The AIDS Policy Project

AIDS Cure Research For Everyone

A Beginner's Guide to How It's Going And Who's Paying for It.

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AIDS CURE RESEARCH FOR EVERYONE

By Kate Krauss, Stephen LeBlanc, and John S. James, of the AIDS Policy Project

Dedicated to our friend and fellow activist Edward Zold

"Luck in science smiles on prepared minds." – Louis Pasteur, via Luc Montagnier

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Introduction

Who knows exactly what's going on with AIDS cure research? Not many people outside the research community. 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 that the cure is decades out of reach. And most importantly, not people with AIDS themselves, millions of whose lives are at stake.

Who is funding the effort to find a cure, and how much are they spending? Almost no one knows that.

For these reasons, we have written this simple report to share what we have learned, so far, about the search for a cure for AIDS.

This section of the report will discuss the scientific and cultural landscape that affects this research. Here, we will offer analysis and make recommendations.

The second part of the report will survey the avenues of scientific research being pursued in the US. Future versions of this report will broaden its scope to include international research and funders.

How Is the Research Going? The Berlin Patient and the Future

The first thing to know about AIDS cure research is that the science is going well.

There are two major approaches presently under investigation.

1. To activate long-lived, infected cells in viral reservoirs (pockets of cells the drugs can't reach) so that they can be detected and killed.

2. To change people's immune systems to have a mutation that makes the person largely unable to be infected by AIDS (for example, the CCR5 deletion mutation). One approach is to use gene therapy to create this mutation in people; another approach is to replace the person's immune system using a stem cell transplant with an outside donor who was born with the mutation. (More on this later in the report.)

What is the CCR5 deletion?

The CCR5 Deletion is a mutation that makes cells highly resistant to AIDS. Cells with a double CCR5 deletion lack the CCR5 cell surface protein, one of the two entry points that most HIV needs to infect T-cells. A double CCR5 deletion (double because it was passed down from both sides of the family) is present in about 1% of Northern European people. People who are born with the CCR5 double deletion are highly resistant to AIDS.[1] Those who inherit this mutation from just one side of the family are likely to progress more slowly if they become infected with HIV.

The Berlin Patient.[2] The second strategy has yielded an important breakthrough. There is one HIV-positive patient in Berlin, Germany who also had leukemia. He received a stem cell transplant from a donor who was born with the CCR5 double deletion. The procedure is considered risky, but the patient already needed a stem cell transplant as a treatment for leukemia. The stem cell transplant apparently cured him of AIDS. He is now healthy, AIDS and leukemia free[3], and living in the US. Despite extensive and sophisticated testing, more than 3 years after the treatment researchers cannot find AIDS virus in his body. Because of the danger inherent in this type of stem cell transplant, this is not a practical cure for millions of people, but it *is* a scientific milestone.

The AIDS Policy Project and San Francisco Supervisor Ross Mirkarimi give Gero Hütter, MD, the physician who treated the Berlin Patient, an award on the steps of City Hall in June, 2010.

This "proof of concept" that a stem cell transplant with the CCR5 deletion can cure AIDS is a critical advance in AIDS cure research. In this respect, AIDS cure research differs from AIDS vaccines or AIDS microbicides research, both of which currently lack a "proof of concept" experiment.

Important new research is following up on the implications of this case. There are other studies that are attempting to activate dormant, infected cells that form long-lasting reservoirs, the last vestiges of AIDS in the bodies of people who have no detectable viral load in their blood. Activate them, the theory goes, and you can detect them. If you detect them, many researchers believe that you can kill them or that the activated cells will die off on their own. And that is a cure.

Following the Money

The second thing to know is that AIDS cure research is astonishingly underfunded. Many of us assumed that it was awash in money but that the scientific problems were just too complicated to solve. In fact, we have learned something quite different. Here is the definition of an AIDS cure as the NIH, and we, define it:

A cure:	Permanent remission in absence of requirement for therapy.
A functional cure:	Control of virus rather than elimination, without requirement for therapy**.**

--The Division of AIDS, US National Institutes of Health

Here's total AIDS spending at the NIH's National Institute of Allergy and Infectious Diseases (NIAID), and at the Division of AIDS, which is part of NIAID:

Table 1. Total AIDS Spending at NIAID[a] and the NIH's Division of AIDS

Year	NIAID	Division of AIDS (subset of NIAID spending)	
2005	**$1.450 Billion**	**$ .986 Billion**	
2006	**$1.475 Billion**	**$1.011 Billion**	
2007	**$1.490 Billion**	**$1.001 Billion**	
2008	**$1.498 Billion**	**$1.044 Billion**	
2009	**$1.541 Billion**	**$1.012 Billion**	

[a] *National Institutes of Health's National Institute of Allergy and Infectious Diseases*

NIAID's self-identified spending on AIDS *cure* research (includes contract and intramural research aimed at both a cure and a functional cure):

Again, these are NIH numbers based on the NIH definitions of a cure, above:

Table 2. NIAID [a] AIDS Cure Spending, Including Contract and Intramural Research

Year	NIAID
2005	$51,325,393 ($51 million)
2006	$47,964,320 ($50 million)
2007	$41,115,662 ($41 million)
2008	$29,276,461 ($29 milion)
2009	$40,652,172[b] ($41 milion)

[a] *National Institutes of Health's National Institute of Allergy and Infectious Diseases* [b] *2009 includes one-time funding of $9,590,297 from ARRA—President Obama's economic stimulus program*

What percentage of its research budget did the National Institute of Allergy and Infectious Diseases spend on AIDS cure research? Let's look at 2009, the most recent year for which the NIAID has full data.

