Is "Cure" Still A Four-Letter Word?

AN HIVISION PUBLIC FORUM

"There is so much to be gained by putting the resources we need into HIV research in all areas—including, I strongly believe, finding a cure."

—Rowena Johnston

On May 19, 2011, San Francisco AIDS Foundation held a public HIVision forum provocatively titled, "Is 'Cure' Still a Four-Letter Word?" The forum acknowledged the controversy that has surrounded the quest for a cure for HIV and explored the latest research and challenges in this field.

In his introduction, foundation CEO Neil Giuliano recalled that, following years of disappointment, "cure" became a taboo topic in HIV research and advocacy. Scientists, clinicians, and people with HIV feared it was a promise that would never be realized, and argued that limited resources for HIV/AIDS should instead be targeted toward prevention and care. Indeed, in 2007, Anthony Fauci, longtime director of the National Institute for Allergy and Infectious Diseases at the National Institutes of Health (NIH), famously declared, "This is a hugely exciting time in the world of AIDS research. We've got incredibly potent treatments on the horizon, possible vaccines in the pipeline, and new options for using these things in ways we haven't before. But, as for a 'cure,' let's just stop talking about it."

Today, HIV cure research is enjoying a resurgence, with momentum it hasn't seen in years—including a new $70 million funding initiative by the NIH. The HIVision forum highlighted promising research and funding developments, as well as challenges anticipated on the road to a cure. Invited panelists included **Rowena Johnston,** PhD, vice president and director of research at amfAR, the Foundation for AIDS Research; **Steven Deeks,** MD, professor of medicine in residence at the University of California, San Francisco (UCSF), and faculty at the Positive Health Program, San Francisco General Hospital; **Moupali Das,** MD, MPH, director of research in the HIV Prevention Section at the San Francisco Department of Public Health and assistant clinical professor of medicine at UCSF; and **Matt Sharp,** longtime HIV treatment advocate and person with AIDS. The panel was moderated by **Shalini Eddens,** executive director of the Well Project.

Why do we need a cure for HIV?

"We could prevent every new infection tomorrow and still there'd be roughly 34 million people in the world living with HIV.…We absolutely need a cure."

—Rowena Johnston

With the availability of effective, more tolerable antiretroviral drugs, HIV has come to be viewed by many as a just another chronic disease; they question whether a cure is really necessary.

Rowena Johnston and Matt Sharp asserted that it is financially unsustainable to provide life-long treatment for the growing number of people living with the virus globally. As Sharp pointed out, "we can't get drugs to everybody as it is now."

In addition, HIV-related stigma persists in the U.S. and around the world, discouraging people from seeking both testing and treatment. Those who do know their status and begin treatment are committed to a lifetime of daily medication, and many are encountering new physical challenges as they age with the virus. Finally, available antiretroviral drugs do not work equally well for everyone.

For these and other reasons, the panelists agreed, it is imperative to find an HIV cure. Perhaps Sharp put it most poignantly: "I've been positive for over 20 years; I don't want to take drugs anymore. I have the right to say that and to want a cure."

How do we define "cure"?

"There's a perception out there of what a cure is going to be, and then there's the reality. I think it's going to take time for those two to meet."

—Matt Sharp

The panelists offered different perspectives on the definition of "cure." Speaking as a researcher and a clinician, Steven Deeks described two broad definitions: a *sterilizing* cure, which refers to the complete elimination of HIV from the body, and a *functional* cure, in which some virus may remain but is kept in check by the immune system.

The latter is generally held to be the more realistic and practical goal; indeed, Johnston argued that what the average person living with HIV wants is to stop taking antiretroviral drugs while maintaining good health and eliminating the risk of transmitting the virus to others. A functional cure is "what the real-world patient is looking for," she said.

