



Talk of HIV cure goes viral

The good news that a baby born with HIV has been functionally cured made international headlines recently, but the wider implications are hard to fathom. David Holmes reports.

Published Online
March 15, 2013

[http://dx.doi.org/10.1016/S1473-3099\(13\)70044-6](http://dx.doi.org/10.1016/S1473-3099(13)70044-6)

For the **Conference on Retroviruses and Opportunistic Infections** see <http://www.retroconference.org/2013>

For more on the **first functional cure of a baby with HIV** see <http://www.retroconference.org/2013b/Abstracts/47897.htm>

For the **WHO statement** see http://www.who.int/hiv/mediacentre/hiv_child_20130305/en/index.html

For more on the **VISCONTI cohort** see <http://pag.aids2012.org/abstracts.aspx?aid=16010>

For the paper by **Stephen Kent** see [Online/Review](http://dx.doi.org/10.1016/S1473-3099(13)70043-4) [http://dx.doi.org/10.1016/S1473-3099\(13\)70043-4](http://dx.doi.org/10.1016/S1473-3099(13)70043-4)

On Monday, March 4, the world woke to the welcome news that doctors in the US state of Mississippi had made medical history after presiding over the first documented functional cure of a baby born with HIV.

The extraordinary outcome is the chance result of two decisions, by turns incisive and unorthodox, first by staff at the University of Mississippi Medical Centre (UMMC), then by the baby's mother. Presenting the case at the Conference on Retroviruses and Opportunistic Infections in Atlanta, Georgia, Johns Hopkins' virologist Deborah Persaud detailed how the baby's mother was unaware she was HIV-positive until the results of a routine test came back during the later stages of labour, by which time she was too close to delivery to risk using antiretrovirals. Given the substantial risk of mother-to-child transmission, the medical centre's paediatric HIV specialist Hannah Gay opted for an aggressive course of treatment: a three-drug cocktail of intravenous zidovudine, lamivudine, and nevirapine (replaced with lopinavir plus ritonavir at 7 days) at a therapeutic rather than a prophylactic dose and, crucially, given just 30 h after birth.

Tests on two separate blood samples taken before therapy was started confirmed that the baby was infected with HIV, and plasma viral load tests on samples taken at 7, 12, and 20 days were also all positive before the viral load became undetectable using standard assays at 29 days. The child continued on antiretrovirals until, for reasons not disclosed, the mother withdrew

“Is this child simply an ‘elite controller’ who would have done well anyway? Would an adult with such acute HIV-1 infection respond in the same way as this neonate?”

the then 18 month old child from therapy. When the mother and child resurfaced and the child was tested again at 24 months, there was unexpectedly still no sign of HIV.

At this stage clinicians at the UMMC contacted collaborating laboratories at the National Institutes of Allergy and Infectious Diseases and the University of California San Diego, who were able to bring ultra-sensitive tests to bear to find out whether any traces of HIV could be detected.

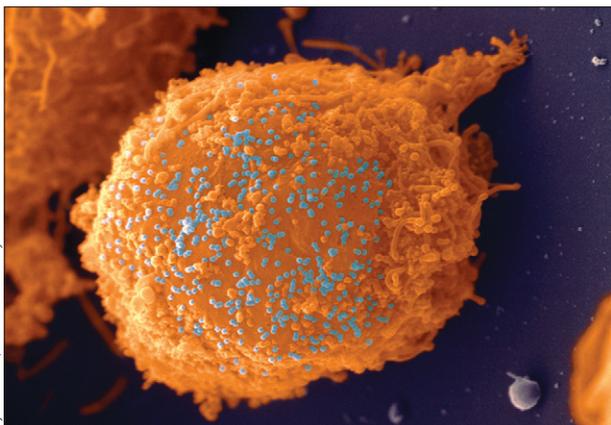
They found a single copy of HIV RNA in plasma, but no replication-competent HIV in 22 million co-cultured purified resting CD4 T cells. Testing did detect a reservoir of HIV DNA in peripheral blood mononuclear cells, but no evidence that the virus was replicating. So although all traces of HIV had not been eradicated (known as a sterilising cure), researchers concluded that the child could be considered functionally cured.

The only adult known to have been functionally cured of HIV is Timothy Ray Brown, widely known as the Berlin patient. Brown had been infected with

HIV for over 10 years when, in 2007, he was given an allogeneic stem-cell transplant to treat leukaemia. The procedure replaced Brown's immune cells with cells from a donor with a rare mutation that rendered their, and subsequently Brown's, CD4 cells immune to HIV. After Brown's leukaemia entered remission and he stopped antiretroviral therapy, his HIV plasma viral load did not rebound, and he remains functionally cured.

Both cases have important implications in the search for a wider cure, according to Oxford University's John Frater. “The Berlin patient proves that with sophisticated, expensive (and even life-threatening) measures it is possible to eradicate HIV from a patient with a chronic infection—but this is proof of principle, and although not relevant to the general population, is vital evidence for researchers. The Mississippi child suggests that there may be something critical in the lifecycle of the virus that means that in the first few hours after transmission the infection hasn't fully taken hold and can be aborted using standard therapy”, he says.