In 2009, NIAID spent $40,652,172 on AIDS cure research. The total AIDS spending of NIAID in 2009 was $1.541 Billion. Thus, NIAID spent less than 3% of it AIDS budget on cure research.

The National Institutes of Health's National Institute of Allergy and Infectious Diseases is spending a maximum of 3% of its *research budget* on the cure for AIDS? This is completely unacceptable. Only a small fraction of people with AIDS around the world are receiving treatment, and few will be able to access AIDS medications for the rest of their lives. Without a cure, nearly every one of them will be dependent on fickle world leaders and international charities to fund access to the medications they need to stay alive.

Meanwhile, even people with access to AIDS drugs are still dying of AIDS, their lives are shortened. Even with excellent treatment, we are learning that they may suffer from dementia and other diseases of premature aging and are predisposed to die of heart attacks and liver cancer as a result of a persistent virus that causes long term inflammation.

The aggressive and well-funded search for a cure for AIDS is a human rights issue.

NIAID spent only 3% of its budget on AIDS cure research in 2009, according to data from the Division of AIDS. Also, roughly a quarter of the money they did spend was one-time Obama economic stimulus money. Without it, the number would be much smaller.

There are only **12 clinical trials** at the Division of AIDS focused on a cure **since 2005.** Of those, only 3 are enrolling (1 since 2006, 1 since 2007 and for 1 there is no information), 3 are in development, and 3 are "pending." This means that there is little translation of basic science into producing AIDS cures that could be used by people.

The other money (97% of the research budget) spent on **AIDS research at the N.I.H.** goes to vaccines, health disparities research, treatments, microbicides, and other research. AIDS cure research, *the cure for AIDS,* is at the bottom of the NIH's list of funding priorities.

We also have data from the National Institute of Mental Health. In this case, the grants cited as "cure" or "functional cure" research seem a bit suspect. For instance, one study is called, "Novel Adjunctive Therapies for NeuroAIDS." This seems like a treatment study to us.

Here is the amount of money for cure research reported by the National Institute of Mental Health:

Table 3. AIDS Cure Research at the National Institute of Mental Health

Year	NIMH
2005	$22,841,478
2006	$26,974,653
2007	$21,964,728
2008	$11,511,912
2009	$18,464,014

There is additional AIDS cure research in small amounts in several other NIH institutes:

- The National Institute of General Medical Sciences is studying HIV/AIDS structural biology and transcription.

- The National Heart, Lung, and Blood Institute is conducting HIV gene therapy research and studying macrophage biology.

- The National Center for Research Resources has some AIDS cure research tied to other NIH funded projects.

- The National Cancer Institute is also conducting gene therapy studies.

None of these institutes responded to our repeated requests for spending data. We have been told by the Division of AIDS that this research amounts to little additional funding.

The US spends about $20 billion every year on AIDS (both for programs in the US and globally). The money is keeping millions of people alive around the world and preventing millions of infections. But a cure is needed, and it is unacceptable that something less than 0.5% (less than about $100 million) of U.S. spending on AIDS is funding AIDS cure research.

The current budget for AIDS vaccine research is $564 million. The NIH and other funders have spent billions of dollars overall on AIDS vaccine research, because an effective AIDS vaccine would be a critical tool for ending the AIDS epidemic. Some researchers believe that the prospects for finding and AIDS vaccine and for a cure are about equal.

- Vaccine trials take years and thousands of patients. AIDS cure trials may require only a few dozen patients. The US government spends ***$1.6 billion***[4] every year to pay drug

companies for AIDS meds via the AIDS Drug Assistance Program, which makes AIDS drugs available to many Americans living with HIV.

- The US spends over ***$15.7 billion*** every year on care for Americans living with AIDS, which **is an amount equal to 1/2 the budget of the entire National Institutes of Health,** which is currently at $30 billion.[5] Combined with global AIDS spending, we spend 2/3 of the budget of the NIH on caring for people with AIDS in the US and abroad.[6]

Functional cure vs. Sterilizing cure? *A functional cure is when a person still has HIV but the body's immune system can now control it without drugs. A sterilizing cure is when there is no HIV in a person's body anywhere. In our view, these options are both light years ahead of taking AIDS medications for the rest of one's life. We support them both—for us, it is not an either/or issue. We'd prefer to have no AIDS at all, but hey—both are great. A treatment that allows your body to control AIDS for five years? Also great. It's all great. Let's move on.*

Who else funds AIDS cure research?

The California Institute of Regenerative Medicine (California's public stem cell agency) recently funded two, four-year studies for a total of $35 million to follow up on the Berlin Patient case. In contrast, a typical NIH study might be $2 million.

The Foundation for AIDS Research (amfAR) has funded AIDS cure research cumulatively totaling $5.8 million since 2002.

Gilead, Merck, Bristol Myers Squibb, and Sangamo are four drug companies that are currently investing in AIDS cure research. However, these companies consider the funding level they are investing in AIDS cure research to be proprietary information and don't disclose it.

We are collecting information about additional sources of AIDS cure research. Please see Appendix A for more information about funders.

Why is AIDS cure research so underfunded?

