microglia, are permanent residents of the brain, where they are supposed to protect this organ.

Unlike T-cells, m/m do not quickly die when infected with HIV. The virus takes over m/m and turns them into mini-factories that produce HIV and viral proteins and chemical signals of inflammation—all of which have a harmful effect on brain cells. For instance, a healthy T-cell or m/m communicates with brain cells, each different type of cell releasing chemical signals and proteins that keep the other cells in good working order. But once HIV infects an m/m, instead of releasing chemical signals that stimulate the well being of neurons, the infected m/m releases compounds that injure brain cells.

In the previously mentioned American study, researchers focused only on macrophages. In part, this focus arose because of previous studies linking HIV-infected macrophages to neurocognitive impairment.

Study details

Researchers enrolled 19 HIV-positive participants, all of whom were taking ART and most of whom had a viral load in the blood of less than 50 copies/ml. Participants were free from the following:

- major mental health issues
- head injury
- a history of substance use

Participants underwent limited neurocognitive testing and technicians conducted MRI scans of the brain. Also, specialized laboratory testing that focuses on detecting HIV-infected monocytes in blood samples was done. The study team zeroed in on these cells because previous studies have found a connection between relatively high levels of infected monocytes in the blood and an increased risk for neurocognitive impairment and dementia.

Specifically the team assessed the amount of HIV DNA in monocytes. Technicians were able to identify monocytes in blood samples because these cells displayed the protein CD14 on their surface. Their assay for this had a lower limit of detection—10 copies per million cells. This assay is available for research use only.

The average profile of participants in the study was as follows:

- 18 men, 1 woman
- age – 55 years
- CD4+ count – 500 cells
- lowest ever (nadir) CD4+ count – 170 cells
- 18 out of 19 participants had a viral load less than 50 copies/ml; the remaining person had a value of 158 copies/ml
- length of HIV infection – 16 years

Results

The study team was able to divide participants into two groups, as follows:

- 10 participants without detectable HIV-infected cells in the blood
- 9 participants with detectable HIV DNA in the blood, an average of 132 copies per million cells

Technicians also took high-resolution MRI scans of the brains of participants. Among people with detectable HIV-infected cells in the blood, scientists found a modest degree of brain shrinkage or atrophy. Among people without detectable HIV-infected cells in the blood, there was generally no noticeable brain atrophy. This difference between the two groups was statistically significant.

Statistical analysis found no relationship between decreased brain size and any of the following factors:

- age
- educational level
- current CD4+ count
- lowest-ever CD4+ count

Participants with decreased brain size seemed to perform worse on some neurocognitive tests. But, bear in mind that only a limited number of such tests were done in this study.

Results in perspective

The findings from the present study linking the number of HIV-infected monocytes in the blood to modest reductions in brain size make some sense. HIV-infected monocytes can travel to and accumulate within the brain. More HIV-infected monocytes within the brain may burden this organ with large numbers of HIV and viral proteins. Moreover, that the loss of brain tissue occurred in people with very little production of HIV in the blood (that is, a viral load generally less than 50 copies/ml) is somewhat concerning.

The disappearance of brain tissue was termed "cortical thinning" by the U.S. team. This problem has been found in other studies with HIV-positive people, however, those studies have not always controlled for substance use, mental health issues and other factors that could also affect the health of the brain.

What are the implications?

The greatest degree of cortical thinning in the present study occurred in a part of the brain called the bilateral anterior insula (or simply insula for short). This tissue is involved in many higher functions such as:

- control of vocal cords
- processing information about the sense of touch, pain and temperature
- processing information about the position of the body
- hand-eye coordination
- attention

Based on experiments both with mice and with HIV-negative people, the U.S. team suggests that damage to the insula may result in these problems:

- problems concentrating
- difficulty assessing risk in different situations
- impaired visual memory

The U.S. team noted that the insula is connected to several other regions of the brain, such as:

- cingulate cortex
- orbitofrontal cortex
- temporal pole
- superior temporal sulcus

In the present study, MRI scans revealed a degree of shrinkage in these regions of the brain in people who had HIV-infected monocytes detected in their blood. Damage to these additional parts of the brain could, the researchers stated, have the following impacts:

- decrease control and coordination of muscles
- affect judgment and control of impulsive behaviour
- reduce a person's ability to remember pictures, objects, faces and possibly some words

The present study focused mostly on the insula, but much more research is needed on the different parts of the brain affected by HIV infection and how this might affect a person's neurocognitive function and personality, as well as ways to slow or reverse this damage.

