WINTER 2017/2018 | THE CURE ISSUE

POSITIVELY AWARE

HIV TREATMENT, PREVENTION, AND SUPPORT FROM **TPAN**

THE CHALLENGE OF DEFINING AN HIV CURE

BRINGING RESEARCH INTO THE REAL WORLD

SPEAKING THE SAME LANGUAGE

WOMEN ARE ESSENTIAL TO FINDING A CURE

WHAT DOES AN HIV CURE MEAN TO YOU?

CHARLES SANCHEZ, star and co-creator of the HIV musical comedy web series, *Merce*, in a scene about a cure for HIV.

WINTER 2017/2018

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JOURNALISM. INTEGRITY. HOPE.

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A WORLD POSITIVELY AWARE
OF HIV AND RELATED CONDITIONS.

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TPAN was founded in 1987 in Chicago as Test Positive Aware Network, when 17 individuals gathered in a living room to share information and support in response to the HIV/AIDS epidemic. POSITIVELY AWARE is the expression of TPAN's mission to share accurate, reliable, and timely treatment information with anyone affected by HIV.

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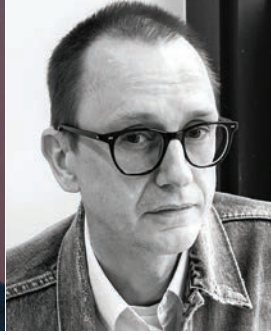


GUEST EDITORS' NOTE
DAVID EVANS &
RICHARD JEFFERYS

Handle with care

Speaking the language of an HIV cure

Welcome to this special issue of POSITIVELY AWARE on HIV cure research.

Coming of age in New York and San Francisco in the early 1990s, we lived through the horrors of the early epidemic just like so many, and the idea that three decades later we'd be centrally involved in the search for a cure is sometimes surreal.

For a long time, the challenge of curing HIV infection was seen as so insurmountable that *the c-word* was almost never mentioned. But that has changed over the past decade, and this area of research is now a central priority within the overall HIV/AIDS portfolio, especially the U.S. government's research arm and private industry. Encouragement has come from a single case of an HIV cure—Timothy Ray Brown—and subsequently, several examples of prolonged remission from detectable virus in the absence of ongoing treatment.

But the science remains complex and challenging, as is the relationship that many have with the words *cure* and *remission*. Those concepts have varied and nuanced meaning for people living with HIV and the diversity of affected communities from which they come. Meaning that is sometimes different from scientists and funders. We've tried to provide some insights from across the spectrum, from the nerdily scientific to the practical and human.

There is so much work underway that it is not possible to fully capture all the knowledge relevant to the pursuit of an HIV cure within these pages, or all the candidate interventions being evaluated. We encourage those interested to seek additional information online. We're both fortunate to work at HIV/AIDS advocacy organizations that have collaboratively played some role in pushing for the renewed emphasis on cure research, and the websites of Project Inform (projectinform.org) and Treatment Action Group (treatmentactiongroup.org) are potential jumping off points for delving deeper into the subject, as is the online version of this issue of POSITIVELY AWARE.

One word of caution about mainstream media coverage of HIV cure research: while it's good that there is interest, the eagerness of news websites to draw visitors has led to some wildly misleading headlines (in the language of the internet: *clickbait*).

Given how much we all want a cure, it's understandable that people embrace and share encouraging stories (such as one that promised a gene therapy cure within three years), but it's also important to be alert to the possibility of hype, in order to avoid the emotional rollercoaster that can result from cycles of hope and disappointment and the risk of contributing further to that cycle.

But evaluating media coverage can be difficult, even for those of us who live and breathe the research. One thing to always look for is perspectives from independent scientists who are not involved in whatever work is being described. The HIV cure research website created by the National Association of People with HIV Australia (hivcure.com.au) has some additional helpful tips for sorting fact from fiction.

More than anything, we come from a long tradition of people living with HIV and their allies who insisted on playing a role in the design and conduct of biomedical research, and not in being compliant patients who were relegated to taking whatever pills happened to make it to market. We hope you will see this issue of POSITIVELY AWARE as an invitation to take part in that tradition.

DAVID EVANS

RICHARD JEFFERYS

THE CHALLENGE OF DEFINING

Different roads to the holy grail

BY RICHARD JEFFERYS

WHAT DOES A CURE for HIV infection look like? It sounds like a simple question, but because of the way the virus can persist in the body, there are significant challenges associated with trying to define if a cure might have been achieved. As the research effort to develop a safe, effective, broadly accessible HIV cure expands, the issue of how to measure success remains central, and is important to understand.

TIMOTHY RAY BROWN

THERE IS ONE INDIVIDUAL who is considered to be the first and, so far, only person to be cured. The case of Timothy Ray Brown has been widely publicized, but is worth revisiting.

Brown had been HIV-positive since 1995 and on combination antiretroviral therapy (ART) for four years when, in 2006, he developed the life-threatening cancer acute myelogenous leukemia (AML). The diagnosis led to the need for a stem cell transplant, a risky treatment that essentially creates a new immune system in the recipient by transferring bone marrow cells from a donor. Chemotherapy drugs and radiation are used to wipe out the existing immune system and make way for the donor cells. The procedure is limited to use in life-threatening cancers because it carries a high risk of death, approximately 20–30% (one out of five to one out of three individuals undergoing it).

Brown's doctor, Gero Hütter, had the idea to look for a donor with a rare genetic trait called the CCR5Δ32 (CCR5 delta 32) mutation. People who inherit this mutation from both parents are described as homozygous for CCR5Δ32, and the consequence is that their cells cannot produce a particular protein named CCR5 (people who inherit the mutation from only one parent have lower levels of CCR5).

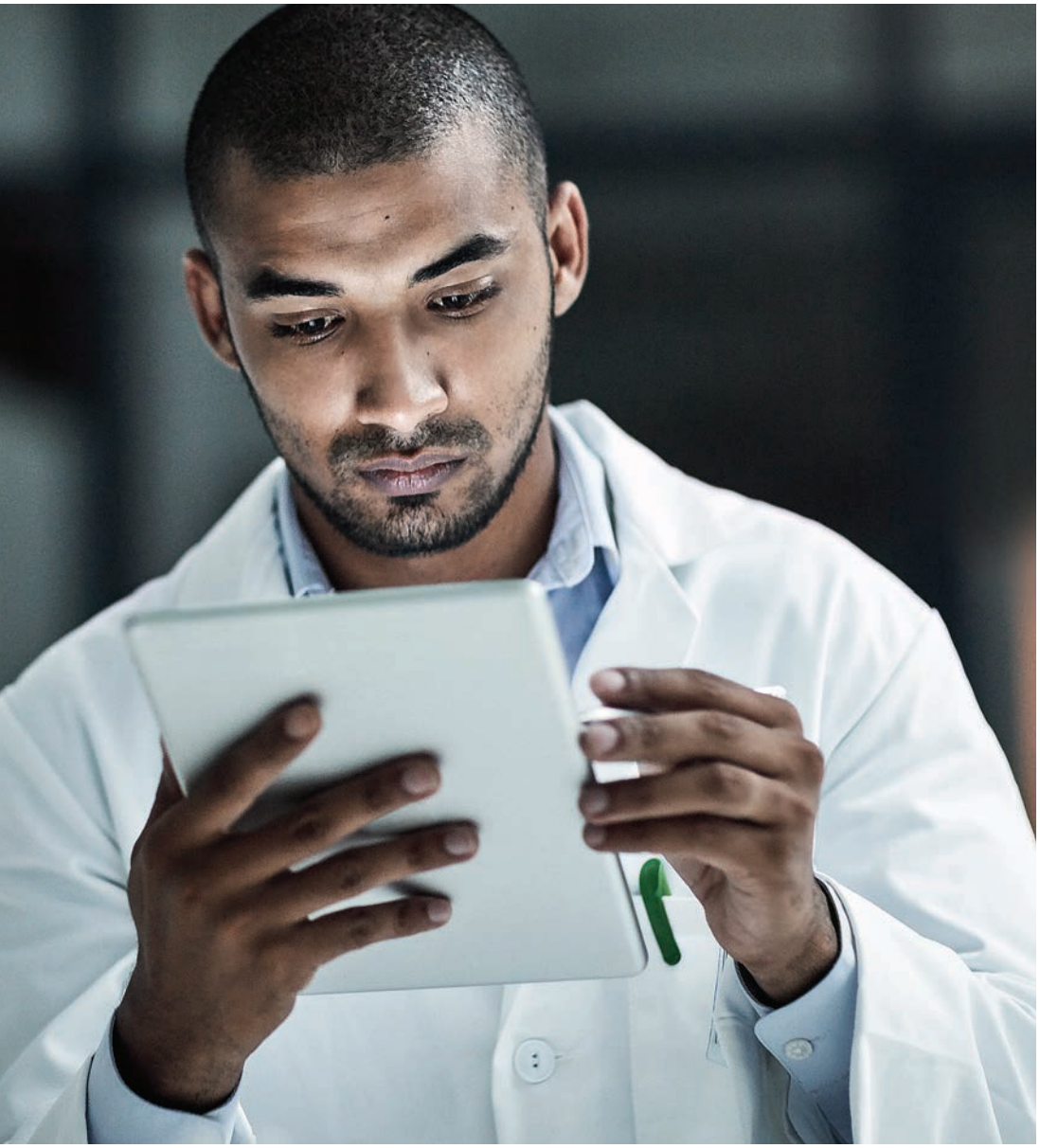
The relevance for HIV is that the most common strains of the virus use CCR5 as a latch to gain entry into the cells it targets for infection—predominantly CD4 T cells, which are a vital component of the immune system. Scientists studying gay men who had been highly exposed to HIV but remained uninfected discovered the CCR5Δ32 mutation in the mid-1990s.

