New Clue in Cause of PI Adverse Effect, HIV Self-Testing Ineffective, Hepatitis B Drug Warning

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By AIDS Reader [1]

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New Clue for Cause of Protease Inhibitor-Related Adverse Effect

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Physicians have been puzzled by the cause of adverse effects seen with PIs and other AIDS drugs, including lipodystrophy, raised cholesterol levels, high blood pressure, and increased risk of diabetes. These adverse effects are found worldwide in tens of thousands of patients with AIDS, said Dr Charles Flexner of Johns Hopkins University School of Medicine, Baltimore, who was not involved in the study.

In a study conducted by researchers from Purdue University, West Lafayette, Ind, and the University of California, Los Angeles, in which mouse and human cells were exposed to a PI, investigators found accumulations of a very clumpy protein called “prelamin A.” The PI had blocked the action of the protein ZMPSTE24, which converts prelamin A into a useful form. Cells with lower ZMPSTE24 were preferentially affected by PI therapy. Blocking this protein could explain some of the metabolic adverse effects seen with PIs, said study coauthor Christine Hrycyna. The same protein accumulation is seen in the cells of patients with early aging syndromes, including Hutchinson-Gilford progeria syndrome, continued Hrycyna, but it is not clear how cellular metabolism is affected (Coffinier C, Hudon SE, Farber EA, et al. Proc Natl Acad Sci U S A. 2007;104:13432-13437).

In further studies, other HIV drug classes did not produce the protein accumulation, said researchers, even though these drugs can trigger similar adverse effects in patients. The researchers now want to evaluate whether PIs that do not block ZMPSTE24 could cause fewer adverse effects. [CDC HIV/Hepatitis/STD/TB Prevention News Update, Monday, August 27, 2007]

HIV Self-Tests Ineffective in High-Risk Persons

In a recent study involving 350 persons who were HIV-positive or at high risk for HIV infection, self-testing for HIV infection was found to be ineffective (Reuters. August 28, 2007).

At 2 HIV testing centers in Singapore, Dr Vernon J. Lee of Tan Tock Seng Hospital and colleagues examined the use of the Abbott Determine HIV-1/2 test among at-risk persons. Before testing, 90% of the participants said the instructions were easy to read and follow. Nonetheless, 85% failed to perform all HIV test steps correctly or were unable to perform the test at all, invalidating 56% of test results (Lee VJ, Tan SC, Earnest A, et al. User acceptability and feasibility of self-testing with HIV rapid tests. J Acquir Immune Defic Syndr. 2007;45:449-453). In addition, 12% of the participants incorrectly interpreted their test results, with 2% incorrectly believing they tested HIV-positive and 7% incorrectly believing they were HIV-negative. The investigators found that when correctly used, the test is as accurate as the manufacturer claims.

Researchers noted that “blood sampling via a capillary tube was difficult for participants.” Participants who were known to be HIV-positive achieved accurate results more often, which might reflect their “exposure to and experience with blood tests.” Among the study participants, 18% cited inconvenience and long waiting times as deterrents for HIV testing at health care centers. The team concluded that the “implementation of self-testing should be reconsidered until kit design and
downstream issues have been adequately addressed.” [CDC HIV/ Hepatitis/STD/TB Prevention News Update, Wednesday, August 29, 2007]

**FDA, Bristol-Myers Squibb Issue Warning on Hepatitis B Drug**
The FDA is warning doctors of the potential for the hepatitis B drug Baraclude (entecavir), marketed by Bristol-Myers Squibb (BMS), to lead to the development of drug-resistant HIV infection in patients coinfected with HIV and hepatitis B virus (HBV) (Reuters. August 16, 2007). The FDA also added a black box label warning, the strongest caution possible, with this message.

In its letter to doctors, BMS cautioned that patients with both hepatitis B and HIV infection should not take Baraclude unless they are taking standard antiretroviral therapy. Drug-resistant HIV might develop in a coinfected patient taking Baraclude who was not being treated for HIV, a company spokesperson said. BMS also recommends that anyone about to begin treatment with Baraclude should be tested for HIV. (To read the BMS letter, visit [http://www.fda.gov/medwatch/safety/2007/Baraclude%20DHCP_aug1607.pdf](http://www.fda.gov/medwatch/safety/2007/Baraclude%20DHCP_aug1607.pdf).)

Worldwide, about 2 million people are infected with HBV, according to the World Health Organization. The CDC reports that about 1.25 million Americans are chronically infected with HBV, although the number of new infections is on the decline. [CDC HIV/Hepatitis/STD/TB Prevention News Update, Tuesday, August 21, 2007]

**HIV’s Double Hit on Brain Cells**
New research suggests that the HIV protein gp120 not only can kill off mature brain cells but also may prevent the production of replacement cells (BBC News. August 15, 2007). Antiretroviral therapy has proved successful in reducing HIV RNA levels, thus helping reduce HIV-related dementia in patients, but it is hard for current anti-retroviral drugs to reach the brain. As persons who are being treated live longer, neurological conditions are becoming more common.

In a recent mouse study, investigators from the University of California, San Diego, showed that the HIV protein gp120 slows the production of new brain cells in the hippocampus, a region key to learning and memory. Normally, these newer cells would become integrated into existing brain circuits and, it is thought, contribute to memory and learning.

The researchers knew that the gp120 protein could disrupt the internal chemistry of brain cells, killing them, but these results show that the same gp120-related chemical disruption in brain cells blocks the regenerative process. “It’s a double hit to the brain. The HIV protein both causes brain injury and prevents its repair,” said Dr Marcus Kaul, a study coauthor. “This indicates that we might eventually treat this form of dementia by either ramping up brain repair or protecting the repair mechanism,” continued Kaul (Okamoto SI, Kang YJ, Brechtel CW, et al. Cell Stem Cell. 2007;1:230-236).

“The discovery that HIV affects stem cell proliferation in the brain is bound to add to concerns that people with HIV doing well on antiretroviral therapy may nevertheless face a higher risk of dementia in years to come,” said Keith Alcorn, senior editor of the British HIV information service NAM (National AIDS Manual). “It may be that low-level infection is enough to interfere with the regeneration pathways in the way shown in this experiment.” [CDC HIV/Hepatitis/STD/TB Prevention News Update, Tuesday, August 21, 2007]

**University Team Zeroes In on HIV Vaccine Development**
Researchers conducting a genomewide analysis of HIV-positive patients whose immune systems control the virus without treatment found a portion of the genome that could account for this rare host response (Chen M. Herald-Sun. Durham, NC. July 20, 2007). The international research team, led by Bart Haynes of the Center for HIV/AIDS Vaccine Immunology (CHAVI), pooled 486 untreated HIV-positive patients to determine why they were not affected by the virus.

CHAVI, a $300 million project of the NIH, “came from a frustration in the field three years ago that progress was not being made fast enough,” said Haynes, a professor at Duke University Medical Center, Durham, NC. “CHAVI was funded to speed the work, do the business in a different way. The different way was to be open and collaborative and work to help the field. This study is an embodiment of that field,” Haynes said.

While previous research has looked at a few genes at a time, CHAVI researchers were able to view

Among the patients, CHAVI scientists found variations associated with the genome that encodes the HLA system, part of the immune system that identifies foreign material for destruction. While HIV shuts down similar genes and prevents them from recognizing the virus as invasive, HLA-C was apparently not influenced by HIV. HLA-C may be HIV’s “Achilles’ heel,” knowledge that could be key in the effort to develop an HIV vaccine, researchers said. [*CDC HIV/Hepatitis/STD/TB Prevention News Update*, Tuesday, August 28, 2007]

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