We have a couple theories. One theory is that researchers were stung by several rounds of publicity about promising developments in the 1990s that did not turn out to be cures.

Because of this, researchers learned a lesson not to be too confident. As years passed, a cure for AIDS came to be seen as a hope that might never be realized. Even now, researchers are loath to publicly admit that they are actually searching for a cure for AIDS: In the scientific community, it is considered naïve. Even if now the science is actually, almost secretly, going well.

(There is no such stigma in saying that you are working toward a vaccine against AIDS. Nor should there be.)

Meanwhile, AIDS treatments became more and more effective and the medications became simpler for patients to take every day. So many researchers started focusing on perfecting treatments, and AIDS cure research started to take a back seat. But it never went away—leading researchers quietly continued to push for a cure.

(One of our goals is to bring the search for a cure for AIDS out of the closet.)

Another theory is that some drug companies, which have a lot of money to spend on research, concluded that the safest investment for them was to put money in AIDS treatment, not AIDS cure research. There was a greater chance to find an effective treatment than to find a cure for AIDS, and less chance of losing their money. Over time, with researchers moving between drug companies and universities as they do, treatment research became more and more the focus. For scientists, it was easier to find research money for treatment studies, not a cure. And it came to be seen as a cooler thing to work on. Less naïve. And again, the search for a cure took a back seat.

*"You start with something complicated and **with** time you take measures that make it easy."*—NIH administrator, talking about evolution of a cure for AIDS

To this day, much of the AIDS cure research takes place in universities and at the NIH, instead of at drug companies—though some drug companies, like Gilead, are in fact initiating important AIDS cure studies.

The National Institutes of Health has been underfunded since 2003[7]. Money is scarce, especially for risky new ideas that might not pan out or young and uninfluential researchers. When push comes to shove, AIDS cure research slides to the bottom of the list. And the red tape to even apply for funding from the NIH is legendary.

And this is cutting-edge research: Several principal investigators, including those who have successfully received NIH funding, have commented that sometimes grants are turned down simply because the grant review panel doesn't understand the science.

How Much Should a Cure for AIDS Cost?

The AIDS cure treatment for the one patient who has apparently been cured, known as the Berlin Patient (he was treated in Berlin, Germany), cost $100,000. Some researchers believe that they must only develop inexpensive cures that can be distributed to millions of people. But that's a fallacy—many treatments, including protease inhibitors, were initially very expensive. As one NIH administrator and researcher put it, "You start with something complicated and with time you take measures that make it easy."

Researchers should be exploring every avenue to find a cure regardless of the cost of the resulting therapy. Once they have a cure that is safe and effective, the scientific, manufacturing, and advocacy communities can work to make it cheaper, and find ways to scale up production and distribution to the millions of people who need it. But researchers should not think that they have to develop a cure that is cheap right out of the box. Even Model T cars were originally made by hand.

Also, if US AIDS treatments cost $15,000-$20,000 per person per year, a cure that costs $100,000 is only the same price as five years of treatment and care in a Western nation. If we look at the international community, where treatment is much cheaper due to generic competition and deals struck by nonprofit foundations, billions of dollars are also spent on AIDS care and treatment that could eventually be re-deployed to pay for cures. Cures that are expensive at first and become cheaper over time.

What Research Is Funded?

When thinking about designing an AIDS cure study, researchers are compelled to consider whether or not the NIH or other funder will actually pay for it. If they don't think the funder will pay, they may move on to another idea—possibly an inferior idea. And accordingly, researchers may try to gear their research toward what money is available.

One problem is that US researchers believe that the NIH, FDA and Institutional Review Boards (advisory boards that must OK research at research facilities) will turn down studies that don't provide current standard of care for patients. Many of them believe that people with AIDS will not volunteer for studies that might result in below standard-of-care treatment, even if for a brief period and even if it's to help find a cure for AIDS.

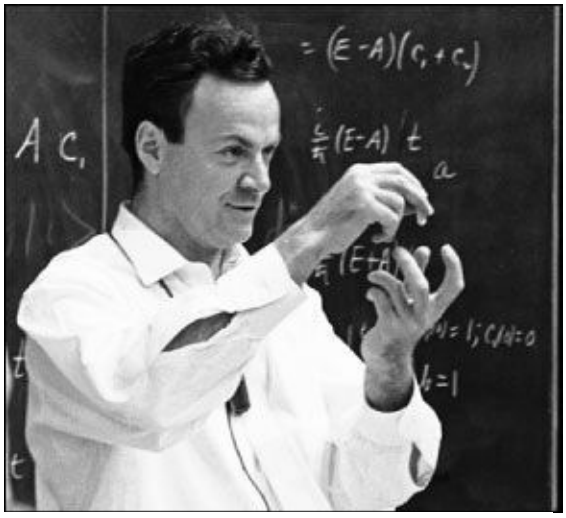
The recruiting practices of a recent, important gene therapy study illustrate this. The study tried to enroll patients in Philadelphia, without informing them that the focus of the study was to find a cure for AIDS. The study site did not enroll a single patient.

A second study site, in San Francisco, explained the purpose of the study to patients and easily enrolled the same study, with a waiting list.

Without seriously considering studies that might result in some patient risk, however small, the NIH may deny them funding or an institutional review board may turn them down. These studies, some of them critically important, are not even getting off the drawing board. Patient rights and informed consent are essential, but the cure for AIDS should not wait because researchers, funders, and institutional review boards presume to take away patients' choice to make informed decisions.

