From Mice Into Men

The gap between groundbreaking scientific discoveries and a game-changing cure has never been greater. And yet, researchers say we could be closer to a cure than many have dared believe. To close that gap, and increase the chances we'll see the end of AIDS in our lifetimes, we need more advocacy, a lot more money and the courage to get as many viable options out of mice and into humans. You in?

September 27, 2010 By Tim Horn and Regan Hofmann

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Cure. It's a word few have been willing to pair with AIDS since we thought we had the virus kicked in '96. For nearly 15 years, talk of a cure has been verboten. Those who have dared utter it (including on the pages of this magazine) were dismissed as dreamers. Since the late 1990s, research, advocacy and funding around HIV/AIDS have focused almost exclusively on prevention and treatment. And yet, it has become clear that we can neither treat nor prevent our way out of the pandemic. The ethical, logistical, sociological and financial barriers to trying to end AIDS with pills and awareness campaigns are proving too great.

The cost of providing antiretrovirals (ARVs) indefinitely to all people globally who will need drugs to survive is staggering; it's estimated to be in the tens of trillions of dollars, not accounting for inflation, an ever-growing caseload and future drug prices. Not even the combined coffers of all the global health funds, the biggest health care foundations and the richest nations and individuals around the world are prepared to foot that bill. (The price tag also poses the question: Even if we could raise the tens of trillions of dollars, why would we spend that much money on treating HIV when it could take far less to find a cure?)

The biggest, pinkest elephant in the room is that since no one, especially in this global economy, is likely to spend the money required to keep the 33.4 million people UNAIDS estimates to be living with HIV today alive—tens of millions of men, women and children are going to die of AIDS in the near future. Unless we find the cure.

So where is the bloody thing? There has been talk of conspiracy. Woefully inadequate funding for cure research. Risk-adverse venture capital investors. Abandoned biotech babies. And precious little advocacy. While the HIV community was focusing on everything from improving treatment options to funding lifesaving programs like the Ryan White CARE Act and the AIDS Drug Assistance

Program and developing a National HIV/AIDS Strategy, it seems we forgot to demand the one solution that could eliminate the need for all the rest: the Big C.

But though the subject of an AIDS cure has long been unmentionable, that doesn't mean it isn't possible, or even probable. In fact, surprisingly, given the lack of adequate funding, AIDS cure research has produced some really exciting breakthroughs. In an interview with *POZ* at the XVIII International AIDS Conference (IAC) this past July in Vienna, Kevin Frost, the CEO of the Foundation for AIDS Research (amfAR), said, "The research around a cure has been going very well. It's one of the great, untold stories of AIDS today. Much of [AIDS cure] research is headed in a very positive direction, and there's genuine enthusiasm in the scientific community about the possibilities of how we get there. We're not going to get there tomorrow or next week, but there's a growing sense of excitement about our progress that, for the first time, shines a light on the pathway to [the cure]."

Optimism for a cure within the scientific community is at an all-time high. The challenge is getting the myriad possible options beyond a laboratory setting—and into human trials. In today's medical research there is an gap (known as "the valley of death") between exciting new scientific discoveries and the dollars, leadership and advocacy needed to turn those ideas into medicine we can use. Within the world of AIDS research, a prime example is the case of Paula Cannon, PhD, who works at the University of Southern California. She is using zinc-finger nucleases (ZFNs)—synthetic DNA-binding proteins developed by Sangamo BioSciences—to genetically alter stem cells capable of producing CD4 cells that don't have CCR5 receptors. The big deal? HIV can't bond with, and infect, CD4 cells that don't have these receptors. The procedure worked well in mice that were specially bred to be born without immune systems so that they could receive transplants with ZFN-modified stem cells and then be exposed to HIV. Cannon, Sangamo and John Zaia, MD, are ready to conduct a similar experiment in HIV-positive patients with lymphoma who undergo chemotherapy. People living with HIV are willing to be subjects in Cannon's trial. Cannon and her colleagues have been given an initial grant of $14.5 million from the State of California. But the rest of the money needed to turn her theory into practice is not looming on the horizon. For now, her hope for a cure remains trapped in the bodies of her mice.