"'Cure,' in the community, is a very loaded word," added Sharp. "We've been through a period of time in the epidemic where there was no possibility there would ever be a cure. It was this dogma that existed both in the scientific community and then among people living with HIV." He sees more optimism today: "The more we all learn as a community,…the more accepted it is that there's a possibility for a cure."

Das added that a potential cure can also be viewed in terms of eradication at a *population* level, as has been achieved for other life-threatening diseases. She argued that, in additional to an individual-level cure, it is essential to consider approaches to eliminating all transmission of HIV in order to truly end the pandemic.

What have we learned from the "Berlin Patient"?

"What this case has done is inspired and given optimism and hope that curing HIV really is possible and is something that we absolutely should pursue."

—Rowena Johnston

To date, only one person appears to have been cured of HIV infection: Timothy Brown, an American formerly living in Germany—and formerly living with HIV.

When Brown, previously known only as the "Berlin Patient," needed a stem cell transplant to treat leukemia, his doctor located a donor with the rare CCR5-delta-32 mutation. This genetic mutation renders the immune system's CD4 cells unable to produce CCR5, a protein that serves as a receptor for HIV and permits the virus to enter and infect cells.

Brown underwent strong chemotherapy to essentially kill off his own HIV-infected immune cells, then received an infusion of donor stem cells, which ultimately produced new CD4 cells that lacked the CCR5 receptor. His new immune system was, in effect, resistant to HIV infection. Four years after his stem cell transplant, Brown remains off antiretroviral drugs and has no detectable HIV in his blood, lymph nodes, rectal tissue, cerebrospinal fluid, brain tissue, or other known viral reservoirs.

Stem cell transplants carry serious health risks and cannot be "scaled up" and used for everyone. But despite the fact that Brown's cure cannot be generalized, it has provided scientists with key insights about what to look for in a cure.

What strategies are currently under study for curing HIV?

"Ultimately, a cure will likely involve a combination of various approaches….If HIV taught us one thing, it's that typically when you're going after a hard thing to accomplish, bringing in more than one approach works."

—Steven Deeks

As Johnston explained in her overview presentation, current HIV cure research falls into three general categories: gene therapy, pharmaceutical treatment, and immunotherapy. All three approaches have been tested in clinical trials, with varying degrees of success.

Gene Therapy

Gene therapy techniques attempt to manipulate the genetic material, or DNA, inside an individual's cells in order to resist infection or manage disease. One such strategy that has reached the clinical trial phase for HIV infection attempts to mimic the CCR5-delta-32 mutation that renders a person's CD4 cells resistant to HIV infection.

In two related trials, CD4 cells were filtered out of participants' blood and modified using a zinc finger nuclease, a protein engineered to cut DNA strands at the region coding for the CCR5 gene. These modified cells were then re-infused into trial participants, where they grew a new population of CD4 cells lacking the gene for CCR5 and therefore resistant to HIV infection.

The first results from these trials were promising, with all but one participant showing significant increases in overall CD4 cell counts after receiving the modified cells. Researchers also reported increases in the number of CCR5-negative CD4 cells over time, indicating the potential for these cells to replace non-modified CD4 cells over time.

One of the greatest limitations of this approach comes from our own immune system. The vector used to deliver the zinc finger nuclease to CD4 cells is a virus related to the common cold. This virus is relatively harmless in itself, but some individuals who have prior immunity to it may mount a cellular defense to attack and destroy the vector—and the zinc finger nuclease along with it.

This was the case for the one individual who experienced no CD4 cell count gains during the gene therapy trial, suggesting that this particular cure strategy may be of limited use for individuals with prior exposure to the virus used as a vector.

Pharmaceutical Approaches

Researchers have long known that HIV can remain hidden inside cells for many years. In an approach that has come to be known as "shock and kill,"

chemical compounds are used to nudge HIV out of its hiding places in the body, followed by antiretroviral drugs or other treatments to rid the body of newly flushed-out virus.