AIDS Research for AIDS Researchers Only

There is another problem that afflicts medical research overall: One has to be a career AIDS researcher to do this work. There aren't a lot of scientists guest starring from other fields to work on the problem. Scientists are needed who might have expertise in physics or group problem solving, or stem cell transplants for breast cancer or who know about research methodologies used in multiple sclerosis. The Nobel Prize-winning physicist Richard Feynman worked briefly in biology, making several important discoveries before returning to physics. We need physicians and scientists from other disciplines to contribute their ideas to a cure. It is notable that Gero Hütter, the physician who treated the Berlin patient, was a young leukemia doctor and not an AIDS researcher. The patient he treated, who remains free of HIV, was the first HIV-positive patient he ever had.



Nobel-Prizewinning physicist Richard Feynman worked in biological research during a sabbatical, making several important contributions.

Conclusion

AIDS cure research receives only 3% of the NIH's NIAID research budget; less than 1/9 the funding of AIDS vaccines, yet it is at least as promising. AIDS eradication research is marginalized inside the research community by a scientific establishment that believes that treatments are a more practical thing to study. Outside the research community, almost no one knows about it.

And yet—there is exciting research happening as a result of the Berlin Patient, who is apparently the first person to be cured of AIDS. [Even writing that sentence is stunning.] Other promising research is attempting to activate and kill the last, latent AIDS-infected t-cells in the body of a person with AIDS.

A cure for AIDS would save the lives of millions and millions of people—including many in developing countries who may never receive the decades of treatment they need to stay alive. And cure clinical trials require only a small number of participants and can be conducted in a relatively short span of time.

The cure must be pursued as aggressively and funded as fully as AIDS vaccines—but not by moving money out of their budget.

What is missing from this equation is proper funding for the National Institutes of Health and just as importantly, attention within it to target a cure. Whether there is the political power from the advocacy community to compel this funding is an open question.

But if we can properly fund this research, and researchers are given opportunities to work together and share data; if we encourage innovators--we have a real chance of finding a permanent cure for AIDS. Soon.

RECOMMENDATIONS

What can we do to foster a cure for AIDS?

1. Congress must fully fund the National Institutes of Health. The Treatment Action Group of New York has shown that the NIH has been struggling under essentially the same funding level since 2003, yet facing 13% in cumulative biomedical inflation, which erodes its purchasing power by billions of dollars. The NIH is arguably the world's leading research institution for AIDS, cancer, schizophrenia and many other scourges. US Congress must properly fund this critical medical research that can improve, or even save, their lives.

   We are calling on Congress to increase NIH funding overall by 20% to $37 billion, to begin to start to make up the funding gap from the past 8 years. [Based on White House estimated NIH FY 2010 spending = $31,089,000,000 + 20%= $37.3 billion *http://online.wsj.com/public/resources/documents/WSJ-20100201-Health.pdf*]

   As a first step, we must educate members of Congress. Do they realize that we are spending $20 *billion* dollars per year on AIDS care, (2/3 of the budget for the entire National Institutes of Health) and only $60 *million* on promising AIDS cure research? Do they know how AIDS cure research is actually going? If they did, perhaps they would support the funding we are requesting.

2. The National Institute of Allergy and Infectious Disease must bring the budget for AIDS cure research up to the level of other major AIDS initiatives. **To start, the budget** should **quadruple for FY2011 to $240 million and reach $600 million within five years.** We want the cure for AIDS to happen as soon as possible, not as part of a scale-up plan headed for 2020. However, this money should not come from AIDS vaccine or microbicides research or other badly needed funding, and doesn't have to.

3. **The NIH must create a new tracking code for AIDS cure research and produce an annual progress report on the push for a cure for AIDS.** Advocates should not be forced to file FOIA requests or enlist celebrities or members of Congress to obtain basic budget information about NIH spending on a cure. The NIH is a taxpayer-funded institution.

4. **Support the scientists!** Right now, the cure is the scientific goal that dare not speak its name. These researchers, some of whom are demoralized by the difficulty in getting funding, are devoting their careers to a goal that could potentially save the lives of 33 million people and alter the lives of their families and future generations of people with AIDS. This research is very, very important and deserves money, attention, and respect. **Charitable foundations could work together to establish two, high profile annual**

prizes: One for the most progress toward a cure, and one for the most intriguing research, whether it pans out or not.

5. **Streamline the NIH system for moving from basic research to clinical trials, and improve patient access to cure trials.** Researchers, funders, and institutional review boards need to remember that a cure is urgently needed, and that they have a responsibility to offer informed patients the opportunity to enroll in AIDS cure studies with reasonable risks. It's not ethical to take those studies off the table.

6. **An X Prize:** A $10 million dollar award to the first person or team that can keep 90 out of 100 men and women functionally cured for 3 years using a treatment with less than a 2%, cure-related mortality rate (comparable to the mortality rate of treated people with AIDS). Judged by an independent research panel.

7. **Find ways to involve people who are not AIDS researchers in the pursuit of a cure.** Host AIDS research seminars and workshops (at the American Association for the Advancement of Science?) that explicitly include a cross-section of different types of established researchers and physicians. Develop cross-cutting academic curricula. Create a $100,000 per year Feynman Fellowship for a major scientist who wants to enter the field of AIDS cure research for two or three years, partnering with an AIDS researcher. Create smaller fellowships for post-docs and physicians.