In 1996, scientists thought they'd hit the cure jackpot with the debut of a new class of drugs called protease inhibitors (PIs) that made it possible to construct potent combinations of drugs equipped to attack HIV at multiple stages of its lifecycle. Protease-based combination therapy profoundly reduced the amount of HIV in the body. Many researchers believed PIs could permanently snuff out the virus after just a few short years of treatment. The hype increased when David Ho, MD, famously suggested, as did a December 1996 cover of *Newsweek*, that combination therapy could prove to be the cure. But the bubble of hope burst with the discovery that even people with undetectable viral loads harbor a small population of immune system cells that are literally "sleeping with the enemy." These cells, a group of 1 million or so "resting" memory CD4 cells—semi-retired holdouts from earlier immune system battles with microorganisms—are infected with HIV and go largely untreated by today's crop of antiretroviral drugs. (ARVs only protect uninfected cells or keep active CD4 cells from producing new HIV.) Thanks to these cells, when most people stopped taking their multi-drug cocktails, the virus bounced back with a

vengeance. Because it can take decades for the infected memory cells to either wake from their slumber (and allow HIV meds to do what they do best) or die a natural death, eradication via ARVs alone would require more than 60 years of uninterrupted therapy. The fact that HIV was capable of hiding in this manner—"latency" in medical terminology—dashed the hope that combination therapy could eradicate HIV from the body.

When protease-based combination therapy proved not to be the cure, scientists and funders turned primarily to the development of a vaccine, the refinement of new treatment options and improved prevention tools. These areas offered greater hope for glory—and greenbacks. As a result, today we have many highly effective and better-tolerated ARVs. We have made important discoveries on the preventive and therapeutic vaccine fronts. And we are closer than before to developing effective microbicides (drug-infused gels that can be applied vaginally and/or anally and serve as a barrier to HIV infection). Meanwhile, we have spent relatively precious little money and effort on cure research.

The National Institutes of Health (NIH) reports that it has spent $45 billion on all forms of AIDS research in the past 28 years. (In 2009 alone, the United States spent $20 billion on AIDS prevention and treatment for people stateside and abroad.) According to a report released recently by The AIDS Policy Project (APP), the NIH spent a mere 3 percent of overall AIDS spending (or $41 million of $1.5 billion) on AIDS cure research in 2009. The APP is calling the NIH to increase AIDS cure research funding five-fold—to $240 million—in 2011 and to $600 million a year within five years. Currently, the NIH spends nine times as much looking for a vaccine as it does looking for a cure. But the APP does not suggest the NIH "borrow from Paul to pay Peter" but rather that it ups the ante across the board; the APP suggests Congress should increase NIH funding (as President Obama promised during his campaign) by 20 percent, effective next year.

A vaccine that is therapeutic (meaning it could help people's immune systems keep HIV undetectable without ARVs) could constitute a "functional cure." But there is a strong case to be made that recent knowledge on other research fronts begs as much devotion as our search for a viable vaccine. For too long, too many people have given up on the cure. The APP's report claims that few outside the research community are aware of what's going on with AIDS cure research, "not members of the general public, nor most health reporters. Nor the United States Congress, which decides how much to fund the National Institutes of Health. Not even most AIDS activists, who assume the cure is decades out of reach. And, most importantly, not people with AIDS themselves, millions of whose lives are at stake."

Why should we cure AIDS? While every disease deserves to get adequate funding to be cured, there isn't enough money to cure all ills. Since we have to make brutal choices anyway, one way to do it is to fund solutions that will save the most lives. HIV/AIDS is the No. 1 cause of disease and death among woman and girls ages 15 to 44 worldwide. Nothing kills more women in the prime of their lives. And given that nearly 50 percent of the 33.4 million people estimated to be living with HIV on the planet are men, the death rate for men isn't far behind.

Also, unlike many fatal diseases that affect people at life's end, HIV impacts young people,

especially in the developing world. Which means HIV is drastically undermining the global workforce. And, when young people die, they often leave behind infants or young children and aging parents who, in turn, become a cost burden to society. And, by striking down millions in their prime, AIDS can greatly reduce nations' gross national products.