Disulfiram is one compound being tested for this strategy that has reached the clinical trial stage, having already been shown to flush latent HIV out of cells in a laboratory setting. Panelist Deeks is currently testing the compound in humans, in collaboration with Robert Siliciano, MD, PhD, from Johns Hopkins University. The trial recently finished enrolling participants.

As with gene therapies, this approach faces obstacles. Shocking cells to shed HIV can be tricky, as multiple systems within cells work to keep the virus latent; a given compound might address one of those systems, but the others could compensate to prevent cells from shedding the virus. Similarly, HIV may infect multiple types of immune cells; a strategy effective for CD4 cells may not work for macrophages or glial cells. And different strategies may be necessary to shock HIV out of cells in the body's different systems or regions, such as the nervous system and the digestive tract. Lastly, it may be difficult to clearly define doses that shock cells effectively without causing cellular damage.

The "killing" poses additional challenges. After shocking cells into shedding HIV, it is essential to neutralize the virus quickly. As Johnston put it, "you don't want that HIV to go on and infect even more cells that had not been previously infected."

Little is known about the most effective strategies for eliminating newly shed virus. Scientists assume treatment with antiretrovirals, in combination with the body's own antibodies and cytotoxic T cells, will be sufficient for the job. More will be known when results from the disulfiram study become available.

Immunotherapy

Immunotherapy strategies attempt to enhance the body's own immune mechanisms to better respond to HIV infection. Such strategies have been used successfully against cancer, setting a precedent for trials of an immune-based cure approach. The EraMune02 trial, ongoing at sites in the U.S. and Europe, is assessing whether intensified antiretroviral treatment combined with an immune-boosting vaccine—using either DNA or the cytokine interleukin-7—can provide a functional cure.

In contrast to a traditional vaccine, which is administered prior to exposure and aims to *prevent* infection, therapeutic vaccines are intended to help control HIV in those already infected by amplifying the body's natural immune response.

A therapeutic DNA vaccine contains genes for specific HIV proteins. When the body's cells take up these genes, they begin producing these HIV proteins. Researchers hope that the body's immune system will recognize these proteins as harmful agents and mount a powerful anti-HIV response. Similarly, cytokines help regulate immune response and modulate the growth and activity of specific immune cells.

The goal of immunotherapy strategies is to help individuals control their HIV for extended periods and reduce their need for antiretroviral treatment. Essentially, this approach would create long-term non-progressors—people who naturally suppress viral replication without drugs. As scientists continue to learn more about immune function, immunotherapy strategies may become centrally important in the quest for a functional cure.

A Combination Cure

Each of the promising strategies currently being tested in HIV cure research attacks a different aspect of HIV infection. For this reason, Deeks suggested that an eventual cure will likely involve a combination of two or more approaches: "I can't really say upfront which of these three different approaches is most promising, but I doubt that any of them alone will work—what will work is a combination."

In the quest to end the pandemic, what is the place of cure research relative to other responses to HIV, including efforts around prevention, testing, and access to care?

"We need to do all *of it."*

—Moupali Das

Despite promising new developments, some of the fiercest opposition to cure research comes from scientists and advocates who are reluctant to take on cure research because they fear it will divert resources from other areas of HIV work. Particularly given the availability of effective and increasingly tolerable antiretroviral drugs, not everyone is certain that funneling already limited resources into cure research is worthwhile.

Johnston, however, is convinced of the necessity. "If we don't do any research to *find* a cure," she reasoned, "we can guarantee that there will not *be* a cure." She argued that debates over the benefit of preventive vaccine research versus treatment research versus cure research are based on the assumption of a "fixed-size pie." Rather than haggle over limited resources, Johnston said, "what we really should be doing is seeing what we can do about increasing our resources and really getting to a point where we can address the epidemic in the ways it needs to be addressed," including cure research and intensified efforts around testing, treatment, and linkage to medical care.

