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.

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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

with men). Half of them received daily oral tenofovir/emtricitabine (TDF/FTC) as PrEP and the other half received LA-CAB 600 mg intramuscularly every 2 months. After 2 years of follow-up, 72 out of 2248 individuals using LA-CAB versus 25 out of 2244 on TDF/FTC became infected with HIV (HR 0.34; CI 95% 0.22-0.54; $p < 0.001$).

Interestingly, only seven breakthrough infections in the LA-CAB arm occurred in subjects despite on-time dosing, appearing the rest in persons with delayed injections. Furthermore, new incident HIV infections depicted an unusual delayed antibody production and low viral load values (*Marzinke et al. J Infect Dis 2021*), which precluded to introduce antiretroviral therapy earlier and favored the selection and accumulation of integrase resistance mutations. These results reinforce the need to check periodically plasma HIV-RNA and HIV antigen/antibody in all subjects on PrEP. In persons receiving LA-CAB as PrEP, viral load testing is now recommended every 2 months, along with each intramuscular injection. Nevertheless, due to its high efficacy, LA-CAB as PrEP should still be considered in settings where HIV-RNA screening is not readily available.

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Unexplained hepatitis in children after lifting COVID-19 pandemic restrictions

Since January 2022, almost 150 cases of acute hepatitis with epidemic features have been reported among children aged 1-15 years old, mostly below 5 years old. A wide range of symptoms has appeared, but a subset of these children has progressed to liver failure and required liver transplantation and at least one death has been reported already.

Common hepatitis viruses that cause food-borne (hepatitis A or E viruses) or nosocomial infections (hepatitis B, C, or D viruses) have been ruled out. Furthermore, a possible relationship with COVID-19 vaccines has similarly been excluded, since all these children had not been vaccinated. Other less probable causes, including poisoning, seem unlikely.

Recent evidences suggest that infection by human adenoviruses (HAdV) is the most likely cause of these unexplained childhood hepatitis. Adenoviruses could be involved in up to 80% of cases that were tested. (*Christie B. BMJ 2022; 377:o982*). The fact that this idiopathic hepatitis has been identified in countries that first lifted social restrictions to control the COVID-19 pandemic support an epidemiological link. This is the case for the United Kingdom, Denmark, The Netherlands, Holland, the United States, and Spain.

HAdVs are double-stranded non-enveloped DNA viruses, well known to be associated with pediatric illnesses. More than 100 different types of HAdV have been described, designated by consecutive numbers, which are grouped into seven species, designated by letters from A to G. Adenoviruses are capable of infecting a diverse number of human cells, hence their use as vaccine vectors (for example, those from Astra-Zeneca, Janssen or Sputnik for COVID-19 vaccines). Interestingly, distinct HAdV species may display a differential cellular tropism.

The transmission of HAdV is similar to that of other respiratory viruses, by drops or aerosols, or through direct inoculation in the conjunctiva or oral-nasal mucosa. Moreover, infection may occur throughout the fecal-oral route or through contact with contaminated objects. After an incubation period of 2-14 days, acute self-limited infection occurs. Occasionally, HAdVs can persist in the respiratory or digestive tracts, and reactivate after long periods of host latency.

HAdVs can produce very different clinical manifestations, depending on the age group, community setting, immune status, and viral species. Primary infection by HAdV usually occurs after 6 months of birth and within the first 5 years of life, following the steadily vanishment of the protection given by passively transferred maternal anti-HAdV antibodies. The most characteristic HAdV infections in young children are acute respiratory tract infections. They are often accompanied by gastrointestinal symptoms. Most childhood HAdV infections are mild; however, especially in older children, they can depict more severe manifestations, including non-purulent conjunctivitis, hemorrhagic cystitis, and mesenteric adenitis. Occasionally, they evolve with respiratory sequelae such as prolonged bacterial bronchitis or bronchiectasis.

Immunity against HAdV depends on innate mechanisms, as well as adaptive immunity, both humoral and cellular immune responses. Immune protection against HAdV begins from the 1st year of life and is strengthened with successive infections until it becomes