What's Up Doc: Notes for the Informed Patient

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KS May Improve with Protease Inhibitor Therapy Use of highly active antiretroviral therapy (HAART), which can decrease HIV RNA load and increase CD4 cell counts, may also improve or prevent symptoms of Kaposi's sarcoma in HIV+ people, according to a European group.

Clearance of human herpes virus 8 (HHV-8), the pathogen implicated in KS, has been reported in HIV+ patients following treatment with HAART, say Dr. Angelo De Milito of the Karolinska Institute in Stockholm, Sweden, and his colleagues in Italy.

To further investigate this, they evaluated six coinfected patients over time, four with KS and two without KS, by measuring levels of plasma HIV RNA, HHV-8 DNA, and CD4 t-cells. All of the subjects received a HAART regimen that contained a protease inhibitor. At baseline, four of the six patients had active KS.

"A specific anti-HHV-8 role for [protease inhibitors] was not consistently found, since fluctuation of HHV-8 viral load over time appeared to be independent of treatment," they report in the February issue of the Journal of Medical Virology.

However, in two of the patients with KS, Dr. De Milito's group observed a regression of lesions following the commencement of HAART. And a third KS patient developed no new lesions, which they believed was associated with indinavir treatment. The fourth patient, who had severe cutaneous KS lesions, experienced no improvements following saquinavir therapy.

Dr. De Milito's group observed decreased levels of plasma HIV RNA and increased levels of CD4 cells in the three KS patients who improved. This was not seen in the fourth patient, who was suspected of being noncompliant with therapy.

The clinicians also noted a "temporal correlation between increasing CD4+ cell numbers and falling HHV-8 DNA levels" in four subjects, which supports the "hypothesis that CD4+ lymphocytes play a role in controlling HHV-8 replication." The researchers believe that KS probably results from a "complex interaction of viral and immunological factors." Therefore, the effects of protease inhibitors on KS may be associated with decreases in HIV replication and restoration of immune function, as well as decreases in HHV-8 load.

Protease Drugs Are Reducing Overall Care Costs Despite the high costs of protease inhibitors, HIV+ people who are taking these drugs have fewer days in the hospital and lower overall healthcare costs, according to a report in the January 1st issue of the Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology.

Treatment with protease inhibitors has been associated with lower rates of opportunistic infections and increased survival, Dr. Philip Keiser of the University of Texas Southwestern Medical Center in Dallas and associates explained. "Statistical models predict that decreased complications will be

associated with decreased hospitalization costs," they added.

To investigate the relationship between protease inhibitor use and HIV-related hospital usage and costs, Dr. Keiser's group evaluated patients at the Dallas Veteran Affairs Medical Center, a facility that provides comprehensive care to patients with HIV infection, between January 1995 and July 1997. Specifically, they examined the mean number of days in the hospital and outpatients visits, along with costs of these services.

Dr. Keiser's group observed a "decrease in hospital use and overall costs by HIV-infected patients that was associated with increased [protease inhibitor] usage." The number of hospital admission days markedly decreased, and although smaller, there was also a decrease in the number of outpatient visits. There were slight increases in outpatient treatment costs, which were attributed to the cost acquiring protease inhibitor drugs.

They found that the reductions in total HIV costs were primarily due to decreases in hospital stays. During the time interval examined, Dr. Keiser's group reports that the monthly costs of HIV care per patient declined from an average of US$1905 at the beginning to $1122 at the end.

In addition, Dr. Keiser's group noted an "inverse relation between [protease inhibitor] use and total HIV costsbut no relation between nucleoside use, stage of disease or financial class." Although they point out that these findings may not be generalizable to all HIV healthcare facilities, they believe that further investigation of the impact of protease inhibitors on HIV costs is warranted.

Scientists Highlight Adherence Concerns at Conference Stepping up the drumbeat of concern about the impact of problems that will be caused by non-adherence to AIDS treatment regimens, several scientists at this year's annual meeting of the American Association for the Advancement of Science took the stage to warn that wide use of drugs that suppress HIV could end up making the epidemic even worse.

