The Cure For HIV Is Not Around the Corner

Cutting through the hype and hyperbole.

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The news broke in April 2013. Danish researchers were mere months from finding a cure for HIV. As other media outlets eagerly picked up the Telegraph's electrifying report, word coursed lightning-swift online and through social media, stoking hopes that talk of ending the HIV epidemic, increasingly common of late, might soon become reality.

There was one snag: The U.K. paper's astonishing headline, "Scientists on Brink of HIV Cure," wasn't true. Researchers at the Aarhus University Hospital in Aarhus, Denmark, were, and still are, researching an HIV cure—that much was a fact. The Danish facility is one in a collection that is investigating cancer drugs known as histone deacetylase (HDAC) inhibitors as a means to flush the virus from the so-called latent reservoir where it hunkers down, craftily evading antiretroviral (ARV) treatment. But the Aarhus University research is only in an early phase of the multi-year process of human trials. And there is no guarantee that the investigators are more than scratching the surface of the daunting task of finding a broadly applicable cure for such a complex viral infection as HIV.

The Telegraph, which eventually revised the online article while the hospital released its own correction (the paper does not appear to have run one), is hardly alone in claiming, or at least implying, that an HIV cure is imminent. Nor is HIV the only health concern to inspire such erroneous hyperbole. Ever since President Richard Nixon announced the "war on cancer" in 1971, news outlets have repeatedly raised hopes of major victory on that front.

A typically tantalizing HIV-related headline comes from the website Medical Daily, which in March enthused that a functional cure—wherein the virus is not totally eliminated from the body but is under control without ARVs— was a "step closer to reality."

However, Michael Farzan, PhD, a prominent HIV cure researcher and a professor at Scripps Research Institute in Florida, says, "It's hard to say how far along we are, from start to finish" in the quest for an HIV cure. "Who knows; we could have moved one inch in a 100-mile race."

Zhi Hong, PhD, head of infectious disease research at GSK (GlaxoSmithKline), which is one of several pharmaceutical companies investing in cure research, puts the matter more definitively: "There's no

illusion that [a cure] is not going to take decades to come to fruition."

Overzealous members of the media are hardly the only ones contributing to public misperceptions of cure research. Perhaps unintentionally—his words ran contrary to all other public messaging from his global health-focused foundation—Microsoft co-founder Bill Gates told attendees of the World Economic Forum in January that both an HIV vaccine and the means to save people living with the virus from the need to take daily ARVs would arrive by 2030.

Richard Jeffreys, an HIV vaccine and cure expert at Treatment Action Group, scrutinized Gates's words in a post on TAG's website, reasoning that "hope does not equate to inevitability."

"Gates's buoyancy," Jeffreys wrote, "does have some scientific basis—there have been encouraging signs of progress on both the vaccine and cure fronts in recent years—but the challenges that lie ahead must not be underestimated."

Then there's the exuberant fundraising messaging coming from amfAR, The Foundation for AIDS Research, which sends frequent emails signed by CEO Kevin Frost in which he characterizes the nonprofit's "Countdown to a Cure" initiative as devoted to "unlocking HIV's final mysteries" or clearing the "final hurdles" blocking an HIV cure.

A high-concept fundraising video published on the foundation's website in April says that the fight against HIV has made it to "the final mile of an epic journey," and that "a cure for all is so close. The end is finally in sight. All we need to do is grab the torch and take it over the finish line." Only at the very end of the 1,000-word promotional text does amfAR pivot from its repeatedly underlined claim that the foundation's goal is to find "a broadly applicable cure for HIV by 2020" to finally clarifying that it actually aims to help establish the "scientific underpinnings of a cure" by then. The initial amfAR news release announcing the cure initiative in February 2014 never made such a clarification.

Meanwhile, Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health (NIH), says that success on the cure front is a matter of "if" rather than "when."

"That doesn't mean that there's any giving up on trying," he says. "But you've got to realize where you are in the process."

