POSITIVELY AWARE
HIV TREATMENT, PREVENTION, AND SUPPORT FROM **TPAN**
SUMMER 2018

# BRAVE NEW WORLD

As human remission trials start, can we reprogram the immune system to control HIV?

# GUEST EDITOR'S NOTE

ANNE-CHRISTINE D'ADESKY
GUEST EDITOR

WITH **RICHARD JEFFERYS**
GUEST CONTRIBUTOR

**Welcome to a special issue of** POSITIVELY AWARE**, prepared for AIDS 2018—the 22nd International AIDS Conference in Amsterdam.** Given developments in the field of HIV cure research (see the Winter 2017 issue of POSITIVELY AWARE), we thought it would be interesting and exciting to go behind the scenes for a close look at a planned clinical trial that aims to assess whether a combination of new interventions can enhance control of HIV in the absence of ongoing treatment.

The trial is an example of a growing interest in exploring combination approaches that pair novel vaccines and experimental agents aimed at the small dormant pool of residual virus, called the latent HIV reservoir. A number of such studies are planned or already underway around the world.

Our choice was San Francisco, an early epicenter of the AIDS epidemic, where the trial protocol has been developed by a University of California at San Francisco (UCSF) team led by HIV cure pioneer Dr. Steven Deeks, under the auspices of the amfAR Institute for HIV Cure Research. The goal is to probe the possibility of achieving a period of remission, or "post-treatment control" off antiretroviral therapy (ART), a scenario short of a full cure, or complete eradication, but a major step. Scientists hope that it might one day become feasible to induce strict long-term control of HIV by the immune system.

The research partly builds on studies of elite controllers—rare individuals whose immune systems control HIV to very low levels without ART. These individuals offer clues about the types of immune protection that researchers may need to try and mimic or further improve in new trials.

Other lessons are being learned from even rarer cases of individuals with only trace amounts of HIV in their bodies due to extremely early HIV treatment, or stem cell transplants for cancers. Such people have been able to interrupt treatment and go for an extended period before the virus rebounds. In this issue, we spotlight the stories of Clark Hawley and Luis Canales, who are among the earliest treated adult cases. Both men kindly talked to us for this issue about why they are participating in cure research.

It's important for us to stress that the proposed clinical trial we highlight in the magazine is only one among many such studies and narratives playing out in the cure research field. We wanted to give a sense of what's behind the development of a cure study: the scientific questions, logistical hurdles, and intersecting human stories—a window into the process. It's not to single out UCSF as being above any other research institution, or to imply that this remission study is more likely to succeed than another.

At press time in early May, the UCSF trial was moving ahead, but it hadn't yet been given final FDA approval. Right now, the trial is expected to enroll in the fall.

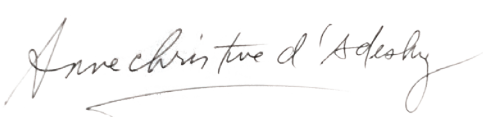
At this early stage of our cure efforts, it's often the case that important lessons are learned, even when interventions don't work. This study will look at the safety and efficacy of new interventions in humans. We wanted to take you to the new frontlines of the battle.

In February, the UCSF team allowed us unfettered access to meet with community volunteers at their SCOPE cohort who play a heroic role in their studies, and the various teams of scientists, doctors, nurses, technicians, and watchdog groups who are now collaborating to plan the new trial. What's readily apparent is a shared passion and global concern for ending HIV, doing science right, and making sure vulnerable and impacted communities are invited in now to become engaged partners in this effort.

We're also hoping this special look at what's coming down the pipeline will inspire you to learn more about HIV cure and remission research, and to share this information with others in your community. We need HIV-positive individuals and the global public to actively participate and help shape such research.

A final note: We'll be putting an expanded digital version of this special issue at positivelyaware.com.

In solidarity,



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A WORLD POSITIVELY AWARE
OF HIV AND RELATED CONDITIONS.

**SINCE 1989.** PUBLISHED BY
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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.

# SUMMER 2018

VOLUME 28 NUMBER 4 positivelyaware.com @posaware


## BRAVE NEW WORLD

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ON THE COVER
KEITH STRYKER, PHOTOGRAPHED BY JOHN GRESS: '**WHAT YOU LEAVE BEHIND.**' HAVING LOST LOVED ONES TO THE AIDS EPIDEMIC, MANY OF THE VOLUNTEERS AND MEDICAL PROFESSIONALS TAKING PART IN CLINICAL STUDIES ARE DETERMINED TO HELP SHAPE THE FUTURE OF HIV RESEARCH.

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## CONTRIBUTORS

**ANNE-CHRISTINE D'ADESKY** is an author, journalist, documentary filmmaker, and gender and human rights activist. She works as a freelance reporter for KQED's science and health blog, *Future of You*, and recently published her fourth book, *The Pox Lover*, an award-winning memoir of '90s-era AIDS activism. She began covering the epidemic in the early 1980s.