Gero Hütter assessed many potential stem cell donors for Timothy Ray Brown and was fortunate to eventually find a match who was homozygous for CCR5Δ32. The treatment was tortuous, with Brown requiring two stem cell transplants and experiencing graft-versus-host disease (GVHD), which occurs when the newly transplanted immune system attacks the recipient's cells, requiring management with immune suppressants.

Ultimately, however, the stem cell transplants succeeded and the AML was cured. Brown's new immune system was made of cells homozygous for CCR5Δ32, so they lacked CCR5. ART was stopped during the procedures and—although Hütter had cautiously hoped for the outcome—it was nevertheless a welcome surprise to find that HIV viral load had not rebounded despite the absence of ongoing treatment.

The first report on Brown's case was made in a poster presentation at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2008. For those unfamiliar with scientific conferences, much of the action takes place in sessions where researchers orally present results to a seated

AN HIV CURE



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audience. But there are also poster halls, where studies deemed preliminary or potentially less important are described on paper pinned to plasterboards. Hütter's poster described Brown's case, and noted that—at that point—he had been off ART without detectable HIV rebound in blood, bone marrow, or rectal mucosal tissue for over 285 days—nearly 10 months.

Many people failed to notice the presentation, or perhaps were skeptical. But activist Martin Delaney, founder of Project Inform, was already advocating for a renewed research focus on curing HIV infection and he drew attention by writing about the results for the organization's website. The news exploded into public awareness about a year later, with articles in the *Wall Street Journal* and a formal case report published by Hütter in the *New England Journal of Medicine*.

Brown, who had initially remained anonymous (referred to in reports simply as "The Berlin Patient"), disclosed his identity shortly afterward and has become a champion for the search for a cure. He has also been incredibly selfless in agreeing to participate in studies aiming to better understand his case. There was briefly some controversy in 2012 when analyses of blood and multiple body tissues by several different laboratories identified a few samples that appeared to contain trace amounts of HIV genetic material, but Brown recently celebrated a decade since his stem cell transplants with no sign of any HIV viral load rebound, and this remains the best evidence that a cure has been achieved.

Even now, though, it is not possible to know for sure if all HIV capable of replicating has been eradicated, or if there is some residual inactive virus—technologies capable of surveying the entire body do not exist.

'THE MISSISSIPPI BABY'

WHILE CLEARLY GREAT NEWS and encouraging for the HIV research field, Brown's example also highlights that, currently, the question of whether a person is cured can only be answered by following them for many years. This has also been underscored by a number of individuals who have shown signs of being cured, only to later experience viral load rebounds after months or even years off ART.

The most famous of these remission cases is "the Mississippi baby." Born to a mother whose HIV infection

CAN WE DO IT AGAIN?

ATTEMPTS TO REPEAT TIMOTHY RAY BROWN'S OUTCOME IN ADDITIONAL HIV-POSITIVE INDIVIDUALS REQUIRING STEM CELL TRANSPLANTS

Understandably, researchers are pursuing the possibility of duplicating the results obtained in Timothy Ray Brown in other HIV-positive people who require stem cell transplants to treat cancers. Several ongoing research programs (such as the amfAR-supported international IciStem collaboration) are attempting to find appropriate donors who are homozygous for the CCR5Δ32 mutation for HIV-positive individuals in this situation. A number of transplants have been performed but, so far, no other cases of HIV cures have been publicly reported.

A publication by Gero Hütter has summarized six cases in which HIV-positive individuals received stem cells from donors homozygous for the CCR5Δ32 mutation, but all died due to either the cancers or complications of the procedures—illustrating the risks of the approach, and its limited applicability as a curative intervention.

—RICHARD JEFFERYS

was not diagnosed until in labor, the neonate was started on ART within hours of delivery. The treatment was maintained for around 18 months, at which time the mother and baby temporarily stopped attending medical follow-up visits. When they returned, doctors learned that ART had been interrupted in the infant but, surprisingly, HIV viral load remained undetectable. The case drew widespread media coverage, and there was optimism that it represented another cure.

The initial theory was that the rapid institution of ART may have prevented the formation of the HIV "reservoir," which consists primarily of long-lived CD4 T cells that have become infected by the virus but then entered a deactivated or resting state that allows HIV genetic material to persist in a silent or "latent" form (see "Latent Tendencies" on page 7).

Latently-infected CD4 T cells, as they are called, can become active if ART is interrupted, leading to renewed virus production and viral load rebound. In essence, the cells act as a hiding place for the virus, from which it can emerge when the coast is clear of ART. For this reason, they are seen as the most important obstacle to accomplishing an HIV cure.

The Mississippi baby remained off ART for a little over two years with no measurable HIV, but then experienced a return of detectable viral load necessitating the restarting of treatment, confounding the hope that the virus had been cleared. Researchers believe that the very early start of ART had greatly limited the size of the reservoir of latently infected CD4 T cells, but a few likely were present in a resting state, and eventually one or more became activated, leading to renewed HIV production. Resting CD4 T cells can become activated for a number of reasons, most commonly due to encountering an infectious agent or other substance that they recognize and respond to—part of their job as immune system cells.

The outcome in the Mississippi baby emphasized that HIV can persist at levels undetectable by current technologies (see "Measuring the HIV Reservoir," page 6) and that long-term monitoring is essential even if it might initially appear that an individual has been cured.

THE BOSTON PATIENTS

SEVERAL ADULT CASES have since mirrored the experience of the Mississippi baby. The closest echo is a recent report of an individual who was diagnosed with HIV extremely early (within approximately 10 days), due to acquiring the infection during a short window of time between screening for a pre-exposure prophylaxis (PrEP) demonstration project and the day they were started on the first dose of the PrEP drug Truvada.

Combination ART was begun as soon as the diagnosis was confirmed and maintained for 34 months before an analytical treatment interruption was undertaken (see "Time Out" on page 11). HIV remained undetectable for 224 days off ART, but then viral load rebounded.

The Boston patients are two HIV-positive men who, like Timothy Ray Brown, required stem cell transplants to treat cancers. They did not receive cells from donors with the CCR5Δ32 mutation, but nevertheless HIV became undetectable after the procedures. ART was maintained throughout, leading researchers to suspect that their new donor-derived immune system cells may have been protected from the virus. Both individuals, like Brown, also developed some GVHD after their transplant, which was thought to have potentially contributed to the clearance of HIV-infected cells. ART was eventually interrupted, and in one case HIV remained undetectable for 12 weeks, and in the other 32 weeks, before viral load reemerged and treatment was reinstituted.

At the 2017 CROI, researchers from Mayo Clinic in Rochester, Minnesota described another HIV-positive man with similarities to the Boston patients. Also a recipient of a stem cell transplant from a donor lacking the CCR5Δ32 mutation as part of treatment for cancer, the individual continued on ART after the procedure and displayed declining levels of HIV reservoirs that ultimately became undetectable. A little over two years after the procedure, an analytical treatment interruption was performed leading to a period of remission from detectable HIV that lasted 288 days. Viral load tests then revealed that HIV replication had restarted, and the individual resumed ART.

These five cases of temporary remission are linked by the fact that all appeared to result from the HIV reservoir being very small at the time of ART interruption. The size in the two Boston patients has been estimated as 290–2,900 latently infected cells and 40–730 latently infected cells, respectively (an estimated reduction of more than 1,000-fold compared to the pre-transplant baseline).

This is important because it indicates that a central goal of HIV cure research—shrinking the size of the HIV reservoir—can at least significantly delay the rebound of HIV when ART is interrupted. Mathematical modeling studies suggest that achieving even greater reservoir reductions—on the order of over 10,000-fold (greater

than 99.99%)—could lead to a lifelong cure in the majority of individuals. So while the task may be daunting, there is a target to aim at. Another implication of the modeling work is that complete eradication of latent HIV—which some scientists believe is likely impossible—may not be a prerequisite for a cure.

The experience of the Boston and Mayo Clinic patients also provides evidence that receipt of a stem cell transplant from a donor homozygous for the CCR5Δ32 mutation was likely key for Timothy Ray Brown's cure, which offers encouragement to researchers pursuing gene therapy approaches (see "Gene Therapy in HIV Cure Research," page 10).

REMISSION VS. POST-TREATMENT CONTROL

THE OTHER LINK among these five cases is that the period of remission seems to have been caused by the few latently infected CD4 T cells that were present remaining dormant (asleep), rather than the immune system actively controlling HIV.

No significant immune responses against HIV could be detected in any of the individuals, which was expected by researchers because of the swiftness with which ART was started in the Mississippi baby and PrEP demonstration project cases (suppressing the virus before the immune system mounted a response), and due to the fact that the Boston and Mayo Clinic patients developed new immune systems—which had not yet encountered HIV—from their HIV-negative stem cell transplant donors.

The absence of immune responses appears to make this type of remission distinct from a somewhat different form that has also received attention in mainstream media coverage of HIV cure research.

Typically referred to as virologic remission or post-treatment control, the best-known examples are the VISCONTI cohort, an unusual group of HIV-positive individuals identified in France who began ART early in infection, continued for several years, and then interrupted and have maintained viral loads at low or undetectable levels, in some instances for over a decade.

A number of other individual case reports have broad similarities, including a perinatally infected French teenager and a nine-year-old South African child who have displayed control of HIV viral load for 12 and 8.75 years, respectively, after limited periods of ART.