Caution needed when interpreting data

The present study had several limitations, as follows:

- It was cross sectional in nature. This is analogous to taking a picture and trying to build a complete profile of a person. People change over time, and so monitoring over time with multiple MRI scans and neurocognitive testing over a period of years is needed. Cross-sectional studies are cheaper and perhaps simpler to run than longitudinal studies. However, cross-sectional studies can only provide limited information.
- The number of participants was relatively small.
- Only limited neurocognitive assessments were performed.

Due to these limitations, the U.S. team cannot prove that the loss of brain tissue was directly caused by a greater burden of HIV-infected monocytes in the brain. However, the present study does provide a foundation for a bigger, longer and more intensive study of how HIV infection could affect different parts of the brain.

If another study confirms the present study's findings, one implication arising from such research is that it might be helpful to begin anti-HIV therapy as early as possible after HIV infection. Such early initiation of therapy could help to reduce the burden of HIV-infected monocytes in the brain and to preserve this vital organ.

Later in this issue of *TreatmentUpdate*, we will report on a potential therapy for protecting the brain from the effects of HIV infection.

REFERENCES:

1. Pulliam L, Rempel H, Sun B, et al. A peripheral monocyte interferon phenotype in HIV infection correlates with a decrease in magnetic resonance spectroscopy metabolite concentrations. *AIDS.* 2011 Sep 10;25(14):1721-6.

2. Valcour VG, Shiramizu BT, Shikuma CM. HIV DNA in circulating monocytes as a mechanism to dementia and other HIV complications. *Journal of Leukocyte Biology.* 2010 Apr; 87(4):621-6.

3. Shiramizu B, Williams AE, Shikuma C, et al. Amount of HIV DNA in peripheral blood mononuclear cells is proportional to the severity of HIV-1-associated neurocognitive disorders. *Journal of Neuropsychiatry and Clinical Neurosciences.* 2009 Winter;21(1):68-74.

4. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *Journal of Infectious Diseases*. 2002 May 15;185(10):1409-16.

5. Parisi SG, Andreis S, Mengoli C, et al. Baseline Cellular HIV DNA Load Predicts HIV DNA Decline and Residual HIV Plasma Levels During Effective Antiretroviral Therapy. *Journal of Clinical Microbiology*. 2011 Nov 30. [Epub ahead of print]

6. Piketty C, Weiss L, Assoumou L, et al. A high HIV DNA level in PBMCs at antiretroviral treatment interruption predicts a shorter time to treatment resumption, independently of the CD4 nadir. *Journal of Medical Virology*. 2010 Nov;82(11):1819-28.

7. Fink GR, Frackowiak RS, Pietrzyk U, et al. Multiple nonprimary motor areas in the human cortex. *Journal of Neurophysiology*. 1997 Apr;77(4):2164-74.

8. Eckert MA, Menon V, Walczak A, et al. At the heart of the ventral attention system: the right anterior insula. *Human Brain Mapping*. 2009 Aug;30(8):2530-41.

9. Jones CL, Ward J, Critchley HD. The neuropsychological impact of insular cortex lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2010 Jun;81(6):611-8.

10. Jones CL, Minati L, Harrison NA, et al. Under pressure: response urgency modulates striatal and insula activity during decision-making under risk. *PLoS One*. 2011;6(6):e20942.

11. Kuhnen CM, Knutson B. The neural basis of financial risk taking. *Neuron*. 2005 Sep 1;47(5):763-70.

12. Fineberg NA, Potenza MN, Chamberlain SR, et al. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. *Neuropsychopharmacology*. 2010 Feb;35(3):591-604.

13. Berlin HA, Rolls ET, Kischka U. Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain*. 2004 May; 127(Pt 5):1108-26.

14. Pourtois G, Vocat R, N'diaye K, et al. Errors recruit both cognitive and emotional monitoring systems: simultaneous intracranial recordings in the dorsal anterior cingulate gyrus and amygdala combined with fMRI. *Neuropsychologia*. 2010 Mar;48(4):1144-59.

15. Dhar M, Pourtois G. Early error detection is generic, but subsequent adaption to errors is not: evidence from ERPs. *Neuropsychologia*. 2011 Apr;49(5):1236-45.