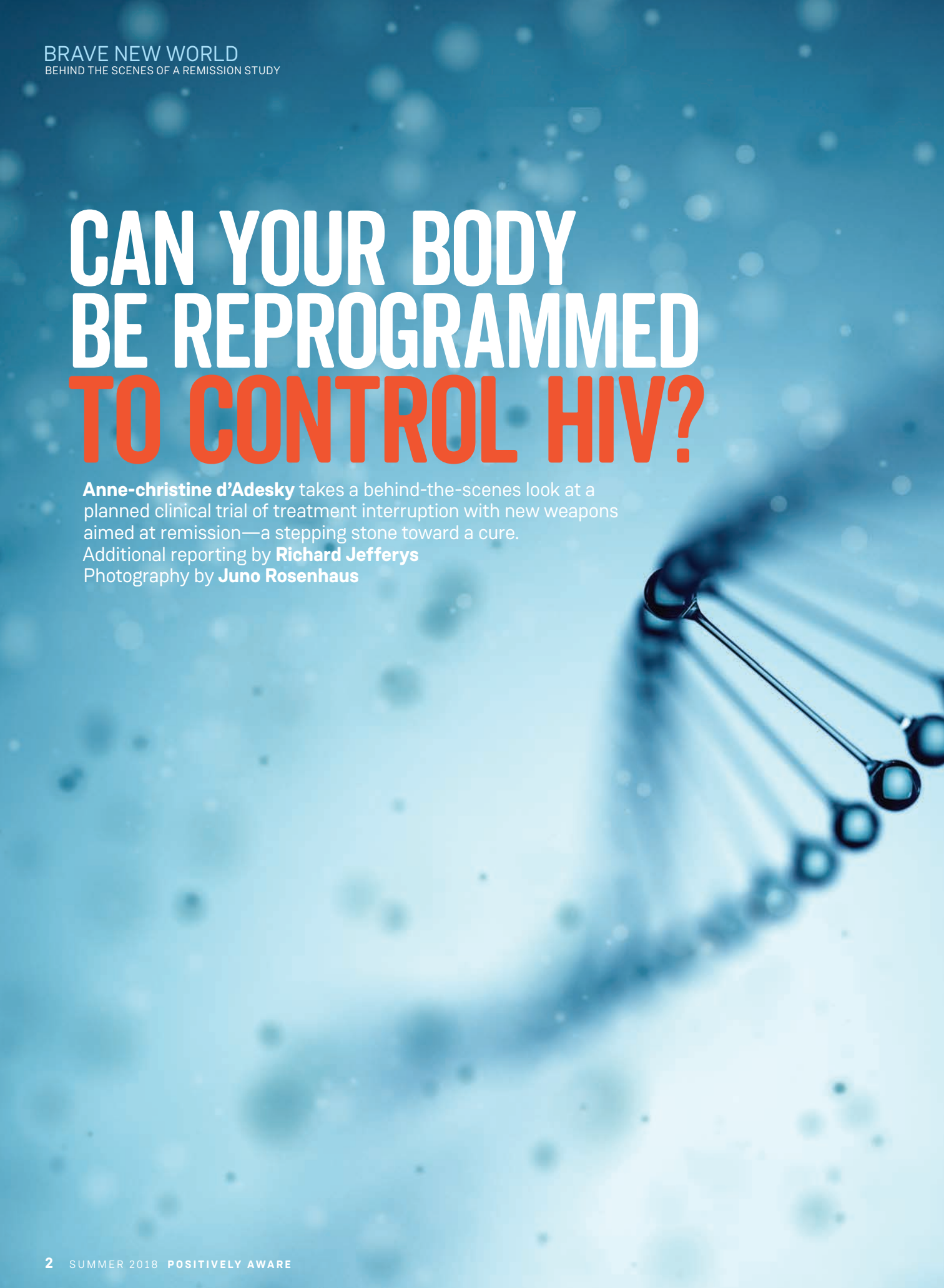
**RICHARD JEFFERYS** began working in the HIV/AIDS field in 1993 as a volunteer at the nonprofit AIDS Treatment Data Network in New York City. He joined Treatment Action Group (TAG) in 2001, and directs TAG's Basic Science, Vaccines, and Cure Project. He was guest editor of POSITIVELY AWARE's Winter 2017 Special Issue on HIV cure research. Disclosure: Richard is currently a member of the CAB for the DARE Collaboratory, which Lynda Dee also co-chairs. Steven Deeks is a principal investigator for the DARE Collaboratory.

