A 2nd Man's HIV Is in Long-Term Remission, but Is He Cured?

Timothy Brown may have company after a man's virus went into remission following an HIV-resistant stem cell transplant to treat his cancer.

March 5, 2019 By Benjamin Ryan

Timothy Ray Brown, aka "the Berlin Patient," may now have company as researchers report that a second HIV-positive man has no signs of the virus following successful treatment for life-threatening cancer with a stem cell transplant of immune cells that are naturally resistant to the virus. At this time, researchers have categorized this second man, a British individual dubbed "the London Patient," as in a state of viral remission.

If scientists are to officially categorize him as cured, the British man will need more follow-up to ensure that his virus does not rebound—thus far, he has gone 18 months without antiretroviral (ARV) treatment with no such resurgence of HIV.

In 2013, excitement shot around the globe when researchers suggested a baby in Mississippi had been functionally cured of HIV after clinicians started her on an atypically aggressive ARV regimen soon after birth. While an initial case report found no evidence of replicating virus in the child after she spent months off ARVs, she ultimately experienced a viral rebound 27 months after she was taken off HIV treatment.

In the years since that particular disappointment, researchers have become more measured about the language they use when referring to outcomes in the effort to cure HIV. Many investigators in the field prefer terms such as "viral remission" or "posttreatment control of HIV" as the ultimate goal of such research. Familiar from cancer treatment, the term "remission" acknowledges at least the outside possibility of a return of the virus.

Scientists, however, are so certain that Brown's virus is gone that they have asserted he is indeed cured of HIV.

Both Brown and the London Patient received stem cell transplants with immune cells from donors drawn from an international registry who lacked the gene that expresses the CCR5 coreceptor on the surface of CD4 cells. Most HIV attaches to that coreceptor in order to begin the process of infecting cells. (Such HIV is known as CCR5-tropic virus to distinguish it from CXCR4-tropic virus, which attaches to the coreceptor on the surface of CD4s of that name.) The technical term for the

donor's genetic profile is that he or she is homozygous for the CCR5-delta32 mutation. This genetic abnormality tends to occur among about 10 percent of those of Northern European ancestry.

Brown now takes Truvada (tenofovir disoproxil fumarate/emtricitabine) as pre-exposure prophylaxis (PrEP) to ensure he does not contract HIV. The London patient has received counseling regarding use of PrEP, but at this time has opted not to take it.

The case of the London Patient is remarkable given that it follows years of concerted efforts on the part of researchers to replicate the success seen with Brown with similar strategies. (Brown's case was first reported in 2007.) There have been numerous reports of failures to prompt extended viral remission in people with HIV using stem cell transplant methods.

There are, in fact, a handful of people around the world outside of the London Patient who are in a state of years-long viral remission after beginning ARV treatment early in the course of their infection and later interrupting their HIV regimen. These include the members of the VISCONTI cohort, a young French woman and an African child.

Promisingly, the British man received a much more tolerable treatment to condition him for his stem cell transplant compared with the brutal conditioning that Brown endured prior to the two transplants he had to receive to beat his own case of acute myeloid leukemia. Brown nearly died from his cancer treatment.

Note that in both cases the men received highly toxic treatments that would be appropriate only for individuals facing potentially fatal cases of cancer. It would not be ethical to put other people with HIV through a comparable treatment if they did not similarly have cancer.

Findings from the case study of the London Patient will soon be published by the journal Nature and will be presented on March 5 at 11:45 Pacific Time by Ravindra K. Gupta of University College London at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle. On March 4, The New York Times and other news outlets broke an embargo restricting the release of the paper's findings.

Ravindra K. Gupta of University College London presenting his findings from the London Patient case at CROI 2019 Benjamin Ryan

The British man was diagnosed with HIV in 2003 and started treatment for the virus in 2012 with Atripla (efavirenz/tenofovir disoproxil fumarate/emtricitabine). Not long after, he received a diagnosis of advanced Stage IVB Hodgkin lymphoma. He was initially treated for the cancer with chemotherapy and several other salvage therapies, but these treatments were unsuccessful.