There are those who argue that a cure isn't needed because treatment has rendered HIV infection a manageable, chronic condition. It can be for those who can get, afford and tolerate care. ARV treatment has been so successful that public health officials and researchers are considering "treatment as prevention." By lowering people's viral levels to a point at which they become considerably less infectious, the thinking goes, treatment could help stop the spread of AIDS. The use of ARVs to protect HIV-negative people from the virus (an approach known as "PrEP" for "pre-exposure prophylaxis") is also being studied. (It has already been proved that when HIV-negative people take a 28-day course of ARVs starting within 72-hours of potential exposure to HIV, their risk of infection is greatly reduced. This approach, known at "PEP" for "post-exposure prophylaxis," was the grounds for PrEP.)

But for many reasons, lifelong treatment is far from the optimal solution for dealing with HIV. As we've already mentioned, it's prohibitively expensive. The estimated lifetime cost of ARV medications can top more than $600,000 per person in the United States, according to a November 2006 study conducted by Cornell University researchers. And treatment doesn't alleviate the many tough issues people living with HIV face. Pills don't eliminate the threats of stigma, discrimination and criminalization. They don't take away the fear that people will be unwilling to be your friend, to date or marry you or to take you home to their families. ARVs don't remove the worry that you may inadvertently transmit the disease to someone else, including your baby. And given that we don't know the long-term impact of the drugs themselves, compounded by the fact that people with HIV and on treatment are still at a higher risk than HIV-negative people for certain life-threatening diseases—like cardiovascular disease and cancer—ARVs are no guarantee against sickness and death.

Ideally, all people living with HIV should be aware of their status, be educated about treatment options and be given access to care should they choose to take it. But, the drugs aren't the ultimate answer for those of us lucky to get our hands on them. And they're certainly not the answer for the 5.5 million people who need drugs right now to stay alive and can't get them.

Stopping AIDS with treatment may seem like a sound public health strategy, but at this point it's purely academic theory. Universal access to treatment for all who require it has, to date, proved impossible. According to UNAIDS, less than half of the 33.4 million people with HIV who need ARVs are on them. Not only have we fallen short to meet current need, but we're highly unlikely to play catch up considering that for every two people we put on treatment, three more become infected. And then there are the challenges associated with getting people tested and linking them to care. In the United States, one person in five living with HIV doesn't know his or her status, and of the nearly 750,000 Americans who know they have HIV, an estimated 350,000 of them are not accessing care and treatment. If we can't achieve universal access in the United States, our prospects for achieving it globally seem dim.

Ironically, the survival of more people with HIV makes it less likely, long term, that we will be able to care for them. And, because there are few new classes of treatment in the drug development pipeline, the number of people who exhaust the current set of treatment options will only grow. And more and more people contract HIV every day. The problem is getting exponentially worse on many fronts, daily.

Positioning treatment as prevention is a persuasive argument for justifying the cost of getting the drugs to everyone who needs them. Given that universal access is an integral part of one of the United Nations' eight Millennium Development Goals, anything that supports that goal is likely to be embraced by global health leaders. But as noble as the goal of treating all who require it is, putting the entire global population of positive people on pills seems to be virtually impossible.

All roads, it seems, lead back to the necessity for a cure.

Which is why perhaps, after many years of the cure being viewed as a pipe dream, the word is increasingly on the tips of more people's tongues today. Are we close? While we're not likely to see a cure in the near future, what we do in the next year or two will impact whether the cure comes soon—or not soon enough. To fast track the cure, we've got to get more people talking about it.

As proof of how reticent people have been to say "cure," consider that mainstream media barely covered the recent case of a man who has possibly been cured of HIV (albeit through impractical means). While speculation that combo-therapy could ring in the end of AIDS once appeared on the cover of *Newsweek*, data showing that HIV may have been eradicated for the first time in a person appeared on a small poster at the far end of the exhibit hall at the 2008 Conference on Retroviruses and Opportunistic Infections in Boston.

The poster told the story of an HIV-positive American, living in Berlin, who received a bone marrow transplant to cure his leukemia. The procedure, performed by Gero Hütter, MD, a German hemotologist at Berlin's Charité Medical University, had a twist: The doctor re-introduced stem cells taken from a person with a certain genetic mutation that renders them (and theoretically the person to whom their cells are given) incapable of producing CCR5 receptors. Because HIV needs CCR5 to connect to and infect CD4 cells, not having it essentially renders a person immune to HIV.