**JUNO ROSENHAUS** is a portrait, art, and documentary photographer; website creator; andro-queer feminist; anti-racist/anti-fascist activist; and drummer. Originally from New Jersey, she has lived in the San Francisco Bay Area for more than 30 years, and is based in Oakland.


THIS ISSUE IS SUPPORTED
BY FUNDING FROM GILEAD SCIENCES, INC.

# CAN YOUR BODY BE REPROGRAMMED TO CONTROL HIV?

**Anne-christine d'Adesky** takes a behind-the-scenes look at a planned clinical trial of treatment interruption with new weapons aimed at remission—a stepping stone toward a cure.
Additional reporting by **Richard Jefferys**
Photography by **Juno Rosenhaus**



On a recent March morning in the neighborhood of Potrero Hill in San Francisco, the day dawned cold but bright. The main entranceways to the sprawling Zuckerberg San Francisco General Hospital and Research Center were blocked by construction, forcing employees and visitors to groan and take the long way around a warren of massive red brick buildings and pavilions that make up the century-old medical complex. Few of them were likely aware that, in the wake of the 1906 earthquake, the original hospital that stood here was razed and rebuilt to rid it of plague-infested rats. Construction has rarely stopped since.

Upstairs inside Building 80, however, the mood was one of calm. A sign in the hallway alerted new visitors to the special history of this unit, famous Ward 86, the world's first dedicated HIV clinic. It opened in 1983, when HIV was still called GRID—gay related immune disorder—and quickly became a model of compassionate clinical care that was linked to collaborative research. Today, Ward 86 serves 3,000 patients, mostly locals, including women; 80 percent are on HIV treatment. Some 80 people including staff, volunteer providers, and faculty work there. It's also a field site for nearly 2,400 volunteers of an observational study of HIV called SCOPE that's emerged over time as a unique cohort of long-term survivors and a younger generation of the Bay Area's LGBTQ community.

Ron Malone, a gay man of 69, is among them. He first arrived at this clinic in 1993, breathing heavily eight years after his HIV diagnosis. At 5'10", his body was weakened by *Pneumocystis carinii* pneumonia (PCP), a marker of failing


ISTOCK

**Zuckerberg San Francisco General Hospital and Research Center's Building 80**, home of the world's first dedicated HIV clinic, serves over 3,000 patients and is the center for a new clinical study of remission—a step toward a cure.

immune health and AIDS. Up to that point, he'd eschewed experimental drugs that had major side effects. At Ward 86, he met Dr. Steven Deeks, a young turk in the AIDS ward who asked if he'd like to join a clinical trial of a promising new drug: a protease inhibitor. "I'm glad I said yes to that question," Malone chuckles. In 1995, when the first HIV protease inhibitor was approved for prescription use, Malone was among the Lazarus-like cases of recovery. "That's how I got into the pipeline for drug research," he adds. "These folks saved my life."

Malone makes the trip from his home in South San Francisco to the clinic pretty often. Sometimes it can take him longer than forty minutes. But traffic was light today; he's on time. Most SCOPE participants are seen quarterly for a check-up, including blood work. Volunteers like Malone sign up to go the extra mile. "I'm happy to do whatever they need," said Malone, who calls himself a Ward 86 vet. "It gives me a sense of purpose. This place and these people are sort of like family to me by now. It's an opportunity to contribute what I can to the fight. At this point I don't even feel like just a patient; I consider myself a member of the team. We're in this together."

Today Malone is contributing a tissue sample from his left groin lymph node. The operation is called a sonogram-guided FNA, or Fine Needle Aspiration, and it's a relatively easy procedure, but it involves multiple syringes and requires him to lie very still. This is Ron's second FNA. Before this, he's had an excision of one of his lymph nodes, tissue removed from his lower colon, and given copious amounts of blood. Such specimens have contributed to an impressive SCOPE repository of biologic specimens used by researchers around the world. To date, the SCOPE cohort has supported over 100 cure-related studies. Malone heard that scientists were short on lymph node tissue and white blood cell samples needed for new studies and quickly signed up.

**Right now Malone is** sitting in a corner chair of inpatient Ward 5B on the hospital's fifth floor as he chats, having a routine blood draw and his vitals taken as prep for the FNA. Minutes later, he's lying down in a hospital bed as the nursing team quietly files in, a picture of efficiency and best practice techniques. They clean their hands and don gloves. A smiling male technician from the FNA team shifts a sonogram machine into position just across from Dr. Poonam Vorha, a pathologist, and adjusts the room's pink curtain; the morning light is interfering with a clear view of the monitor. Dr. Vorha smiles at Malone and quickly reviews what will take place. She'll be taking several samples today. The procedure shouldn't hurt—a little pinch—and will be over pretty quickly. "Try to stay still," she reminds him. Malone nods. He's a study vet: been here, done this. Piece of cake.

