Antinausea Drug Stops HIV Too

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The antinausea drug Emend (aprepitant) doesn't just help settle the stomach—it also has fairly potent anti-HIV activity when combined with protease inhibitors (PIs). This finding was published in the November 27 issue of *AIDS*.

Although the current antiretroviral (ARV) drugs exhibit remarkable activity against HIV, typically reducing HIV replication to the minutest levels, they do not shut down HIV completely. When the drugs are stopped, the virus nearly always comes roaring back to life within days.

Researchers have determined that there are sanctuary sites, such as the brain, genitals and other compartments in the gut, which ARVs fail to reach fully. Not only do these sanctuary sites offer HIV a place to hide out from the drugs and the immune system, but they also serve as a source of ongoing immune inflammation that can lead to cardiovascular disease, cancer and cognitive disorders.

Not long ago, scientists discovered that a class of drugs used to fight nausea might also have HIV-fighting potential. These drugs, called neurokinin-1 receptor (NK1R) antagonists, reduce inflammation by blocking substance P, a neurotransmitter, from binding with neurokinin-1 receptors in the brain. Not only does blocking substance P reduce nausea, it also reduces the ability of HIV to infect immune cells. It accomplishes this by causing the cells to display fewer coreceptors on their surface. When fewer coreceptors, such as CCR5 or CXCR4, are present, HIV has a more difficult time infecting the cell.

Given that cognitive disorders and brain inflammation are sometimes quite high despite effective ARV therapy, it is hoped that the NK1R antagonist Emend might exert particular antiviral and anti-inflammatory pressure against HIV in the brain.

To take these findings one step further, Mark Manak, PhD, from SeraCare Life Sciences Inc., in Gaithersburg, Maryland, and his colleagues, tested the anti-HIV activity of a handful of NK1R antagonists against common strains of HIV in cell cultures. They found that Emend, which is approved in the United States for patients with chemotherapy-associated nausea, had the most antiviral activity.

Manak's team next challenged the infected cells with Emend, combined with a number of ARV drugs. They found that when Emend was combined with Invirase (saquinavir) and Norvir (ritonavir) at the same time, it boosted their HIV-fighting ability by more than five times. This effect was not

seen with any other class of drug, leading the team to conclude that Emend must be combined with PIs to achieve its HIV-fighting potential. They also concluded that Emend's antiviral properties were likely achieved by several mechanisms, only one of which was blocking substance P.

While Emend has few side effects when given at the dose used to treat nausea, the authors stated that higher doses will be needed in HIV. Also, the drug can interact with a number of other drugs. In fact, it can significantly boost the blood levels of Norvir.

The authors concluded by saying that Emend's safety, in combination with HIV medication, must now be tested in humans, and they revealed that a Phase Ib clinical trial is currently under way to do exactly that.

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