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## Infection with Second Strain of HIV Compromises Treatment

Howard Hughes Medical Institute researchers are reporting that a patient undergoing experimental therapy for HIV infection became superinfected with a second strain of the virus, which compromised his treatment.

This finding has strong public health implications because it means that if you are already infected with HIV you can become infected with a second strain of the virus, said the study's senior author Bruce D. Walker, a Howard Hughes Medical Institute investigator at Harvard Medical School and Massachusetts General Hospital. We now know that superinfection is possible, but we still need to determine how frequently people become infected by a second virus upon exposure.

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— **Bruce D. Walker**

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Walker cautioned that the findings in no way undercut the importance of developing an effective HIV vaccine. But they do emphasize that vaccine developers are likely to be locked in a long-term duel with a continually mutating virus, he said.

Walker and colleagues from Los Alamos National Laboratory, Duke University Medical Center, University of Wisconsin and Oxford University published their article in the November 28, 2002, issue of the journal *Nature*.

The patient described in the article was enrolled in a clinical trial of an experimental antiviral drug therapy known as supervised treatment interruption, or STI. The regimen aims to boost anti-HIV immune response in patients with acute infection. During treatment, physicians periodically interrupt antiviral therapy to allow the patient's immune system to mobilize to help control the infection. Doctors carefully monitor the level of virus present in the patient's blood. Drug therapy is reinstated if levels of the virus rise significantly.

Walker and his colleagues found that even though the patient's immune system showed enhanced responses and prolonged immune control following treatment interruption, he abruptly developed an increase in the level of virus in his bloodstream.

After a prolonged period of relative control, we saw a sudden increase in viremia that necessitated reinstatement of therapy, said Walker. When we interrupted therapy again, the virus came back even quicker than in previous interruptions and rose to an even higher level. After a final interruption in antiviral treatment, in which the virus level rose and persisted, the patient chose to end the therapy.

When this patient experienced sudden increase in the level of virus in his blood, we originally thought it was probably due to the virus slowly evolving a new variant that could escape the existing immune response, said Walker. He and his colleagues pursued the cause of the sudden rebounds in viral load, recognizing that the answer might yield insight into how HIV infection persists.

Initial analysis of the patient's HIV-fighting immune cells, called CD8+ T-cells, indicated that they were not responding to infection as they should. This raised the possibility that a distinct, unrelated variant of the HIV virus had infected the patient.

The case for superinfection being the culprit was strengthened when the patient reported that he had unprotected sex with a partner before the appearance of new symptoms and coincident with the predominant rise of the new virus. Indeed, genetic analyses of blood samples from the patient confirmed the presence of a second type of HIV in the patient. Walker and his colleagues then showed that even though the patient's immune cells had some cross-reactivity with the new virus, this was not sufficient to control the secondary infection.

While the scientists' findings may influence the direction of future vaccine development strategies, Walker cautions that patients with superinfection present unique challenges. For one thing, we studied the immune system in a person who is already infected, and that amount of immunity in somebody who actually harbors HIV may be very different functionally than the immunity if you could induce it with a vaccine before the patient encountered HIV.

Importantly, our study doesn't say that a vaccine is not possible, said Walker. It says that the cross-protective immunity generated by natural infection is not that great. Particularly striking, said Walker, was that even though the two strains of virus were only about 12 percent different genetically, the difference in the surface proteins targeted by the immune cells was 50 percent. This broader immunity-related difference was what rendered the new virus unrecognizable by the existing immune response, he said.

This has important basic research implications, because investigators have long believed in a phenomenon of innocent bystander activation, in which if

you boost immunity to one viral strain, it will boost immunity to others, he said.

While there had been previous reports of superinfection of people by different strains of HIV from disparate regions of the world, the report of superinfection from two relatively close North American strains of HIV is especially cautionary, said Walker. This study emphasizes the importance of achieving broad cross-reactive immunity and incorporating immune responses to as much of the virus as possible to counteract these problems, he said.

Although the emergence of documented cases of superinfection suggests that no single HIV vaccine is likely to be completely effective for all strains of the virus, if patients develop even partially effective cellular immunity, they may end up with lower viral load than they would otherwise have and will do better, said Walker.

Walker said that strategies to develop HIV vaccines may need to take a cue from influenza, where efforts to develop new vaccines are ongoing because new strains of the virus are emerging continually. On the other hand, said Walker, we're learning an incredible amount about the immune system and how it deals with chronic viruses. I think that these kinds of insights are going to lead to effective new strategies just by having a better understanding of how the virus does its damage.