Nearby, a small rolling table is set up with five syringes, and plenty of alcohol swabs. Malone's groin area is swabbed with antiseptic, then gel for the sonogram wand. A Ward 5B nurse reviews the informed consent form. The paperwork is in order. Time to start.

For several minutes, all eyes focus on the enlarged image of Malone's lymph node as the first needle gently penetrates his skin, then the perimeter of the node. Dr. Vorha's hand moves imperceptibly. The needle moves to an inner chamber of the node called the cortex that contains T cells and B cells of the immune system. T cells are among the primary target cells of HIV infection.

'At this point I don't even feel like just a

Malone smiles, encouraging her to carry on. He's curious about what she'll find. He's been on successful daily HIV treatment for 25 years, and his HIV levels remain undetectable on standard viral load blood tests. That means he can't pass on the virus to others, a finding confirmed in major clinical trials. It prompted the slogan: *U=U, undetectable equals untransmittable.*

But *is* he totally free of HIV? Here, many studies have shown that a small residual pool of HIV may still exist in individuals on therapy. Copies of the virus—a few here and there among millions of cells in tissue—are trapped inside dormant immune cells. This latent pool is known as the HIV reservoir (see page 15). Studies show this latent virus almost always ignites a rapid viral load rebound in individuals should they stop therapy. Unfortunately, standard HIV tests can't detect HIV in tissue compartments.

In recent years cure researchers have been hotly focusing their efforts on eradication and control of HIV in the latent HIV reservoir. It's the new frontline of the AIDS

patient; I consider myself a member of the team. **We're in this together.'**
—RON MALONE

war. While the Holy Grail is complete eradication of every last particle of HIV—also known as a *full* cure—many research groups are targeting the next best thing: remission, or a *functional* cure. This approach combines novel antiviral agents with vaccines and immune-boosting agents designed to keep HIV in check. The goal is to try to build on the immune protection seen in "elite controllers"—rare individuals exposed to HIV with undetectable or very low HIV levels who typically go years, even decades, before developing symptoms; some cases of "exceptional control" may never see disease progression.

To date, only one person is deemed completely "cured" of HIV: the famous Berlin Patient, Timothy Ray Brown. He was cured of both HIV and a serious cancer in 2007 after getting a stem cell transplant from a donor with a genetic resistance to HIV. In another case, Mayo Clinic scientists in Rochester, Minnesota induced remission for 288 days after stopping HIV therapy in an individual who also received chemotherapy and a stem cell transplant. There are also growing reports of individuals treated with HIV drugs very soon after exposure who have seen periods of remission from months to years after stopping therapy. They include cases referred to as the "Mississippi baby" and two Boston patients. The SCOPE cohort includes a significant number of elite controllers; Timothy Ray Brown also joined the cohort.

At Ward 86, Malone's longtime doc Deeks is embarking on a new clinical trial aimed at remission in both newly infected individuals and long-term survivors. Malone is jazzed, though he may not qualify, being almost 70. "It keeps me active to be in the medical world, and I feel like I'm getting something out of it too," says Malone. "It keeps me hopeful."

**In 1992, AIDS deaths in** San Francisco reached an epidemic zenith, peaking at 1,641, becoming the leading cause of death in U.S. men aged 25–44.[i] Back then, Steven Deeks was a fresh-faced doc training at the inpatient ward at San Francisco General. There were only three approved HIV drugs, AZT, ddI and ddC, and little to halt the spread of disfiguring Kaposi's sarcoma lesions or creeping blindness from cytomegalovirus—two illnesses linked to HIV's attack on immune defenses. The weekly death toll was high. Deeks recalls the environment as very depressing. The picture shifted when Dr. Paul Volberding, a cofounder of Ward 86, invited him to work at the outpatient clinic. Deeks found his calling.

"This position started off in 1993 as a one-year job for me in between my residency and fellowship," recalls Deeks. "I got to know this cohort of young men who were highly engaged in the disease. It was a very inspiring time for me because that's when things started to get better."

It's mid-March. Deeks is sitting—hiding out, he jokes—in a narrow cubicle office of Ward 86, fielding phone calls and preparing to meet patients. He's a super busy guy, and soon he'll be even busier with the launch of a major clinical trial sponsored by amfAR's Institute for Cure Research. Deeks is the study's PI, or Principal Investigator; he'll work closely with Volberding, now co-chair of the Center for AIDS Research at the University of California, San Francisco (UCSF) with Warner Greene (read the online-only feature about Warner Greene on positivelyaware.com), longtime collaborators Peter Hunt and Teri Liegler, and Afam Okoye, an Oregon Health & Science University staff scientist. With the trial still a few months away,


**SCOPE VOLUNTEER** RON MALONE UNDERGOING A GROIN LYMPH NODE FINE NEEDLE ASPIRATION (FNA) PROCEDURE.

Deeks says he's "putting all our ducks in a row," to address regulatory and logistical issues.