Two-plus years after the procedure, "the Berlin patient" as the American is colloquially known, remains apparently HIV-free. Certainly many questions remain. Has the patient really been cured? The jury is still out. Doubters wonder whether the diagnostic tests that probed for latent HIV in places like the lining of his gut and his brain were effective, meaning that he could still harbor the virus. There is discussion about whether it was the high-dose chemotherapy, the CCR5-deficient stem cells or a combination of the two that seems to have chased HIV from his body.

No one knows whether the procedure can be successfully replicated, and the cost (up to $200,000 per patient) and health risks of such a procedure are high.

One thing's for sure: Whether the Berlin patient proves that a "functional cure"—near-complete

immune system control of HIV in the absence of HIV treatment—is possible or whether his body holds the grandest grail of them all—a "sterilizing cure" in which every scrap of HIV is eradicated from the body—he is proof of concept that HIV may be able to be controlled by something other than ARVs.

Few, including Hütter himself, are willing to say that AIDS has been cured, functionally or otherwise. But the findings of the Berlin patient and the research that contributed to Hütter's gambit now inform current research. And they have helped invigorate the discussion around the cure.

The case of the Berlin patient also illuminates another key point: It's not up to the NIH alone to find the cure for AIDS. And money does not necessarily force scientific discovery, and throwing cash against research projects with little promise is a waste. The high-stakes and high-cost responsibility should be spread between mighty giants like the NIH and other outfits like amfAR (of which Hofmann is a board member), ADARC, AVAC, IAVI, France's Agence Nationale de Recherches sur le Sida, the Canadian HIV Trials Network and independent academic centers throughout the world. It will take the combined efforts and resources of multiple governments and a lot of public-private partnerships. Private funding of independent biotech companies has always been a critical link in the solution to any disease. In a recession-struck world, high-risk funding dries up quickly whether that's on the part of individuals, venture capital firms or even the pharmaceutical companies themselves. It is unfortunate, to say the least, that at a time when we need to spend most aggressively, we face a dearth of resources and willingness.

Though we have long passed the tipping point at which it became clear that we needed to pour considerable funds into cure research, we haven't invested the money. (Here's where people cry, "Conspiracy!") Indeed, the creation of a global market of tens of millions of patients who could live a full, healthy life as long as they took pills every day for the rest of their days does seem to be a pharmaceutical company's dream. It is important to point out that the global HIV drug market is potentially becoming less profitable for the companies that make the drugs. If there were a way to pay for ARVs for 33.4 million people for the course of their lifetimes, it would pay to make the drugs. But given that the need for treatment expands as the resources to pay for the meds shrink, pharmaceutical companies are being forced to lower their prices (even abandoning patents earlier than before or, in some cases, coming straight out of the R&D pipeline to low-price-tag generic formulations). A *Wall Street Journal* opinion piece by Alec van Gelder suggested that "trampling over intellectual property rights removes drug companies' incentives to invest billions of dollars in the development of the next generations of [ARVs]." And, as imperfect compliance leads to more drug resistance, there is an ever-increasing need for new compounds in general, and for getting a wide variety of drugs to the world at large. Historically, drugs with expired or nearly expired patents were offered to the developing world. Now, brand new formulations are required increasingly by nations and people who can't pay for them. It's another giant pink elephant in the room. Drug companies are for-profit. What will happen when it is no longer lucrative for them to make and distribute the meds? Already, we are seeing it happen. The pipeline for new treatments for HIV is nearly empty.

Thankfully, the biotech and pharmaceutical industries stand to see a very healthy return on AIDS cure investments. In other words, finally, a cure may prove more profitable for them than a world of people on ARVs for the rest of their lives. And governments and insurance companies, which also bear the brunt of paying for HIV treatment, have a vested interest in heralding in a cure. One challenge is that the system itself is not set up to facilitate a cure for HIV. The same organizations (NIH) that fund basic biomedical research have no financial incentive to get a possible therapy to market. They are paid to discover the basic science, not develop it. And groups such as venture capital investment firms and pharmaceutical companies that could financially benefit from such development are shying away from investing in AIDS cure research, partly, because it has proved so expensive and challenging. One hope is that the epiphany that the global market for ARVs may not always prove lucrative may drive venture cap and pharmaceutical companies to get some skin in the cure game.

