HIV Reservoir in the Brain Doesn't Respond to Treatment Intensification

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Adding a new antiretroviral (ARV) drug with the ability to penetrate into the brain to an existing regimen doesn't reduce residual HIV in the brain or brain inflammation in people who have good suppression of HIV elsewhere in the body, according to a study published in the December 15 issue of the *Journal of Acquired Immune Deficiency Syndromes*. These data suggest that the brain does serve as a protected reservoir of HIV infected cells, and that simply adding ARVs that penetrate into the central nervous system (CNS) may not shut down residual virus or reduce brain cell inflammation.

In 1996, researchers dramatically pronounced that they believed they could eradicate HIV in a person's body within two to three years with combination ARV therapy including protease inhibitors (PIs). That same year, the first batch of PIs was approved.

Within a few years, however, this optimistic eradication hypothesis was laid to rest because researchers discovered that reservoirs of virus go unscathed by ARV therapy. And in recent years, these reservoirs have been tied to ongoing cellular inflammation, responsible for all kinds of harmful effects, including cardiovascular disease, cognitive problems and certain cancers.

This has led to the question of whether the virus is actively replicating within the reservoir or if the cells are simply releasing virus that is trapped within the cells. Answering this question is important. If ongoing replication is occurring, then simply adding more potent drugs could shut it down. If there is no active replication, and infected cells are simply releasing intact virus, then the only way to get rid of it will be to purge these infected cells entirely.

One of the suspected reservoirs is the CNS, where virus has been found despite undetectable levels in the blood. To better understand what is happening in the brain, Aylin Yilmaz, MD, PhD, from the University of Gothenburg in Sweden, and his colleagues tested the strategy of treatment intensification in 20 people living with HIV who had undetectable levels of HIV in the blood, but detectable levels in their brains.

The study involved adding one of two types of intensified ARV drugs for six weeks, and then switching over to the other type for an additional six weeks. One type of ARV, Fuzeon (enfuvirtide), doesn't penetrate well into the brain. It's chemical structure is too large. The other type of ARV—in this case either Selzentry (maraviroc) or Kaletra (lopinavir plus ritonavir)—does penetrate well into

the brain.

The research team's theory was that if active replication were occurring in the brain, then intensifying treatment would shut it down. If intensification didn't work, then the experiment would prove that active reproduction was not the cause of residual virus.

Yilmaz's team found that the latter was true. Intensifying treatment did not reduce the level of HIV present in the brain, nor did it reduce the level of cellular inflammation. The use of a drug for six weeks that did not cross over into the brain was necessary to ensure that whatever effect they found was not a result of virus reduction in other parts of the body, but what was actually occurring only in the CNS.

The authors argue that their results have two implications. First, the data indicate that the tiny bit of detectable HIV in the brain is not due to active reproduction, and that new strategies will be needed to get rid of it. Further, the data suggest that a trend toward seeking and using ARV regimens with good brain penetration might not have the intended effect of lowering HIV and reducing cellular inflammation there.
