PLOS Science Wednesday: Hi reddit, we're Nathan and Stacey, and we published a case study of a patient whose HIV was undetectable and may have been cured after allogeneic stem cell treatment – Ask Us Anything!

PLOSScienceWednesday [1] and r/Science AMAs[1]

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Abstract

Hi Reddit, My name is Nathan Cummins, and I am the Research Chair in the Division of Infectious Diseases at the Mayo Clinic Rochester. My research focuses on studying how HIV prevents cell death in some cells that it infects, and repurposing drugs to modify those effects. And my name is Stacey Rizza and I am the Chair of the HIV Clinic at Mayo Clinic, Rochester. My work focuses on HIV and solid organ and stem cell transplantation. We recently published a paper titled "Extensive virological and immunological characterization in an HIV-infected individual following allogeneic stem cell transplant and analytic cessation of antiretroviral therapy: a case study" in PLOS Medicine. This manuscript examined the immunologic and virologic changes that occurred in a patient with chronic HIV infection who was diagnosed with ALL, and who underwent Allo-PBSCT. We found that the amount of HIV that was present in this patient was reduced to undetectable levels, and that his serologic tests for HIV were reverting to negative, suggesting that he may have been cured from HIV infection. Ultimately, we stopped his HIV therapy, and observed no HIV rebound for 288 days following treatment interruption, when a viral species that was unrelated to his pre-transplant virus rebounded. We will be answering your questions at 1pm ET – Ask me Anything!

the WINNOWER

REDDIT

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PLOSSCIENCEWEDNESDAY R/SCIENCE

Hi Reddit,
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We recently published a paper titled "Extensive virological and immunological characterization in an HIV-infected individual following allogeneic stem cell transplant and analytic cessation of antiretroviral therapy: a case study" in PLOS Medicine. This manuscript examined the immunologic and virologic changes that occurred in a patient with chronic HIV infection who was diagnosed with ALL, and who underwent Allo-PBSCT. We found that the amount of HIV that was present in this patient was reduced to undetectable levels, and that his serologic tests for HIV were reverting to negative, suggesting that he may have been cured from HIV infection. Ultimately, we stopped his HIV therapy, and observed no HIV rebound for 288 days following treatment interruption, when a viral species that was unrelated to his pre-transplant virus rebounded.
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Hi Nathan and Stacey, and thank you for doing this AMA.

This story is obviously reminiscent of Timothy Brown's story, who was also cured of HIV during the course of his treatment for acute myeloid leukemia.

In cases like these, though, it has never been clear to me that the stem cell transplant is actually mediating the cure. What would the mechanism for this be? Graft vs. HIV? Would this mechanism make sense for reservoir cells (I imagine they don't present many HIV-pMHC molecules at the cell surface)?

A simpler explanation would be that myeloablative chemotherapy would have drasticlly reduced the number of reservoir cells. This would seem to be consistent with the data shown in Fig. 1A, where the viral loads decrease in the peri-transplant period *before* the transplant actually takes place. Can you distinguish between these possibilities in your research?

Also, my impression was that people have since tried HSCT with CCR5 modified cells and have struggled to reproduce the results seen with the Berlin patient. What do you think is happening here?

SirT6

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Thank you for your comments and questions. It is unknown which aspect of the Timothy Brown's treatment course led to his HIV cure. Depletion of latently infected cells by chemotherapy and anti-thymocyte treatments, transplantation of immune cells resistant to HIV infection, and graft versus HIV effects have all been hypothesized to contribute, and are individually being investigated. It may have been a combination of factors. Indeed, other CCR5 null transplants have failed to induce another cure. This may be due to pre-existing X-4 tropic viral variants that escape the CCR5 null pressure.

Dear Nathan,

I am wondering why you are clearly misrepresenting the results of your study? When someone's cancer is initially rendered to undetectable levels using chemotherapy they are not considered cured. Neither with HIV. Especially not if they have a relapse.

From the abstract of your publication it is undeniably clear that this patient still had HIV.

He remained aviremic off antiretroviral therapy until ATI day 288, when a low-level virus rebound of 60 HIV-1 copies/ml occurred, which increased to 1,640 HIV-1 copies/ml 5 days later, prompting reinitiation of ART. Rebounding plasma HIV-1 sequences were phylogenetically distinct from proviral HIV-1 DNA detected in circulating PBMCs before transplantation.

Later in the paper you explicitly state:

Together, these data suggest that the rebound viremia originated from a viral variant that was not detected in the peripheral blood compartment at any earlier time point, possibly implicating reactivation of an archived provirus harbored by one or more cellular or anatomical reservoirs that were distinct from CD4 T cells circulating prior to transplantation.

The bottom line is only slight novelty was uncovered in this publication.

Why would you lead with such a grossly misleading and audacious claim such as the patient "may have been cured".

Do you think these kinds of things foster **trust** between the public and the scientific community?

glacierelement

Thank you for your comments. Indeed, there is an ongoing debate in the field regarding what would constitute an HIV cure. Does that require complete eradication of all infected cells? Or is reducing HIV to undetectable levels and immunologic control that does not require antiretroviral therapy, i.e. functional cure, sufficient? There is not universal agreement, and both goals are being actively investigated.

There's a threshold for "undetectable", and we know that this threshold is higher than the absolute number of viruses in the body.

With a treatment like stem cell transplantation, which tends to be 'wait and see', at what point does "May have been cured" officially transition to "We have a cure"?

antiproton

Thank you for your question. It remains unclear at what point one can declare a patient "cured". So far, there are no reliable biomarkers to define a cure. The gold standard at this point would be to stop antiretroviral medications and monitor for relapse. The question then, is how long does a person have to remain undetectable to be declared cured? In our opinion, based on a number of similar reports, this

would have to be at least one year, and probably longer.

Will there be an HIV vaccine one day?

MudButt2000

Thank you for the question. There is a definite need for an effective HIV vaccine, both preventative and therapeutic, and a significant effort is ongoing to find one or more candidates.

What selection are you placing on the virus? As in, which changes to the virus would escape this treatment? (I.e., a new receptor for entry, RT/PR/IN mutations, etc.) And knowing this, could infection occur with a different virus clade or tropism?

priceQQ

Thank you for your question. Our approach in this situation was not targeting a specific viral or host protein, and therefore we think the prolonged viral control was likely due to a significantly reduced reservoir size, combined with some immunologic control for a defined period. Therefore, it is unlikely that this selected any specific escape mutants, and antiviral resistance genotyping performed at the time of rebound did not find any known drug resistance mutations.

Will a treatment like this be always and forever only available to rich people?

ProfessorRiffs

Thank you for this question. Anthony Fauci (NIH) has elegantly stated the criteria for a universal HIV cure would include being "simple, safe and scalable". We, and others, do not consider stem cell transplantation to meet this criteria, but represents a means to identify novel mechanisms and targets to study in patients who need this therapy for other medical reasons.

Would this treatment work for other viral infections like chronic epstein-barr ME/CFS?

WeAreButStardust

Thank you for your question. Different viruses have different mechanisms of persistence, and infect different cells, so it is unlikely that there would be a one-size-fits-all solution to many chronic viral infections.