It is not sufficient to say, “Whoever finds the cure for AIDS will be rich.” Unless we spend enough money on the search, not enough people will look, and we will be less likely to find it. It takes a lot of money to look. And it takes a lot of money to get basic scientific discoveries translated into potential therapies that are ready to enter clinical trials and, if all goes well, get FDA approval. Consider this: The cost of researching and developing a single drug, from molecular discovery to pharmacy shelves, has been estimated as between $500 million and $2 billion—and that’s using the dollar value from a decade ago.

The AIDS Policy Project’s executive director Kate Krauss sums it up best: “We have a chance to dismantle this pandemic. What we do now as activists could determine whether the AIDS pandemic lasts another seven years—or 30—and who will outlive it. We need nine times more money than we have right now for scientists to pursue genuinely original ideas. We need to build a pipeline to test in people not just one or two treatments but a steady and growing list of potentially curative therapies. A workable cure may involve more than one approach, so collaboration—virologist-immunologist, Parisian-New Yorker—is critical. Researchers collaborate in real time in multiple sclerosis research, why not also with AIDS? New funding has to reward new ideas and real teamwork. Is the scientific world ready to promote and encourage another Gero Hütter? Not yet. But it should be. This [moment] is a rare opportunity for philanthropists to step up and do something pivotal in the history of the AIDS pandemic.”

In addition to awareness, advocacy, cash and scientific breakthroughs, we need to revolutionize the way we conduct AIDS research if we’re going to find the cure.

To create a bigger, bolder, more diverse pipeline, we need to put as many promising options for the cure into pilot studies within the next two years as possible. The days of five-year, three-country, 5,000-patient studies should be numbered. As long as we can establish legitimate baselines of safety, we should be able to forge ahead faster and more nimbly to get the answers millions desperately need. Let’s see some five-month, five-people trials. Researchers can no longer toil alone in their ivory towers, holding their ideas and discoveries close to their chests. We need to encourage openness and collaboration. We need to give people incentives to work together. And we need to share learning between groups along the way, not just when all is said and

done—and published in medical journals. What about a centralized database of cure research projects, perhaps one that could allow researchers to share findings—and best practices—ideally mid-study?

We need to lure new talent from other areas of biomedical research (remember, the first man to perhaps technically cure AIDS was neither a virologist nor an immunologist). We need long-term, stable and flexible approaches to funding to allow scientists to focus on doing research, not applying for grants.

We need to better track AIDS research around the world, across our nation and within the NIH. The AIDS Policy Project identified that the NIH had trouble tracking AIDS cure research, in part, because it had no code to do so. It does now. It has been suggested that advocacy efforts include appealing to the Office of AIDS Research, led by Jack Whitescarver, PhD, at the NIH, to better follow the arc of AIDS cure research and that an annual report should be issued highlighting progress toward a cure.

We need the United States' National HIV/AIDS Strategy to more clearly spell out a plan for AIDS cure research. And to encourage its stewards to ensure that that happens. We need to educate members of the U.S. House of Representatives and the Senate about AIDS cure research so they will fund it properly.

Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), a division of the NIH, recently announced a NIAID research grant named in honor of legendary treatment activist Martin Delaney. The grant allocates $8.5 million a year for five years to search for a functional cure. Sean Strub, POZ's founder, said in response to the grant, "If Pharma [sic], the public health establishment and AIDS service organizations lobbied for funding for cure research the way they lobby (directly and indirectly) for 'routinizing' testing, PrEP, 'Test and Treat,' etc., this would be $8.5 billion rather than $8.5 million. "

Referencing the power of lobbyists for AIDS vaccine research, Françoise Barré-Sinoussi (who codiscovered HIV) said, "There is no equivalent for research into remission or [a] functional cure [for AIDS]." Barré-Sinoussi, who will head the International AIDS Society beginning in 2012, led a two-day workshop on the cure just before the IAC in Vienna.