Post-treatment controllers generally display immune responses against HIV, including antibody and CD4 and CD8 T cell responses, although there is considerable individual variability. The prevailing belief is that these cases represent some sort of active containment of HIV replication by the immune system. Attempting to induce immunological control of HIV is another avenue being pursued by cure researchers (see "Enhancing Immunity," page 8).

ELITE CONTROLLERS

ONE CONCERN about post-treatment control as a model for an HIV cure relates to the parallels with rare HIV-positive individuals known as elite controllers, who suppress viral replication to undetectable levels for many years without ART. This phenomenon is associated with strong and effective immune responses targeting the virus, particularly CD8 T cells and CD4 T cells. Certain genetic traits that influence the performance of CD8 T cells are known to increase the likelihood of becoming an elite controller.

Unfortunately, however, studies have found that elite control is not necessarily completely protective against disease progression. The efforts of the immune system to control HIV can be associated with increased levels of inflammation and a slow decline in CD4 T cell numbers, ultimately leading to AIDS, albeit it at a far slower pace than is observed in individuals with higher viral loads.

Prospects for long-term health may therefore be better in instances where remission is associated with latently infected cells remaining dormant (or, ideally being eliminated entirely), as opposed to HIV being actively controlled by immune responses—it is early days, however, and firm conclusions cannot yet be drawn.

Notably, there is a subset of elite controllers who exhibit extraordinarily strong control of HIV, and they may offer cure researchers a model of immune-mediated containment without the potential for detrimental effects.

LOOKING AHEAD

THE COMPLEXITIES associated with discerning what an HIV cure looks like with some degree of certainty can be headspinning, but should not be disheartening. Even having cured just one person, and attained temporary remission in several more, is a far from trivial achievement. The increasingly global expansion of cure research promises to bring answers to the difficult questions that still face the field, and hopefully draws an easily taken, effective, and scalable cure ever closer. PA

CHEAT SHEET

KEY POINTS TO KNOW ABOUT HIV CURE RESEARCH

One person, Timothy Ray Brown, is considered cured and there are several other cases where HIV viral load did not rebound for an extended period after an ART interruption (referred to as remission)

These outcomes remain rare and resulted from exceptional circumstances—stem cell transplants for HIV-positive people with cancers or extremely early initiation of ART—but they are providing important clues to researchers working to develop a cure

There are more numerous—but still relatively rare—examples of individuals who have controlled HIV viral load to low levels either naturally (elite controllers) or after an ART interruption (typically after beginning treatment early), but it is uncertain how long this immune-mediated control can last and if it may come at some cost to long-term health

While many different therapeutic approaches are being studied, so far no broadly usable interventions have led to cures or remission—the best reported results involve small reductions in the HIV reservoir (its hiding places in the body) and some cases of short-term control of HIV viral load to low levels after ART interruption

MEASURING THE HIV RESERVOIR

Current tests for sizing up viral hideouts

BY **RICHARD JEFFERYS**

For researchers working to develop an HIV cure, it is important to have some way of measuring the effects of a potential therapy. In particular, there is a need to accurately quantify the pockets of virus (latent HIV reservoir) that persist in the body after ART suppresses viral load to undetectable levels. There are a variety of technologies available that are currently employed in studies, but each has pros and cons.

The "gold standard" test for assessing the size of the latent HIV reservoir is called the **quantitative virus outgrowth assay (qVOA)**. Performing qVOA requires taking a large blood sample (in the range of 120–180 ml) and extracting resting CD4 T cells, which are then activated in the laboratory in order to induce HIV production by any latently infected cells that are present. The amount of HIV generated is measured, and a statistical approach used to calculate the number of latently infected CD4 T cells that were in the sample—the result is expressed as infectious units per million cells (IUPM). The test takes a total of 14 days to perform.

The advantages are that qVOA measures latent HIV that is capable of replicating (described as "replication-competent")—this is important because it has been shown that the majority of HIV DNA that can be found integrated into the DNA of resting CD4 T cells is mutated in ways that render it defective. These defective HIV DNA copies cannot produce new viruses capable of infecting other cells.

The disadvantages of qVOA include the requirement for large volumes of blood and the length of time it takes to perform, as well as the cost (approximately $1,000). Additionally, it has recently been discovered that activating resting CD4 T cells—the key step in the test—does not induce HIV production by all the replication-competent latent HIV that is present in the sample. It is now estimated that there is likely about 60–70 times more replication-competent latent HIV than is detected by qVOA.

At least two improved variants of the qVOA that are cheaper and require less blood volume have more recently been described—including **a new assay that may address the problem of underestimating the frequency of latently infected cells** (developed by Anwesha Sanya and colleagues at the University of Pittsburgh)—but these new approaches have yet to undergo extensive evaluation.

The **Tat/Rev-induced limiting dilution assay (TILDA)** is a relatively new (but increasingly popular) approach to quantifying the HIV reservoir. TILDA has some similarities to qVOA but measures particular forms of HIV RNA after CD4 T cells are activated in the laboratory—it is thought to preferentially capture replication-competent HIV but may also pick up some defective viruses.

Several more straightforward tests look for HIV genetic material in different ways. The most common measures levels of HIV DNA in a sample using **polymerase chain reaction (PCR)**, but this technique cannot distinguish between defective and replication-competent HIV. A more complicated adaptation of this approach can specifically quantify HIV DNA that is integrated into the genome of CD4 T cells, but also cannot ascertain if it is replication-competent or not. Nevertheless these tests are frequently employed to give a rough idea of the size of the HIV reservoir.

Attempts to accurately measure the HIV reservoir are complicated by the fact that the vast majority of latently infected cells are known to reside in lymph tissues rather than the blood. For this reason some studies look to collect lymph biopsies, and new technologies are being developed to better quantify the amount of virus in tissues. Sampling from the central nervous system (CNS) is another challenge, considered important due to evidence that HIV may persist in the brain. There is uncertainty regarding whether HIV can become latent in cell types other than CD4 T cells, such as macrophages, and whether additional tests may be needed to evaluate the contribution of non-CD4 cells to the reservoir—ongoing research is aiming to answer this question.

An overarching problem with HIV reservoir measurement is highlighted by the cases of temporary remission described in "The Challenge of Defining an HIV Cure" (see page 2). In these individuals, the HIV reservoir could not be detected by any current test, even for a period after an ART interruption. But we know from the eventual viral load rebound that latently infected cells were still present somewhere in their bodies. This limitation in the ability of scientists to detect small HIV reservoirs is a big part of the reason why ART interruptions are still considered important in some cure research studies (see "Time Out," page 11). PA

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Latent tendencies

NEW STRATEGIES TARGET DORMANT HIV

WHEN COMBINATION ANTIRETROVIRAL THERAPY (ART) first became available in the mid-1990s, there were hopes that suppressing HIV replication for a few years would be enough time for all virus-infected cells to die off, resulting in a cure. Those hopes were dashed by the discovery that HIV can persist in long-lived cells in a latent (dormant) form—particularly in a type of immune system cell called a memory CD4 T cell. As their name suggests, the normal job of memory CD4 T cells is to remember a past infection and respond quickly if it recurs (vaccines work partly by generating memory CD4 T cells against a particular infectious agent).

How HIV latency works

EVERY CELL IN THE BODY, with the exception of red blood cells, contains a copy of the entire genome. The genome consists of DNA and can be thought of as a production line capable of manufacturing all the protein components that make up your body (this is done via an intermediate step, wherein the DNA makes RNA which then makes proteins). Different cells just employ the parts of the DNA production line that they need to make the proteins that allow them to do their job, e.g. kidney cells make the proteins they use in clearing waste and immune system cells like CD4 T cells make proteins involved in the work they do responding to infections.

Memory CD4 T cells can be in an activated state when they are responding to something—this requires the DNA production line to be busy, making the proteins the cell needs to go about its work. But memory CD4 T cells can also de-activate into a resting state, which causes the DNA production line to largely shut down.

HIV prefers to replicate in activated memory CD4 T cells, because it hijacks the busy DNA production line to manufacture more viruses, which can then exit and infect other cells. But if HIV infects a memory CD4 T cell when the DNA production line is in the process of shutting down (or is shut down), the virus essentially becomes trapped in the machinery, and can only start making viruses if the CD4 T cell becomes activated again and the DNA production line cranks back up.

In technical terms, HIV DNA becomes integrated into the DNA genome of the resting memory CD4 T cell. While the cell remains resting, HIV stays latent and is invisible to the immune system because no virus proteins are being made. The total number of latently infected CD4 T cells in the body that contain replication-competent HIV is around 100 million, according to recent estimates.

Reversing HIV latency

A MAJOR FOCUS OF HIV CURE RESEARCH is on reversing HIV latency—essentially switching on the latent virus's DNA machinery so that it starts making proteins. The aim is to cause the death of the latently infected cell, either by making it visible to the immune system because HIV components are being produced, or due to the toxic effects of viral activity.

A variety of approaches to reversing HIV latency are being studied, referred to collectively as latency reversing agents (LRAs). Among the leading candidates are HDAC inhibitors, a type of cancer drug that has demonstrated an ability to induce the production of HIV proteins by latently infected memory CD4 T cells. The HDAC inhibitors vorinostat, panobinostat, and romidepsin are all currently being tested in clinical trials but are being given in short courses because they can cause a range of unpleasant side effects including headache and gastrointestinal upset.