Unlike Brown, the London patient did not receive total body irradiation, a process that prepares an individual for stem cell transplant in which the immune system is suppressed or destroyed. Specifically, the British man received induction therapy with lomustine, cyclophosphamide, cytarabine and etoposide (LACE). Reduced intensity conditioning with anti-CD52 (alemtuzumab) depleted his CD4 cells. He was also treated with cyclosporine-A and short-course methotrexate to prevent graft-versus-host disease, a major inflammatory reaction that can occur following a stem cell transplant.

While Brown received two transplants, the London patient received only one. Additionally, Brown experienced severe graft-versus-host disease, while the London Patient had only a mild, grade 1 case of the condition, which was localized in his gut. Specifically, he experienced fever and gastrointestinal symptoms 77 days after his stem cell transplant.

While he was receiving chemotherapy, the London Patient’s ARV regimen was switched to Tivicay (dolutegravir) plus Truvada (tenofovir disoproxil fumarate/emtricitabine). Then, after he developed

mutations that confer resistance to the two components of Truvada (known as K65R and M184V) during a short period when his viral load was detectable—he had a five-day ARV treatment interruption in 2015—he was put on dolutegravir and rilpivirine (the drugs in Juluca) plus Epivir (lamivudine).

In September 2017, 16 months following his stem cell transplant, the London Patient went off his ARV regimen. He received weekly viral load monitoring for the first three months after stopping HIV treatment and monthly thereafter. A viral test that has a threshold of 1 copy of the virus per milliliter in peripheral CD4 cells has remained undetectable for 18 months. Extremely sensitive tests have not detected signs of the virus in his body.

Researchers drew CD4 cells from his body and found that CCR5-tropic HIV could not infect his cells but that CXCR4-tropic virus could. (The man had CCR5-tropic virus prior to his cancer treatment.)

Like Brown, the British man was successfully treated for his cancer.

HIV antibodies have declined in the London Patient, following a similar pattern previously seen in Brown’s case.

Timothy Ray Brown, aka the Berlin Patient, watches as Ravindra K. Gupta presents findings about a new case of likely cure of HIV at CROI 2019.Benjamin Ryan

The British man is actually one of 38 HIV-positive individuals who have received stem cell

transplants (this includes six people whose donors did not have the CCR5 mutation) that researchers hope will lead to long-term remission of the virus among them. Another study presented at CROI concerns one of these individuals, referred to as "the Düsseldorf Patient," who has been off ARVs for four months without a viral rebound.

"[At] 18 months posttreatment interruption it is premature to conclude that this patient has been cured," the study authors concluded about the London Patient in the Nature paper. However, they stressed that this case study suggests that a single treatment with stem cells conferring resistance to HIV "may be sufficient to achieve HIV remission with reduced intensity conditioning and no irradiation, and the findings further support the development of HIV remission strategies based on preventing CCR5 expression."

Additionally, the researchers concluded that their report "demonstrates that the Berlin Patient was not an anomaly."

Gupta told conferencegoers he was reluctant to say how long a period of viral remission would be needed in order for him to officially consider the London Patient cured. He did, however, say that perhaps two to three years of viral remission would be sufficient to determine whether Brown does indeed have company in the HIV cure club. In other words, this designation could come between the fall of 2019 and the spring of 2020.

The researcher nevertheless expressed confidence that the London Patient is indeed a second case of HIV cure.

That said, Gupta said it was possible there were some HIV-infected cells left in the London Patient's body. But it is probable that such cells contain virus that is defective and cannot yield viable new copies of HIV. Even if cells do contain virus that is capable of producing viable HIV, this virus would be CCR5-tropic. Therefore such virus could not spread throughout the body given the fact that the London Patient has a new immune system that is resistant to CCR5-tropic HIV.

To view a webcast of the conference presentation, click here.

To read the New York Times article, click here.

To read a press release about the study, click here.

To read the study abstract, click here.

And for a related POZ article, read "Reactions to the News of Another Person Possibly Cured of HIV."

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