Bucking the trend of overly effusive reports on cure progress, CNN ran a headline on its website in July quoting the French virologist Françoise Barré-Sinoussi, PhD, co-discoverer of HIV, who argued that "to develop a cure is almost impossible."

Headlines are by their nature reductive, certainly because of space constraints, but perhaps more so because journalists' efforts to lure readers often subvert nuance or specificity in the text. In this case, CNN left many with the dispiriting impression—just as inaccurate as the notion that a cure is around the corner—that Barré-Sinoussi thought all hope was lost. But as the interview clarifies, the Nobel laureate's claim was more pragmatic than pessimistic, and hinged on her description of the extreme difficulty of eliminating every last HIV-infected cell from the body. (When referring to success in such a feat, many scientists use more specific terminology, calling it a sterilizing cure.) She argued that what she called remission, in which the virus is brought to very low levels and kept there without daily meds, is a more viable goal, one that others call a functional cure.

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Of course there is one person who has been cured of HIV: Timothy Ray Brown. The 49-year-old American is also known as the Berlin Patient, after the city in which he was treated for leukemia and given two bone marrow transplants, in 2007 and 2008, from a donor whose immune cells were naturally resistant to HIV thanks to an inherited genetic mutation about 1 percent of Caucasians possess. (Leukemia is cancer of the bone marrow, which manufactures immune cells. A bone marrow transplant gives an individual someone else's immune system after theirs has been intentionally destroyed, typically by chemotherapy.)

Until Brown's case was first reported, and then widely heralded, in 2008, a cure for HIV was the research ambition that dared not speak its name. The absence of replicating virus in Brown's body established what scientists call a proof of principle—in this case, that a cure is possible—and it jolted the cure field to life. More scientists got on the bandwagon, and research grants flowed.

The challenge before them is formidable. The principal foe is the viral reservoir, an amorphous entity made up of cells infected with the virus in an unreplicating form, and which may also include infected cells out of reach of standard treatment, such as in the brain. Standard HIV treatment doesn't eliminate the reservoir because ARVs only work when a cell is replicating, and because not all the meds can cross the so-called blood-brain barrier.

Unfortunately, Brown's cure is not widely applicable. Such cancer treatments, which are highly expensive, have a steep fatality rate; post-Brown, similar efforts to cure HIV and cancer simultaneously in six others have failed, or the individuals have died before researchers could establish if the HIV cure pursuit was successful. Attempts to prepare the body for a bone marrow transplant with less potentially lethal means have also failed to vanquish HIV.

A critical obstacle facing cure efforts is that scientists haven't developed tools refined enough to determine with absolute certainty that there are no latently infected cells hiding out in someone's body that might years later come to life, start producing new copies of HIV and ultimately repopulate the reservoir. A major element of the search-and-discovery work that largely characterizes the cure field today is the attempt to map the reservoir, and to develop tests that can accurately measure its presence. Nascent versions of such tests are helping scientists determine the success of current attempts to at least reduce the size of the reservoir.

The disappointing case of the famed Mississippi Baby illustrates not only the pitfalls of this inability to properly detect and measure the reservoir, but also the scientific community's lack of standards for describing an HIV cure, or anything in that general ballpark.

At the 2013 Conference on Retroviruses and Opportunistic Infections (CROI) in Atlanta, Deborah Persaud, MD, a pediatric infectious disease researcher at Johns Hopkins Children's Center, set off a media frenzy when she announced that a then-18-month-old child in Mississippi had been functionally cured of HIV.

In some ways, the qualifier "functional" acknowledges the impossibility of declaring success in achieving a sterilizing cure. Again, a functional cure is generally defined—there is no official definition—as a case in which someone is not infectious, and although he or she still harbors HIV, the virus is under control without the need for ARVs.