So far researchers have evidence that HDAC inhibitors can activate latent HIV to some degree in people, but it has not significantly affected the size of the HIV reservoir. This has led to studies of the "shock and kill" or "kick and kill" approach, which combines HDAC inhibitors (or potentially other LRAs) with immune-based therapies intended to help promote clearance of latently infected cells that have been induced to produce HIV (see "Enhancing Immunity," page 8).

Beyond HDAC inhibitors, scientists are also looking at other candidate LRAs, including compounds known as PKC agonists, but only very limited testing has taken place in people due to concerns regarding potential side effects.

The design of safe and effective LRAs remains a major goal for HIV cure researchers.

Block and lock: Latency reversal in reverse

A NUMBER OF RESEARCH GROUPS are investigating whether it might be possible to pursue a strategy that is the opposite of reversing HIV latency: locking down latent HIV to prevent it from being able to ever reactivate. For an interview with Susana Valente from the Scripps Research Institute, a leader in these efforts, go to the online version of this special issue of POSITIVELY AWARE.

—RICHARD JEFFERYS

Block-and-lock strategy for an HIV-1 cure

A schematic diagram of the approach under development by Susana Valente and colleagues at the Scripps Research Institute in Florida. A drug called a Tat inhibitor is being employed to try and permanently prevent latent HIV from being able to reactivate and produce new viruses (a state they describe as "deep latency").

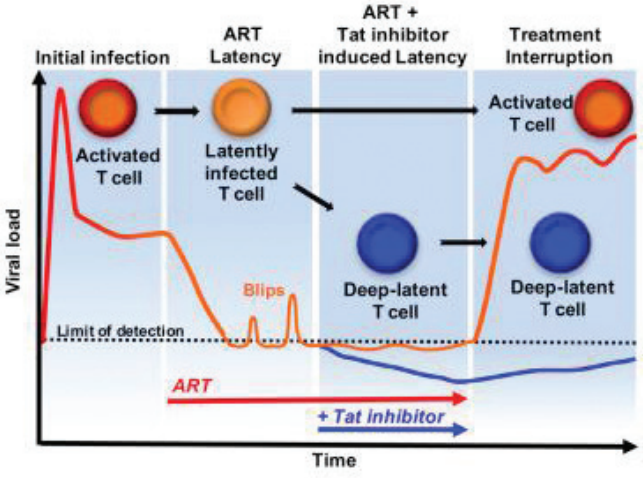
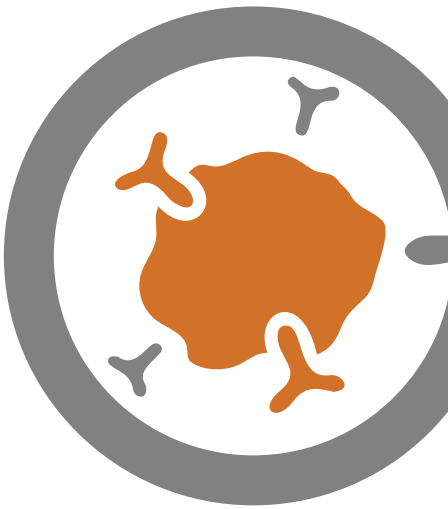


DIAGRAM COURTESY OF CREATIVE COMMONS

Enhancing **immunity**

MANIPULATING THE IMMUNE SYSTEM TO TACKLE HIV

BY **RICHARD JEFFERYS**



The immune system can be a potent weapon against disease, and a major avenue of cure research involves attempting to enhance the immune response against HIV. The task is challenging, not least because one of the properties of the virus is that it infects and compromises CD4 T cells, the component of the immune system normally responsible for coordinating anti-viral immunity.

Multiple clinical trials are investigating whether immune-based approaches can deliver the "kill" in "kick & kill." This strategy combines latency-reversing agents (the "kick") with interventions designed to enhance the ability of the immune system to recognize and destroy the latently infected cells that are stimulated to produce HIV. Researchers are also studying whether immune-based therapies can promote control of viral load after ART is interrupted. **(SEE CHART NEXT PAGE)**

Collaborating for a cure

SIX GROUPS FOCUSED ON THE TASK

AS MENTIONED in the main article in this issue, Martin Delaney of Project Inform, who died on January 23, 2009, was a staunch advocate for cure research, stating in a 2001 magazine article: "It's time once again to make 'Cure AIDS now!' the primary goal of treatment activism." Delaney subsequently co-authored an article in the journal *Science* calling for the funding of collaborative research programs specifically focused on developing a cure for HIV.

In 2011, the US National Institutes of Health (NIH) announced the funding of the first three such programs, named the Martin Delaney Collaboratories in his honor. Last year the number was expanded to six, which are supported for the next five years:

BEAT-HIV: Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy - Wistar Institute, Philadelphia

BELIEVE: Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication - George Washington University, Washington, D.C.

CARE: Collaboratory of AIDS Researchers for Eradication - University of North Carolina, Chapel Hill

IC4: Combined Immunologic Approaches to Cure HIV-1 - Beth Israel Deaconess Medical Center, Boston

defeatHIV: Cell and Gene Therapy for HIV Cure - Fred Hutchinson Cancer Research Center, Seattle

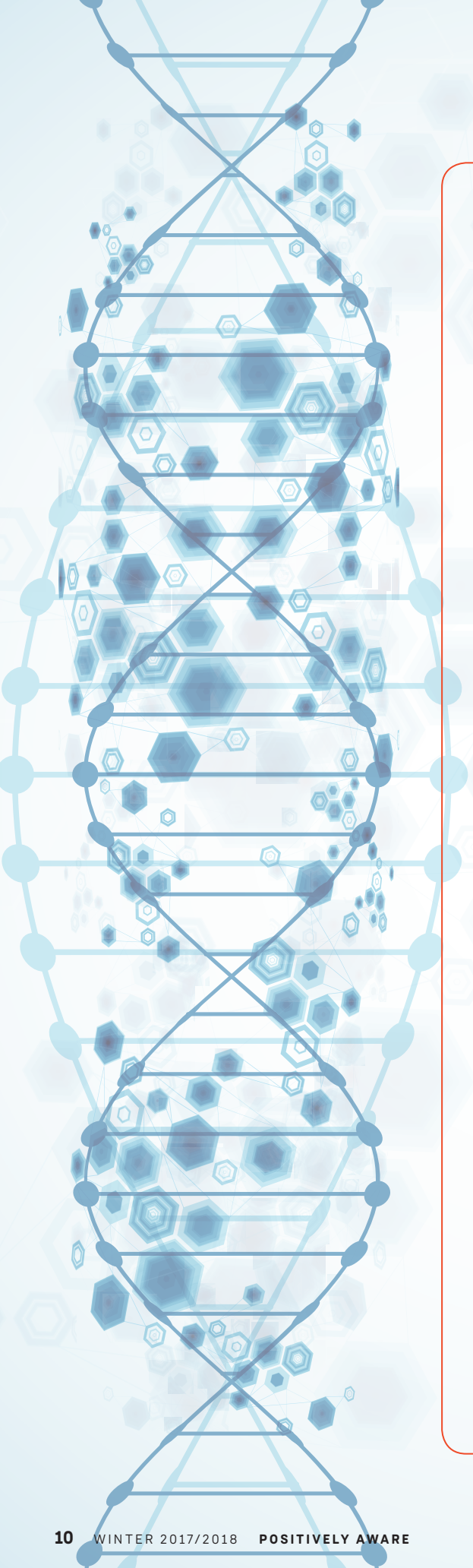
DARE: Delaney AIDS Research Enterprise to Cure HIV - University of California, San Francisco (UCSF)

MORE INFORMATION ON THE SPECIFIC RESEARCH FOCUS OF EACH COLLABORATORY CAN BE FOUND ONLINE.

