# Discordant HIV Levels in the Brain and Blood Are More Common Than Expected

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Up to 10 percent of people on antiretroviral (ARV) therapy have active HIV replication in the brain and spinal fluid despite having undetectable HIV levels in the blood, according to a study published online November 4 in *The Journal of Infectious Diseases*. This could explain why low-level inflammation and cognitive decline persist in people being successfully treated with HIV drugs. It may also have implications for treatment recommendations and the ongoing study of different treatment strategies.

A number of studies in recent years have documented two key findings about HIV in the brains of people taking ARVs. First, that HIV reproduction in the brain and central spinal fluid (CSF) is sometimes different from what occurs in the blood; and second, that immune inflammation and cognitive decline are frequently detected in people who otherwise have very good control of their HIV on ARV therapy.

Another key factor that some researchers believe can significantly affect HIV's activity in the brain and CSF is the ability of individual drugs to cross the blood-brain barrier. Some ARVs cross easily, while others have poor penetration into these compartments.

In an effort to explore the interaction of these three factors—differences in viral replication in blood and brain, signs of immune inflammation, and the brain penetration potential of a person's regimen—Arvid Edén, MD, from the Sahlgrenska Academy at the University of Gothenburg, in Sweden, and his colleagues examined blood and CSF samples from 69 HIV-positive people taking ARV therapy.

The blood and brain samples were taken between 2002 and 2010. To be included in the study, in which CSF levels were obtained by a lumbar puncture, a person needed to have been on ARVs for at least six months and to have had undetectable HIV levels in the blood for at least three months. All of the people were taking either Sustiva (efavirenz), Norvir (ritonavir)-boosted Reyataz (atazanavir) or Kaletra (ritonavir plus lopinavir). These drugs were combined with either Viread (tenofovir), Ziagen (abacavir) or Retrovir (zidovudine), plus either Emtriva (emtricitabine) or Epivir (lamivudine).

Edén and his colleagues found that 10 percent of the participants had detectable HIV levels in CSF, many more than they expected. When the team compared the characteristics of those with measurable virus in CSF with those who did not have measurable virus in CSF, they found that people with measurable CSF levels were more likely to have been on ARVs longer, to have had periodic increases in HIV in the blood (blips), and to have taken a treatment interruption.

Edén's team also found that people with measurable CSF HIV levels were more likely to have high levels of brain inflammation, as determined by measuring neopterin levels.

The makeup of the ARV regimen was not statistically meaningful in regards to discordant viral load responses in the blood and brain. However, there was a trend toward an increased risk of HIV replication in the brains of those who took either Viread or Ziagen compared with those who took Retrovir.

Interestingly, a new method of calculating the likelihood of good ARV control of HIV in the brain, called the central nervous system penetration effectiveness (CPE) rank, was not a good predictor of neither discordant blood and brain HIV levels nor the likelihood of brain inflammation.

Though the brain penetration of the regimens did not significantly affect the likelihood of having discordant HIV levels in the blood and brain, other studies have found that it does. In an accompanying editorial, David Clifford, MD, from Washington University in St. Louis, said this issue needs critical attention, as the most commonly used ARVs today often have only minimal to moderate brain penetration. "If these findings are replicated by others, suggesting 10 percent failure rate of current therapy in the critical CNS compartment, this would be a serious shortcoming for present therapy," he warned.

"This topic also touches on the interaction of HIV with aging, particularly as it affects the brain and cognitive status," he continued, noting that cognitive decline from HIV replication and activation could hasten or worsen age-related cognitive problems.

"If control of virus in the brain becomes increasingly difficult to maintain over time," he concluded, "this implies that increasing neurologic symptoms associated with the virus might augment the cognitive decline of aging, resulting in much more serious late-life neurological issues for HIV-infected patients."

Ultimately, both doctors, along with Edén's colleagues, emphasize that this is a very important area of exploration that demands larger studies going forward.

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