Early on, Deeks found he enjoyed collaborating with his patients and other doctors (see "The Team Player," page 18). He's a team player, one who enjoys wearing multiple hats. He's a professor of medicine at USCF with a patient caseload at Ward 86, and co-director of the SCOPE cohort. He's a fan of translational research—a "bench to bedside" model that seeks to apply insights from basic science—the bench—into tools useful to doctors with patients—the bedside. "I've never seen myself as an immunologist or virologist or clinical trialist or this or that, but someone who tries to merge these in the same program," says Deeks. "It's always at those transition points in science that I find the environment to be the most exciting and the chance for innovation to be the greatest."

That's the approach Deeks has taken to the pending trial, where he's tried to "bring the best brains in the room together" to debate and help shape its design. Today Deeks co-chairs the International AIDS Society's Toward an HIV Cure Initiative and is a Principal Investigator in the Delaney AIDS Research Enterprise (DARE), as well as a member of amfAR's original Research Consortium on HIV Eradication (ARCHE) collaboration. Longtime colleagues at UCSF and the Gladstone Institutes are key collaborators in the study.

**Deeks got the idea** for his newest cure-related trial last fall after reading a December 2016 *Nature* paper by Dan Barouch, a leading immunologist at the Beth Israel Deaconess Medical Center (BIDMC) who's been developing novel HIV vaccines for years. In his groundbreaking paper, Barouch published the results of a two-year pre-clinical animal study involving 36 primates that was specifically aimed at achieving long-term remission—sustained control of SIV (HIV's simian counterpart) off antiretrovirals. His approach combined two vaccines—an adenovirus vector vaccine (Ad26) and an attenuated vaccinia virus vector vaccine (modified vaccinia Ankara strain, or MVA)—and an investigational drug called a TLR7 agonist that can boost virus-specific immune responses.

The animals were first given antiretrovirals for six months to bring their viral levels to undetectable. They were then divided into four groups including a control group that received no drugs. One group got the combo vaccine; the other just TLR7; a third the cocktail of vaccine plus immune booster. Three animals in the last group remained undetectable for a sustained period after therapy was stopped. The study stands as an early proof of concept for the feasibility of what some prefer to call "post-treatment control"—life without HIV pills.

The study also helped pinpoint the specific immune responses that make up what scientists call the "immunologic correlates" of protection against a possible HIV rebound. Other groups have also published data on potent TLR7 and TLR9 agonists.

While Barouch was testing his novel cocktail, Deeks and colleagues at the amfAR Institute were also tinkering with TLR7 agonists, which are well known to cancer researchers. In fact, cancer is seen as a model for HIV cure research. Deeks began working with Bob Seder at the Vaccine Research Center, and colleagues at the Infectious Disease Research Institute in Seattle, as well as industry colleagues at Gilead. "That paper in *Nature* really stimulated our group," says Deeks.[ii] "We began to design a way to model a therapeutic intervention after the Dan Barouch work."

Last December, Barouch was awarded the 2017 Drexel Prize in Immunology for his vaccine work. By then Deeks had laid out the blueprint for an ambitious study using the same combo cocktail as Barouch's group, but with a twist. AmfAR colleagues wanted to add one more ingredient: broadly neutralizing antibodies, or bNAbs for short. They're derived from B cells of the body that can target proteins on HIV's surface. Neutralizing means kill: studies have shown a single bNAb can lower HIV levels in individuals. But HIV is also a tricky virus; its genes mutate as it reproduces, limiting the potency of single bNAbs. In the September 29, 2017 issue of *Science*,[iii] lead author Ling Xu of the National Institutes of Allergy and Infectious Disease (NIAID) tackled that problem by genetically creating a "trispecific" antibody hybrid of three bNAbs that each target a different region

'It is by far the most complex and challenging study **I've ever done**.'
**DR. STEVEN DEEKS**, SCOPE STUDY PRINCIPAL INVESTIGATOR

of HIV. His "super antibody" provided complete protection against SHIV, a simian-human virus. Xu works in the lab of NIAID head Dr. Anthony Fauci, a longtime collaborator with Barouch's lab, too.

The broadly neutralizing antibodies now being tested in various trials target fixed, or conserved, regions of the virus, making them effective against 99% of HIV viral strains including drug-resistant ones—a welcome addition to the arsenal. On March 4, Barouch's lab presented more promising data from a rhesus monkey study at the 25th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. A combination of a TLR7 agonist made by Gilead Sciences and a bNAb known as PGT121 resulted in a six-month period of remission.[iv]

Now come the human studies. Deeks plans a novel combination of a DNA vaccine, an MVA boost, a TLR9 agonist, and a potent bNAb, administered sequentially. That approach will allow researchers to evaluate the impact of each single intervention, and their combined power.