8. **Introduce and propagate *multiple*, alternate scientific research models to the current competition and peer review model.** Provide an alternative to the goal of peer-review publication with *progress toward a cure* as measuring stick and finish line. Competition between labs is one important model, but has its limitations. (Right now, the lack of shared information is slowing the overall effort.) Models—such as one used in multiple sclerosis research-- that focus on high-level scientific collaboration in real time are also needed.

   The NIH's Division of AIDS just established a new, public/private partnership to find a cure. The Martin Delaney Collaboratory, named in memory of an important California AIDS activist, is a welcome innovation and shows great follow-through from the NIH. However, the first-year funding is only $8 million, which is only enough money for one or two projects. ***Multiple* research models should be explored and developed.**

9. Publicize the state of the research, and its funding crisis, in the mainstream and scientific press to build public support and awareness.

Cell-Based And Genetic Engineering Therapies

One promising avenue for a possible AIDS cure is using cell-based therapies to treat HIV. Unlike all presently existing AIDS therapies, cell-based therapies transform human cells to either make those cells resistant or immune to HIV infection or to make the cells able to target and kill HIV infected cells. Currently proposed AIDS cellular therapies combine the proven medical technique of stem cell transplantation with genetic engineering.

Stem cell transplantation has become a mainstream treatment for many cancers. More than 10,000 stem cell transplants are currently performed in the United States each year, with many thousands more performed around the world. A majority of these transplantations are self-donor transplantations, also called autologous transplants. In self-donor transplants, some of a patient's stem cells are removed from his or her body and then the patient is given harsh radiation and chemotherapy to kill any cancer cells that are present. This chemotherapy also kills most of the stem cells in the patient's body that would replenish the patient's blood supply. After the radiation or chemotherapy is completed, the patient is given back his or her own stored stem cells (which have usually been frozen) and those cells then reproduce and repopulate the patient's bone marrow.

The AIDS cellular therapies currently being studied use exactly the same proven self-donor stem cell transplant techniques to remove stem cells from a patient's body and later reintroduce them. However, in AIDS cellular therapies, while the stem cells are outside of the body, they are genetically modified to resist HIV. These genetically transformed cells are then given back to the patient.

Genetic engineered therapies have not yet become widespread treatment for any diseases. One reason is that problems can arise when genetic engineering techniques are tried on cells that are inside a patient's body. In proposed HIV cellular therapies, however, this is not a problem because the genetic engineering techniques are not done inside a patient's body, but are applied to the cells outside the body. Thus, there is some reason to hope that HIV could be the first serious disease to be treatable with genetic therapy. HIV might also be an especially good candidate for this type of genetic therapy because the transformation of only one cell type, CD4 T-cells, might be enough to dramatically improve a patient's HIV disease, or even lead to a cure. The very thing that made HIV disease so mysterious during the early years of the epidemic, its ability to precisely target one very specific type of immune cell, might make HIV the first disease to be effectively treatable with genetic engineering.

Dr. Gero Hütter and the Berlin Patient

(A donor transplantation of stem cells with a natural CCR5 deletion.)

The Berlin patient, described in the introduction, is widely regarded as a proof of concept that CD4 cells that are altered so that they have the CCR5 deletion (and are immune to AIDS) might lead to an effective or curative AIDS treatment. The donor stem cells received by this patient were not modified by genetic engineering, but were received from a patient who was born with cells that lacked the CCR5 cell surface protein, one of the two entry points that HIV needs to infect T-cells. This mutation (called a CCR5 double deletion) is present in about 1% of Northern Europeans. As has been widely reported and discussed above, three years after receiving the transplant, the patient has no evidence of HIV in his body. [8]

There are a number of things about the Berlin Patient's treatment that make that particular treatment not appropriate for people with HIV who do not also have leukemia. First, the patient received harsh partially ablative (immune cell killing) chemotherapy and radiation therapy to treat his leukemia. This would have also cleared out many cells that could harbor latent HIV infection. Such partially ablative therapy is likely too risky for HIV+ patients who are otherwise doing well on anti-HIV drugs. Second, the patient received donor cells that were *all* CCR5 double deleted. In proposed HIV cellular therapies, only a portion of the cells would be transformed. Third, the patient received cells from another person, not an autologous transplant in which his own cells would be removed, stored, and replaced after chemotherapy. These donor cells may have been more active at killing any remaining latently HIV infected cells through mild graft versus host disease.

However, there are a number of things about the Berlin patient that could be seen as hopeful for CCR5 gene therapies. First, the Berlin patient did not receive the most ablative radiation and chemotherapy prior to his first transplant. A number of cells (such as macrophages) in the patient that are widely believed able to harbor HIV survived the radiation and chemotherapy and were detected in the patient 159 days after transplantation.[9]. HIV proviral DNA was detected on the 20th and 61st day[10], but was not detected in the three years since. This suggests that it is possible that the CCR5 deleted T-cells and the patient's reconstituted immune system were able to recognize and eliminate other HIV infected reservoirs. Second, the Berlin patient did not receive any treatment specifically targeting any of the other possible reservoirs for HIV infection. Researchers have long believed that low-level HIV infection can occur in a number of different cells, including macrophages, heart cells and brain cells. The fact that the Berlin patient shows no evidence of HIV several years after treatment suggests that it might be possible to rid the body of HIV by only transforming CD4 blood cells.

