



GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY NEWS

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INFECTION WITH DRUG-RESISTANT HIV ON THE INCREASE, GLADSTONE RESEARCHERS FIND

A rising number of San Franciscans are being infected with HIV that is already resistant to some classes of antiretroviral drugs, report researchers from the Gladstone Institute of Virology and Immunology in the July 10th issue of the *Journal of the American Medical Association*.

The finding gives researchers clues about the effectiveness of anti-HIV drugs and underscores the need for new classes of drugs. In 2000–01, 27.4 percent of newly infected patients had virus that was resistant to at least one class of drugs, said lead author Robert Grant, MD, MPH, assistant investigator at Gladstone and UCSF assistant professor of medicine.

“That means about one in four are acquiring a virus with signs of drug-resistance,” Grant said.

The study supports the use of drug resistance testing before starting antiretroviral therapy, especially in recently infected persons who were found to have high rates of drug resistance in this study.

“This is most true for patients located in places like San Francisco where anti-retroviral therapy is widely used,” he said. Widespread use of antiretroviral drugs means that the virus passed on to a newly infected person is more likely to have developed resistance to one or more of those drugs.

The researchers studied 225 newly infected and untreated patients from June 1996 to June 2001. One way of testing for drug resistance against the three classes of drugs is to study the genetic sequence of the virus. This genotypic test reveals genetic mutations that cause drug resistance.

Most alarming was the increase in transmission of virus resistant to non-nucleoside reverse transcriptase inhibitors (nnRTIs). The nnRTIs are one of three major classes of anti-HIV drugs and are an important weapon in the arsenal against HIV. In 1996–97, none of the patients were infected with nnRTI-resistant virus, according to genotypic testing. In 2000–01, 13.2 percent were infected with nnRTI-resistant virus.

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Transmission of virus resistant to protease inhibitors (PI) also increased. PIs are another class of drugs that have received much attention in the last several years for their potency. Infection with PI-resistant virus increased from 2.5 percent of patients in 1996–97 to 7.7 percent of patients in 2000–01.

“The efficacy of the two most potent classes of antiretroviral drugs is being offset by transmission of viruses resistant to them,” Grant said.

Resistance can also be determined by phenotypic testing to assess the susceptibility of the virus to drugs in vitro. Virus that grows despite the presence of a drug is resistant to that drug, which means that it is less susceptible, but not impervious, to its effects.

Using phenotypic testing, the researchers found a dramatic decrease in the transmission of virus resistant to a third class of drugs called nucleoside reverse transcriptase inhibitors (nRTIs). AZT, the first drug ever to be used in the treatment of HIV infection, is a nRTI. In 1996–97, 20 percent of patients had nRTI-resistant virus. In 2000–01, only 5.5 percent had nRTI-resistant virus.

Phenotypic testing also showed that virus resistant to two classes of drugs was rare. However, genotypic testing showed an increase in the number of people infected with this type of dual-resistant virus, from 2.5 percent of patients in 1996–97 to 13.2 percent in 2000–01.

“This is an area where our data are not yet clear,” Grant said. “The good news is that we only found one person out of more than 200 who was infected with a virus that was resistant to all three classes of drugs.”

Another finding of the study: Drug resistance can be used to predict the time it takes for the drugs to control the virus. Resistant virus takes longer to control in patients who normally take a drug regimen that includes three or more drugs, the study showed.

In patients infected with drug-resistant virus, it took an average of 12 weeks for the antiretroviral drugs to suppress the viral load to below 500 copies/ml. In patients with drug-sensitive virus, it took only 5 weeks. Some viral suppression was possible in the majority of patients in both groups.

“Checking for drug resistance by looking at the genetic makeup of the virus predicts the time to viral suppression during therapy,” Grant said. “However, viral suppression was eventually possible in the majority of patients because the transmitted resistance affected only some of the drugs in the regimen.”

Dr. Grant added, “Although the risk of transmission of HIV-1 resistant to some types of therapy is increasing, the benefits of treatment include prolonging survival for the individual, and there may be benefits for the community as well, which were not directly assessed in our study. Our findings should not dissuade doctors from offering antiretroviral treatments. Rather, our study supports combining treatment with prevention interventions.”

Co-authors also from Gladstone were Maria Warmerdam, BS, senior research associate, and Teri Liegler, PhD, staff research scientist. Co-authors from the Positive Health Program at San Francisco General Hospital Medical Center were Frederick M. Hecht, MD, UCSF professor of medicine, Lea Liu, MS, statistician, and James O. Kahn, MD, UCSF

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associate professor of medicine. Co-author Michael P. Busch, MD, PhD, is UCSF professor of laboratory medicine and director of research at the Blood Centers of the Pacific. Co-author Margaret Chesney, PhD, is co-director of the Center for AIDS Prevention Studies. Co-authors from ViroLogic—a biotech company that helped with phenotype testing and provided the assay for drug susceptibility—were Christos J. Petropoulos, PhD, vice president of research and development, and Nicholas S. Hellmann, MD, vice president for clinical research.

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The Gladstone Institute of Virology and Immunology is one of three research institutes that comprise The J. David Gladstone Institutes, a private nonprofit biomedical research institution affiliated with UCSF. The institute is named for a prominent real estate developer who died in 1971. His will created a testamentary trust that reflects his long-standing interest in medical education and research.

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