Once the drugs are widely used in the community, dosing tends to get increasingly haphazard, which allows resistance to develop and makes the virus even more likely to be passed on, said Sally Blower of the University of California San Francisco. Blower said that even in carefully controlled clinical trials, some people did not take their drugs as directed, giving the virus a chance to mutate into drug-resistant forms.

"It could have beneficial effects, but it is also likely that if treatment increases, the likelihood of drug resistance increases," Blower said.

Blower and her colleagues used advanced mathematical models and data from clinical drug trials, to show the course of the AIDS epidemic. When mathematicians take this rate and apply it to what is known about how people take drugs in day-to-day life, Blower said the picture is a grim one.

"If we increase treatment rates considerably and keep a tight, tight rein on how (the drugs) are handed out, you would have a beneficial effect on 15% of new infections," she said.

In others words, 15% of new HIV infections, on average over 10 years, would be prevented. But if someone does not monitor patients very closely, Blower's model predicts a 20% increase in new infections over 10 years.

Viruses and bacteria become resistant to drugs by mutating. Each time an organism reproduces, a few mistakes creep into the genetic code. Some of these will allow the microbe to evade a drug's action. The process is slow, and if strong enough drugs are taken for a long enough period of time, the organisms will be killed before this mutation develops. But if a person takes a drug in a hit-or-miss way, or stops taking it before all the bugs are killed, the organisms that have a tendency to resist the drugs will be the ones that survive and multiply. Eventually, the resistant bugs can be passed from person to person-something doctors have seen in hospitals around the world with drug-resistant bacteria and are just starting to see with HIV.

With HIV drugs this is very likely to happen, because the drugs are difficult to take. They only work when used in a cocktail of three, four or even five different compounds, each of which often has to be taken several times a day and at different times of the day. Side-effects include nausea and diarrhea, which can discourage regular use.

"There is going to be drug resistance and we've got to expect that," Blower added, pointing out that antibiotic-resistant forms of tuberculosis have existed since the 1950s. Blower said the answer to the problem is not immediately apparent. "I'm not saying don't treat people," she said. "I think people need to be treated. But we need to do it in a careful manner." Her observations have been borne out with TB. The World Health Organization strategy of training health workers to watch people take their drugs-known as Directly Observed Treatment or DOTS-can work well in developed countries but may lead to more deaths in developing countries because it does not work so well against drug-resistant strains of TB.

The development of resistant viruses because of adherence problems has already arisen with common antibiotics. Years of inappropriate prescription by doctors and failure of patients to take their drugs properly has led to the emergence of so-called "superbugs" that resist virtually everything modern medicine has in its armory.

(Scenarios may be on the horizon wherein common bacterial infections treatable for two generations re-emerge as major health threats in the near future.) Optimism On Vaccine at Recent AAAS Conference Recent advances in efforts to develop an HIV vaccine are promising, Dr. David Baltimore of the California Institute of Technology said at the annual meeting of the American Association for the Advancement of Science.

AIDS researchers have long set their sights on a vaccine that can produce both a cellular response (cytolytic) and a neutralizing antibody response. Vaccine developers have uncovered promising methods of generating HIV-specific cytotoxic T lymphocytes, but stimulating a strong antibody response has proved the greater stumbling block, Dr. Baltimore noted.

"Can we ever make a strong antibody response? We're working on that problema lot of people are working on that problem," Dr. Baltimore said.

Dr. Baltimore applauded recent research published in the journal Science. A group of researchers led by Jack Nunberg at the University of Montana at Missoula, generated gp120-CD4 complexes that are transiently seen when HIV binds to t-cells. These immunogens, which expose gp120 epitopes that are normally hidden, elicited strong antibody responses in a mouse model to all but one strain of HIV

tested.
Although the research offers as many questions as answers, and clinical trials in humans are not even on the horizon, Dr. Baltimore said the results present "exciting possibilities." "It's a good idea and it's an idea that [Nunberg] put into practice and it in fact gave the kind of response that you'd like to see," Dr. Baltimore said. "They give me the sense that there are routes to [an antibody response] that have not so far been tried and that may work." This information is reprinted from We The People Living with AIDS/HIV of the Delaware Valley, Inc. Please visit their website at www.critpath.org/wtp.

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