The 20th Conference on Retroviruses and Opportunistic Infections (CROI) opened in Atlanta with a blockbuster about a Mississippi toddler who appears to be the first child—and only the second person—to have been functionally cured of HIV. The toddler was abruptly taken off treatment after receiving antiviral drugs during the first 18 months of life. Several months later, doctors could find no detectable replication-competent virus in the toddler’s blood or any evidence of disease.

Unveiled at an early press conference and rounded out a day later in an oral abstract session, the case report sparked a rare media firestorm for the organizers of this otherwise low-key, science-heavy meeting. Within 72 hours, a news story by The Associated Press had generated close to 5,000 comments on The Huffington Post website. Deborah Persaud, the Johns Hopkins researcher who presented the findings, seemed ubiquitous on television screens, and Hannah Gay, the treating pediatrician from the University of Mississippi Medical Center who referred the case to Persaud, became an instant celebrity. The story captivated the blogosphere for days.

Even before this remarkable case landed in CROI’s late-breaker pile—reserved for abstracts that are considered after the deadline for submissions—it was clear that HIV cure research was going to be a hot topic at this year’s conference, given how much researchers have lately learned about the cellular reservoirs in which HIV persists despite highly active antiretroviral therapy (HAART). The hope is that this expanding knowledge will one day inform new therapies to better control HIV or even snuff it out entirely (see Primer on Understanding Therapeutic Vaccination, this issue).

Still, despite recent advances, and even a scientific roadmap (see IAVI Report blog, Cure Research: An Update and a Roadmap, July 27, 2012) for the burgeoning field, HIV cure researchers are probably years from achieving their ultimate goal. One of those challenges will be confirming the toddler’s apparent functional cure. But it’s worth the effort. “With this case, we may have not only a positive outcome for the particular child, but also a promising lead for additional research toward curing other children,” said Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases, in an agency release.

So far, not a great deal of personal detail has been disclosed about the toddler, primarily to protect patient confidentiality. We are informed that the child, from rural Mississippi, was born prematurely at 35 weeks to a mother who received no antiretroviral treatment (ART) or prenatal care. Doctors affiliated with the University of Mississippi Medical Center have been treating the child, who is now 2 ½, since birth and the child is reportedly thriving. But Persaud has declined to divulge the child’s gender, the mother’s age, why the mother didn’t receive ARVs during her pregnancy and, perhaps most importantly, why the child was taken off ART after 18 months.

What we do know is that when the baby was 30 hours old, doctors began administering a liquid cocktail of three ARVs—zidovudine, lamivudine, and nevirapine, which was given at a therapeutic dose, which is higher than a preventive dose, according to Persaud. Blood samples obtained the same day confirmed HIV infection. The RNA test showed a viral load of 19,812 copies per milliliter of blood. Subsequent tests, conducted when the child was 7, 12 and 20 days old, showed steadily declining levels of virus in the blood before it became undetectable at 29 days.

The baby was discharged from the hospital at one week of age and switched to an ARV cocktail of zidovudine and lamivudine co-formulated with lopinavir-ritonavir. The liquid regimen continued for 18 months. Then, for reasons that are not clear, treatment was...
stopped and the child was apparently lost to follow up. When Gay, the Mississippi pediatrician, finally saw the child about six months later, she discovered there were still no detectable levels of HIV in the child’s blood, even though the baby had been off ART for about as long. This surprised Gay because previous studies have found that the virus resurges swiftly following treatment interruption.

Gay consulted both Persaud, a researcher at Johns Hopkins Children’s Center, and Katherine Luzuriaga at the University of Massachusetts Medical School, who recommended ultrasensitive RNA and DNA tests that can detect extremely low levels of virus in the blood. Those tests, done at 26 months of age, detected a single copy of HIV RNA in the child’s plasma and extremely low levels of HIV DNA. But plasma viral load, HIV DNA, and HIV-specific antibodies remained undetectable in standard tests, leading Persaud and colleagues to conclude that the child had been functionally cured. This contrasts with the sterilizing cure—complete eradication of all viral traces from the body—initially documented in Timothy Brown, an HIV-infected man known as the “Berlin patient” who received a stem cell transplant from a donor naturally resistant to HIV. However, after some bits and pieces of viral DNA and RNA were discovered last year in Brown’s blood and tissue, scientists now question whether the Brown case really is an example of such a cure. Scientists aren’t sure if the traces are the result of false laboratory readings or indeed evidence that transient virus still exists in Brown’s body.

There have been other reported cases of transient HIV infection in infants, but Persaud said the details of those cases were murky. Indeed, a study published 15 years ago in the journal Science by University of Rochester researchers analyzed 42 cases of suspected transient HIV viremia. It found that most of the results had been misinterpreted.

