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### **Treatment Interruption Shows No Benefit in Drug-Resistant HIV Infection**

Prescribed interruptions in antiretroviral therapy—so-called “drug holidays”—may hasten disease progression in a subset of HIV-infected individuals, namely those whose treatment has been rendered significantly less effective by the development of resistance to multiple anti-HIV drugs (MDR-HIV). This was the finding in a study by researchers supported by the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH).

As reported in the August 28, 2003 issue of *The New England Journal of Medicine*, researchers found that study participants who underwent a four-month structured treatment interruption had more HIV-related complications and poorer immune response than did individuals who took antiretroviral drugs continuously throughout the study.

“Interruption of treatment has become increasingly common among HIV-infected individuals,” says NIAID Director Anthony S. Fauci, M.D. “This study helps to clarify the effects of treatment interruption in one group of patients and emphasizes how important it is for people to join clinical trials to help answer questions that will improve patient care.”

As used in this study, structured treatment interruption involves discontinuing all anti-HIV drugs for a defined period of time to allow the repopulating virus to regain susceptibility to anti-HIV drugs. Previous studies of individuals infected with MDR-HIV have shown that drug-sensitive variants of the virus re-emerge and become predominant after therapy is stopped. Treatment interruptions have also been used to give people time off from multiple medications that may be difficult to take and have toxic side effects.

“We had hoped that a structured treatment interruption would be beneficial for people experiencing treatment failure due to multidrug-resistant HIV,” says study chair Jody Lawrence, M.D., of the Department of Medicine at the University of California, San Francisco. “However, our results indicate that this strategy does not work and should be avoided by this group of HIV-infected individuals. Continuing therapy guided by HIV drug resistance testing proved to be a better approach.”

Conducted by NIAID’s Terry Bein Community Programs for Clinical Research on AIDS (CPCRA), the MDR-HIV study by Dr. Lawrence and colleagues is the first randomized clinical endpoint study to examine the effectiveness of structured treatment interruption in people with few remaining treatment options. The study enrolled 270 participants with MDR-HIV who had HIV levels of more than 5,000 copies per milliliter of plasma. About one-half of the participants were randomized to a four-month interruption of treatment before starting a new optimized anti-HIV treatment regimen. The other half

(the control group) immediately started a new optimized regimen. Physicians were given the results of two types of HIV drug-resistance tests to help them choose the optimized regimen.

After an average follow-up of nearly 12 months, 22 of the 138 individuals in the treatment-interruption group had either died or experienced disease progression, defined by the occurrence of one or more AIDS-defining conditions. In contrast, 12 of the 132 people in the control group (those who received continuous therapy throughout the study) had died or had their disease worsen. Participants in the treatment-interruption group also had persistently fewer CD4+ T-cells—crucial immune cells typically depleted during HIV disease—and showed no benefit in HIV viral load response or quality of life relative to the control group.

“This trial was conducted because community and healthcare providers were interested in finding better treatment strategies for people with treatment failure and multidrug-resistant HIV,” says Sandra Lehrman, M.D., director of the Therapeutics Research Program in NIAID’s Division of AIDS. “The strengths of the study,” she notes, “are the number of volunteers who participated in the study, the length of follow-up and the fact that there was a randomized comparison with a control group. These features allowed the researchers to study the overall impact of structured treatment interruption, including the effects on AIDS-related illnesses, HIV viral load, CD4+ T-cell count and quality of life.”

“It is important to remember,” adds Dr. Fauci, “that the failure of treatment interruption seen in this study pertains only to individuals who had drug-resistant HIV and detectable virus in their blood when they entered the study. For individuals who are being successfully treated with anti-HIV medications, other studies have shown that cycles of treatment interruptions for shorter periods may be of potential benefit to conserve medications and reduce drug-related toxicities.”

The CPCRA is a national community-based clinical trials network whose main goal is to inform healthcare providers and diverse populations of people living with HIV about the most appropriate use of HIV therapies.

NIAID is a component of the National Institutes of Health (NIH), an agency of the Department of Health and Human Services. NIAID supports basic and applied research to prevent, diagnose and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, illness from potential agents of bioterrorism, tuberculosis, malaria, autoimmune disorders, asthma and allergies.

**Reference:** J Lawrence *et al.* Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *The New England Journal of Medicine* 349(9):837-46 (2003).

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