New Study on Brain Disorders and HIV: What Does it Mean?

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Though neurological disorders are common in people with HIV—one in four has a disorder—and are associated with an increased risk of death, a history of an AIDS diagnosis appears to be the most important factor associated with these problems, a new study reports. What's more, HIV-positive people can potentially avoid these problems by starting antiretroviral (ARV) treatment before their CD4 counts are depleted. These data, which also show signs of improvement with respect to certain neurological disorders in recent years, were published online August 24 in the journal *Neurology*.

Modern ARV therapy has worked wonders in terms of reducing illness and death in people with HIV, and this includes many neurological disorders. Rates of some of the most common and debilitating neurological disorders from early in the epidemic—including HIV-associated dementia, progressive multifocal leukoencephalopathy (PML) and distal sensory polyneuropathy (DSP)—have all diminished considerably since the late 1980s and early 1990s.

Experts cite a number of reasons for the decreased rates of many neurological disorders in recent years: Prolonged reduction of HIV replication and consistent gains in CD4 cell counts potentially slow HIV damage to the brain and nerve cells and help prevent central nervous system disease. In addition, today's ARVs are less likely to cause neurological problems than their predecessors.

While rates of many disorders have gone down in the years since the introduction of potent combination ARVs in the late 1990s, a number of recent studies suggest that such disorders are still occurring at much higher rates among people with HIV compared with their HIV-negative counterparts, as have deaths from neurological disorders.

The top neurology researchers working on HIV have hypothesized that the continued elevation in neurological disorders in people with HIV is due in large measure to two factors: waiting too long to start ARV therapy and the inability of many ARVs to fully penetrate into the central nervous system (CNS) and the brain.

The studies that have been reported so far, however, have differed widely in terms of the people being studied, the methods for assessing and diagnosing neurological disorders and the specific disorders that were captured.

To better assess the ongoing risk of neurological disorders in the modern ARV era, Christopher Power, MD, and his colleagues from the University of Alberta in Edmonton, Alberta, Canada, studied the medical records of 1,651 people with HIV who were in active care in Southern Alberta between 1998 and 2008.

Characteristics of the People in the Study

Over the course of the study, 404 of the participants (roughly 25 percent) were diagnosed with a neurological disorder, while 1,247 were not. The two groups were similar in some regards. The average age in both groups was 33, roughly 80 percent were male, and about 67 percent were white. There were more AIDS-related deaths in the group diagnosed with a neurological disorder, however, than those without a neurological disorder. Likewise, CD4s at study entry and lowest-ever CD4 counts (CD4 nadir) were much lower in those with a neurological disorder. Information about the percentage of people on ARVs and the types of ARVs used was not reported.

Over the course of the study, the most common neurological disorders, in order of prevalence, were DSP, seizure disorders, HIV-associated neurocognitive disorders (HAND), severe headaches and migraines, mononeuropathy, toxoplasmosis, minor neurocognitive disorder (MND), myopathy, strokes and tremors. About half of those with a neurological disorder had at least one other unrelated neurological disorder.

What the Study Showed

As with most other studies, Power and his colleagues found that CD4 count and a previous AIDS diagnosis were highly associated with most of the neurological disorders. Viral load, however, was not. People with an AIDS diagnoses were twice as likely to develop a neurological disorder as people without an AIDS diagnosis. Moreover, the likelihood for developing DSP, a movement disorder, a seizure disorder or central nervous system opportunistic infections (CNS-OIs) were all increased in people who weren't diagnosed with HIV until after their CD4 count fell below 200.

Over time, however, the likelihood of developing a neurological disorder fell by more than 50 percent. In 1998, 12 percent of those enrolled in the study developed a new neurological disorder, compared with just 5.7 percent in 2007. This reduction was particularly true for HAND and DSP. However, the rate of new diagnosis of seizures, mononeuropathy and CNS-OIs did not diminish over time.

The authors note that the drop in DSP diagnoses could be largely due to a corresponding drop in the use of drugs known to cause DSP, such as Retrovir (zidovudine) and Zerit (stavudine).

People with a neurological disorder were about twice as likely to die of any cause than people without a neurological disorder, even after accounting for CD4 count and other factors. Much of the increased risk was seen in those diagnosed with HAND and CNS-OIs. It should be noted, however, that the most common causes of death—including malignancies, cardiovascular disease, liver disease and suicide—are not typically caused by neurological disorders. Other factors

associated with premature death included the usual suspects: a drop in CD4 count and an increase in viral load.

Putting the Findings in Context

The authors conclude that while effective and potent ARVs have significantly diminished neurological problems, people with HIV are still at increased risk for many of these disorders.

Given that low CD4 counts and the diagnosis of AIDS-defining diseases were so strongly associated with neurological disorders and deaths, health care providers and community health workers must remain focused on helping people access care before their CD4s drop to dangerous levels (200 and below). One reassuring finding was that there was no difference in the prevalence of neurological disorders between those with very high CD4 levels (over 500) and those with moderately high CD4 levels (200 to 500).

The research community has only recently begun looking at the possibility that people with HIV are experiencing diseases and conditions typically associated with old age at an accelerated rate. Indeed, the average age of those in the study (33 years old) was young, but the authors state that: "The occurrence of neurocognitive impairment herein was comparable to the general population who were 20 years older than the current study group."

Finally, though it is alarming that one quarter of those in the study had some form of neurological disorder, this figure is far lower than other studies, which found that up to 69 percent of those studied had some degree of HAND. The authors conclude that the difference between their study and other studies is that people were only assessed for neurological problems if they had been referred to a neurologist. This means that those with minor symptoms may have been missed.

On a positive note, researchers in the United States and elsewhere are currently engaged in studies to look at whether ARV combinations can be maximized to include those drugs most likely to make it into the brain—and therefore to possibly prevent or reverse some cognitive problems. Moreover, as increasing evidence emerges about the persistence of neurological disorders despite suppression of HIV, pressure to develop ARVs with better brain penetration will grow.

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