Persaud said the Mississippi case suggests that delivering ARVs within days of exposure could potentially induce long-term remission without the need for daily ARVs. But whether this alone accounts for the outcome in the Mississippi case remains unclear, she said.

The next step will be to replicate the result in other high-risk newborns. Persaud, who is the scientific chair of the HIV Cure Committee of the International Maternal, Pediatric Adolescent AIDS Clinical network, said clinical trials are already being planned. “This is a single case,” said Persaud. “But, certainly, if it is replicated, we do think this will transform management of children” born to HIV-infected mothers.

**Monkey business**

But Persaud’s wasn’t the only notable talk on viral clearance. Louis Picker detailed in one of the last presentations at the conference how a novel viral vector vaccine candidate bearing antigens against the simian immunodeficiency virus (SIV), the monkey form of HIV, appeared to have cleared residual virus in rhesus macaques who had been challenged with a pathogenic form of SIV. A professor of pathology at Oregon Health & Science University, Picker has been working for nearly a decade on an HIV vaccine candidate built on a replicating rhesus cytomegalovirus (rhCMV) viral vector. His research has potentially broad implications for the development of both preventive and therapeutic HIV vaccine candidates, though CMV viral vectors have not yet progressed to human HIV trials.

Persistent replicating vectors are attractive to vaccinologists because such vectors are capable of continuously expressing target antigens after delivery. Their persistence is also likely to elicit broader, long-lasting, and more potent immune responses. Further, CMV vectors—which elicit distinct populations of SIV-specific CD4+ and CD8+ T cells—maintain effector memory cell responses at mucosal sites. These cells are retained in tissues where HIV gains a foothold in the early stages of infection and can kill infected cells before HIV establishes a life-long infection. Picker and colleagues reported in 2011 that the rhCMV vaccine, when given alone or in combination with another SIV vaccine vector, stringently suppressed SIV indefinitely in 13 of 24 macaques who had been challenged rectally with a highly pathogenic strain known as SIVmac239.

At CROI, Picker offered proof that the rhCMV-vaccine elicited response hadn’t just suppressed the SIV in protected animals, but cleared it. He and his colleagues took 60 million cells from five SIV-infected animals that had controlled the SIV infection for at least 17 months and injected them into SIV-uninfected animals. When the cells from SIV-infected monkeys on fully suppressive HAART or from monkeys able to control SIV without ARVs were injected into SIV-uninfected animals, their transfer led to rapidly detectable infection. But in the case of the rhCMV vaccine-protected animals, no infection occurred following transfer.

“The implication is that there is no residual SIV in the rhCMV/SIV vector-vaccinated, long-term protected animals,” said Picker. “The SIV infection, which was demonstrable there early on, after challenge, is now gone, cleared, nada.”

So did the CMV vector eradicate the virus? “My partner suggested I not use the ‘E’ word,” he said. “But certainly, the implication is that these animals are virus-free at this point.”

Still, CMV is not entirely benign. Though it is widespread—90% of people in sub-Saharan Africa have been infected with it—and is generally harmless in healthy people, the virus does pose a risk to fetuses and immune-compromised individuals, including those with HIV. Picker has therefore been trying to develop an attenuated CMV vector that does not cause disease but remains effective. He did not report any new results from that effort at CROI.
For women, some mixed signals

Advocates of pre-exposure prophylaxis (PrEP) were recently dealt a blow when an international study of 5,029 women found that a prescribed regimen of ARVs did not prevent HIV acquisition. A University of Washington researcher who presented the findings at CROI said this appeared to be because women in the trial didn’t use the oral and topical PrEP regimens consistently (see IAVI Report blog, The VOICE results, loud and clear: Adherence Matters, Mar. 4, 2013).

Two studies also delivered conflicting verdicts on whether hormonal contraception increases a woman’s risk of HIV acquisition and of transmitting the virus to men. In a study of 99 HIV-infected women from Kenya who adhered to a three-drug ARV regimen for an average of 34 months, HIV viral loads in blood and genital secretions remained suppressed most of the time. University of Washington researcher Summer Day said viral load levels did not differ between women who took the injectable hormonal contraceptive depot medroxyprogesterone acetate (Depo-Provera) and those who did not. Previous studies had suggested Depo-Provera may increase the risk of HIV transmission.

Data from the current study suggest that consistent use of triple-combination therapy seems to counter any increase in viral load induced by the contraceptive, which is popular in developing countries. Day said ARVs should be considered along with condom use as a strategy for decreasing the risk of heterosexual transmission of HIV by infected women who use this form of birth control.