16. Simões-Franklin C, Hester R, Shpaner M, et al. Executive function and error detection: The effect of motivation on cingulate and ventral striatum activity. *Human Brain Mapping*. 2010 Mar;31(3):458-69.

17. Brew BJ, Crowe SM, Landay A, et al. Neurodegeneration and ageing in the HAART era. *Journal of Neuroimmune Pharmacology*. 2009 Jun;4(2):163-74.

18. Chang L, Andres M, Sadino J, et al. Impact of apolipoprotein E ε4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. *Neuroimage*. 2011 Oct 15;58(4):1017-2.

19. Kallianpur KJ, Kirk GR, Sailasuta N, et al. Regional Cortical Thinning Associated with Detectable Levels of HIV DNA. *Cerebral Cortex*. 2012; *in press*.

20. Jernigan TL, Archibald SL, Fennema-Notestine C, et al. Clinical factors related to brain structure in HIV: the CHARTER study. *Journal of Neurovirology*. 2011 Jun;17(3): 248-57.

21. Becker JT, Maruca V, Kingsley LA, et al. Factors affecting brain structure in men with HIV disease in the post-HAART era. *Neuroradiology*. 2011 Mar 22. [Epub ahead of print]

22. Becker JT, Sanders J, Madsen SK, et al. Subcortical brain atrophy persists even in HAART-regulated HIV disease. *Brain Imaging and Behavior*. 2011 Jun;5(2):77-85.

23. Cohen RA, Harezlak J, Gongvatana A, et al. Cerebral metabolite abnormalities in human immunodeficiency virus are associated with cortical and subcortical volumes. *Journal of Neurovirology*. 2010 Nov;16(6):435-44.

24. Tate DF, Sampat M, Harezlak J, et al. Regional areas and widths of the midsagittal corpus callosum among HIV-infected patients on stable antiretroviral therapies. *Journal of Neurovirology*. 2011 Aug;17(4):368-79.

E. Are platelets a window into the brain?

Platelets, the second most common type of blood cell, are tiny disc-shaped cells. The main role that platelets play in the body is that of damage control. When platelets sense injured blood vessels, they become activated and release chemical signals that trigger the formation of blood clots at the site of injury so that blood does not leak.

Researchers have also found that platelets play a role in inflammation, cardiovascular disease and cancer, and they appear to help control infections.

Exactly how platelets do all of these functions is not yet clear but it may have something to do with their ability to display molecules that interact with the immune system as well as germs. Platelets can also serve as mini-warehouses storing chemical signals and proteins that are released when platelets become activated.

There are about one trillion platelets in the blood of an adult. The laboratory range for platelets will vary from one lab to another, but normal levels are usually above 150 billion. When the number of platelets falls below this level, people become at risk for uncontrolled bleeding.

In the time before potent ART became available, less-than-normal platelet levels were a relatively common complication of HIV infection. However,

in the present era this complication is not common among HIV-positive people who are taking ART.

Platelets and the brain

In 2007 a team of researchers announced that it had found a link between declining platelet levels and an increased risk for the subsequent development of extreme HIV-related neurocognitive decline—dementia.

As assessments of neurocognitive function are complex, it would be helpful if there were a simple blood test that could be used to accurately foretell neurological complications among HIV-positive people.

Confirming unusual results is an essential part of the scientific process. Another team of neurologists across the U.S. conducted a long-term study of neurocognitive function and platelet levels in the blood. They did not find any conclusive link between declining platelet levels and HIV-related dementia. However, they did unexpectedly find that among some older people with HIV declining platelet levels might be linked to atrophy of parts of the brain.

Study details

Since 1984, researchers in the U.S. have enrolled nearly 7,000 gay and bisexual men from these cities:

- Baltimore
- Chicago
- Los Angeles
- Pittsburg

Participants were seen twice a year by study staff; at each visit they were interviewed, examined and had blood samples drawn for analysis. From time to time, specialized neurocognitive assessments and MRI scans of the brains of some participants were also done.

For the present analysis, researchers used data from 2,125 HIV-positive men, 250 of whom subsequently developed dementia.

Results—Platelets

Taking many factors into account—including CD4+ cell count, viral load, red blood cell counts, age, education, alcohol and tobacco use, and so on—falling platelet levels were not linked to an increased risk for HIV-related dementia.