Clinical trials are notoriously difficult to put together, time-consuming, and they involve mountains of red tape. But so far, Deeks' protocol has gotten a green light from key review bodies, including the Food and Drug Administration. "I've gotten remarkably little pushback," he says, a bit surprised himself by this fact. "The idea has gone forward pretty damn quickly with a tremendous amount of enthusiasm."

**Last year, at an amfAR** HIV cure summit, Deeks gave a little preview of what he was dreaming up with the trial. "We're gonna put together the best of everything we think

can work and see what sticks," he said, breaking it down for a lay audience. His team jokingly calls it the "kitchen sink" trial or "Jaws"—like a big shark aiming at a chunk of the HIV reservoir mystery. Six different investigative groups are involved in the trial—"each with their own lawyers," Deeks notes, grinning, as well as outside groups.

"We've put together a superstar team of investigators," he adds. "We're doing something no one has ever done before; we're pushing the envelope in terms of trial design with this combination approach. And we have the infrastructure to do a high quality study."

The trial will have two research arms and is expected to take three and a half years to complete. It will recruit 30 individuals in a randomized, placebo-controlled proof of concept study in which eligible subjects will be randomized 2:1 to receive a five-stage combination regimen or placebo. It will also recruit 10–15 individuals with acute/recent HIV infection into a single-arm, open label study using the same regimen. Participants will have been on therapy and undetectable for two years prior to starting the study, with T cell levels above 350. They remain on antiretrovirals for 44 weeks of the study while getting the regimen. They will interrupt therapy after the last dose of their regimen—the added antibody.

Deeks anticipates they'll remain undetectable at least 12 weeks (through week 56) or see low viral loads, based on the Barouch animal data and other studies. By letting viral rebound rise, he hopes to monitor how much virus is cleared from the tissue reservoir, and if it's sufficient to allow boosted immune defenses to kick in and reduce viral load levels to undetectable or very low levels—a proof of concept of sustained remission. That would mimic the immune profile of elite controllers. Study participants will be followed until week 96 and allowed to remain off antiretrovirals if viral load is kept low enough.

The trial is designed to test the safety and efficacy of the regimen; a Safety Monitoring Committee will meet biannually to review any adverse reports. The study will recruit from SCOPE and include males and females ages 18 to 65. There are a few exclusion criteria including prior use of non-nucleoside drugs, having hepatitis B or C or liver disease, and taking active chemotherapy or immunomodulatory drugs. Women who are pregnant, breastfeeding, or unwilling to use birth control are out. So are individuals who have a clotting or bleeding disorder or can't undergo the two-hour leukopheresis, or "leuko pak" procedure. This last item may limit some women's participation; their veins may be too small to handle the large needle used in that process.

While the broad goal is remission, some call it a 2.0 HIV "shock and kill" study of treatment interruption. It's that, too. The trial will also provide an opportunity to develop and test new gene technology and diagnostic tools to better measure and map the reservoir and immune responses to HIV. "It is by far the most complex and challenging study I've ever done" says Deeks. "The amount of resources necessary to launch the clinical trial is overwhelming," he explains.

He's also confident the trial is safe, which, he says, is always his number one priority. "It's highly unlikely we'll do any harm because the components have been pretty much well vetted." Deeks pauses, smiling. "I think people are excited."

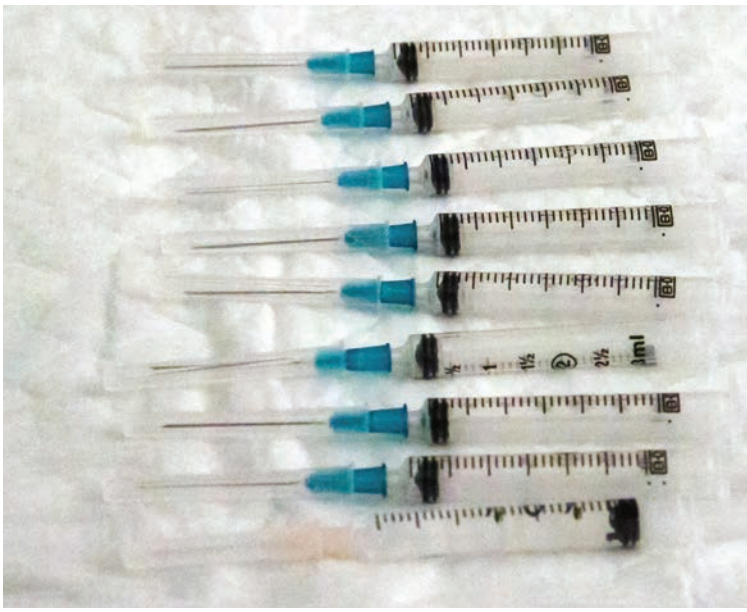
**How likely is it to work?**

Deeks is more hopeful than ever—but he's also wary of over-hyping the possible results. "In order for me to justify putting together a combination approach there has to be a scientific justification, and there's lots of scientific rationale for everything involved in this study," he states, pointing to data from recent monkey models to oncology. "The rationale is solid and no one has ever asked us for additional preclinical studies to support the rationale."