ILLUSTRATION: ISTOCKPHOTO

CURRENT CANDIDATE **IMMUNE-BASED THERAPIES**

APPROACH	DESCRIPTION	EXAMPLES	STATUS
Broadly neutralizing antibodies (bNAbs)	Antibodies capable of potently inhibiting the replication of diverse HIV variants There is evidence that some bNAbs can promote clearance of HIV-infected cells via mechanisms called antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP)—the antibodies bind to HIV proteins expressed on the outside of cells that have been induced to produce virus, flagging them for destruction by the immune system	**VRC01** **3BNC117** **10-1074** **PGT121**	In early phase trials, including in dual combinations Two trials are investigating a "kick & kill" combination of **3BNC117** with the HDAC inhibitor romidepsin, a latency-reversing agent
Therapeutic vaccines	Designed to induce more effective immune responses against HIV than those seen in natural infection Particular emphasis on promoting CD8 T cell (killer T cell) responses capable of recognizing and killing virus-infected cells	**MVA.HIVconsv** **ChAdV63.HIVconsv** **Ad26.Mos.HIV** **MVA-Mosaic** **iHIVARNA-01** **GTU-MultiHIV B-clade** **MVA HIV-B**	Many different clinical trials, including in combinations with the latency reversing agents romidepsin and vorinostat Plans to combine therapeutic vaccination with the TLR-7 agonist vesatolimod
Adoptive immunity	The extraction and expansion of anti-HIV CD8 T cells from HIV-positive individuals, followed by reinfusion	**HIV 1 antigen expanded specific T cell therapy** (HXTC)	In trials both alone and in combination with the latency-reversing agent vorinostat
Immune checkpoint inhibitors	Antibodies targeting molecules known to be expressed by dysfunctional "exhausted" T cells Goal is to revive the activity of these T cells against their targets (e.g. virus-infected cells or cancerous cells) Several are FDA approved as cancer therapies, but carry some risk of life-threatening side effects due to induction of autoimmunity Studies suggest some immune checkpoint inhibitors may also have latency-reversing activity	**durvalumab** (anti-PD-L1 antibody) **nivolumab** (anti-PD-1 antibody) **ipilimumab** (anti-CTLA-4 antibody) **pembrolizumab** (anti-PD-1 antibody)	Almost exclusively being studied in HIV-positive individuals requiring treatment for cancers due to potential risks One trial is studying a single dose of **pembrolizumab** in HIV-positive people without cancer
Toll-like receptor (TLR) **agonists**	Toll-like receptors (TLRs) are elements of the immune system capable of recognizing certain structural features shared by many different pathogens TLRs play a role in generating immune responses to infections, and can be stimulated with products known as TLR agonists There are indications that certain TLR agonists can both stimulate latent HIV and bolster immune responses to the virus	**vesatolimod** (TLR7 agonist) **MGN1703** (TLR9 agonist)	Gilead Sciences is testing the effects of a **TLR7 agonist** in HIV-positive individuals, having seen promising results in animal studies Researchers at Arhus University in Denmark are studying a **TLR9 agonist**
Cytokines	Signaling proteins produced by immune system cells with a multiplicity of potential effects Certain cytokines may be able to bolster anti-HIV immune responses Interest in interleukin-15 due to evidence it can also have latency-reversing effects	**ALT-803** (recombinant human super agonist IL-15 complex) **IL-2** **Alpha-interferon**	Multiple ongoing trials
Anti-$\alpha_4\beta_7$ integrin antibodies	Antibodies designed to target anti-$\alpha_4\beta_7$ integrin, a molecule involved in the trafficking of CD4 T cells to the gut Studies in animal models suggest administration may contribute to enhanced control of viral replication after an ART interruption	**vedolizumab**	Initial trial underway at the National Institutes of Health (NIH)
Chimeric antigen receptor (CAR) **T cells**	T cells genetically modified to better recognize and kill HIV-infected cells (see "Gene Therapy in HIV Cure Research," page 10) May need to be delivered in combination with CD4 T cells genetically modified to resist HIV entry		Preclinical (not yet in trials)



Gene therapy in HIV cure research

Modifying immune system cells to resist, attack, or remove HIV altogether

BY RICHARD JEFFERYS

There is a great deal of interest in exploring the potential of gene therapy to cure HIV. This area of research has received encouragement from recent successes in the cancer field—the FDA has just approved the first two gene therapies for hard-to-treat malignancies.

Multiple different gene therapy strategies for HIV are under investigation. A leading approach involves genetically modifying immune system cells to resist HIV infection, with the aim of preventing the virus from being able to cause disease even if the latent reservoir is not reduced or eliminated.

Sangamo Biosciences has conducted studies involving extracting CD4 T cells from HIV-positive individuals, genetically altering them in the laboratory so that they can no longer display the HIV co-receptor CCR5, and then re-infusing them in large numbers. Some evidence of enhanced control of HIV viral load after ART interruption has been reported, but it appears that further work is needed to increase the number of gene-modified cells.

The company Calimmune is testing a dual gene therapy that inhibits both CCR5 expression and HIV fusion with target cells. In an ongoing trial, CD4 T cells and stem cells are being extracted, genetically modified, and then re-infused.

At least seven clinical trials (including several conducted by the defeatHIV collaboratory) are testing genetic modification of stem cells for HIV-positive people who need stem cell transplants to treat cancers. The hope is to use gene therapy to generate an HIV-resistant immune system, akin to what was achieved in Timothy Ray Brown using stem cells from a donor homozygous for the CCR5Δ32 mutation.

Plans are also afoot to test a type of gene therapy known as a chimeric antigen receptor (CAR) T cell against HIV—this involves equipping immune system cells with receptors that allow them to better recognize and kill HIV-infected targets. The recently FDA-approved gene therapies for cancers comprise CAR T cells engineered to recognize malignant cells.

While trials are likely further down the road, there is excitement about the possibility of using a new gene-editing technique called CRISPR/Cas9 to try and specifically excise HIV DNA from latently infected cells. The approach has shown promise in the laboratory, but it is not yet known if it can be successfully delivered into the body.

For additional information on gene therapy research, see the interview with Paula Cannon in the online version of this issue of POSITIVELY AWARE.

TIME OUT

TREATMENT INTERRUPTION: A risky but essential step in cure research

BY **JOSH TAGER** AND **DAVID EVANS**

ISTOCKPHOTO

If there is ever to be an HIV cure, first there must be people with HIV who are willing to interrupt their antiretroviral therapy (ART). It's a risky maneuver, for sure, but utterly essential to test whether an experimental intervention is effective.

For a study participant, there are several levels of health risk. First, the drug being tested might not be effective, and in any case, it might induce harmful side effects. Second, interrupting ART is a dicey proposition that could bring health risks, both biological and psychological.

But not only are treatment interruptions risky for participants, they are potentially risky for their sex partners. Studies have confirmed the potency of an undetectable viral load in preventing transmission from a person living with HIV to others.

It's a big ask to enroll any HIV positive person in a cure study, especially because the world's top public health experts are finally declaring that people with undetectable viral loads are essentially unable to pass on HIV to

POINT/COUNTERPOINT

Biomedical concerns about analytical treatment interruptions

Immune activation

CONCERN: Chronic immune activation causes more harm to the body than direct killing of immune cells by HIV. In fact, the SMART study and others have shown that HIV keeps the cells so revved up that they can contribute to heart problems, diabetes, cancer, and more. Some experts worry that interrupting ART could increase people's risk for these problems.

CONSIDERATION: Immune activation occurs even when ART suppresses HIV to extremely low levels and in people who naturally control HIV without medication. Treatment interruption studies that allow the virus to rebound to very low levels before resuming treatment may not be worse than staying on ART, but there have been deaths associated with immune activation in studies with longer interruptions.

Expanding the HIV reservoir

CONCERN: As pointed out in "Measuring the HIV Reservoir" in this issue, the size of the reservoir may determine who can achieve a cure or long-term remission off ART. Some experts worry that taking people off treatment, even for short amounts of time, could increase the size of the reservoir —possibly rendering them less likely to benefit from cure/remission strategies in the future.

CONSIDERATION: So far, it does not appear that allowing the virus to return for a period after being suppressed by ART leads to a larger reservoir than was present before ART was stopped.

Acute Retroviral Syndrome (ARS)

CONCERN: Many people have symptoms when they first become infected—a reaction called Acute Retroviral Syndrome (ARS), where the body is working on hyperdrive trying to control the virus. Most often, people simply feel like they've got a bad flu, but the syndrome can sometimes be serious. So, experts worry the risk of ARS could be serious if an ATI allows a person's virus to peak before they resume treatment.

CONSIDERATION: In the natural course of disease outside of HIV cure studies, it's relatively rare for a person to develop serious symptoms if they have an acute reaction to the virus. However, people who start antiretroviral therapy very early (within days or weeks of infection) never develop an immune response to HIV. That means going off treatment could lead to a rapid spike in virus, with a corresponding—and potentially harmful—activation of the immune system.

Studies have proven that people who participate in clinical trials tend to overestimate the likelihood that they'll benefit from the study, even when it's clearly asserted ahead of time that they won't.

others, offering the tantalizing promise for decreased stigma and discrimination for people with HIV.

Reconciling the risks with the benefits—which can vary from one community to another—will require an exhaustive process that includes scientists, ethicists and community advocates. And though biomedical and social science input is required to design and implement these studies, it's community members who are putting their bodies on the line.

Richard Jefferys points out in "Measuring the HIV Reservoir" on page 6 that there is currently no accurate way to measure the reservoir if it reaches extremely low levels. That means the only way to detect whether the virus is still present is to take people off ART...and wait. In scientific parlance this is called an analytical treatment interruption (ATI).

Understandably, much of what's been reported on ATIs, even in the lay press, focuses on the physical health dangers to the study participants. Potential dangers include lasting effects from immune activation (heart problems for one) as well as the potential for the virus to develop resistance to ART medications. Less has been reported about the psychological consequences for participants and the practical implications for their sex lives and relationships.

James McMahon, the Head of the Clinical Research Unit at the Alfred Hospital and Monash University near Melbourne, Australia, has well-considered the knotty challenges of designing studies involving temporary cessation of ART.

"The difficulty with this is that each cure intervention is different, and ATI parameters and frequency of monitoring may need to be individualized for each study," he said.

"At the moment, there is no standard protocol for a clinical study utilizing an ATI. Some studies test viral load and CD4 counts twice a week, others [every two weeks]. Some restart ART when the viral load [first becomes] detectable, others when it reaches maybe 5,000 copies or 10,000 copies for over 2 weeks."

In fact, the AIDS Clinical Trials Group (ACTG), a free-standing HIV clinical trials network funded by the National Institutes of Health, has launched a new study, ACTG5345, that will seek to answer some of these questions. For example, what are the underlying factors that might predict which people can maintain control of the virus when they go off ART?

Liz Barr, an HIV treatment activist and a community advisor to the ACTG, acknowledged the tension between the need to answer some of the critical questions that stand in the way of HIV cure-oriented research and the need to protect people with HIV and their partners from harm.

"Researchers and advocates were torn from the beginning about the study," she said. "We had a lot of conversations about how to proceed, whether to proceed, how to satisfy the most concerns possible. As you know, the hope with the study is to provide some guidance as to where cure research might go in the future."

Barr said that the team of researchers, clinicians and community advisors carefully considered not only the health risks involved for study participants, but also the potential psychological and social repercussions.