Moupali Das agreed, suggesting that "a concerted, coordinated approach" to all of those aspects of HIV work could identify areas of overlap and free up resources "to make sure we have enough funding to try to find a cure while we're trying to take care of the people who are positive and make sure the negative people stay negative." Sharp concurred, observing that the HIV pandemic is "not going to be solved by treatment alone or prevention alone."

How can we ensure that any eventual cure is distributed equitably to all who need it?

"We can learn from the past 30 years of what we've done to advocate for equity, and see if we can use those same approaches to make sure people have access to the cure."

—Moupali Das

In addition to the (sometimes controversial) costs associated with cure research, a major concern revolves around the cost of the cure itself and of its distribution. Johnston frankly admitted, "We don't know how much this is going to cost," and observed that the price of the intervention and whether insurance coverage is available may stratify cure access by socioeconomic status. "There is always the problem of getting treatments to disenfranchised communities," said Sharp.

Deeks suggested that a cure need not be exorbitantly priced, however. "Let's assume a cure will take a combination therapy, a cocktail," he said, involving a daily pill of a chemical compound to flush the virus out of reservoirs, several shots of a therapeutic vaccine to boost the immune system into killing the newly released virus, and a monthly infusion of monoclonal antibodies to help reverse the inflammatory signals that cause the virus to go into hiding. In Deeks' words, "That's scalable. That's doable. That's affordable. That could be done anywhere in the country. That could probably be done anywhere in the world."

However, Deeks cautioned that, regardless of the cost of the cure, the patient characteristics that may ensure its effectiveness are *not* equitably distributed. In his view, an HIV cure may be most effective in those who started antiretroviral therapy soon after becoming infected and have maintained high CD4 cell counts (above 500 cells/mm^3)—certainly not the picture of every person living with HIV.

Panelists feared that, as long as socioeconomic disparities continue to delay HIV testing and frustrate access to treatment and engagement in care, the equitable distribution and success of an eventual HIV cure will face major hurdles. "The people who have other issues that are preventing them from taking medications and taking care of themselves" are likely to also have trouble accessing a cure, argued Das, citing untreated mental health issues, substance use problems, and lack of stable housing as serious obstacles. "We know what those issues are because we've been dealing with them for the past 30 years. They're often the same issues that make it more likely for some groups of people to get HIV."

On a positive note, Das reminded the audience that we can draw on decades of experience advocating for and working toward widespread access and adherence to life-saving antiretroviral drugs. Johnston agreed: "It's going to be crucial for AIDS activists to be involved in whatever comes out to be the cure," she said, "because these are the people who have the interest, the energy, the knowledge, and the will to make it happen."

Is there a conflict inherent in the participation of drug companies in both treatment research and cure research?

"I do think there's a genuine desire at the companies I've worked with to actually be involved in something as transformative as a cure."

—Steven Deeks

The antiretroviral drug industry is a profitable one, driven by the need for life-long treatment, which leads some to suspect that pharmaceutical companies have a strong disincentive to invest in cure research.

Forum panelists had a more pragmatic outlook, however. While they acknowledged the underlying profit motive for all pharmaceutical companies, they agreed that an HIV cure is unlikely to bankrupt any of them. "Most of the companies that have HIV drugs on the market today are making a lot of money, but they're big, big, big corporations, and they make money off of other diseases, as well," said Sharp. "Let's face it, there's always going to be another disease for companies to make money off of!"

Deeks emphasized that, ultimately, pharmaceutical companies do have a financial incentive to pursue a cure: "We do think that [HIV] is ultimately going to be cured, and it's going to be cured with drugs. So some company is going to make money."

"It's disingenuous for us to imagine that there are no drug companies out there that don't enjoy making money and that might feel they might make less money if there were a cure. No doubt there are companies like that," Johnston said. But, she reminded the audience, "there are scientists who *work at* companies, and then there are *companies,"* and the researchers who conduct drug trials within the industry "really are interested in working out how to deal with the epidemic."

What will it take—from advocates, researchers, and funders—to cure HIV?