Thanks to pressure from advocates like the folks at the AIDS Policy Project and others, the tide may be beginning to turn. On August 31, Carl Dieffenbach, PhD, director of AIDS at NIAID, announced in a conference call with activists that "AIDS cure research" would be one of the top four NIH priorities next year. It is up to us to keep the heat on that promise.

Accelerating the cure for AIDS will require more attention; more money; more, and new kinds of research; greater determination—and people living with HIV who are willing to enroll in pilot studies. Because while mice are nice, the fastest way to get to an actionable cure for AIDS is to test potential therapies, when proven safe, as quickly as possible in people living with the virus.

Of all the things we need to do to hasten the end of AIDS, we need to not be afraid to dream of the

cure and to say it out loud. Because when it comes to the cure for AIDS, we've already seen that it doesn't pay to be quiet as a mouse.

THE CURE HUNTERS
A look at some of today's hottest AIDS cure research teams

It would take more pages than are housed in this magazine to even begin to highlight all the innovative work being done around the world that could directly, or indirectly, help us find the cure for HIV/AIDS. But in order to give you a sense of the different types of approaches to AIDS cure research, we highlight a handful of teams hard at work trying to find the cure. Many of these people have yet to make big headlines because their research is still in its infancy. But they're undoubtedly leaders in an ever-expanding pack of scientists dedicated to ending AIDS.

There are currently two basic camps of HIV cure research: cell-based (or genetic) therapies and reservoir-based therapies (to address the issue of HIV hiding out in reservoirs in the body).

But there is also the possibility of a "therapeutic vaccine"—a vaccine for people with HIV that would serve as a functional cure and achieve the same end as other functional cure approaches: no meds, HIV in check.

That's the general overview. Now, on to the specifics.

CCR5 gene modification is a key area of AIDS cure research that is ripe with potential. Working in tandem with Sangamo BioSciences, a research team headed by Paula Cannon, PhD, at the University of Southern California is using zinc-finger nucleases (ZFNs)—synthetic DNA-binding proteins—to disrupt the gene in stem cells responsible for studding CD4 cells with CCR5. The procedure worked well in mice that were specially bred to be born without immune systems so that they could receive transplants with ZFN-modified stem cells and then be exposed to HIV. (Think: mini Berlin patients, with fur.) Cannon, working with Sangamo and John Zaia, MD, (whose other work is featured below), now hopes to conduct a similar experiment in HIV-positive patients with lymphoma who undergo chemotherapy.

Carl June, MD, and his group are working at the University of Pennsylvania on their own Sangamo-supported study exploring what happens when CD4 cells are extracted from HIV-positive people, infected with a common cold virus containing ZFNs, and infused back into the patient. While this approach is less ambitious than Cannon's stem cell method, results involving one patient have been encouraging—his viral load was slow to rebound during a treatment interruption after receiving the ZFN-modified, CCR5-depleted CD4s. June is also developing a gene-modifying technique using technology from England-based Adaptimmune, to enhance the receptors of killer CD8 cells to seek out and destroy all cells in the body infected with HIV.

Zaia, at the City of Hope Comprehensive Cancer Center in Duarte, California, has his irons in many possibly curative fires. In addition to his group's work with Sangamo and Cannon, they've also completed a preliminary study transplanting HIV-positive lymphoma patients with stem cells collected from their immune systems and modified to include genetic material—ribozymes and

“small interfering” RNA (siRNA)—that block HIV from infecting new cells. Though the results were encouraging, additional studies are necessary to determine if this approach has true potential.

Several biotech companies and academic centers are trying to develop the aforementioned therapeutic vaccines, designed to enhance and broaden the immune response to HIV in people already infected with the virus.

Julianna Lisziewicz, PhD, at Genetic Immunity in McLean, Virginia, for example, is developing DermaVir, which transports synthetic viral DNA to dendritic cells through the skin. In fact, dendritic cells are the focus of several vaccine developers. There’s also a vaccine from Argos Therapeutics that uses a patient’s HIV to tailor the immune response.