Okay, so what does he expect? And how much of a picture can we get of what may happen in the reservoir based on lymph node FNAs and gut samples? A snapshot? More?

"To predict a cure in people you have to be able to *cure* people," he stresses. "I mean, I'm interested in what happens when you stop therapy, right? And if we quote-unquote, *cure people and put people in remission*. We're gonna measure a million things that we think will control the reservoir in the absence of ART [HIV drugs], and the only way to figure that out is to stop ART. So it's possible that we will achieve a remission, without affecting the size of the reservoir at all; that's not necessary right up front." This is Deeks the clinician talking, the guy who does translational research so lab data will result in positive patient outcomes.

That's also what worries him the most: the human burden of the trial. Participants will be expected to make 60 to 70 visits to the clinic in 18 months. "It's intense," stresses Deeks. The visits will involve an interview, a blood draw, and then the IV drug administration, a process that may take 2–3 hours. "That is going to be happening once or twice a week for a long period of time," he



**MULTIPLE SYRINGES** ARE NEEDED TO PERFORM A FINE NEEDLE ASPIRATION.

‘To predict a cure in people you have to be able to *cure* people.’
**DR. STEVEN DEEKS**

adds, shaking his head at the thought. “Our concern is that the intensity of the protocol will be so great that it might overwhelm our system,” he admits. “So we’re not entirely sure this will be a single center study.”

**Yet that’s not even the** hardest part. New challenges will come when it’s time for participants to stop taking their HIV medicines. “The monitoring will go sky high and people are going to have to be concerned not only with what is happening to them but about their interactions with loved ones because of the issue of transmission,” states Deeks. “So there is an intensity during the treatment phase and intensity during the interruption phase.”

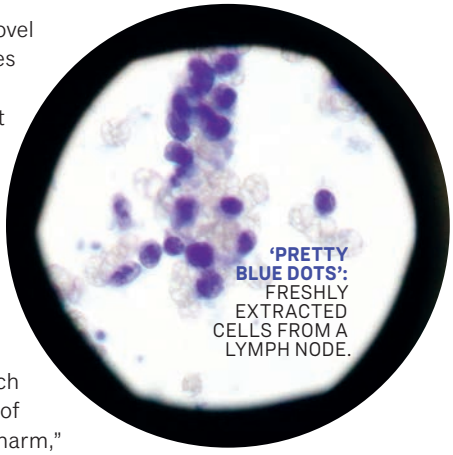
Luckily, Deeks has teams of experts to help him consider the ethics dimensions and needs of participants in the study (see “The Community Watchdog” on page 21). An independent Institutional Review Board has reviewed the draft protocol and made comments. So has an FDA body, and the group Deeks has come to really rely upon since his early AIDS days: the Community Advisory Board, or CAB. It’s co-chaired by longtime treatment activists and HIV-positive individuals well versed in HIV clinical trials. The CAB had early input on the study’s Informed Consent form and process; they advise on such aspects as recruitment, and inclusion and exclusion criteria, to assure it conforms to best practice norms of clinical research.

But this study also pushes the envelope a little. Prior treatment interruption trials have immediately put individuals who showed signs of a viral rebound back on therapy. But we also know from such studies that when the virus initially rebounds back it may shoot up high, then drop down to a stable plateau or viral “set point.” “It’s about six to eight weeks minimum before we know what’s working,” says Deeks. He wants a threshold of 10,000 HIV copies for the trial; if individuals see rebound levels rise above 10,000 for two visits in a row, they’ll have to get back below that level within two weeks.

That spike in HIV, of course, may not only worry participants, but carries a risk of transmission for their sexual partners, making prevention issues a critical component the study must address. “That’s a constant discussion,” Deeks acknowledges. The SCOPE research staff are very experienced in patient support and retention, and a lot of resources are aimed at helping volunteers manage their participation. Not everyone’s a Ron Malone, who’s pretty stoic and up for anything, and has a supportive partner who can help drive him to distant appointments. “We try to plan for everything, but things come up,” Deeks admits.

A good example of that are lymph node biopsies. After doing nearly a hundred lymph node biopsies without incident, two SCOPE volunteers had complications with the procedure. While lymph node biopsies provide a more complete picture of HIV activity in the reservoir than a grain-sized FNA extraction, Deeks has decided to stop collecting the tissue samples for now. “We were pretty surprised,” Deeks said, sighing. “A hundred procedures—no problem. Then, boom. But, look, that’s what can happen.”

