The Case of the Baby & 'Functionally Cured' of HIV: A Detective Story

Was the famous baby really functionally cured of HIV, or was this just a case of post-exposure prophylaxis? Was the child infected at all? Is this actually the first cured baby? The skeptics want answers.

April 1, 2013 By Benjamin Ryan

"A baby is 'functionally' cured of HIV."

Such a claim is so profound and seemingly unprecedented, it should come as no surprise that skeptics would pick over every piece of available data and every last word out of the mouth of the scientists involved with the case.

At the 20th Conference on Retroviruses and Opportunistic Infections (CROI) in Atlanta at the beginning of March, Deborah Persaud, MD, a pediatric infectious disease researcher at Johns Hopkins Children's Center, presented her case study on a 28-month-old child from Mississippi who had received an atypically aggressive antiretroviral (ARV) cocktail shortly following being born to an HIV-positive mother. After remaining off ARVs for the past 10 months of life leading up to the report (more time has passed since then), the child maintains an undetectable viral load—although highly sensitive tests can still detect fragments of virus present.

This appeared to be the first well-documented case in history of a child "functionally cured" of the virus. And to many—in particular the global media, which reacted feverishly to the news—the case was poised to join that of Timothy Brown, also known as the "Berlin Patient," in the pantheon of great HIV medical breakthroughs.

Meanwhile, a coterie of skeptical scientists and HIV advocates around the globe have furrowed their collective brows at what they perceive as an overly sweeping pronouncement. They have expressed doubts ranging from whether the child was actually infected, to whether this represents a functional cure or a prophylaxis preventing infection, to whether going public with such a case is premature when the child's virus might still rebound.

Joseph Sonnabend, MD, a retired HIV clinician and researcher living in London who famously pioneered community-based research of the disease in its early years, is keen to criticize the media for jumping on a case report that has not yet been published in a peer-reviewed journal.

(Persaud says a journal is currently reviewing the case study.)

Sonnabend points to the paper published in PLOS Pathogens only 11 days after the story of the Mississippi baby broke, in which 14 adults who were all treated within two months of infection maintained undetectable viral loads for between 4 and 9.6 years after going off ARVs. The paper did not make explicit claims that any of these individuals had been functionally cured, rather projected how the findings could further future research into functional cures. Which is not to say, however, that the study didn't immediately lead to wide talk that the members of the cohort had been functionally cured.

At CROI, Persaud described her case as a "proof of principle" that a functional cure of an infant may be possible and stressed that more follow-up research was needed. However, the American Foundation for AIDS Research (amfAR), which supported her and her colleagues' research, touted in a release that this was the "first case of a child cured of HIV" while the National Institutes of Health's (NIH) press release headline read, "Toddler 'Functionally Cured' of HIV Infection."

"To make definitive statements about a cure is crazy; it's rash," Sonnabend says. "It's incautious, imprudent—one might even say abusive. You don't want to present hopes to people when you don't have sufficient grounds to do so. That's terrible."

Persaud says she never anticipated how a single case would lead to such a media extravaganza. She stresses how cautious she has been as a researcher, turning over every possible stone throughout the case, and points to her and her collaborators' more than 15 years of study in the field of mother-to-child transmission to buttress their qualifications in the face of such criticism.

"This is going out on a limb for me to report a case like this," she says. "and I would not do it without having the laboratory evidence and confirmation of infection in this child and the knowledge of what we know with respect to exposure, prophylaxis and infectious outcomes in infants, and how we identify them and how we treat them."

While she feels that some of the media coverage got blown out of proportion in reaction to a single case study, leading to false beliefs that this was the beginning of a sea change that would immediately affect many others with HIV, she insists, "I think it would have been irresponsible to sit on a case like this and not report it at CROI."

One in a Million? More Like One in 65 Million

A series of unusual circumstances led to the development of this case—one that is so unique some experts wonder if it can ever be replicated. The child's mother received no prenatal care and was only diagnosed when she arrived at a rural Mississippi medical center in premature labor. The delivery was very short, so there was no chance for her clinicians to administer the IV of ARV prophylaxis that is a standard preventative measure against HIV transmission to the baby during delivery.

