HIV Material Detected in Berlin Patient Samples Spurs Cure Questions, Confusion

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Does a recent conference presentation noting that HIV genetic material has been detected at low levels, in a minority of recent samples taken from Timothy Brown, a.k.a. “the Berlin Patient,” debunk the conclusion that he has been cured of the infection? While one scientist is publicly arguing that Brown “still has detectable HIV in his body” and goes so far to suggest that he may even have been reinfected, others—including the original study presenters—counter that these claims misrepresent the new data and are therefore misleading.

Brown is widely known as the first person with confirmed HIV infection to be cured of the virus. This occurred after he received high-dose chemotherapy to wipe out his existing immune system followed by stem cell transplants from a donor resistant to one of two forms of the virus (HIV that uses the CCR5 receptor, as opposed to the CXCR4 receptor, to gain entry into CD4 cells). His cure, first suggested as a possibility at the 15th Conference on Retroviruses and Opportunistic Infections in Boston in 2008, was ultimately declared as such in a December 2010 follow-up report published in Blood.

At various time points since undergoing the transplants, Brown has donated numerous specimens for testing, all of which have yielded encouraging results: His blood and cerebrospinal fluid (CSF) viral loads have remained undetectable; infectious virus hasn’t been detected in his bone marrow or blood-based cells (PBMCs); his HIV-specific antibody levels have trended downward; and his CD4 cell counts, both in the blood and gut, have normalized.

Whether or not Brown’s HIV has truly been eradicated (a sterilizing cure, with all traces of the virus removed from his body) or more simply controlled (a functional cure, where HIV is still present but unable to cause disease, even in the absence of antiretroviral therapy) has been difficult to determine, however, given the limits of technology to detect trace amounts of the virus in the human body.

To explore this further—and, importantly, to more fully evaluate the strengths and weaknesses of laboratory assays that will be needed in HIV eradication research—teams of researchers representing six different HIV laboratories received new blood, cell, rectal and spinal tap samples from Brown.

Preliminary results were reported by Steven Yukl, MD, on Friday, June 9, at the International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies in Sitges, Spain.

According to Yukl's presentation, most assays conducted by the six laboratory teams were HIV negative. And importantly, no infectious virus—virus capable of reproducing—was found in any of the samples tested by the six laboratories.

Neither HIV RNA nor HIV DNA was detected in PBMC samples, analyzed by four labs. At the lab where rectal samples were tested, HIV RNA was not detected. And at two labs conducting CSF tests, no viral DNA or RNA was detected. The researchers also confirmed an ongoing decline in Brown's HIV antibody levels, now below the level of detection using commercially available assays.

Two of the laboratories did, however, detect HIV RNA in some blood plasma samples, though the actual level was too low to be accurately measured by one lab and extremly low at the other lab compared with what is typically seen in people living with HIV on successful antiretroviral treatment (less than a half copy per milliliter of blood plasma versus 1 to 2 copies per milliliter of blood plasma, respectively). HIV DNA was also found in some rectal samples by one laboratory, though the level was 8 copies per 1 million cells, which is substantially lower than the 780 per 1 million cells typically seen in viral load-suppressed people living with HIV. The researchers also noted in their conference abstract that the sequences of the HIV RNA found in the plasma samples differed from those present before Brown's transplant, and from each other.

The latter set of findings prompted one researcher, Alain Lafeuillade, MD, an HIV cure researcher at the General Hospital in Toulon, France, and the University of Maryland, to publish a hiv-reservoir.net blog post dubbed "The Weird Story of the Berlin Patient" and a press release questioning Brown's cure.

"The only case of a possible sterilizing HIV cure has been challenged today at the 2012 resistance workshop: the patient, actually, could still be HIV infected!" reads the headline of Lafeuillade's blog post.

The study authors specified that it is "impossible to conclude that the subject remains HIV infected," given the low levels of virus detected and the limits of available technology to successfully identify trace amounts of HIV genetic material in the human body.

But Lafeuillade questions the study authors' conclusions, and he offered up two alternative theories. He suggests: "First, the patient has never been cured and is a chimera. Second, he has been cured but reinfected," noting that Brown's rectal tissue was negative for HIV DNA using earlier post-transplant biopsy specimens and the "fact that different circulating viral strains were isolated."

Yukl and his colleagues disagree with Lafeauillade's take on the data. "We weren't trying to say HIV was still there or he hadn't been cured," Yukl told Jon Cohen of ScienceInsider.

In fact, Yukl's team notes in the study's conclusion that assay contamination may have resulted in false-positive HIV RNA detection—which may also explain the gene sequence variations—in the plasma samples. Douglas Richman, MD, who heads the University of California, San Diego, lab participating in the study and whose team did not find any HIV RNA or DNA in the provided samples, concurs. "If you do enough cycles of PCR," he told ScienceInsider, "you can get a signal in water for pink elephants."

Tae-Wook Chun, MD, of the National Institute of Allergy and Infectious Diseases, agrees that nothing is certain. Though Chun's group did find low levels of HIV genetic materials in some of the samples provided, he told ScienceInsider, "I don't really know what to make of it, other than [Brown is] controlling viral replication or he doesn't have HIV that can restart the infection. It's a difficult case to talk about."

All researchers involved agree that additional research is necessary, not only to shed further light on the specifics of Brown's case, but also to better define the laboratory markers that will be needed in the hunt for both sterilizing and functional cures.

"[Brown has] been off ARVs for five years," Richman told ScienceInsider. "That trumps all these assays."

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