A British study was less encouraging. A secondary analysis of the Microbicides Development Programme (MDP301) trial found an increased HIV incidence in women using two different injectable hormonal contraceptives—Depo-Provera and norethisterone enanthate (NET-EN). MDP301 evaluated the microbicide PRO 2000, which was found to be ineffective (see VAX Feb. 2009 Spotlight article, Cannassing CROI).

The sub-analysis included 8,663 women under age 50 from four African countries, who were tested every three months. Researchers identified 417 HIV infections after a year of follow up. Angela Crook, a researcher from the UK Medical Research Council, said initial results showed an increase in HIV incidence among women using the two injectable contraceptives and no increase in HIV among users of oral contraceptives. But after adjusting for various factors, including age, condom use, frequency of sex, study recruitment site, and occurrence of the sexually transmitted diseases chlamydia and herpes simplex virus-2, there was no increased risk of HIV between users of NET-EN or oral contraceptives. Still, researchers found a higher risk of HIV associated with Depo-Provera, though it was less than what the original analysis suggested. The conclusion: More research required.

GLOBAL NEWS by Regina McEnery

First candidate HIV vaccine to employ Sendai vector poised for trials

Mention Sendai and many people think of the 2011 earthquake and tsunami that devastated Japan. But Sendai is the name of an RNA virus that is being used as a viral vector in a recently launched Phase 1 AIDS vaccine trial. This is the first time Sendai is being used in an AIDS vaccine candidate.

The vector carries an immunogen—the active ingredient of a vaccine—derived from the predominant subtype of HIV that circulates in East Africa, clade A HIV. But what distinguishes this vector is its ability to replicate within the body following delivery, and its replication within mucosal tissues. It is in such tissues, mainly in the gut, that HIV establishes a foothold in the early stages of infection. The Sendai candidate, researchers hope, might recruit targeted immune responses to mucosal tissues and provide an edge to the immune system when it is subsequently challenged by HIV.

The randomized, double-blind, placebo-controlled trial known as S001 began screening volunteers in Rwanda in March, is expected to start soon in the UK, and eventually Kenya. The trial is testing the safety and immunogenicity of a prime-boost regimen of the Sendai vector and another HIV vaccine candidate built from an inactivated strain of another virus, adenovirus serotype 35 (Ad35), a common virus that causes colds and respiratory infections. The two candidates will be given to volunteers four months apart.

The four-group study will enroll 64 healthy HIV-uninfected men and women ages 18-50. In the first part of the trial, vaccine recipients will receive a lower dose of the Sendai candidate containing the HIV subtype A gag gene, administered intranasally, followed by an intramuscular injection of the Ad35 viral vector vaccine candidate four months later. The Ad35 vaccine candidate contains four HIV genes: nef, reverse transcriptase, integrase, and gag. Volunteers in the next part of the trial will receive a higher dose of the Sendai candidate vaccine followed by the Ad35 vaccine candidate four months later in the second group, and the Ad35 vaccine candidate followed by the Sendai vaccine candidate in the third group. Vaccine recipients randomized to the fourth group will be given two intranasal administrations of the Sendai candidate.

The Sendai virus was isolated in 1952 in Japan. It is part of the Paramyxoviridae family of viruses, which includes measles, mumps, canine distemper, and human parainfluenza viruses. Though Sendai causes respiratory tract illness in rodents, it is not known to cause human disease. The Sendai viral vector was developed by the Japan-based DNAVEC Corporation and the Ad35 viral vector candidate was developed by IAVI, which is sponsoring the Phase 1 trial and supplying the vaccine candidate to the three clinical sites.

Evidence suggests that replicating viral vectors might be able to elicit broader, more potent, and durable immune responses against the immunogens they carry (see VAX Dec. 2007 Primer on Understanding Replicating Viral Vectors).

Dagna Laufer, IAVI’s Senior Director for Medical Affairs, said one of the aims of the trial will be to see how well intranasal immunization alone or in a prime-boost regimen with the Ad35 viral vector vaccine candidate induces systemic and mucosal immune responses. While different vaccination routes elicit different mucosal responses, nasal immunization may not only stimulate an immune response in saliva, nasal secretions, and other parts of the respiratory tract, but also in more distant mucosal sites, such as the vagina or rectum.
In the late 18th century, the British doctor Edward Jenner scratched some pus from a Cowpox sore into the arm of an eight-year-old boy to see whether exposure to the virus it contained—vaccinia variola—would subsequently protect the child from its far deadlier relative, the smallpox virus. The experiment might have been highly unethical by current standards, but its success revolutionized preventive medicine and established Jenner, in the eyes of many, as the founding father of immunology.

