

## Hot News

### Another patient has cured HIV infection

Up to date, a sterilizing cure of HIV-1 infection has been reported in only two persons living with HIV-1 who underwent allogeneic hematopoietic stem cell transplantations from donors who were homozygous for the CCR5  $\Delta$ 32 gene polymorphism. They are known as the “Berlin patient” (*Hutter et al. N Engl J Med 2009*) and the “London patient” (*Gupta et al. Nature 2019*), respectively. Those cases proved a HIV cure was feasible, but transplants are expensive and dangerous, and donors difficult to find.

HIV elimination has been considered elusive during natural infection. However, in a recent publication (*Turk et al. Ann Intern Med 2021*), an Argentinian woman named Esperanza showed signs of being naturally cured from HIV-1 infection.

Persistent HIV-1 reservoir cells were examined in Esperanza, an elite controller with undetectable HIV-1 viremia for more than 8 years in the absence of antiretroviral therapy. The authors performed a detailed investigation of virologic and immunologic characteristics. No genome-intact HIV-1 proviruses were detected in analysis of thousands of billions of peripheral blood mononuclear cells and 500 million mononuclear cells from placental tissues (the woman became pregnant and gave birth to a healthy newborn). However, seven defective proviruses were detected. A viral outgrowth assay failed to retrieve replication-competent HIV-1 from 150 million resting CD4<sup>+</sup> T-cells. Furthermore, no HIV-1 RNA was detected in 4.5 mL of plasma. Although absence of recognition for intact HIV-1 proviruses in large numbers of cells is not fully confirmation of absence of intact HIV-1 proviruses, a sterilizing cure has been presumably achieved (*Turk et al. Ann Intern Med 2021*). The Esperanza case raises the possibility that a sterilizing cure may be an extremely rare but possible outcome of natural HIV-1 infection.

Esperanza was a scientific curiosity. Despite being diagnosed with HIV-1 in 2013, she had never shown any signs of illness. Moreover, traditional tests failed to turn up evidence that the virus was replicating in her

body. Only the presence of antibodies suggested that she had ever been infected. Since 2017 researchers had been collecting blood samples from her, scanning the DNA of billion cells, searching for HIV-1 genomes dormant, ready to roar to life if the conditions were right. They wanted to do the same with her placenta because even though it is an organ of the fetus, it is loaded with maternal immune cells. Again, they did not find any HIV-1 provirus in the placenta. Thus, the woman appears to have eradicated the virus from her body without the help of antiretrovirals or a bone marrow transplant. Then, the human immune system could be powerful enough to control HIV and eliminate all the functional virus.

The Past year researchers found a subset of elite controllers with intact viral genomes that were integrated into chromosomes at places far from sites of active transcription (*Jiang et al. Nature 2020*). In one patient they examined, a 67-year-old California woman named Loreen Willenberg, the authors did not find any intact virus in more than 1.5 billion of her cells. Willenberg had maintained undetectable plasma viremia and stable CD4<sup>+</sup> T-cells for nearly three decades without the use of antiretroviral drugs. If the Esperanza patient is the second person known to have been naturally cured of HIV, Willenberg is the first.

About a decade into the AIDS pandemic, researchers began to find a handful of patients who tested positive for HIV but experienced neither symptoms nor CD4<sup>+</sup> T-cell declines. They were later found to have very low or undetectable plasma viremia. In Spain, a cohort of 19 of long-term non-progressors was established in 1997 and followed for 6 years (*Rodés et al. AIDS 2004*). At the time, these case studies were presumed to be one-offs; may be these fortunate few caught a glitchy strain of HIV that was not particularly good at replicating, giving their immune systems a rare edge against a disease that was considered universally deadly until the first antiretroviral drugs were developed.

The past few decades have revealed that people with unusually potent immune responses make up around 0.5% of the nearly 40 million HIV-infected people on the planet (*Saez-Cirion et al. Immunol Rev 2013*). In recent

years, elite controllers have become the subject of intense investigation because they represent a model of a cure for HIV. If we can figure out what makes them special, they might be able to bottle it up into medicines or appealing gene therapies (*Herskovitz et al. EBioMed 2021*) that could free millions from a lifetime of antiretroviral drug taking.

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## **The opioid epidemic during the COVID-19 pandemic: Impact on HIV and HCV control**

The opioid epidemic is a tragedy in the United States. In the 12-month period that ended in April 2021, more than 100,000 US citizens died of drug overdose, up almost 30% from the 78,000 deaths in the prior year. The figure has more than doubled since 2015 and it is currently above the toll of car accidents and guns combined. The magnitude of this huge public health crisis has growth during the COVID-19 pandemic (*Baldwin et al. JAMA 2021*).

Drug overdose fatalities have wide repercussions since most deaths occur among people aged 25-55. Overdoses are largely caused by synthetic opioids, and fueled by the widespread use of fentanyl, a fast-acting drug that is 100 times more powerful than morphine. Fentanyl has increasingly been added surreptitiously to other illegally manufactured drugs to enhance their potency (*Dowell et al. JAMA 2017*). Fentanyl's ubiquity, combined with the unique social conditions caused by the COVID-19 pandemic, with stress and isolation, have created a perfect storm.

Besides overdose deaths, the opioid epidemic has been associated to a resurgence of HIV and hepatitis C cases, linked to sharing needles during drug injection practices and increased sexual risk behaviors (*Lerner and Fauci. JAMA 2019*).

The increasing use of drugs is a brake on the control of HIV infection. In the US, nearly 35,000 new HIV infections occurred in 2019. Although there is a decline of 8% compared to 2015, driven by a broader use of

antiretrovirals for both prevention and treatment, preliminary numbers for 2020 show that HIV declines have vanished during the COVID-19 pandemic. Access to HIV prevention, testing, and treatment have been compromised in many places (*Rick et al. HIV Med 2021*).

COVID-19 has also resulted in many hepatitis C elimination programs slowing or stopping altogether. A 1-year delay in hepatitis C diagnosis and treatment could result by 2030 in nearly additional 45,000 liver cancers and 75,000 deaths from HCV globally (*Blach et al. J Hepatol 2021*).

In 2016, the CDC issued new guidelines for prescribing opioids for pain, which has caused doctors to prescribe them less and health insurers to place more restrictions on the payment of these painkillers. Its over-prescription has largely been behind the opioid crisis, since oral consumption in patients with pain has easily passed to recreational intravenous use, especially by relatives and friends. The dependence on opiates has favored moving to illegal heroin and fentanyl use in certain populations. The new addicts are mainly unemployed adolescents and young people, with limited economic resources and low educational level (*Campbell et al. J Infect Dis 2017*). They are the "NEETs" ("not employment, education, or training)."

In 2019, a pharmaceutical company was convicted for the first time of marketing oxycodone, a morphine derivative. In addition to significant financial compensation, the ruling forced Purdue Pharma to fund an addiction treatment center. The US court battle with drugmakers has only begun, for failing to report the addictive effect of their opioid painkillers. However, a recent sentence dismissed responsibilities for Johnson & Johnson and Teva.

It is urgent to resume harm reduction programs for injection drug users. Treatment of opioid use disorders using methadone, buprenorphine, and extended-release naltrexone remains standard care, but gaps persist, with only an estimated 20% of persons in need receiving these medications.

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