For one, studies have proven that people who participate in clinical trials tend to overestimate the likelihood that they'll benefit from the study, even when it's clearly asserted ahead of time that they won't. This dynamic could be even more complicated with HIV cure trials that involve an indefinite period off ART, and where the desire to be cured is so intense.

If someone goes off of antiretroviral therapy and maintains viral suppression for even a couple of months, it's understandable they might wonder if they've been cured, or even convince themselves of it, whether or not it's true. Gary Steinkohl, an HIV-positive New Yorker who interrupted therapy following a stem cell transplant, had exactly this experience. As his virus stayed suppressed for weeks and then months, he reported feeling a profound sense of ease and hope. When the virus returned, he recounted feeling "devastated."

The stakes are further raised in an ATI study, because a person's viral load could climb high enough to transmit the virus but before it's detected by the study investigators.

"Even if there was the potential for long-term viral control off ART due to the study intervention, the risk of onward transmission may still be there," said McMahon. "If potential participants are correctly informed and have concerns about onward transmission they may well choose not to participate. "

When asked about whether PrEP could be given to a participant's sex partners, he points out the practical and ethical challenges. Should people with HIV who'd like to participate be turned down if their sex partners refuse to use PrEP? Should HIV-negative partners be asked to consent to the study too?

We're in uncharted territory, which both Barr and McMahon humbly acknowledge, though both have the same solution for now—extensive discussion among all stakeholders, especially people living with or at risk for HIV.

"I'm not sure how this is best practically done," McMahon said, although he echoed some of the ACTG study practices. "Clear, open, and honest communication will be critical to the successful conduct of these trials. PA

POINT/COUNTERPOINT

Psycho-social concerns about analytical treatment interruptions

Increased transmission risk

CONCERN: A person with fully suppressed HIV has effectively no chance of transmitting the virus to sex partners, such that top health experts have joined the declaration that undetectable equals untransmittable (U=U). But a person who interrupts ART could have a rapid viral rebound, thereby losing the certainty that they can't pass on HIV to others.

CONSIDERATION: Even constant monitoring for viral rebound (2–3 times per week) won't eliminate the risk that the virus could climb high enough to allow someone to transmit HIV to their partner(s) before it is detected and they can restart ART. Right now, top researchers are grappling with what to do about this, including possibly providing full prevention services—including PrEP and PEP—to HIV-negative partners of study participants.

Emotional and psychological harms

CONCERN: The likelihood of receiving any health benefit, let alone being cured or achieving very long-term remission, is exceptionally low with early HIV cure-oriented studies. Experience in the few people who've had at least a few months of viral control before rebounding has shown that people often have profound emotional reactions when the virus eventually returns.

CONSIDERATION: Unfortunately, there aren't existing protocols for how to prepare people for this kind of emotional blow if they are one of the rare individuals who sustains viral suppression off of ART for several months or longer. While models for this do exist, particularly in cancer, there have been too few HIV cure studies that involved an ATI for guidelines for researchers and trial designers to be developed.

Difficulties reinitiating ART

CONCERN: People who have an interruption in a health-maintenance behavior (exercise, diet, medicine taking, etc.) often struggle to resume that behavior at the end of the interruption. Resuming ART is no different. There have been too few cases to know if this will be difficult after ART interruptions from HIV cure studies, but previous non-cure-related ATI studies have found this to be true, and can lead to emergence of HIV drug resistance.

CONSIDERATION: There are a number of interventions that have proven effective in helping people reinitiate health-maintenance behaviors, including restarting ART after stopping for one reason or another. Ensuring that they are incorporated into HIV cure studies could minimize risks in this regard.

LOUELLA: "IT'S A TIGHTROPE WE ALL MUST LEARN TO WALK. KEEPING A BALANCE BETWEEN HOPE AND CURRENT REALITY."

SPEAKING THE SAME LANGUAGE

Advocate Michael Louella talks about '50 shades of cure'

BY **JOSH TAGER**

An HIV cure is a real possibility, but not a given. One way to hasten effective research is to make certain cure researchers and the community speak the same language. What's the difference if one researcher says "cure" and another says "remission," and what do various community members hear?

The application of technical jargon versus plain language (depending on context) carries staggering consequences, both positive and negative. Take the word "remission." That word alone could make the difference between a person consenting or declining to participate in a clinical trial; it can determine whether a person living with HIV decides to try a new treatment; it can have community-wide implications in subverting HIV stigma.

Effective cure-oriented research mandates that scientists—especially those who don't live with HIV—listen to those who do with perfect sincerity and seriousness. In turn, the community must ask questions, and ask more still so they can serve as effective advocates and get the results they want: a meaningful cure.

Michael Louella, a 50-year-old educator and activist, is spurring the conversations that need to be had. He currently serves as both the Outreach Coordinator for the Seattle AIDS Clinical Trials Unit as well as the project coordinator for one of six NIH-funded public/private HIV cure science collaborations. A close witness to the factors that lead some communities to distrust science or feel disengaged from it, he's applied his natural facility for poetry and storytelling to examine how people with HIV respond to the complex terminology of cure science, and most importantly, to help medical scientists and the community speak the same language.

As someone who's been engaged in the cure social sciences since the beginning, what are some of the biggest changes you've seen in how different groups talk about an HIV cure, in particular, words like "cure" or "remission"?

People working in the cure social sciences have become cautious, more precise in the ways we describe the research effort. It's a tightrope we all must learn to walk. Keeping a balance between hope and current reality.

You want people to hear the good news, you want them to get informed, get inspired, and get involved with the cure effort. But if you're not careful, in a heady rush of excitement you may find yourself beginning to sound like a preacher preaching a gospel of cure.

That's when you begin to use qualifiers, or different words altogether. The danger here is that people notice the shift in tone, and often suddenly are plunged into despair. You want people to understand fully the scientific challenges facing us. But to be able to do this effectively, while not squashing all hope.

Do you think when medical scientists talk about cure they mean the same thing as people living with HIV or affected communities?

PHOTO COURTESY OF MICHAEL LOUELLA

No. I think when scientists talk, they implicitly understand that there are fifty shades of cure. Because they talk science and think science all the time, they better understand how both clinical research and the human body work, and better appreciate the limits to each. They know science is baby steps, and that progress toward a cure will be lots and lots of baby steps. They know this and accept this.

Non-scientists don't know this. Not understanding the processes and methods of a scientist allows them to think of science as more akin to magic.

What are the consequences of this?

The real disconnect comes from serostatus and the stigma, rejection, and discrimination people confront in varying degrees every day and, many assume, for the rest of their lives. To live with HIV is far different than to work in HIV. Scientists may feel empathy, but I bet if they lived with HIV in their bodies, they might talk about and use the c-word differently.

When people with HIV hear "functional cure" or "remission," I can sometimes sense an immediate distrust rising, a silent accusation in the way they start to look at me that says, *"Wait a sec, your eyes done slipped from the prize."* They don't want us to rest at remission or functional cure. When we talk about remissions, they think we've given up on cure. And that's unacceptable to them. To them, functional cure is like sitting with a time bomb that could go off at any moment, hurting themselves of course, but what's most dreaded is the idea of transmitting the virus and hurting someone they love.

Alright, so what are the benefits of using language that is consistent with how most people living with HIV and their communities think about that language?

Speaking the same language opens up the potential to collaborate and grounds relationships to endure in the face of challenges and setbacks.

What about the opposite? What are the consequences if language isn't consistent?

I often think back to 2014 when we were lucky to have Dr. Robert Siliciano—who was visiting Seattle to present a science talk—agree to participate in a community Q&A about HIV cure research. The defeatHIV CAB partnered with BABES Network-YWCA to bring 70 of our community members together to listen and to ask questions about the science. Dr. Siliciano fielded a wide range of questions from our audience with grace, and answered them plainly and clearly.

That night I think Seattle finally grasped that sometimes when scientists say *cure* they really mean *remission*—and by *remission* what people hear, is *temporary*.

Our emcee, a local journalist named Nina Shapiro, captured this startling revelation of the night in a blog post the next day in *Seattle Weekly*: "HIV 'Cure' Likely to Be Temporary, Says Leading Scientist Robert Siliciano."

How does it play out when people react that way?

There will be no people to participate in studies and help scientists determine a curative strategy that works for everyone. There will be distrust. Conspiracy theories will be seen as truth. Disparities will grow. Despair will rule our hearts, and dreams will be deferred.

Remember, no one longs to listen to a litany of data from a scientist. What we really want is what all humans beings love above all else, which is *a good story* told by *a good storyteller.* HIV cure research has some great stories that await to be told. Just be careful with the things you say and the way you tell it, because we are all listening—especially people living with HIV. PA

PHOTO COURTESY OF LESHERRI JAMES

WHAT DOES A CURE MEAN TO YOU?

Four individuals share their hopes and fears

BY **JIAN HUANG**

LeSherri James

LeSherri James is a 35-year-old mother of two. She's been living with HIV since 2000 when, at the age of 17, she was raped by an HIV-positive man who later died of AIDS.

Today, James works to support other HIV-positive women at the AIDS Foundation of Chicago. She echoes the sentiment that a cure for HIV would change the world, and that talking about it is essential.

Her 14-year-old daughter and four-year-old son are both HIV-negative. LeSherri's HIV-status is especially difficult for her daughter because of the social stigma that comes with the disease.

"Growing up in the black community, what happens at home stays at home," she says. She says the culture of not talking about HIV extends to other ethnic groups as well. Cultural factors can intensify the loneliness for many people, and she says lots of women with whom she works are afraid to talk about HIV with family; instead, they struggle alone.