Dr. Paula Cannon and the Los Angeles Mice

(An animal model of treatment with stem cells modified using zinc finger technology from Sangamo, a California biotech company)

The second major proof of concept for an AIDS cure has occurred in engineered mice and was just announced and published on July 2, 2010 in *Nature Biotechnology*. [11] The procedure was performed by Paula Cannon, Ph.D., Associate Professor of Molecular Microbiology & Immunology at the Keck School of Medicine of the University of Southern California (USC). The research team used mice that were specifically bred and treated to have no natural immune system. The mice received human stem cell transplants to give them a human immune system—one that is susceptible to HIV infection. One group of the mice was given a stem cell transplant with human stem cells that had been genetically modified to remove the CCR5 gene, thus partly duplicating the treatment that cured the Berlin patient. The mice were then infected with HIV. The mice with the altered CCR-5 deletion stem cells regained their normal T cell counts afterwards and maintained their health without any additional medications. The mice that were infected with HIV and had normal human stem cells showed signs of HIV-weakened immune systems and HIV disease.

The genetic engineering technique used in Dr. Cannon's research used zinc-finger nuclease (ZNF) editing of stem cells. ZFNs are proteins that can be used to generate a double-stranded break in DNA at a precise location, such as the location of the CCR5 gene. This work was conducted along with a team of scientists at City of Hope, a medical center in Duarte, California; and Sangamo Biosciences, near Oakland, California.

Human Trials Of Combination Gene-Therapy: Dr. John Zaia

In a different research trial, conducted by John Zaia and City of Hope Hospital in Los Angeles, human stem cells were treated with gene therapy to provide them with three different mechanisms to resist HIV infection. In this treatment, self-donor (autologous) stem cells were modified outside the body using an engineered lentivirus that programmed the cells to produce three new molecules (in this case RNA sequences) that fight HIV. One of the molecules disables the CCR5 in cells, but by an entirely different method than the ZFN technique discussed above. The second molecule hides a protein that the virus uses to replicate, and the third knocks out a key piece of genetic machinery that HIV needs to maintain itself. (These three techniques are referred to as (1) **CCR5 ribozyme, (2) tat/rev short hairpin RNA, and (3)TAR decoy.)**

In the study, researchers at the City of Hope extracted stem cells from the blood of four people with AIDS-related lymphoma, a blood cancer, and modified some of them to carry anti-HIV genes. The altered cells were returned to the patients' blood without harming them and remained there for two years, a sign that if given in greater number, they might be able to suppress the AIDS virus.

By hitting multiple sites of the virus with different types of gene therapy, the researchers hope that resistance to one type of gene therapy doesn't make it resist others. Because the transplant procedure was risky, it was only attempted on HIV patients who needed it already to treat their cancer. All four patients remain free of their lymphoma about two years after the treatment.

The number of gene-modified cells returned to the patients in this pilot study was too small to cure or even improve their HIV infections. The next step is to replace a much larger portion of a patient's stem cells with gene-modified cells and see if they can substantially reduce their HIV level.

CD8-Cell enhancement: Drs. Carl June and Pablo Tebas

A team of researchers in Philadelphia, Pennsylvania is using genetic engineering of self-donor cells to fight HIV in an entirely different way. The team is creating CD8 killer immune system cells that are substantially better able to eliminate HIV infected-cells from the body than normal CD8 killer cells. A small-scale clinical trial has been announced using this technique. The trial will be led by Carl June, MD, of the University of Pennsylvania's Abramson Family Cancer Research Institute and the Department of Pathology and Laboratory Medicine. He will work with Pablo Tebas, MD, Director of the Adult AIDS Clinical Trials Unit (ACTU), Department of Infectious Diseases Division, also at the University of Pennsylvania.

In this technique, CD-8 killer T cells are modified to better recognize all versions of a key HIV molecular fingerprint on the surface of infected cells. The modified CD-8 cells are able to clear HIV infection in the laboratory cell cultures. The modified CD-8 cells target HIV about 450-fold more strongly than unmodified CD-8 cells. Adaptimmune Ltd, a United Kingdom-based company, owns the rights to the technology.

More Cure-Related Research

This overview includes notes on three research projects happening now that are relevant to a possible cure for HIV infection. In addition there are many other possibilities--many mechanisms in viral growth or HIV disease development that might be targeted successfully.

Clearing the HIV Reservoirs: Infected Resting CD4 Cells

Modern antiretroviral treatment works well to suppress viral replication, sometimes leaving no evidence of new HIV in the blood. But even after years of seemingly complete suppression, if the drugs are stopped the virus quickly returns. Clearly HIV is preserved somewhere in the body, beyond the reach of current AIDS drugs or the immune system, in "reservoirs" (known or unknown), where it may replicate at very low levels or not at all.

The best-known and most studied HIV reservoir is in resting CD4 memory cells [note 1]. In persons with HIV, only about one in a million of these cells is infected. But those cells can live for many years. And since the HIV in them is completely inactive inside the DNA, it is invisible to the immune system, and unaffected by current antiretrovirals. (An HIV "reservoir" may refer to a certain kind of cell, as above -- or to an organ or other location in the body, such as the brain.)

Occasionally one of these infected resting cells becomes activated, [note 1] and produces infectious HIV. If the patient is still taking antiretrovirals, the new HIV can be suppressed like the original infection. But without the antiretrovirals, the new virus will set off cycles of replication, restoring a high viral load.