After the mother was then transferred to the University of Mississippi Medical Center, Hannah B. Gay, MD, an associate professor of pediatrics, followed the current U.S. guidelines for determining HIV infection in a high-risk, HIV-exposed newborn: She performed two separate blood draws, the first taken at 30 hours of life, the second at 31, to detect for HIV RNA and DNA, both of which came back positive. The baby's viral load was about 20,000.

According to U.S. guidelines, newborns at risk for HIV infection should be placed on a prophylactic dose of AZT; nevirapine is added in high-risk situations. Gay decided that because the baby was at such an usually high risk of HIV infection she would prescribe a much more aggressive "therapeutic" dose of ARVs—in this case, AZT, lamivudine and a higher dose of nevirapine—and then wait until more information about the infant's infection became available.

Viral load tests taken in the following weeks showed the persistent presence of HIV in the blood of the infant and a steady drop to undetectable levels. The child continued on the drugs for 18 months, but then, for unexplained reasons, disappeared from care.

After five months off therapy, the child returned to care and Gay found that there was no evidence of replicating virus in the child (ordinarily, the virus will rapidly rebound after a treatment interruption), although highly sensitive screens called PCR tests could still detect traces of virus. At the time of the CROI report, 10 months had passed since stopping therapy, and the child maintained an undetectable viral load. The reasons for this are unknown.

Since the fall, Persaud and a research team that includes Gay, Katherine Luzuriaga, MD, at the University of Massachusetts Medical School in Worcester, and several others, have studied the case, working under a grant from amfAR to explore the potential for curing children (the grant was established shortly before Gay alerted them to this case).

Some Questions Have Easier Answers

"We can't know with certainty that the baby was really infected," Sonnabend says, echoing the questions of many skeptics.

This is a position that "mystifies" Rowena Johnston, PhD, the vice president and director of research at amfAR.

"If you want to question whether this infant was infected, you have to question whether any infant was infected, using today's current standards of how to define infant infection," Johnston says. "Furthermore, the infant then went on antiretroviral therapy and had subsequent viral load tests which went down in exactly the way that you would predict if the antiretroviral therapy were having an effect."

Some have also argued that this is not actually the first instance of a baby born to an HIV-positive mother clearing the virus. In particular, they point to three published reports from the pre-ARV cocktail era, two in 1995 and another in 1996, which seemed to suggest the potential for a

“transient” HIV infection that would disappear on its own.

However, subsequent questions about the accurateness of the diagnostic tools available at the time have led many scientists to question these findings as suspect. A 1998 paper published in Science found that 42 supposed cases of viral remission involved contaminated samples or laboratory error. Written by Lisa M. Frenkel, MD, a professor of pediatrics at the University of Washington, the paper had 28 coauthors, including such bold-faced names as the Aaron Diamond AIDS Research Center’s David Ho, MD, and the NIH’s Richard Koup, MD. They also questioned reports of transient infections that did not conduct tests to confirm “viral relatedness” between the mother and child.

An opinion piece in the journal Nature about a 1995 case study of a transient infection in one infant, signed by a collection of British scientists, called into question the paper’s findings due to what the authors described as insufficient diagnostic confirmation of the infants’ HIV infections at birth.

The lead author of that case study, Yvonne Bryson, MD, chief of pediatric infectious disease at David Geffen School of Medicine at University of California, Los Angeles Mattel Children’s Hospital, says she still stands by her research, although she acknowledges that her team waited a year to draw the blood sample from the mother that they used to more fully confirm the source of the virus initially found in the infant. She disputes arguments that culture tests commonly used in the early 1990s were supposedly unreliable.