For James, deepening the conversation about HIV with an awareness of how women and people of color think differently about the virus is a

major part of the cure. HIV is still heavily stigmatized and there is often little support, even from families. James says a cure means these families would get their loved ones back.

For her personally, a cure would come with many emotions: knowing that her children could live without stigma, that James herself would not have to take daily medications, cost savings from doctor visits, and most importantly, a second chance at life. "I wouldn't be 'LeSherri James with HIV' anymore," she says. "I would just be LeSherri James again."

Adaora A. Adimora, MD, MPH

We've come a long way in treatment and prevention since the height of the HIV epidemic, but for Dr. Adaora Adimora, the need to find a cure is obvious in the work she does.

Adimora is a physician at the University of North Carolina at Chapel Hill, and has been working in infectious diseases since the 1980s. In 2013, she was appointed to the President's Advisory Council on HIV/AIDS.

"I have been close to a lot of people who have HIV, in the course of my work and my personal life," she says. "One thing that may be very powerful around having a cure, and may be the most important thing, in addition to the obvious health benefits, is the extent to which it will get rid of the stigma that has so often and unreasonably been associated with HIV."

The road to finding a cure is a complicated process and past research has primarily included men. Though she doesn't describe herself as a cure researcher, she has given it a great deal of thought.

"As a physician, my major motive is to eliminate pain and suffering in whatever way possible and [a cure] would go a long way towards this," she says. For Adimora, it is important for research to be inclusive from the beginning rather than to have a cure developed that benefits one segment of the population, such as men, and not others, such as women. Likewise, research must include people of color and take into consideration the widening disparities in our access to health.

Adimora reminds us to keep in mind both how far we have progressed in HIV research and treatment, but how fragile our gains are. She is particularly worried about the constant threats now to tear down the health care and social service programs that have begun to cut infections and deaths in a significant way, programs needed to help deliver a cure.

When asked what we could do to help find a cure, Adimora offers this suggestion. "I urge people to stay 'woke,'" she says. "We are in danger. They need to make sure that they stay abreast of this stuff and pay attention and go to the polls. And support access to healthcare for all—and research."

Jack Shallow

Jack Shallow wants today's young people to keep HIV in the conversation. He tested positive in 1985 and has been living with HIV for more than three decades, but for him, the war is not over. He sees HIV awareness, and the search for a cure, as paramount.

At 71 years old, Shallow has lived through some of the worst periods of the epidemic, and fears that as more people from his generation disappear, the conversation about a cure diminishes in priority.

Shallow was among the first in San Francisco to receive Social Security Disability resulting from his AIDS diagnosis in the 1980s. Prior to testing positive, he had spent 20 years building a successful career as an engineer. Then he lost everything. Shallow and his partner sold their two homes and many of their possessions to pay for expenses.

He fought to stay alive after the diagnosis and volunteered his time helping others to do the same. At Project Inform, Shallow answered calls from thousands of people across the United States to help them make informed treatment decisions.

When asked what it would mean to have a cure, Shallow, whose long-time partner remains HIV-negative, struggled to hold back tears. "I can't even imagine, but I do have hope."

Ken Lazarus

Ken Lazarus is a minister in Atlanta, Georgia. Now 54 years old, he was diagnosed with HIV in 1986.

With a background in Public Health and Social Justice, Lazarus' goal to bring more equity for the most vulnerable populations extends to the conversation around HIV.

As an African American man living with HIV, Lazarus is aware of the added stigma and social pressures HIV/AIDS has within communities of color. He believes community engagement in discussions about an eventual cure for HIV are a necessity. This includes mentoring more people of color, and bringing them into leadership and decision-making positions. More funding is needed and shifts in allocation must happen as well, he says. Lazarus knows it is a difficult task to achieve, but it is also well worth the effort.

Lazarus is unsure that a cure will happen in his lifetime, though he remains hopeful. For him, a cure would mean freedom from the disease physically, emotionally, and financially. He estimates that his current medication costs are up to $20,000 annually. "A cure would bring back a state of normality and health," he says. "It would mean I wouldn't have to be subjected to my daily regimen of medication. I would be able to return to a different place."

Until a cure is found, Lazarus wants health care professionals, government, communities, and individuals to keep having this important conversation on the need for a cure. "Let's have a cure," he says. "Let's kick this out!"

JACK SHALLOW

PHOTO COURTESY OF JACK SHALLOW

BETTER LATE THAN NEVER

PIONEERING SCIENTISTS PROVE WOMEN ARE ESSENTIAL TO FINDING A CURE

BY **DAVID EVANS**

ALTHOUGH WOMEN who are not of trans experience, ciswomen, make up more than half of the 34.5 million people living with HIV globally, a 2016 review of the scientific literature found that they made up only 21% of the participants in HIV cure-oriented studies, and that a substantial number of studies recruited no women at all. For transgender women, the numbers are even worse. Out of more than 15,655 participants in the 2016 review, only one person was identified as transgender. But the failure to include cis- and transgender women doesn't just pose medical and social harms to them, it runs the risk of crippling the search for a cure for all.

Human biology 101

Eileen Scully, MD, PhD, an assistant professor of medicine at Johns Hopkins University, is both a laboratory scientist and clinician. Initially interested in looking at models of the human immune system in the lab, she did what most systems scientists strive to do: remove variables that might be so distracting that they prevent the truth from shining through.

She observed early on, however, that although her colleagues often went to great lengths to control for variations in the immune system associated with age or length of HIV infection, one of the biggest differences—a person's sex—kept getting pushed to the side.

She makes the point somewhat ironically, joking, "Maybe short people and tall people are just as different so we should control for height," but then continues in a more serious vein.

"No one in the world would argue that sex hormones don't have a huge effect... on our physical appearance, of our neurological makeup, and this is true across the board whether you are cis or trans," she says, "To suggest that it [might not] have an impact on other biological processes is really farfetched."

And we've actually known this for a long time. Ciswomen tend to respond much more robustly to vaccines of all types. They are also more prone to diseases that are related to a hyperactive response to one's own cells or tissue, such as lupus and irritable bowel disease.

And with HIV, we see that ciswomen's immune systems exert much stronger control over the virus soon after infection, but later burn out due to over-activation.

More recently, Scully and a colleague, John Karn from Case Western University, confirmed the significant impact of female hormones on the persistence—and possibly one day the elimination—of HIV. What Karn found, based on intensive screening,

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is that the female hormone estrogen diminished the effect of drugs designed to kick HIV out of its resting and hidden state. Scully followed up on this work soon after, and determined that female sex had a profound role on the state of the immune system in ciswomen compared with cismen and how sex differences affected the reservoir of latent HIV.

'No one in the world would argue that sex hormones don't have a huge effect... on our physical appearance, of our neurological makeup, and this is true across the board whether you are cis or trans. To suggest that it [might not] have an impact on other biological processes is really farfetched.'

—EILEEN SCULLY, MD, PHD

These striking results, which Scully and others have stressed should not be surprising, have finally led to resources to determine their significance to the HIV cure research enterprise. In fact, she is now heading up a study sponsored by the AIDS Clinical Trials Group that will see if blocking estrogen production with the anti-cancer drug tamoxifen could boost the activity of vorinostat, which has been used in other studies to "kick" the virus.

It's good news that at least some researchers are devoted to understanding how sex and sex hormones impact how the HIV reservoir persists despite being driven down by antiretroviral drugs to just one infected cell per million cells, and are committed to constructing studies that account for sex and gender.

But Karn's finding in 2015 that sex hormones affected the activity of a drug that has been under investigation in HIV cure research for nearly ten years—and that we didn't know it—has two worrisome implications. Most obviously, it leads one to question how other strategies being used will help or harm cis- and transwomen. But if sex hormones affect the immune system and its battle with HIV so much, then promising strategies that didn't work in men could have been prematurely discarded, simply because they were never tested in women.

Why does science perpetually struggle to include women?

Catalina Ramirez is the Director of the University of North Carolina's site for the Women's Interagency HIV Study (WIHS), a decades-old cohort of women living with HIV who return every six months to provide blood and tissue samples and to complete surveys. WIHS has contributed some of the most important findings on HIV and HIV-related complications in the history of HIV research. It is also historical in another way, in that it has routinely managed to keep more than 85% of its all female participants engaged for five or more years.

Because of this, Ramirez disputes that enrolling and retaining women in studies is a challenge that can't be overcome. Nor does she believe it has anything to do with a lack of desire to participate.

"I don't necessarily think that there are sex or gender differences related to levels of altruism, but there are things that we can do to make someone's participation fair and equitable," she says.

Scully concurs, saying, "Many years ago I saw a patient with a new diagnosis and she was isolated in many ways. I offered her entry into a clinical trial... and she declined.

"Then she came back two weeks later... she had read about how women don't participate in clinical trials and she came back to me and said, 'I feel so bad that I didn't do this. I didn't know how helpful it could be.' "

The key, says Ramirez, is attending to what women want and need. "If you want women to be in research then you have to listen to what will help them do it."

She says, "We ask people to come and do things that may take hours and if you couple that with the demands of a person's employment and childcare...we just have to be cognizant of that and build that into our research paradigm for how we treat research participants."

That means having a budget for the things that women might need and ask for, Ramirez says, which in WIHS can include not only transportation or reimbursement for expenses, but also food if an appointment is going to take a long time. According to Ramirez, the median yearly income of women in the WIHS study is less than $12,000. Studies have found that food insecurity is rife among people with HIV and alone can contribute to poor health outcomes. Asking someone who may be struggling to eat enough under normal circumstances to go without food for hours is asking quite a lot.