One approach to clearing the reservoirs is to look for drugs that could activate the infected cells [note 1], without also activating too much of the immune system or otherwise causing intolerable side effects. When the infected cell is activated it will be destroyed, but first it will produce new HIV, which needs to be blocked by antiretroviral drugs.

For years there has been interest in prostratin (a drug from a Samoan medical plant used by traditional healers to treat hepatitis) for activating the infected cells, and possibly eradicating this reservoir of HIV.

More recently, prostratin is being tested in combination with other drugs, such as SAHA (used in cancer treatment). These two types of drugs seem to work particularly well together, allowing doses to be reduced. Researchers are now searching for more

tolerable substitutes for prostratin and SAHA that show the same synergy. Researchers are also looking for new agents entirely. The idea is to achieve a cure by activating these last infected cells in HIV reservoirs while conventional antiretrovirals protect the patient from the HIV released. Then, with HIV completely eradicated, the AIDS drugs could be discontinued.

How could the activation be made specific to cells infected by HIV? The following study suggests one possible answer.

A recent laboratory study[12] screened many substances and found one that activated latent HIV-infected cells, without also turning on pro-inflammatory genes. Apparently it took advantage of the fact that just a few copies of one part of HIV (called the Tat protein) can cause the production of many more copies, a positive feedback loop that causes the HIV genome within the human DNA to create more and more HIV, even starting from very few copies [note 2].

An Accidental Discovery

In a different approach to helping clear HIV reservoirs, high-dose intravenous immunoglobulin (IVIG) (an approved but scarce drug, made from human blood) looked promising in a very preliminary study[13]. No one understands exactly how it works. This study was suggested by treatment of a patient who was given IVIG for other reasons, then decided to stop his antiretroviral treatment because he wanted to; his viral load remained under 50 copies per mL while off treatment for several months, which is quite unusual. The small study to follow up on this did not stop the antiretroviral treatment, because of concerns about asking patients to do so, but other evidence from that trial suggested that the IVIG might be activating HIV-infected cells in reservoirs that are then killed off.

Restoring Immunity to Help Control HIV

In this approach toward a functional cure (disease control without ongoing therapy, but short of eradication of HIV), one possibility is to restore certain immune functions to help the body control the low levels of HIV released from the reservoirs during successful antiretroviral treatment. If these occasional virions (particles of HIV) cannot cause a new infection, then it might not be necessary to continue daily treatment.

There are thousands of published papers on HIV and immunity [note 3]. More will be presented at the International AIDS Conference in Vienna. It is often difficult or impossible to know which ones may be relevant to a cure.

Vienna Reservoirs Workshop

An HIV Reservoirs Workshop (focused on AIDS cure research) will take place July 16 and 17, 2010, in Vienna, Austria, just before the International AIDS Conference[14].

The AIDS Policy Project will be blogging about AIDS cure research from this workshop and from the main conference.

Follow our Cure Blog: http://aidspolicyproject.blogspot.com/

Twitter: www.twitter.com/aidspolicyproj

Facebook: http://www.facebook.com/pages/The-AIDS-Policy-Project/187761083716

YouTube: Later this summer, the Reservoirs Workshop will post videos of each of its public meetings on AIDS cure research that can be accessed here: http://aids2008.org/Default.aspx?pageId=349

Other Suggested Publications on Cure Research

Cohen, Jon. Can AIDS Be Cured? *Technology Review*. 2010 Jun 22; http://technologyreview.com/biomedicine/25563/[abstract]

Deeks SG. HIV Eradication: Is it feasible? *Aids2031 Working Paper No. 7*. 2008 Nov; http://www.path.org/publications/details.php?i=1644 [full text]

Gandhi RT, Bosch RJ, Aga E, et al. No evidence for decay of the latent reservoir in HIV-1-infected patients receiving intensive enfuvirtide-containing antiretroviral therapy. *J Infect Dis.* 2010 Jan 15;201(2):293-6, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2887684/[full text]

Keedy KS, Margolis DM. Therapy for Persistent HIV. *Trends Pharmacol Sci.* 2010 May;31(5):206-11. Epub 2010 Mar 5; http://www.ncbi.nlm.nih.gov/pubmed/20207023 [abstract].

Margolis DM. Mechanisms of HIV Latency: an emerging picture of complexity. *Curr HIV/AIDS Rep.* 2010 Feb;7(1):37-43, http://www.ncbi.nlm.nih.gov/pubmed/20425056 [abstract].

O'Connell KA, Brennan TP, Bailey JR, Ray SC, Siliciano RF, Blankson JN. Control of HIV-1 in elite suppressors despite ongoing replication and evolution in plasma virus. *J Virol.* 2010 Jul;84(14):7018-28. Epub 2010 May 5. http://www.ncbi.nlm.nih.gov/pubmed/20444904 [abstract].

Richman DD, Margolis DM, Delaney M, Greene WC, Hazuda D, Pomerantz RJ. The Challenge of Finding a Cure for HIV Infection. *Science.* 2009 Mar 6; 323(5919):1304-7, http://www.ncbi.nlm.nih.gov/pubmed/19265012 [full text, with free registration].

Trono D, Van Lint C, Rouzioux C, et al. HIV Persistence and the Prospect of Long-Term Drug-Free Remissions for HIV-Infected Individuals. *Science.* 2010 Jul 9; 329(5988):174-180. http://www.sciencemag.org/cgi/content/short/329/5988/174 [abstract].