Thus far, results from therapeutic vaccine studies have been mixed—though they perk up the immune system and several have been shown in Phase II studies to reduce viral load, they haven’t yet exerted substantial HIV control over long periods of time without treatment.

Another ambitious goal is to force latent HIV out of its hiding places in the body.

Soon after reservoirs of sleeping HIV-infected CD4 cells were discovered, researchers set out to wake them with powerful immune-based therapies. While this helps purge HIV and render it susceptible to ARVs (a good thing), the process also causes people’s immune systems to go haywire, with potentially serious consequences (a bad thing).

David Margolis, MD, and his colleagues at the University of North Carolina at Chapel Hill have been taking a kinder, gentler approach to lure out HIV and squash it. His group is experimenting with FDA-approved drugs that block histone deacetylases (HDACs)—a group of enzymes that keep HIV quiet in resting cells. Initial experiments using the HDAC inhibitor Depakote (valproic acid)—a med that treats epilepsy—were encouraging. Margolis and his team are now seeking funds to conduct a 20-person study of Zolinza (vorinostat), an approved chemotherapy for a type of lymphoma.

Targeting HDAC, however, is just the beginning. A number of proteins and pathways believed to be responsible for HIV latency are also in scientists’ crosshairs. One such example is the ominous-sounding “programmed death-1” (PD-1), a protein found in high numbers on cells harboring HIV. By blocking PD-1 or the way it interacts with a molecule called PD-L1, it may be possible to purge the virus within. Fortunately, such compounds are in development for other diseases; unfortunately, very little is known about their potential regarding HIV.

The process of screening an infinite number of drugs and natural compounds that can coax HIV out of latency can be expensive and time-consuming. Which is why the work of Robert Siliciano, MD, PhD, and his team at Johns Hopkins University at Baltimore is important. They have developed a lab protocol that can rapidly determine whether a chemical agent can get at HIV in resting CD4 cells, a process that can potentially shorten the development time of curative interventions by 10 or more years.

Merck Research Laboratories, under the direction of Daria Hazuda, PhD, is also checking its

collection of compounds using streamlined testing procedures.

Another potential problem with HIV infection isn't that the immune system doesn't work hard enough to clear the virus, but that it's working too hard. According to Joseph McCune, MD, at the University of California at San Francisco, an overabundance of immune system activation to HIV simply ends up creating new targets for the virus to attack, causing HIV to overstay its welcome.

McCune and his team are studying an enzyme called indoleamine-2, 3-dioxygenase (IDO) to determine if it plays a role in this vicious cycle. If so, the results may point to a new therapeutic strategy that could both decrease levels of immune activation—itself associated with some of the diseases commonly seen in HIV infection—and lower the amount of virus that persists, bringing us closer to a cure.

The possibility of "functionally" curing HIV—in which the virus is present in the body but kept at undetectable or nearly undetectable levels—is real. About 1 in 300 people living with HIV are "elite controllers" and don't require antiretroviral (ARV) therapy to keep their HIV undetectable, many of whom are enrolled in the International HIV Controllers Study, run by Bruce Walker, MD, at Harvard Medical School.

The goal of HIV treatment research—and, indeed, HIV eradication research—is to develop therapies that enable all people living with HIV to control their virus without the need for ongoing ARV therapy. A critical step, however, is to understand what it is about elite controllers and other long-term nonprogressors that renders them nearly impervious to the effects of HIV. Walker and his team are searching for that answer.

And, finally, it has been found that drugs that stimulate the immune system to either eradicate or functionally cure HIV infection may only stand a chance if HIV replication is stopped dead in its tracks. Therefore, before these agents are tried, it may first be necessary to intensify already potent HIV drug regimens with the use of additional tried-and-true agents.

Brigitte Autran, PhD, is hard at work with her colleagues in Paris on two studies known as "ERAMUNE" designed to show a possible benefit of intensifying therapy with Isentress (raltegravir) and/or Selzentry (maraviroc). In ERAMUNE 01, patients will receive intensified ARV therapy plus Merck's recombinant Ad5-based vaccine. In ERAMUNE 02, patients will receive treatment intensification plus Cytheris's immune-boosted interleukin-7 (IL-7). Both trials began in July.

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