Frenkel, who is also an investigator at Seattle Children’s Research Institute, is on board with the position of scientists such as Mark J. Siedner, MD, an infectious disease postdoctoral fellow at Harvard Medical School, who argued in a recent Wall Street Journal opinion piece that the Mississippi child was not cured of HIV but exposed to the virus and then given what amounted to prophylaxis that prevented an established infection.

Frenkel argues, “It’s been showed many times with animals, with monkeys, that if you intervene with [ARVs] you can prevent the establishment of a long-term reservoir. And that’s what I think happened in this baby, most likely.”

Even Anthony S. Fauci, MD, the director of the National Institute of Allergy and Infectious Diseases (NIAID), a division of the NIH, which has long been funding Persaud and her collaborators’ research in this field of study, says, “The weight of the evidence supports that the baby was actually truly infected, with virus replicating within the baby’s cells in the body. But I think there’s a slight chance, and I wouldn’t say it’s a big chance, but there’s still a possibility that what we were seeing was really a transfer of virus from mother to the baby and this might not actually be a true cure of an infected baby, but a very aggressive prophylaxis.”

Debating the Use of Words: Prophylaxis vs. Cure

Part of the major bone of contention among scientists examining this case involves

verbiage—debating the proper use of “transient” or “acute” infection versus “established” or “chronic” infection, as well as “cure” versus “prophylaxis”—and, by extension, how those choice of words apply to the continuum that begins with HIV exposure and runs through to the virus’s establishment as a permanent fixture in body.

According to the current scientific understanding, when someone contracts HIV, the virus typically remains at the infection site for a time—restricted, for example, to the genital mucosa. Next, the virus succeeds in replicating more broadly throughout the body. And in turn the virus infects what is known as the reservoir—the tissues and cells that remain largely off limits to the reach of ARVs and the body’s immune response.

A prophylactic approach to ridding the body of the virus attacks this process at its earliest stages. However, exactly where in the continuum of infection an attempt at prophylaxis becomes an attempt at cure appears unsettled among the scientific community.

Daniel R. Kuritzkes, MD, a professor of medicine in infectious diseases at Harvard Medical School, who also argues this is likely a case of aggressive post-exposure prophylaxis following a non-established infection, says he defines HIV infection as dependent on the establishment of a reservoir.

Persaud, meanwhile, reacted to such a statement saying, “I’ve not heard that definition to date,” stressing, “Infection is defined as detection of replicating virus and HIV nucleic acid—DNA and RNA—present in an infant. Maybe definitions will change over time with this case, but using our standard definitions and what we know about the pathogenesis of HIV infection, this meets criteria for infection.”

Robert F. Siliciano, PhD, a professor of medicine at Johns Hopkins, believes that the baby was indeed cured of HIV and that one need not begin with a reservoir to achieve a cure. He says that the child’s cure was actually made possible because infants are born without what are known as memory T-cells, which are a key component of the latent reservoir. Since the baby was aggressively treated before there was a potential for HIV to establish a reservoir in these cells, the door was opened for a functional cure.

Unfortunately, there is no way to demonstrate if the child had actually had a pool of latently infected cells before beginning ARVs, or if the child had any such pool at a subsequent point in time. Currently, however, all available evidence indicates that there is no reservoir or virus with the potential to replicate in the child. And while recent research out of Siliciano’s lab has suggested that some virus may take a year to emerge from reservoirs, almost that amount of time passed before the CROI report with no sign of viral emergence in the child.

Still, Fauci says, “Be careful, cure is only as good as the length of time you’re off therapy.”

Some have also pointed to the child’s relatively low viral load at birth, which seems to suggest a recent infection—possibly within a few days before birth—and possibly a “transient” or “acute”

one which would indicate the child received a successful prophylaxis and not a cure from the ARV treatment.

Frenkel posits that it's possible the baby experienced what is known as a "mixed lymphocyte reaction." One the one hand, the mother had a high CD4 count and low viral load of only 900 at the time of labor. However, in the event that the mother's blood crossed the barrier of the placenta and infused into the baby—which sometimes occurs during delivery, or, more infrequently, during pregnancy—the mother's cells may have reacted to the baby's as if they were foreign pathogens, stirring a reaction that would have produced greater amounts of virus.