Endnotes

Note 1. Memory cells recognize an infection the body encountered earlier, and can respond quickly to it; this is how ordinary vaccination works. Resting memory cells are not currently active, but become activated if they meet the particular infection they recognize. Unfortunately, about one in a million of these resting memory cells also has HIV silently integrated into its DNA, and activation causes the HIV to start reproducing, re-establishing the infection even after it had been suppressed for years by antiretrovirals. This is one way that HIV persists, making patients keep taking the drugs.

Note 2. Apparently this "hit-and-run stimulation" worked by raising the level of NF-kappaB for just a short time, causing a very small amount of Tat protein to be produced. But that Tat caused the HIV genome to produce more Tat, in a self-perpetuating cycle [1].

Note 3. Over 10,000 references from found from a PubMed search on July 8, 2010. Visit http://www.ncbi.nlm.nih.gov/pubmed/, search: HIV immunity

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[11] Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 1996;86:367-377.; See Also Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene, Letters to Nature, Nature 382, 722-725 (22 August 1996) ; R Landau, Homozygous Defect in HIV-1 Coreceptor Accounts for Resistance of Some Multiply-Exposed Individuals to HIV-1 Infection, Cell - 9 August 1996 (Vol. 86, Issue 3, pp. 367-377)

[2] ***"A Doctor, a Mutation and a Potential Cure for AIDS",*** The Wall Street Journal, November 7, 2008 http://online.wsj.com/article/SB122602394113507555.html

[3] Hütter G, Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation, N Engl J Med. 2009 Feb 12;360(7):724-5. PMID: 19213682

[4] National ADAP Monitoring Project Annual Report, http://www.nastad.org/InFocus/InfocusResultsDetails.aspx?infocus_id=329 (May 3, 2010)

[5] Department of Health and Human Services Fact Sheet: *http://online.wsj.com/public/resources/documents/WSJ-20100201-Health.pdf page 78*

[6] HIV/AIDS Policy Fact Sheet, Henry J. Kaiser Foundation, http://www.kff.org/hivaids/upload/7029-06.pdf

[7] Flat-Lined: How Flat NIH Funding Undermines Research on HIV, TB and Viral Hepatitis, Report by the Treatment Action Group of New York, May, 2009, Page 1. http://www.treatmentactiongroup.org/publication.aspx?id=3052

[8] Hütter G, Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation, N Engl J Med. 2009 Feb 12;360(7):724-5. PMID: 19213682

[9] Hütter G, p. 695

[10] Hütter G, p. 695

[11] Paula M Cannon, Human hematopoietic stem/progenitor cells modified by zinc-finger nucleases targeted to CCR5 control HIV-1 in vivo, Nature Biotechnology 2 July 2010 | doi:10.1038/nbt.1663

[12] Wolschendsorf F, Duverger A, Jones J, et al. Hit-and-Run Stimulation: A Novel Concept to Reactivate Latent HIV-1 Infection Without Cytokine Gene Induction. J Virol. 2010 Jun 10 [Epub]. http://www.ncbi.nlm.nih.gov/pubmed/20538859 [abstract].

[13] Lindkvist A, Edén A, Norström MM, et al. Reduction of the HIV-1 reservoir in resting CD4+ T-lymphocytes by high dosage intravenous immunoglobulin treatment: a proof-of-concept study. AIDS Res Ther. 2009; 6:15. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713257/ [full text]. Also see earlier interview with senior author Magnus Gisslén, M.D., Ph.D. High-Dose Intravenous Immunoglobulin May Reduce Latent HIV Reservoir in Resting CD4+ Cells, Study Suggests. The Body Pro. February 10, 2009; http://www.thebody.com/content/confs/croi2009/art51696.html [full text]

[14] "TOWARDS A CURE": HIV RESERVOIRS AND STRATEGIES TO CONTROL THEM. Pre-Conference Workshop: 16 - 17 July 2010, Vienna, Austria. http://www.hiv-travel.org/Default.aspx?pageId=349.

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Appendix A

FUNDING SOURCES FOR AIDS CURE RESEARCH
(We are just beginning to compile this list; feel free to contact us with additional information)

US National Institute for Allergy and Infectious Diseases:
$40 million in 2009 (see report for earlier years)

US National Institute for Mental Health
$20 million in 2009

The California Institute of Regenerative Medicine (California's public stem cell agency) has funded two, four-year studies for a total of $35 million to follow up on the Berlin Patient case.

The Foundation for AIDS Research (amfAR) has funded AIDS cure research cumulatively totaling $5.8 million since 2002.

Gilead, Merck, Bristol Myers Squibb, and Sangamo are four US drug companies that are currently investing in AIDS cure research. However, these companies consider the funding level to be proprietary information and don't disclose it.

Objectif Recherche VACcin Sida (ORVACS)
http://clinicaltrials.gov/ct2/show/NCT00976404
http://clinicaltrials.gov/ct2/show/NCT01019551

Istituto Superiore di Sanità
http://www.iss.it/

Medical Research Council
http://www.mrc.ac.uk/index.htm

Institut National de la Santé et de la Recherche Médicale
http://www.inserm.fr/

Agence Nationale de Recherches sure le SIDA et les Hepatites Virales
http://www.anrs.fr/