This difference between the present and past studies is interesting and may have arisen because of these factors:

- In the present study, participants had been monitored for up to 25 years. In the previous study, which reported its results in 2007, participants had been monitored for only a few years.
- The present study was larger and used only men with a broad range of CD4+ cell counts. The previous study had both men and women, and many participants had less than 300 CD4+ cells.

Results—MRI scans

In a subset of 83 HIV-positive men in the present study who were more than 51 years of age, there was a link between declining platelet levels and shrinkage of part of the brain, specifically gray matter. This term describes parts of the brain involved in thinking and memory.

Keep in mind that in the present study, only one MRI scan was done. Had multiple MRIs been done over several years, then a more robust link between brain atrophy and platelet counts might have been made.

Why platelets?

It may seem unusual that a cell not obviously connected with the brain, such as a platelet, might have an impact on this organ. However, as explained previously, platelets perform many roles in the body. Also, researchers have found that platelets release chemical signals that aid in the development and survival of immature brain cells. Researchers have found that in monkeys infected with SIV, which causes an AIDS-like disease, declining platelets have been linked to severe SIV-related brain infection. Still other researchers have found that a decline in the health of the bone marrow is somehow linked to the presence of dementia in HIV-positive people. So the connection between platelets, which are made in the bone marrow, and brain health is not as far-fetched as it may seem.

For now, the evidence to support a relationship between low levels of platelets in the blood and subsequent severe HIV-related neurocognitive impairment in people remains contested. Until researchers can refine their studies to find a clear and consistent relationship between platelet count and HIV-related neurocognitive impairment, platelet counts by themselves are not likely to be reliable indicators of future decline in cognitive functioning.

REFERENCES:

1. Wachtman LM, Skolasky RL, Tarwater PM, et al. Platelet decline: an avenue for investigation into the pathogenesis of human immunodeficiency virus -associated dementia. *Archives of Neurology*. 2007 Sep;64(9):1264-72.

2. Peng F, Dhillon N, Callen S, et al. Platelet-derived growth factor protects neurons against gp120-mediated toxicity. *Journal of Neurovirology*. 2008 Jan;14(1):62-72.

3. Wachtman LM, Tarwater PM, Queen SE, et al. Platelet decline: an early predictive hematologic marker of simian immunodeficiency virus central nervous system disease. *Journal of Neurovirology*. 2006 Feb;12(1):25-33.

4. Potula R, Dhillion N, Sui Y, et al. Association of platelet-derived growth factor-B chain with simian human immunodeficiency virus encephalitis. *American Journal of Pathology*. 2004 Sep;165(3):815-24.

5. Ragin AB, Wu Y, Storey P, et al. Bone marrow diffusion measures correlate with dementia severity in HIV patients. *AJNR American Journal of Neuroradiology*. 2006 Mar;27(3):589-92.

6. Ragin AB, D'Souza G, Reynolds S, et al. Platelet decline as a predictor of brain injury in HIV infection. *Journal of Neurovirology*. 2011 Oct;17(5):487-95.

F. Can a drug for psoriasis and MS help protect the brain from HIV's toxicity?

Researchers have found that a compound called dimethyl fumarate (DMF) can, in lab experiments with cells and HIV, suppress the production of HIV and cause HIV-infected cells to reduce production of compounds that harm brain cells. Before we detail these experiments, we first present some background information on antioxidants and HIV infection, followed by a brief history of DMF's application and recent therapeutic developments with this compound.

Antioxidants

Cells make a compound called GSH (glutathione) from the amino acids cysteine and glutamine. Then, using minerals such as selenium and zinc, they make GSH-containing enzymes. The purpose of these enzymes is to protect cells from the harmful effects of highly reactive molecules. Many such molecules are produced in the everyday activities that cells undergo.

GSH is particularly important in protecting key organs such as the liver and kidneys when faced with toxicity from excess acetaminophen (Tylenol). A liquid formulation of N-acetyl-cysteine (NAC) is licensed for the treatment of acetaminophen toxicity (cysteine is converted into GSH) in Canada and other high-income countries.

Antioxidants and HIV

Since the mid-to-late 1980s, some researchers have theorized that antioxidants—substances that protect the body from the harmful effects of highly reactive molecules—may play a role in protecting the body from some of the effects of HIV infection. Researchers found that HIV-positive people have less-than-normal levels of GSH in many tissues and fluids such as blood, the lungs and many different types of the immune system's cells, including CD4+, CD8+, natural killer and monocytes/macrophages. In general, the greater the degree of HIV-related immune deficiency, the lower the concentration of GSH.

