Brain-Penetrating ARVs Don’t Improve HIV Neuro Problems, Says Ontario Study

July 20, 2011 By Tim Horn

Drugs known to penetrate the central nervous system do not appear to offer much in the way of added protection against neuropsychological (NP) problems associated with HIV infection, according to a new Canadian study reported Monday, July 18, at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Rome.

When the researchers used one particular list categorizing different drugs’ central nervous system (CNS) penetration effectiveness, or CPE, they did show a positive effect on one NP outcome: working memory, or the ability of people to perceive the space around them and to remember and work with this information. However, they also reported a negative effect on another NP outcome: motor functioning, or the ability to perform complex muscle-and-nerve acts needed to produce seamless movements.

As explained by Sean Rourke, PhD, on the University Toronto and Ontario HIV Treatment Network, the widespread use of combination antiretroviral (ARV) therapy has led to a significant drop in the number of new cases of AIDS-related dementia, but the prevalence of two milder neurological disorders—asymptomatic neurocognitive impairment (ANI) and HIV-associated mild neurocognitive disorder (MND)—remains high.

Though mild, they can still affect people’s lives. According to Rourke, these neuropsychological deficits can affect job functioning and decrease work performance, reduce the ability to carry out complex tasks, and reduce medication adherence. They may also increase mortality rates.

To minimize the effects of HIV on the brain, researchers have turned to the potential benefits of ARV therapy which, according to another study reported in the same session at IAS 2011, seems to have reduced the prevalence of these mild neurological declines—often characterized together as HIV-associated neurocognitve disorder (HAND)—at least in an Italian cohort. But a central question remains: Should HIV treatment regimens contain ARVs that penetrate the CNS to prevent or reverse HAND?

Not all ARVs are created equal with respect to CNS penetration. One research team, under the direction of Scott Letendre, MD, of the University of California at San Diego Medical Center, has

produced two CPE tables—one based on criteria established in 2006 and another based on criteria established in 2010—listing the drugs most likely to penetrate the CNS. Generally speaking, Retrovir (zidovudine), Viramune (nevirapine) and Crixivan (indinavir) are the best CNS penetrators, whereas Viread (tenofovir), Aptivus (tipranavir) and Fuzeon (enfuvirtide) are unlikely to penetrate the CNS.

Whether drugs that penetrate the CNS also affect NP functioning, however, isn't clear. While Rourke pointed to studies showing that these ARVs do decrease viral load in the CNS, the relationship between the drugs' effectiveness at penetrating the CNS and their influence on NP outcomes hasn't been determined. In turn, Rourke's group set out to assess the association of CNS penetration of ARV regimens and NP function in a people living with HIV in Ontario.

The researchers evaluated 529 the 5,000 people living with HIV participating in the Ontario HIV Treatment Network Cohort Study (OCS). All participants in the current study had undergone NP testing as part of annual data collection, had detailed medical information available and were on a standardized combination of ARVs.

Those included in the analysis were, on average, 49 years old. Roughly 83 percent were male, 13 percent had used illicit substances six months before enrolling and more than 11 percent had symptoms of depression.

Rourke's group analyzed testing scores—which included a battery of tests—in the context of the CPE scores devised by Letendre's group. The 2006 CPE scoring system classifies ARVs with little or no CNS concentration as "0," drugs with some degree of CNS penetration as "0.5" and ARVs with adequate penetration as "1.0." The 2010 CPE scoring system ranges drugs on a scale of 1 to 4.

About 47 percent of those in the Ontario study were on CNS-penetrating regimen using the 2006 scoring with a cutoff of 1.5, whereas 60 percent were on a CNS-penetrating regimen using the 2010 scoring with a cutoff of 7.

Across the board—at least among those who completed two rounds of NP testing—neuropsychological impairments were just as likely to be documented among those using effective ARV therapy compared with those not on treatment. Rates of NP impairment exceeded 50 percent in both groups. Interestingly, the rate of NP impairment was highest—63 percent—among those on sub-standard ARV treatment.

Rates of NP deficiency were also similar among those using regimens with a high CPE score compared with a low CPE score. Fifty-six percent of patients in both groups had evidence of NP impairment during testing while on treatment, though it should be noted that those who received regimens with a high CPE score were more likely to have NP impairment before beginning treatment.

Rourke also noted that one CPE scoring table failed to perform better than the other in terms of predicting ARVs that would work best in preventing or reversing NP impairment. However, the scoring system developed in 2006 did help predict important changes in two of three major NP

outcomes: working memory efficiency and motor efficiency. Using a regimen with a high 2006 CPE score improved working memory efficiency, which means study volunteers experienced better visual learning and memory while using a CNS-penetrating regimen. However, they were also more likely to have decreased motor efficiency, meaning that their nervous system experienced delays signaling muscles to complete tasks that require thinking.

As daunting as these data seem, Rourke noted in his concluding remarks that NP impairment is a “downstream” problem—it can occur many years into HIV infection and its occurrence may not necessarily reflect the CNS effects of the ARVs being used at the time. A lot more information, including factors such as when treatment is started and how long CNS-penetrating drugs are used, along with the effects of other diseases like hepatitis C virus infection, will need to be gathered to better understand whether ARV treatment has the ability to minimize the likelihood—and to treat—neuropsychological problems.

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