Is It Ethical to Take People Off HIV Meds for Cure Research?

Cure studies typically require a temporary break in HIV treatment, often with little promise of a personal benefit to the participant.

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In recent years, researchers have firmly established that people living with HIV can best protect their health by starting antiretroviral (ARV) medications as early as possible in the course of their infection. From then on out, it's important to adhere well to the daily drug regimen indefinitely. Even structured breaks from ARVs—the so-called drug holidays that were once in vogue—were proved harmful in the mid-2000s.

So why are the investigators behind so many studies in the HIV research field these days experimenting with taking people off their ARVs for periods of time?

They do it in the name of finding a cure. Or if not a cure—meaning total eradication of HIV from the body—then some form of viral remission or post-treatment control of the virus without daily ARV treatment. Such outcomes may include a scenario in which HIV is still clearly present but the immune system suppresses the virus well on its own. Or perhaps the population of virus in the body has been so decimated it fails to bounce back, at least for an extended period. (In this article, the umbrella term "HIV cure" applies to research into prompting any such outcomes.)

Analytical treatment interruptions (ATIs), as they are often known, are an integral facet of the kind of search-and-discovery work that characterizes HIV cure research in this early stage of the game. (The overall HIV cure research endeavor may stretch across decades, hopefully yielding progressive successes along the way.) Because a central goal of cure research is to allow people freedom from daily drugs, a primary reason scientists work ATIs into such studies is to analyze how the virus behaves in the absence of such suppressive medications.

Unfortunately, today's cure studies typically cannot promise any major personal benefit to their participants. Rather, the hoped-for benefit is usually restricted to a contribution to greater scientific knowledge. And even though ATIs in these studies involve very close, rigorous monitoring of participants to mitigate risks, the risks—in particular long-term ones—may be unknown.

"Ultimately, this kind of research really relies on people being willing to take on some risk for the

benefit of others," says Seema Shah, JD, an associate professor of pediatrics at the University of Washington and faculty member in the Treuman Katz Center for Pediatric Bioethics. "That is ethically complex."

Research into HIV-positive people's reasons for wanting to participate in cure research has found that altruism is in fact a major motivating factor, which is a promising sign that cure studies will continue to find willing participants.

ATIs: Helping solve the mystery of the viral reservoir

Standard ARV treatment is highly effective at suppressing viral replication. However, the stubborn persistence of the viral reservoir keeps treatment from curing, or eradicating, the virus. While researchers are still hard at work characterizing just what makes up the reservoir, they've known since early on that HIV is able to harbor copies of itself below the radar of ARVs. The perseverance of these hidden stores means that when an individual stops his or her daily treatment, a once-undetectable viral load almost always bounces back up, typically within weeks.

A cornerstone of the reservoir is the collection of long-lived immune cells that are latently infected with HIV, meaning that they have virus integrated into their DNA but are not replicating, that is, not producing new copies of the virus. HIV treatment works only on replicating cells, meaning that ARVs cannot attack virus in latently infected cells, which may remain in a resting state for years before springing back to action and churning out viral copies.

Today's HIV cure studies run a very wide gamut in their approaches. Some seek to shrink the size of the reservoir through a process known as "kick and kill," waking up unreplicating cells and then attempting to destroy them. Others give individuals some sort of gene-based or antibody-based treatment intended to prime their body to better control the virus without daily drugs. There are also studies of people, both those who contracted HIV as adults and children born with the virus, who were treated very early in the course of their infection and who may as a result have a very small, or possibly even nonexistent, reservoir. These early-treated individuals may be able to go off their ARVs and spend considerable time—sometimes many years, as researchers have seen thus far in a handful of cases—without the reservoir prompting the viral load to rebound.

When it comes to studies that take participants off daily ARVs, researchers structure the research projects to analyze one of two factors: 1) the time until the virus rebounds; or 2) the level of equilibrium the virus ultimately reaches in the body after a rebound, known as the viral set point. Scientists hope to use data on individuals in these studies to help, for example, estimate the size of an individual's reservoir. (A smaller reservoir likely means a longer time to rebound, likely because the chances are smaller that at any given time one long-lived, latently-infected cell will wake up and succeed in producing viable copies of virus). And very importantly, they are looking for biomarkers to use as the basis for tests that in the future could help predict whether an individual is likely to experience an extended period without a viral rebound after an ATI and how long that period is likely to last.

Studies that measure the time to viral rebound during an ATI expose participants to much less risk

than the viral set point studies.

Steven Deeks, MD, a professor of medicine at the University of California, San Francisco and a major player in the HIV cure research field, says, “If someone’s willing to go through the rigors of careful monitoring, which means having viral loads tested two or three times a week, and willing to start antiretroviral therapy the minute the viral load goes to 51 copies, I think that then an interruption can be done pretty safely. The risks are really minimal. They’re not zero; there’s never zero risk.”