Clinical trials

In the early 1990s, researchers at Stanford University in California conducted an eight-week randomized, placebo-controlled study of NAC in HIV-positive people. The dose of NAC used was about 4,400 mg daily. After the initial eight weeks, all participants were offered NAC for six months. Researchers collected data on the survival of participants for several years after they stopped using NAC. They found that this supplement significantly increased GSH levels within CD4+ cells. However, NAC did not significantly raise CD4+ cell counts. The data also suggested that people who used NAC were twice as likely to survive over the next two years compared to people who did not ever use NAC. At the time of the study, powerful anti-HIV drugs such as protease inhibitors were not available and most participants used AZT (zidovudine, Retrovir) with or without another nuke (nucleoside analogue). Due to the study design, firm conclusions about the effect of NAC on survival cannot be drawn and it is important to note that a large proportion of NAC users did eventually die. However, the trial did heighten interest in the use of antioxidants.

Researchers in Montreal also tested whey protein concentrates, which are rich in cysteine, in HIV-positive volunteers and found that they improved weight. In the time before ART was available, a sustained increase in weight was unusual in HIV-positive people.

Researchers in Toronto and Ottawa led a randomized, placebo-controlled study of mixed carotinoid supplementation in HIV-positive people who were also taking ART. Mixed carotinoids are often responsible for the colour of pink, red, orange and yellow vegetables and fruit and can function as antioxidants. An example of a carotinoid is beta-carotene; this particular

carotinoid can be converted into vitamin A by the body. Mixed carotinoids contain the full range of carotinoids, not just beta-carotene. Researchers in this study found that participants who received the supplement of carotinoids survived longer than people who received placebo.

These and other studies suggest that some antioxidants and foods rich in the amino acid cysteine seem to have beneficial effects in people with HIV infection.

The Canadian HIV Trials Network is sponsoring a trial of micronutrients and antioxidants in people with HIV infection. It is still recruiting people. To find out more about this study, visit this link:

http://www.hivnet.ubc.ca/clinical-studies/canadian-hiv-trials-database/ctn-238/

Psoriasis

In the late 1950s, researchers in Germany found that compounds containing chemicals related to fumaric acid (mostly dimethyl fumarate, or DMF) were useful for the treatment of psoriasis. However, it was only decades later, in the late 1980s, that clinical trials were conducted to prove this beneficial effect. Subsequently, regulatory authorities in Germany approved a tablet formulation containing DMF and other compounds, sold as Fumaderm, for the treatment of psoriasis. Fumaderm has not been approved by regulatory authorities in Canada, the U.K., U.S. and many other high-income countries.

Now the Biogen Idec biotechnology company, whose headquarters are in the U.S., has completed two large Phase III trials of DMF (code named BG-12) for the treatment of multiple sclerosis (MS). Both trials, code-named Define and Confirm, found that BG-12 at a dose of 250 mg twice daily was effective at significantly preventing relapse of MS; and in Define, the drug significantly prevented worsening disability in some participants. The side effects were mainly diarrhea and flushing of the skin. German researchers who have used DMF for treating patients with psoriasis have stated that the drug's side effects are lessened after the first month of use.

Based on the promising results from Define and Confirm, Biogen Idec plans to seek regulatory approval of BG-12 in at least the U.S. in 2012.

Dimethyl fumarate (DMF) and HIV

Researchers at the University of Pennsylvania have performed extensive laboratory experiments with HIV and a group of the immune system's cells called macrophages. As explained earlier in this issue of *TreatmentUpdate*, macrophages play an important role in helping HIV spread throughout the body, including to the brain. Moreover, macrophages likely play a critical role in HIV-related neurocognitive impairment.

The Philadelphia researchers found that DMF had the following impact:

- HIV-infected macrophages produced fewer chemical signals that could harm brain cells.
- It restored the ability of HIV-infected macrophages to produce their own antioxidants.
- It reduced production of HIV.
- It had an anti-inflammatory effect.

In part, DMF exerts its protective effect by activating genes within macrophages that carry instructions for making GSH.

The research team speculated that perhaps DMF treatment might also have suppressed the ability of macrophages to display co-receptors such as CXCR4 and CCR5. HIV uses one or sometimes both of these receptors, together with another receptor called CD4, to gain entry to and infect cells. Proof of this will require further experimentation.