After the Mississippi Baby was infected at birth by her mother, doctors quickly started her on an atypically aggressive cocktail of ARVs. Her mother eventually interrupted the treatment, and by the time Persaud first presented the case to fellow scientists, the girl had spent 10 months off ARVs without a viral rebound. Highly sensitive tests could, however, still detect traces of the virus in her body. Persaud says she used the word "functional" at the time because she felt not enough time had passed to confirm that the child was, simply, cured.

This period came to a close after 27 months, when the child's viral load rebounded and she was put back on ARVs in 2014.

"The field has to really stop and think about terminology and expectations," reflects Persaud, who is among the leaders of a trial seeking to replicate the Mississippi case in newborns infected at birth around the world.

There is hope that other children will fare better than the Mississippi Baby (whose case, along with other failed cure attempts, has taught scientists a great deal and helped shape and propel future research). July's International AIDS Society Conference in Vancouver, British Columbia, heard news that an 18-year-old French woman has 12 years of remission under her belt after being born with HIV, initially receiving prophylactic treatment, and then spending six years on ARV combination therapy before quitting treatment. Researchers can still find some HIV DNA in her body, but she has no detectable viral replication in her plasma.

Another dozen French individuals, known as the Visconti cohort, have been in a state of remission for a median decade after stopping the ARV treatment all of them started within six months of contracting HIV. Scientists believe that, in each of them, such prompt treatment prevented the viral reservoir from significantly entrenching itself.

Asier Sáez-Cirión, PhD, of the Institut Pasteur in Paris, first presented data on the Visconti cohort at CROI 2011; but, in his words, the news went "almost unnoticed" at the time. In recent years it has garnered more interest, but nothing compared with the Mississippi Baby. The vast disparity in attention directed at Sáez-Cirión's and Persaud's respective announcements may be attributable to semantics. Sáez-Cirión has from the start eschewed the glamour and excitement of the word "cure," with or without a qualifier, and has steadfastly insisted on characterizing these French individuals as being in a state of remission.

The word "remission," Sáez-Cirión reasons, evokes a concept people are familiar with from cancer: The disease is gone, but there's always a chance it could return. "When you use the term 'functional cure,'" he adds, "sometimes the 'functional' part is dropped and the 'cure' part remains. It creates some confusion."

Indeed, many of the headlines concerning the Mississippi Baby stated only that she was cured, thus stripping the message of any nuance. Touting its contributions to the case (another possible reason the case received so much media attention), amfAR stated in a press release that "confirmation of the cure was made possible" in part by an amfAR grant supporting Persaud's research.

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In marked contrast to the foundation's fundraising pitches, amfAR's director of research, Rowena Johnston, PhD, strikes a measured tone when describing the current state of HIV cure research, saying,

“Thoughts around the key challenges are starting to coalesce. Not that [researchers] have necessarily found answers or all of the answers. But that people are really starting to agree what the challenges are.”

One major element that is increasingly coalescing is money. According to a July report from the global HIV advocacy group AVAC, worldwide public and philanthropic investment in cure research leaped by 82 percent between 2012 and 2014, from $88 million to $160 million. The lion’s share comes from the United States, mostly in the form of NIH grants, with $114 million given in 2014 and an estimated $127 million slated for 2015. AmfAR intends to rapidly scale up its annual cure funding from $4.4 million in 2014 to give researchers a total of $100 million over a six-year period starting in 2015. The Gates Foundation granted about $9 million to cure research in 2014.

Such figures are still paltry compared with recent HIV vaccine research investment; the NIH spends over half a billion dollars annually on that front. According to Fauci, the disparity between cure and vaccine funding is not a reflection of the agency’s lack of enthusiasm for the cure cause. Rather, vaccines get more money because the field is more advanced; vaccines are primarily in the development, rather than discovery, phase.

“The investment goes up once you have specific leads to pursue, and the relatively greater NIH investment in HIV vaccine research at this point in time reflects that,” Fauci says.

