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"Blips" in HIV Treatment Are No Cause for Alarm

Intermittent "blips" of increased viral load in the bloodstream of patients receiving antiretroviral HIV treatment are clinically insignificant statistical fluctuations, according to new studies by Howard Hughes Medical Institute researchers at The Johns Hopkins University School of Medicine.

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— **Robert F. Siliciano**

Blips have caused considerable concern among clinicians and patients, who thought that they could signal either the development of drug resistance by the virus or reduced drug efficacy. Such concerns have led to patient anxiety, costly repeat testing, or unnecessary alterations in therapy, said the researchers.

A research team led by Robert Siliciano, a Howard Hughes Medical Institute investigator at Johns Hopkins, published its findings in the February 16, 2005, issue of the *Journal of the American Medical Association*. Siliciano and his colleagues at Hopkins collaborated on the studies with researchers from the Bloomberg School of Public Health at Johns Hopkins, and the National Institute of Allergy and Infectious Diseases.

Highly active antiretroviral therapy (HAART) has been successful at suppressing HIV, enormously reducing viremia, which is a measure of the concentration of viral particles in the bloodstream, said Siliciano. "The goal of treatment now is to suppress viremia below fifty copies per milliliter,

which is the limit of detection of the best available assays,” he said. “It’s pretty clear that if viremia is consistently above that level, drug resistance—the overwhelming problem in HIV infection—will develop. It’s also pretty clear that if a patient is below fifty copies and doing well, that drug resistance doesn’t develop.”

Resistance arises because the proliferating virus evolves molecular changes that evade the suppressive effects of the drugs. “So, when a clinician suddenly sees a measurement of one hundred and twenty (copies), the clinician and the patient tend to get extremely upset about it,” he said. “But then typically, a repeat measurement would register below fifty without any intervention.

“Some clinicians have wondered whether in these cases they should change the patient’s drug regimen. This could be a problem, because usually the patient has been on what has been selected as the optimal drug combination for his particular situation. Any change will lead to use of a combination that’s less optimal, so you don’t want to change unless you need to,” he said.

One of the significant problems in detecting drug resistance is that genotyping tests are only sensitive down to levels of about 1,000 copies per milliliter. So, without the ability to test for resistance at 120 copies, clinicians are left in the dark about the significance of the blips with regard to resistance, Siliciano said.

Siliciano and his colleagues hypothesized that the small increases in viral load represented by the blips were only random statistical fluctuations in measurement of a viral load that was clinically well managed. Such fluctuations would have no clinical significance, they theorized.

They also believed that they would not detect any evidence of developing drug resistance based on their considerations of the likely source of the blips. “We had shown that there is a latent reservoir for HIV in resting CD4 immune cells that is not affected by drugs,” he said. “This stable reservoir will continue to spit out low levels of virus. This is a likely source of low levels of virus in the blood, rather than ongoing viral replication, which might lead to drug resistance.”

To confirm their hypotheses, they tested the viral levels in 10 patients every 2-3 days—a much more frequent interval than the standard practice of testing once every several months. To determine whether the blips were statistical fluctuations, they submitted the samples to two independent laboratories for testing.

They also performed ultrasensitive genetic analyses of the HIV strains in the patients to see if they could detect development of drug resistance at levels of 50 copies of the virus per milliliter of blood. And, they gathered data on the patients’ immune status due to other illness or vaccination, drug levels, and adherence to drug regimen.

“The lab results did show blips in nine of the ten patients,” said Siliciano. “But importantly, the blips were not reproducible between the two labs, not occurring in the same samples. This is consistent with the idea that the blips are simply statistical fluctuations in the assay.”

Most importantly, Siliciano noted that the ultrasensitive tests showed no evidence of the development of drug resistance among the HIV samples obtained from patients in the study. Nor did the blips show any association with drug levels, drug regimen adherence or immune status.

“So, these results indicate that an isolated blip below about two hundred copies per milliliter, with subsequent negative finding, is very unlikely to be clinically significant or to be associated with new drug resistance,” concluded Siliciano.

Since the patients studied had late-stage disease before beginning treatment, further studies will aim at confirming the findings in patients who began treatment earlier in the course of their infection, said Siliciano. Additional studies will seek to determine with greater precision the definition of a “clinically significant” level of persistent viremia.