Jintanat Ananworanich, MD, PhD, who directs research in the HIV cure field in her capacity as the associate director for therapeutics research at the U.S. Military HIV Research Program, says that thanks to such close monitoring of participants in these time-to-rebound studies, “at least in the short term we do not see adverse events in terms of clinical symptoms.” She says that those under her care—she is researching ATIs among those who started HIV treatment very early—don’t experience a drop in their CD4 count and after they restart ARVs ultimately get their viral reservoir back to the size it was before the ATI. (Granted, tools for accurately measuring the reservoir are limited.)

“We’re learning a lot,” says Ananworanich of the benefits of using ATIs in cure research.

Regarding studies designed to look for the viral set point established during an ATI, Deeks says, “That’s where risks become much more substantial. But the knowledge gained is also much more substantial.”

These types of studies usually involve an experimental treatment crafted to prompt the immune system to control the virus on its own after the participant goes off ARVs. The ATI needs to extend long enough to allow the virus to surge, possibly up to a viral load in the tens of thousands, and for the immune system, buoyed by the experimental therapy, to bring it back down to an eventual viral set point. Such an extended period of a high viral load—these ATIs typically last about six weeks—introduces the possibility of the kind of flu-like symptoms associated with acute HIV infection. Additionally, during this period, CD4s may drop, and individuals become significantly infectious to their partners.

In fact, one individual in a recent vaccine trial that involved an ATI transmitted the virus to his partner during this time. According to Deeks, there is a movement afoot to add the practice of offering Truvada (tenofovir disoproxil fumarate/emtricitabine) as pre-exposure prophylaxis (PrEP) to the sexual partners of participants in studies involving ATIs.

Allowing the virus to replicate, particularly if for an extended period of several weeks, may raise health risks associated with the harmful chronic inflammation to which even fully suppressed HIV gives rise. Scientists believe chronic inflammation is a major contributor to the raised risk, most notably, of cardiovascular disease among those living with the virus. In theory, allowing for a greater level of inflammation during an ATI could, for example, lead to lasting damage in tissue-based immune cells in the gut or lymph nodes.

Then there's always the risk that the virus could develop resistance to ARVs during an ATI, compromising the effectiveness of future daily treatment regimens. The virus of an individual who takes such a break in ARV treatment may also become less responsive to a future cure therapy.

Informed Consent

The point at which potential participants of medical studies are informed of all the potential associated risks and benefits—and sign on the dotted line if they agree to participate—presents a vital opportunity for researchers to ensure that HIV cure studies are conducted in the most ethical manner possible.

Unfortunately, according to Deeks, "The informed consent process is broken, in my opinion." He criticizes the insistence of financial backers of HIV cure research on drafting consent forms that include everything plus the kitchen sink and run as long as 15 to 20 pages. "No one really reads those," he says.

Deeks argues that a more ideal informed consent process involves drawn out, fully interactive communication between study investigators and potential participants. The ultimate goal is to make sure those considering enrolling in such research studies fully understand the risks, potential benefits as well as the benefits that are unlikely (such as an actual individual cure) to result from such participation. Fortunately, many cure study investigators do indeed engage in such careful and thoughtful dialogue to ensure that potential participants are fully informed before agreeing to participate.

Word choice regarding long-term research goals is also very important. Many researchers worry that even using the term "HIV cure" can inflate hopes and motivate participants in such trials to take on more risk than they would otherwise be comfortable with.

Potential participants of such studies who wrongly presume they may be cured "are not making a rational choice, balancing the potential risks and benefits," says Richard Jefferys, Treatment Action Group's cure research expert.

Keeping such expectations in check is a major reason why researchers in the field are moving away from the use of words like cure, sterilizing cure or functional cure and toward terms like "viral remission" and "post-treatment control of the virus."

"HIV cure to me is eradication" from the body, says Ananworanich, "which is our long-term goal and not something we can hope for at the moment with the interventions we have. The more near-term goal is HIV remission."

And as the research community saw most recently, at the 9th International AIDS Society Conference on HIV Science in Paris (IAS 2017), such viral remission is in fact possible today, at least in rare cases. Conference attendees learned of a 9-year-old South African child who was treated with ARVs for just 40 weeks after being born with HIV and has since spent more than eight years off treatment with no viral rebound.

According to Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), during the 2020s, researchers may indeed find ways to prompt such a state of remission in more than just a lucky few. Fauci believes that those whose early treatment (started within a few months) after contracting the virus has blunted their viral reservoirs are the most likely to benefit from such a treatment advance.

Scientists will certainly not rest on their laurels following such success. Going forward, thanks in no small part to the participants of HIV cure studies, scientific knowledge will hopefully continue to expand, yielding ever-expanding ways to liberate people living with the virus from ARV medications.

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