AVAC’s overall cure research figures don’t account for industry spending. GSK recently pledged $20 million over five years for a joint effort with the University of North Carolina (UNC), Chapel Hill. Additionally, Merck, Gilead Sciences, Janssen, and the biotech companies Sangamo BioSciences and Calimmune are all in the search.

The field is increasingly collaborative. In 2011, the NIH established the Martin Delaney Collaboratories, which has encouraged cooperation between academia and the private sector. There also is collaboration between amfAR grantees.

When it comes to research that goes beyond background study and progresses into actual curative therapies, the biggest focus is on a method known as shock and kill, or kick and kill. In the first part of this strategy—the shock or kick phase—an agent, or combination of agents, spurs the machinery of latently infected cells back into action. The subsequent challenge—the kill part—is to find ways to clear the body of those newly active cells.

Unfortunately, ARVs don’t kill HIV-infected cells. Nor does the immune system, in part because these particular cells have so few HIV antigens on their surfaces. (Antigens flag a cell as infected and help summon an immune response.) Confounding the issue, a person’s immune response to HIV may have lessened after years of taking ARVs, and the virus in latently infected cells may have mutated to resist the immune system’s primary line of attack.

The lab of Robert Siliciano, MD, PhD, at Johns Hopkins University, leads the shock-and-kill field, which includes efforts from more than two dozen groups around the world, such as the UNC-GSK team and the Danish lab that spawned those erroneous headlines. Researchers are testing at least six latency-reversing agents in humans, including the HDAC inhibitors vorinostat, panobinostat and romidepsin.

Scientists on the kill front are exploring various means of boosting the immune response in order to give

rise to immune cells or antibodies that can more effectively attack the reawakened infected cells.

According to David Margolis, MD, who heads up the UNC effort, shock and kill is still in "in its infancy," but it has enjoyed some recent advances. "The biggest limitation to forward progress right now," Margolis says, "is that we haven't yet really developed safe and effective ways to substantially deplete the reservoir that we can measure." In other words, with research into the kill part of the strategy only just beginning, any results are particularly insufficient. "I think that after hopefully not too long, maybe a year or two, we will have forward motion in that regard."

Fauci, however, is "not at all sure" that the overall shock and kill approach will prove successful.

Delving further into the realm of science-fiction-come-true is research into curative genetic therapies. Researchers are trying to recreate Tim Brown's case (or at least partially so), but without the danger and impracticality of a traditional bone marrow transplant.

Brown's donor had a genetic mutation that prevented development of what's called the CCR5 coreceptor, which is located on the surface of the CD4 immune cells that HIV targets. Without CCR5, most copies of HIV can't latch onto the immune cell, much less infect it. So scientists at Sangamo and the Fred Hutchinson Cancer Research Center, among others, are experimenting with drawing out an HIV-positive individual's immune cells, or immune cell-producing stem cells, and editing their genetic code to ultimately prevent the development of the CCR5 coreceptor.

Sangamo has had some promising results from the company's genetic treatment, with one 32-year-old man off ARVs for over a year and a half following an infusion of edited, HIV-resistant immune stem cells. He isn't cured—the virus is still actively replicating—but his viral load is only about 500 and his CD4 level has remained stable.

This is an example of the partial success that researchers may build upon as they reach for the pie in the sky. Each of these individual steps may offer new and exciting health benefits to people living with HIV. Ultimately, multiple approaches may be required to beat back the virus further than ARV treatment is already able to do.

"There are many routes of attack" in the cure quest, says the Nobel prize–winning virologist David Baltimore, PhD, a professor at the California Institute of Technology and the founder of Calimmune, "and from my point of view, the word cure is perhaps misleading. What we want to do is make this a less and less debilitating disease. And what that means is limiting the effects of the virus and also moving toward forms of therapy that are less debilitating to the patient."

