Hot News

A cure for HIV on the horizon

Since the first effective jump from chimpanzees to humans in West Africa during the early 1900s, HIV has infected more than 80 million people. The current estimates for persons living with HIV are of 38 million worldwide and two-thirds in Sub-Saharan Africa. Despite dramatic advances in antiretroviral therapy, the virus cannot be eradicated from infected carriers. Although persisting lifelong, treated patients neither progress to AIDS nor transmit the virus to others. In contrast, individuals unaware of their HIV infection (roughly 15%) may develop AIDS and spread the virus. Indeed, roughly 1.5 million new infections occur each year. Therefore, HIV testing must be encouraged as much as possible and repeated in persons acknowledging any risk practices (*De Cock et al. Emerg Infect Dis 2021*).

Five cases of cure of HIV infection have challenged the paradigm of indefinite chronic infection. These cases provide hope for new strategies that pursue HIV eradication from carriers. In particular, new gene editing techniques, based on CRISPR/Cas9, are one the most promising strategies to achieve this goal (*Herskovitz et al. EBiomedicine 2021*). However, before becoming a real option, several limitations of current methods, including of-side effects, need to be addressed (*Herskovitz et al. Methods Mol Biol 2022*).

The five HIV cures

In 2009, the first patient cured from HIV infection was reported. The "Berlin" patient was Timothy Brown, an adult male that had been diagnosed with leukemia in 2005. After chemotherapy and a first bone marrow transplant, leukemia relapsed. A new bone marrow transplant was then performed, this time from a homozygous donor with the Δ32 deletion at the CCR5 gene. The patient improved and multiple studies investigating the presence of HIV after stopping antiretroviral therapy showed that the virus had disappeared (*Hütter, et al. N Engl J Med 2009*). Timothy passed away in 2020 from another cancer, remaining HIV-negative.

In 2017, another case of HIV cure was reported in a 40-year-old male from Venezuela that was living in London. As in the previous case, the "London" patient received a bone marrow transplant from a histocompatible donor who had in homozygosis the

Table 1. HIV cure reports

No.	Name	Date	Location	Procedure	Reference
1	Timothy Brown	2008	Berlin	Bone marrow transplantation of homozygous Δ32 CCR5 donor	Hutter et al. *NEJM 2009*
2	Adam Castillejo	2017	London	Bone marrow transplantation of homozygous Δ32 CCR5 donor	Gupta et al. *Nature 2019*
3	? (middle aged woman)	2019	New York	Bone marrow transplantation of homozygous Δ32 CCR5 cord blood	Hsu et al. *CROI 2022*
4	Loreen Willenberg	2020	California	Elite controller	Jiang et al. *Nature 2020*
5	Esperanza	2022	Argentina	Elite controller	Turk et al. *Ann Intern Med 2022*

Δ32 deletion at the CCR5 gene. After ablative chemotherapy for leukemia, the donor graft was unable to maintain viral replication and HIV was no longer demonstrated during the following months, even after stopping antiretroviral treatment (*Gupta et al. Nature 2019*).

At CROI 2022, which took place in Denver last March 2022, a third case of HIV cure was reported. This was a middle-aged woman, with parents of different races, although she lived in New York. She also received a bone marrow transplant from a histocompatible donor, this time supplemented with umbilical cord cells with the Δ32 deletion in homozygosis at the CCR5 gene. The patient had been diagnosed with leukemia 5 years earlier. After initial repopulation with the adult bone marrow transplant cells, the cord blood HIV resistant cells expanded and replaced the patient's hematopoietic cells. HIV was no longer detected after stopping antiretroviral therapy.

Two years ago, the case of Loreen Wallenberg, a woman from California who was part of a group of elite controllers, was reported. She had been known to be HIV-positive for several years, but always had an undetectable viral load and a normal CD4+ T-cell count. The doctors who treated the patient extensively examined the presence of provirus in different cells of her body and concluded that she was actually sterile for HIV (*Jiang et al. Nature 2020*). This situation is unprecedented and represents the first evidence that natural HIV infection can be eliminated by the immune system.

More recently, the spontaneous eradication of HIV infection has been reported in another woman, Esperanza, who lives in Argentina (*Turk et al. Ann Intern Med 2022*). The patient had developed HIV antibodies but had always undetectable viral load and preserved immunity (Table 1).

More cases of possible cure of HIV infection, either after transplantation or following natural infection, have been reported (*Casado et al. Sci Rep 2020*). Although the available information or follow-up period are not as long as in the five cases described above, the list of HIV cures is likely to increase in the coming months.

Ana Treviño and Vicente Soriano
UNIR Health Sciences School & Medical Center, Madrid, Spain
Received in original form: 02-04-2022
Accepted in final form: 16-04-2022
DOI: 10.24875/AIDSRev.M22000048

News from CROI 2022 – caveats using antiretrovirals as HIV prophylaxis

The annual conference on retroviruses and opportunistic infections was held in Denver, CO, last February. Most sessions were attended by virtual attenders, due to restrictions forced by the COVID-19 surge caused by the Omicron variant. A general feeling emerged: the pace in HIV therapeutics is slowing down and seems to have reached a certain plateau. The future steps may require drastically distinct approaches.

Islatravir is a promising new antiretroviral belonging to a first class of inhibitors of the HIV polymerase. The molecule exhibits a long half-life and depicts high barrier to resistance (*de Mendoza et al. Lancet HIV 2019*). At CROI 2022, the results of the MK8591-016 trial were presented. This is a multicenter, randomized, double-blind, and placebo-controlled Phase II trial of monthly oral islatravir for HIV prevention. Two doses were compared to placebo in 250 uninfected adults. Despite overall good tolerance during the first 6 months, all studies with islatravir as prophylaxis have been placed on hold due to unexpected lymphocytopenia.

Lenacapavir is a capsid inhibitor with potent antiretroviral activity. At CROI 2022, results from two trials conducted in HIV-infected patients were presented. In the Phase II trial CALIBRATE, 1-year treatment with an every-6-month subcutaneous dose of the drug in a dual treatment combination in drug-naïve HIV individuals provided 88% undetectable viral loads. The drug was well tolerated, with two out of 182 people developing drug resistance to lenacapavir and one person developing a nodule at the injection site. Lenacapavir shots can be given into the abdomen and are designed to be simple enough to be administered at home, resembling insulin.

On December 2021, Gilead announced that the FDA had placed a clinical hold on the use of injectable lenacapavir in borosilicate vials in all ongoing clinical studies as HIV pre-exposure prophylaxis (PrEP). There were emerging concerns about the compatibility of these vials with the lenacapavir solution, which could potentially lead to the formation of glass particles. Other studies using oral formulations of lenacapavir are continuing.

Updated results at 52 weeks of long-acting cabotegravir (LA-CAB) as PrEP were presented at CROI 2022. The HPTN-083 study was a Phase III trial that included 4566 HIV-negative individuals engaged in high-risk behaviors (most were men having sex