Speaking at a press conference Persaud said the timing of the treatment was decisive in establishing the functional cure, noting that “perhaps the initiation of very early antiretroviral therapy prevented the formation of the viral reservoirs in central memory CD4 T cells that are the barriers to cure, and really sets the stage for a paediatric cure agenda going forward”. Persaud is now planning trials to test whether the approach can be effective in other high-risk newborns—but many questions need to be answered before broader conclusions can be made says Frater: “It is not clear what really happened. Will the virus come back eventually? Is this child



Early treatment may prevent latent HIV infection developing in T cells

simply an 'elite controller' who would have done well anyway? Would an adult with such acute HIV-1 infection respond in the same way as this neonate?" WHO said in a statement it would keep current recommendations in place advising the "early HIV testing of pregnant women and provision of ARVs to all HIV positive mothers, along with infant prophylaxis, to prevent HIV transmission to the infant".

Researchers have known for some time that starting patients on antiretrovirals soon after infection can, in some instances, enable patients to maintain low viral loads after discontinuing therapy despite having a reservoir of latent disease. This was recently reported to be the case in the VISCONTI (virological and Immunological Studies in controllers after treatment interruption) cohort of 12 patients. But such early treatment is not possible in most cases, and only seems to confer an ability to naturally control the disease in a few patients.

Although antiretrovirals have revolutionised the control of HIV, problems with their cost, potential toxicity, drug resistance, and treatment fatigue, mean that a cure will probably need to be found in the long term. Most efforts have focused on ways to eliminate the reservoir of latent HIV that is able to evade antiretrovirals by hiding in cells. From a strategic perspective, this can be approached in four ways explains Frater: "exhaust (activate the proviral reservoir in conjunction with antiretroviral therapy), kill (target latently infected cells), silence (silence transcription from the proviral reservoir), or replace (engineer a new population of HIV resistant cells)". Of these, the exhaust and replace approaches have received most attention, and Jerome Zack, Director of the UCLA Center for AIDS Research, and his team are one of many pursuing the exhaust strategy. "The goal is to find agents that induce expression of the latent virus while

the patient is on antiretrovirals to inhibit spread of new virus, which should either expose the cell to the immune system or make it targetable by virus-specific reagents such as immunotoxins", he explains.

In a Review in *TLID*, Stephen Kent and colleagues report that researchers have already shown that latent virus in patients on antiretroviral therapy can be activated with a single dose of vorinostat, an anticancer drug that inhibits the enzyme histone deacetylase. But the studies are still in the "early developmental stages", says Zack, and there are still fundamental questions about the basic biology of HIV that remain unanswered. "We still do not know all of the potential reservoirs of virus, and how to attack them", he says, "and we are also still learning about how HIV causes disease". For now, at least, a cure remains a hope rather than an expectation.

David Holmes

Infectious disease surveillance update

Anthrax infection in the UK

A heroin user from Suffolk, England has died after being infected with anthrax. Europe has seen a recent outbreak of anthrax: 13 cases have been identified since early June 2012, including seven in the UK—five in England (including four fatalities), one in Scotland, and one in Wales. The Health Protection Agency (HPA) claims the source of the infection is heroin contaminated with anthrax spores. Whether the British cases were linked to the European outbreak, which has affected drug users in Denmark, France, and Germany is unclear.

Syphilis in New Zealand

From 2011 to 2012 the number of infectious syphilis cases in Christchurch increased fourfold, and this year 16 people (six infectious) have been treated for the disease.

Most people with infectious syphilis are men who have sex with men, and many use social media sites or smartphone applications such as Grindr to search for sexual partners. Sexual health physicians warn that the government should take action before the infection spreads into the heterosexual community.

Hepatitis E in South Sudan

More than 88 cases of hepatitis E have been reported in 27 days in the Doro refugee camp in South Sudan, and three pregnant women have died. According to a medical officer, five or six cases of hepatitis E are being reported per day at various units in the camp. Symptoms include yellowing of the eyes, joint pains, and general body weakness. Hepatitis E spreads in environments with poor sanitation and contaminated water. The outbreak spread to Doro

from the Jammam, Jandrassa, and Yusif Batil camps because of contact between the residents. In 2012, Médecins Sans Frontières started an awareness campaign in Doro.

Salmonella in England

An outbreak of salmonella has been linked to a Newcastle food festival that took place between Feb 28, and March 2, 2013. So far, 250 people who attended the festival have reported symptoms including diarrhoea and abdominal pain, and eight have tested positive for salmonella. Although most people with salmonella recover without treatment, sometimes the illness can become more serious and need hospital admission. The HPA are working closely with the organisers of the event to establish the source of infection.

Natalie Harrison

For more on **anthrax infection in England** see <http://www.hpa.org.uk/NewsCentre/NationalPressReleases/2013PressReleases/130308SuffolkpatientwithAnthrax/>

For more on **syphilis in New Zealand** see <http://www.stuff.co.nz/national/health/8402842/Syphilis-back-with-vengeance>

For more on **hepatitis E in South Sudan** see <http://radio.tamazuj.org/en/article/over-88-cases-hepatitis-e-doro-camp>

For more on **salmonella in England** see <http://www.coventrytelegraph.net/news/national-news/2013/03/08/salmonella-cases-rise-after-event-92746-32951359/>