Another incremental advance that cure research may achieve is to reduce the kind of low-level viral replication that occurs even in the presence of successful ARV treatment. Scientists suspect this activity from the virus may spur the immune system into a state of chronic inflammation, which is believed to contribute to the increased risk of age-related disorders among people living with the virus. Another shorter-term ambition is for treatments that would allow for periods of extended viral remission, giving HIV-positive people a safe way to take time off from the toxicities of ARVs.

Vastly shrinking but not totally eliminating the reservoir may allow for such extended remission. Case in point, the members of the Visconti cohort don't have zero reservoir; it's just very small in each of them. (Scientists do have the tools to determine this.) A recent study found that if someone stops taking ARVs,

on average, a week will pass before at least one latently infected cell successfully reactivates and is able to kick start a viral rebound. Considering the vast number of cells in the typical reservoir, the implication is that any given cell only rarely jumps into significant action. Based on these observations, the paper's authors estimated that a 50-to-70-fold reduction in the size of the reservoir could extend the time between stopping ARVs and a viral rebound to an average of one year. Siliciano has made his own projection that some people with HIV may experience lifelong remission with as little as a 1,000-to-10,000-fold reservoir reduction.

"We might get interventions that work a good part of the time in good sections of the people," says amfAR's Johnston. "And so it will be this interactive process over time until you get to an intervention that cures most people most of the time. Maybe that's as good as we can hope for."

Assuming such advances do come, there is the pressing question of access. The new $100,000 hepatitis C cures are threatening state Medicaid and prison health budgets nationwide, and insurers have been restricting who can receive treatment.

The process required to draw out, edit and reinfuse an HIV-positive person's immune cells is quite expensive, and the cost can't necessarily be brought down simply by pharmaceutical companies allowing generic production, as with ARVs used in poorer nations. (Although compared with lifelong ARV treatment, the cost for such a cure might be a bargain, especially if a one-time curative therapy is all that's required.) With the ultimate goal of expanding such a potential opportunity to populations beyond the wealthy Western world, researchers hope that a similarly successful outcome wouldn't require such a complicated process, and instead would come from a generalized vaccine-like shot, or maybe a series of shots.

"At the end of the day, if you have what you're calling a cure or a sustained virologic remission, it's got to have the three S's: safe, simple and scalable," says NIAID's Fauci. "Otherwise you're going to cure a handful of people that are going to make the front page of The New York Times, and then you can't do much else for the 36 million other people who are infected."

HIV Cure Research, In Short

HIV cure research is in what's known as the discovery phase. The field is largely characterized by efforts to better understand just what scientists are up against in their quest to cure the virus.

Major avenues include:

- Characterizing the viral reservoir. What kind of cells are in the reservoir and where in the body are they located?
- Developing tests to measure the reservoir. This is vital to be able to measure the success of attempts to reduce the size of the reservoir.
- Determining how the reservoir manages to persist.

Current therapeutic pursuits include:

- “Shock and kill” or “kick and kill,” in which an agent or combination of agents, such as cancer drugs called HDAC inhibitors, are used to flush the virus out of latently infected cells. Then another method is used to prompt the body to better eliminate those cells.
- Genetic therapies. Researchers are trying to recreate the Berlin Patient’s cure by editing immune cells or immune-cell-producing stem cells to ultimately populate the body with HIV-resistant immune cells.

Common terms:

- Sterilizing cure: totally ridding the body of HIV.
- Functional cure: There is still some virus in the body, but it’s under control without the need for daily meds.
- Remission: Some researchers prefer to use this term instead of “functional cure,” because it is familiar to people from the world of cancer and implies that the virus may rebound, as was the case with the Mississippi Baby.

International investment in cure research:

2012: $88 million
2013: $105 million
2014: $160 million

These figures do not reflect for-profit investment. Many biotech and pharmaceutical companies are pursuing cure strategies. For example, GSK recently pledged $20 million over five years to the University of North Carolina, Chapel Hill.

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http://beta.docker.poz.com/article/HIV-cure-update-27811-1952