It also gave us the word “vaccine,” which is today used to describe a variety of substances administered to prevent disease—such as the live-attenuated or inactivated viruses contained in flu shots, or the molecular fragments of HIV that are used to make AIDS vaccine candidates. Though experimental and approved vaccines that fail to prevent infections might well dampen the severity of their targeted diseases, vaccination is generally associated more with the prevention of infection than its treatment (see VAX May 2009 Primer on Understanding How Partially Effective Vaccine Candidates are Evaluated).

But an entirely different sort of vaccine has lately become the focus of intense scientific research: the therapeutic vaccine. Such vaccines are currently being devised to harness the immune response to treat diseases ranging from cancer to multiple sclerosis. AIDS researchers too have sought to develop therapeutic vaccines in hopes of delaying or preventing the onset of AIDS in the HIV-infected. The first person to try this was the French scientist Daniel Zagury, who in 1986 inoculated two HIV-infected women from Zaire (now the Democratic Republic of the Congo) with a genetically engineered version of an HIV protein. To deliver the HIV fragments, Zagury used a viral vector based on the vaccinia virus used in the smallpox vaccine. Soon after, Zagury tested the candidate in eight more HIV-infected individuals.

Zagury’s research, however, provoked controversy because his vaccine wasn’t adequately tested in preclinical studies, and because he did not obtain French regulatory approval for the trial. To make matters worse, three of the vaccinees died from severe, progressive necrosis that developed at the injection site, a reaction triggered by the recombinant vaccinia virus that was used as a vector. (The rare complication has also occurred in immune-compromised individuals vaccinated against smallpox.) This set back the pursuit of therapeutic vaccination, and the field languished for years.

The dawn of HAART

It took the introduction of highly active antiretroviral therapy (HAART) in 1996 to revive the field, and therapeutic vaccination is now being considered by some researchers as a potentially valuable component of investigational therapies to cure HIV infection. The three or more drugs simultaneously used in HAART potently suppress viral replication in the blood, allowing the body to rebuild its immune system. But such regimens cannot by themselves cure HIV infection, since the virus weaves itself into the chromosomes of resting CD4+ T cells, creating a population of latently infected cells known as the viral reservoir. Because the virus in these T cells doesn’t replicate, it is unaffected by HAART.

While it is not entirely clear how these latent reservoirs form or are maintained, they have become the central focus of HIV cure research. Scientists believe that one way to cure HIV could be to locate and drain the reservoirs. In one recent clinical trial conducted in HIV-infected people on HAART who had undetectable viral loads, for example, a chemotherapy drug named vorinostat was used to rost HIV from latent cells in hopes of depleting such reservoirs and clearing the virus. More recent studies suggest, however, that single or multiple doses of this drug were unable to clear infected cells, suggesting that multiple strategies will likely be needed to do the job.

Scientists and pharmaceutical companies have also been evaluating other drug compounds to ferret out latent HIV and eradicate it or expose it to immune attack. The hope is that even if such approaches leave patients with a residual HIV infection, they will have suppressed the virus sufficiently to achieve what’s referred to as a functional cure.

So where does therapeutic vaccination enter into all of this? Scientists believe that the active recruitment of an immune cell known as the CD8+ T cell, which destroys virally infected cells, would help ensure that exposed cells of the viral reservoir are eliminated. Unfortunately, previous studies have found that the CD8+ T-cell responses induced in HIV-infected individuals were not sufficiently broad or potent to control the virus. Researchers are now trying to address this deficiency by boosting CD8+ T-cell responses through therapeutic vaccination.

The hope is that by first administering compounds to expose latent virus and then following up with therapeutic vaccination, it might be possible to suppress HIV indefinitely without relying on daily ARVs. Scientists are also evaluating therapeutic vaccine candidates as a single strategy for suppressing HIV after HAART is stopped. One candidate recently tested in a Phase I trial contained subsets of dendritic cells. These specialized immune cells act as first responders by detecting viruses and recruiting immune responses to target them. Unfortunately, this vaccine candidate, tested in a small group of individuals in Spain, did not work well enough to keep HIV-infected individuals off of HAART for very long (see VAX Jan. 2013 Global News).

Scientists have also shown in animal studies that therapeutic vaccination could further reduce and actively suppress the levels of residual virus following HAART. While the animals were on ARVs, the vaccine additionally lowered the average viral load of the monkeys to about 100 copies per ml of blood. When ARV treatment was stopped eight weeks after the final vaccination, the mean viral load did not rebound in the vaccinated animals.

Though they still have a long way to go, researchers hope that therapeutic vaccines may one day offer an alternative strategy to the daily grind of HAART for people infected with HIV.