Based on their results, the Philadelphia scientists propose that DMF (or BG-12), when used together with combination anti-HIV therapy, may protect brain cells and macrophages from the harmful effects of HIV and its proteins. DMF also has potential to help reduce the excess immune activation seen in HIV infection. This excess activation may play a role in some of the co-morbidities seen in HIV infection, such as cardiovascular disease, diabetes and bone thinning.

Clinical trials to explore these ideas in HIV-positive people, at least in North America, may have to wait until regulatory agencies such as the U.S. Food and Drug Administration and Health Canada approve DMF for the treatment of MS. The good news is that data collected over the past 14 years from patients in Germany suggest that DMF generally has not caused serious or permanent side effects.

REFERENCES:

1. Eck HP, Gmünder H, Hartmann M, et al. Low concentrations of acid-soluble thiol (cysteine) in the blood plasma of HIV-1-infected patients. *Biological Chemistry Hoppe-Seyler*. 1989 Feb;370(2):101-8.

2. Buhl R, Jaffe HA, Holroyd KJ, et al. Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. *Lancet*. 1989 Dec 2;2(8675):1294-8.

3. Roederer M, Staal FJ, Osada H, et al. CD4 and CD8 T cells with high intracellular glutathione levels are selectively lost as the HIV infection progresses. *International Immunology*. 1991 Sep;3(9):933-7.

4. Roederer M, Raju PA, Staal FJ, et al. Cytokine-stimulated human immunodeficiency virus replication is inhibited by N-acetyl-L-cysteine. *Proceedings of the National Academy of Sciences USA*. 1990 Jun;87(12):4884-8.

5. Kalebic T, Kinter A, Poli G, et al. Suppression of human immunodeficiency virus expression in chronically infected monocytic cells by glutathione, glutathione ester, and N-acetylcysteine. *Proceedings of the National Academy of Sciences USA*. 1991 Feb 1;88(3):986-90.

6. Bounous G, Baruchel S, Falutz J, et al. Whey proteins as a food supplement in HIV-seropositive individuals. *Clinical and Investigative Medicine*. 1993 Jun;16(3):204-9.

7. Fuchs J, Schöfer H, Milbradt R, et al. Studies on lipoate effects on blood redox state in human immunodeficiency virus infected patients. *Arzneimittel-Forschung*. 1993 Dec;43(12): 1359-62.

8. Walmsley SL, Winn LM, Harrison ML, et al. Oxidative stress and thiol depletion in plasma and peripheral blood lymphocytes from HIV-infected patients: toxicological and pathological implications. *AIDS*. 1997 Nov 15;11(14): 1689-97.

9. Herzenberg LA, De Rosa SC, Dubs JG, et al. Glutathione deficiency is associated with impaired survival in HIV disease. *Proceedings of the National Academy of Sciences USA*. 1997 Mar 4;94(5):1967-72.

10. Austin J, Singhal N, Voigt R, et al. A community randomized controlled clinical trial of mixed carotenoids and micronutrient supplementation of patients with the acquired immunodeficiency syndrome. *European Journal of Clinical Nutrition* 2006 Nov;60(11):1266-76.

11. Lehmann JC, Listopad JJ, Rentzsch CU, et al. Dimethylfumarate induces immunosuppression via glutathione depletion and subsequent induction of heme oxygenase 1. *Journal of Investigative Dermatology*. 2007 Apr; 127(4):835-45.

12. Killestein J, Rudick RA, Polman CH. Oral treatment for multiple sclerosis. *Lancet Neurology*. 2011 Nov;10(11): 1026-34.

13. Mullard A. Success of immunomodulators in MS shifts discovery focus to neuroprotection. *Nature Reviews Drug Discovery*. 2011 Dec 1;10(12):885-7.

14. Cross SA, Cook DR, Chi AW, et al. Dimethyl Fumarate, an immune modulator and inducer of the antioxidant response, suppresses HIV replication and macrophage-mediated neurotoxicity: a novel candidate for HIV neuroprotection. *Journal of Immunology*. 2011 Nov 15; 187(10):5015-25.

15. Seu L, Burt TD, Witte JS, et al. Variations in the heme oxygenase-1 microsatellite polymorphism are associated with plasma CD14 and viral load in HIV-infected African-Americans. *Genes and Immunity*. 2012; *in press*.

Disclaimer

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

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