"I think we, as a community, need to have hope. …If you all leave here tonight and tell somebody about this forum and what you heard, and spread the word—that's what it's going to take on a community level."

—Matt Sharp

The panelists resoundingly agreed on the importance of ongoing advocacy efforts for building public support for cure research, and to ensure that scientists engage in this research and that adequate funding is made available.

Deeks reminded the audience that when news of the "Berlin Patient" first appeared, it was not the scientists who took notice, but advocates. "I was shocked by that—that the scientific community was just not interested, and no one talked about it!" Only after advocacy efforts around the story generated media buzz did scientists became interested, he recalled. Now, it's nearly impossible to talk about cure research without mentioning Timothy Brown's case.

Similarly, Johnston noted that a major obstacle to *funding* cure research is getting the researchers on board. "You might be assuming that scientists are gung ho for this, that they're behind it, that they want to do it," she explained, "but you would be astonished at how fiery and fierce a reaction you can get from a group of scientists if you start to talk about trying to seriously pursue a cure scientifically."

Johnston went on to describe amfAR's unique solution to this problem: the amfAR Research Consortium on HIV Eradication (ARCHE). As the director of ARCHE, Johnston identifies research opportunities and facilitates connections between HIV scientists, with the goal of fostering productive, innovative collaborations. The consortium also offers a shortened application cycle to ensure that promising studies are funded as quickly as possible. Whereas a traditional NIH funding application cycle can take up to two years complete, a recent ARCHE-sponsored collaboration between Deeks and Robert Siliciano sped from developing a study protocol to enrolling participants within six months.

Such innovative solutions will continue to be important in the journey toward a cure. As Stephen LeBlanc of the AIDS Policy Project mentioned during the audience discussion, despite a resurgence in the field, relatively few scientists are pursuing a cure. The community needs to be pushing harder for more money and more trials, he urged.

Advocacy groups such as AIDS Policy Project and Project Inform are already doing much to bring attention to the issue and galvanize support. For example, a recent AIDS Policy Project report highlighted the dearth of funding for cure research. Project Inform and the Treatment Action Group recently organized a clinical research meeting that brought together scientists to discuss cure research.

In addition to advocacy, commitment from scientists, and adequate funding, progress toward a cure depends on the courage and volunteerism of trial participants. As cure research gains momentum (and money), increasing numbers of volunteer study participants will be needed to evaluate cure strategies.

As Deeks explained, no one should expect to be cured in these early clinical trials; however, such altruism is not new to the HIV community. Indeed, audience member Loreen Willenberg thanked panelist Sharp for his participation in a gene therapy trial, and pointed out that long-term non progressors, a community for whom she advocates, have made themselves available for repeated poking and prodding over many years to help scientists learn from their ability to control HIV replication without antiretroviral treatment.

Similarly, Deeks and Das both noted that San Francisco is fortunate to have a well-informed and engaged community of people who are willing to participate in research. Das advocated for greater effort to increase diversity among clinical trial participants: "We could even do better here to increase representation of different racial and ethnic minority groups and people from different neighborhoods and different walks of life in our research projects—and try to do it in a way that empowers people."

Das also reminded the audience that it may take some years before a cure for HIV becomes widely available, and emphasized the need to maximize the benefits, meanwhile, from our existing toolkit: "We need to make sure everybody knows their status, and we need to make sure that everyone who is positive is linked to care, supported in care, and on treatment so we don't have unnecessary death and morbidity while we're waiting for a cure."

Conclusion

As the panel and audience discussion showed, there is renewed hope that a cure is possible within our lifetime. Johnston acknowledged that, over the years, cure advocates have been accused of raising false hope—but as Sharp observed, we need to have hope in order to maintain the current momentum in research toward a cure. "We're not promising [a cure] to anybody in the next year or two…but we're hopeful," Johnston concluded. "I hope that everybody else is hopeful, because this is the right place for us to be traveling."