But could such a reaction have led very quickly to the approximate 1.25 million copies of HIV that Persaud estimates the child had throughout its entire body at birth? This is a level the researcher presents as evidence of a firmly established, or chronic, infection.

Indeed, in a blog post, Treatment Action Group's Richard Jefferys references a 1998 study of 18 infants infected in utero that found the median viral load count for measurements taken within 48 hours of birth was 27,000, which in this small sample would place the Mississippi child's 20,000 copies per milliliter well within the norm.

Jefferys also points to studies of post-exposure prophylaxis used to prevent mother-to-child transmission, none of which found evidence that there was ever detectable viral load among infants who succeeded on the therapy.

What Does a Cure Look Like? What Do You Call It?

While much of the media quickly ditched the qualifier "functional" in favor of the much more exciting "cure," invariably leading to inflated optimism if not outright confusion around the world, the amfAR-sponsored research team has been more careful to couch their findings in non-absolutist terms.

Part of the reason for the use of the word "functional" is that we currently lack, and may always lack, the means to prove with 100 percent certainty that someone who was once HIV infected has no virus anywhere left in his or her body—which is the requirement for a "sterilizing" cure. Some stray particles of virus may still hide out in tissues inaccessible to even the most sensitive tests or invasive biopsies and which could only be found through an exhaustive autopsy.

The term "functional cure" is intended to indicate that immune cells are keeping the virus in check in the absence of ARVs, but that tests still indicate the presence of the virus. (With the exception, that is, of the rare "elite controllers" who are able to maintain control of the virus without ever having taken HIV therapy.) However, in the case of this child, there is no current evidence of an immune response against the virus, and unlike the transplanted cells the Berlin Patient received, the child lacks the genetic abnormality that blocks HIV's ability to latch onto the CD4 cells' coreceptors. So the actual mechanism of the control is unknown. But for lack of another expression, functional cure appears to be the best way to describe the phenomenon. (Provided, of

course, that the child didn't just receive a successful prophylaxis.)

"An HIV cure is not really widespread enough for us to know what it's going to look like or what we're going to call it in different people," Johnston reflects. "We're really, at this point, putting the feelers out there and wondering what a cure would look like and what we'd call it if we saw it."

As for the particles of HIV that do remain in the baby, Johnston speculates that they may be what's known as "replication-incompetent" copies. The virus is notoriously sloppy at reproducing itself, with 99 percent failing to do so. And because ARVs can only attack viruses that are replicating in human cells, the incompetent virus would remain behind, most likely posting no threat to the body since it can't replicate. Persaud also has argued that HIV's very presence in this form is further evidence that this child was infected.

Scientific Baby Steps Forward

"It's a single case," says NIAID's Fauci. "And in medicine, you've got to be really careful not to make broad extrapolations on a single case."

Fauci argues that if nothing else, the findings about the Mississippi baby may lead researchers to revisit guidelines about when to use a prophylactic versus a therapeutic dose of ARVs for a newborn, which are based on an assessment that weighs the risks of toxicity from a higher dose of medications over the likelihood that the child will become infected with HIV.

"Now that you have the possibility that you might cure the baby, this maybe turns the risk-benefit a little more in favor of being a little more aggressive in treating babies at birth," Fauci says.

Such a shift could possibly have significant repercussions in the global fight against HIV. But not before much more research is done.

"Hopefully we can replicate this," Persaud says of her research, acknowledging that 10 months is a very short follow-up. "And if we can't, then we'll be like the Berlin Patient to date. I think what it tells us is that in a rare individual you can clear or prevent establishment of reservoir with specific intervention. It informs knowledge going forward; it raises the bar for science. And we do have to continue toward the mission of achieving remission of HIV for infected children and adolescents and adults. That's our goal."

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http://beta.docker.poz.com/article/functional-cure-23739-6444