Yet, Ramirez says she sees a preoccupation with defining fair compensation in the realm of HIV research that carries higher risk and lower rewards. This alludes to the fear that excessive compensation could unethically induce someone to participate in a clinical trial.

"We need to think of all the other disciplines [that] have done this, such as cancer," she says. "I mean, cancer is indiscriminate, people of all levels of income get cancer, and yet we never seem to have these same discussions about whether compensation is fair."

That's not to say that research in ciswomen in particular is straightforward, especially if it involves the potential for the effect of sex hormones. Female hormones can fluctuate greatly in pre-menopausal ciswomen, and not always on the same calendar. Scully has made the point that designing a study that can accommodate this isn't straightforward.

However, she's managed to design a study with post-menopausal women, which at least is a first step to begin dipping our toes into the influence of hormones on cure, and it's the commitment to be creative that's key.

For 59-year-old Vanessa Johnson, who is the cofounder of Ribbon Consulting Group, and who has been living with HIV since 1990, our failure to make the study of women high enough of a priority to use our ingenuity to overcome any barriers that might exist really comes down to how society feels about women.

"There is an underlying belief that women are not as valued as men," she says. "In fact, it's not belief. It's a reality and that's evident by the funding."

"The problem is that we live in a society that is based on a scarcity model and not an abundance model. Truthfully there should be enough for everyone." PA

PHOTO COURTESY OF EILEEN SCULLY

BRINGING HIV CURE RESEARCH INTO THE REAL WORLD

Looking at the need for including social science

BY **JOSH TAGER**

FOR ADVOCATES, social science is an important component of effective cure research, one that is often undervalued. Whereas biomedical researchers investigate and develop interventions, and establish that they work in optimal conditions, social scientists make sure these interventions are effective in the real world and are embraced by affected communities.

The use of language, even a single word, poses an ethical conundrum in clinical research (see "Speaking the same language," on page 14). Take the word "cure." It may seem like a word most people can agree upon, but that's simply not true. What one biomedical researcher thinks of as a cure can be very different from what a person living with HIV thinks. This disparity can inform who participates in clinical trials; some people might consent to participation underestimating risks while another might decline by overestimating them. The same is true of possible future cures and how they're delivered.

Certainly, biomedical work is at the core of treatment and cure research, but the benefits of this work are amplified and risks mitigated when done in tandem with social scientists and community representatives.

Funders now have a chance to demonstrate forward-looking leadership with grants that foster collaboration between social and biomedical scientists focused on cure. If we fail to integrate social science into HIV cure-related clinical trials, it will be people with HIV who most suffer the consequences of missed opportunities.

Efficacy without effectiveness doesn't cut it. But meaningful, systemic change to the scientific research process will require additional funding of social research that elevates the least represented communities.

A few of these studies have been completed or are underway (see page 9), and more are in the pipeline. Rather than a catalogue of research, we compiled a catalogue of unanswered questions **(SEE "HIV CURE SOCIAL SCIENCE 2.0," PAGE 20)**.

Q&A with Karine Dubé

ASSISTANT PROFESSOR AT THE UNIVERSITY OF NORTH CAROLINA GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

What sparked your professional and personal interest in HIV cure social science research?

I started my research work in the HIV prevention field. I worked in nine African countries—mostly in Mozambique—developing clinical research capacity for future HIV vaccine trials. In HIV prevention research, there was already a rich tradition for biomedically-relevant social sciences and community engagement.

When I started working in HIV cure research, I noticed the lack of research in this area. Most of the HIV cure research field is dominated by biomedical research, with little attention paid to the acceptability of potentially high-risk interventions.

I was interested in factors that would make the implementation of HIV cure research both effective and ethical, and in the patient and community perceptions of this complex body of science.

We've studied people's willingness to participate in HIV cure studies, but I suspect there are many unanswered

PHOTO COURTESY OF KARINE DUBÉ

questions. Which are most pressing?

We want to better understand what motivates people living with HIV who are doing well on treatment to be willing to undergo risk for a specific HIV cure research strategy, and what is the risk threshold for these various interventions. Some risks are predictable, whether they are great or small, while others are merely possible in the long term.

We also still have a lot of unanswered questions about what makes people willing to undergo treatment interruptions.

Sometimes ethicists don't concern themselves with the direct application of an ethical principle in the real world—for instance, they dream up thought exercises to make things simple. But at the pace that cure research is going, how should we think about ethical principles to make sure trials are as safe as possible?

This is a great question that relates to the intersection of social sciences and ethics research. Social scientists are interested in studying humans and their social relationships. Theoretical ethicists more generally study aspects of human culture and its values. As we move forward, I think we need ethics to be less philosophically-inclined, and more grounded in the reality of actual HIV cure studies here in the U.S.

Most HIV cure studies right now will benefit science, but not the physical health of the study participants. Some participants derive tremendous psychological benefits from participating in studies, and that must be better understood. The concept of non-maleficence, which is about doing the least harm possible, is paramount in HIV cure-related research.

KARINE DUBÉ

We must try to minimize the risks as much as possible, while trying to advance this important body of research.

My fear is that the field of HIV cure research will go too far without adequate social sciences and applied ethics research to understand the non-medical harms. In fact, I do not understand why we are not asking these questions concurrently with the biomedical science for the most part.

What will lead the way to better coordination and collaboration between the biomedical and social sciences?

The patient and community voice is so important. One of the obstacles is the significant power difference. We must build knowledge in communities, people living with HIV, and other people who should be included in the process. It's very hard to change cultures, but it must happen and active collaboration between multiple-stakeholders [people affected] is critical to doing it. And of course, community engagement, education, and dialogue must remain a core part of the process along the way. PA

HIV Cure Social Science 2.0

Social science research is now taking place around the globe. In the United States, researchers are targeting geographic locations that haven't been reached, such as the Southeast, as well as populations that haven't been well represented, including younger people, cisgender and transgender women of color, and black men who have sex with men.

Some new social science studies are seeking knowledge about perceptions of HIV cure and cure research from the wider communities that people with HIV come from as well as the health care providers who care for people with HIV.

These projects, scattered across Western Europe, Australia, China, Thailand, and South Africa are seeking answers to questions like these:

- **Are the attitudes, beliefs and motivations of people who are actually in HIV cure trials substantially different than those who answered previous surveys?**
- **How do people with HIV and those affected by HIV in their communities view more controversial issues such as treatment interruptions, which pose risks for sex partners?**
- **What effect does stigma play on willingness to participate in cure studies?**
- **How do mothers of children with HIV, or their guardians, feel about allowing the children to participate in research?**

PHOTO COURTESY OF KARINE DUBÉ

It's important that we keep hope alive

The co-creator and star of the web series *Merce* envisions life with an HIV cure

BY **JIAN HUANG** PHOTO BY **GERALD WARHAFTIG**

Charles Sanchez believes a cure for HIV would change the world, and he's dedicating his artistic and comedic gifts to this cause.

Sanchez (featured on the cover) has been living with HIV for 14 years. In 2003 when he found out, he was told that the disease had already progressed to an AIDS diagnosis. "I got very sick," he says. "I almost died." Then living in Little Rock, Arkansas, he decided to move back to New York City after getting out of the hospital and stabilizing.

Always an artist, musician, and writer, Sanchez started doing solo shows, talking on stage, in part, about "crazy things that happened with HIV." His friend Tyne Firmin brought in a flipcam and eventually the two created something special: a modern HIV musical comedy show.

Five years later, *Merce*, which Sanchez calls a miracle, is now in its second season on YouTube. As with the original solo shows, he wants to talk about HIV in a way that he feels others don't. He created *Merce* as an original campy web series about a middle-aged HIV-positive single man living in New York City. The protagonist Merce (played by Sanchez), his Mama (played by Firmin), and a colorful cast of characters regularly deal with issues such as family, friends, dating, slutshaming, PrEP, and gay marriage, with joyous musical sequences that echo his background in theater.

"Merce is a reflection of me," he said. "I wanted to show a character with HIV who is not sad, sick, or dying. I wanted a character who has a full life with friends, family, and problems that don't have to do with HIV."

Even with contemporary medication, however, which Sanchez says consists today of a single pill, he acknowledges living with HIV can still be a heavy burden both physically and emotionally.

In season two, Merce enters into a relationship with an HIV-negative partner, all while the show expands to a greater conversation about the future of HIV: a cure. "It all started because I had never thought what it would be like to be cured," says Sanchez. "It became a conversation in talking to other people. There's always stuff you find on the internet about some faraway cure, but we never really hear that much about actual scientific research. It got my brain buzzing."

The buzz led Sanchez to write one particular episode which follows Merce after a hip replacement surgery. Inspired from his own experience of having two replacements, the show deals with Merce's struggle with avascular necrosis, a condition that occurs when there is blood loss to the bone. "It's a secondary condition to HIV that we don't talk about much either," says Sanchez. "In the script, Merce is trying to recover and is doing it all by himself. He can't and he realizes he needs help, so he calls his boyfriend and breaks down. He says, 'I wish you didn't see me like this. I wish I didn't need your help.'"

During an emotionally-charged song, Merce's boyfriend replies, "I wish you didn't have this. I wish there was a cure...but until there is a cure, I will be your cure. Love is your cure."

Sanchez says, "It's important to keep that hope alive. You may think you're alone, but you're not."

WATCH *MERCE* AT MERCETHESERIES.COM

I am a friend, a dreamer, and an activist.
And I am living with HIV.

Let's stop HIV together.™

—Hydeia

Hydeia (left) has lived with HIV since 1984.

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