What about the new study? While the four drugs being tested have been safe in prior studies, this one will combine them in a novel way. Deeks anticipates positive, synergistic drug interactions, not negative ones, but it’s still a question mark. Some first generation “shock and kill” drugs caused side effects and weren’t very effective. That’s why the study calls for such intensive monitoring of participants. “Do no harm,” states Deeks, citing medicine’s dictum. “Even though you can’t predict certain aspects of a trial, you plan as much as you can to avoid any adverse outcomes.”


**‘PRETTY BLUE DOTS’:** FRESHLY EXTRACTED CELLS FROM A LYMPH NODE.

**To the naked eye,** Malone’s tissue sample, rubbed onto slides, looks like pretty blue dots. A staining solution has been added to differentiate the cells. One of the nurses carefully packs the samples in a carrying case and, in minutes, is headed down the hallway to deliver them to scientists at collaborating institutions in the trial. Malone’s fresh samples are destined for Dr. Rachel Rutishauser’s lab at Gladstone (read the profile on Dr. Rutishauser on positivelyaware.com). She’s focused on the immune side of the puzzle and vaccines. After Malone, two other SCOPE volunteers will undergo the lymph node FNA today. The team has already completed 50 FNAs for the pilot—an average of five to ten a month.

**From the outside,** the center looks like an ordinary modern office building. But inside, and down a flight of stairs, is a state of the art facility that includes a biosafety level 3 lab—one of a few in the U.S. That’s the kind of lab you see in apocalyptic movies where scientists are heavily suited up in protective clothing and goggles to avoid exposure to a live virus like polio.

The BSRI facility has 9,000 square feet of labs, with a 2,200 square foot freezer room that can store over a million specimens. It’s stacked head to toe with heavy refrigerators and freezers that bear the labels of the specimens inside and who owns them. Here you find Zika, dengue, and of course, HIV. Satish Pillai’s group has laid claim to several big freezers.

The lab team occupies a row of small offices on one floor, but a lot of their time is spent below ground, in the windowless shared lab. It’s a cluttered, busy place, overlit with fluorescent lights that only underscore the lack of daylight. There, senior scientists work with younger graduate students and lab technicians hunkered over microscopes and computers, some listening to music on headphones that help pass the time during long experiments.

**Satish Pillai could easily** be mistaken for one of the younger protégés. A friendly, self-described ex-Deadhead and math geek, Pillai loves music so much that he relies on it to help him relax and

think conceptually about his lab work. He's a rising star in the field of HIV diagnostics and is responsible for the laboratory side of the coming remission trial. Last year, he gained attention for a PCR (polymerase chain reaction) testing method that can assess 1 million cells using a digital droplet technology, compared to prior methods limited to 100,000 cells or less at a time.[i]

Pillai's lab is tasked with developing and testing new technologies and tools that will help assess the impact of the planned regimen. "We want to shrink the size of the virus reservoir and then we want to manipulate the immune system so that, even if we can't achieve complete eradication, the immune system is primed in a way that can control any of the residual virus that escapes after the reservoir reduction that we attempt," Pillai explains. That's the big picture in a nutshell. "My goal is to come up with strategies to measure those things: 'Have we actually reduced the reservoir?' That's number one. 'Have we manipulated the immune system in any way that there is a likelihood that we can control any of the embers that persist?' That's number two."

He's nodding to himself as he ticks off that list, then pauses, his expression reflective. "The thing is, we don't have any off-the-shelf tools we can use to measure that. The HIV reservoir itself is a very nebulous concept," he explains, and the cure field lacks industry standards to measure HIV latency. "That's where we come in. A lot of what we have done in the amfAR Institute is to develop a range of tools to measure the reservoir using different approaches, targeting different components of the virus."

**A key aspect** of the planned combination trial is being able to map and reduce the infectious HIV pool. To do that, we need tests that can distinguish between T cells that harbor a defective HIV provirus, or viral genome, and can't reproduce, and T cells with proviruses that can replicate and are infectious; the latter pose a danger of re-infection (see "The Mapmaker" on page 20). "We really need to be able to discriminate between infectious viral genomes and the replication-incompetent duds," Pillai explains, using more wonky language. "We are trying to get our technology up to the point where you can take clinical samples and actually look to see if our interventions—even if they don't change, for instance, the frequency of HIV DNA in circulation—do they dramatically impact the frequency of replication-competent virus? Because that would be a very meaningful deliverable." Put more simply, he's hoping to measure just how big a bite the trial regimen may take out of the important piece of the reservoir pie.

Timothy Henrich at UCSF is also looking at markers on CD4 T cells that might flag them as harboring infectious HIV (read the online-only feature about Henrich at positivelyaware.com). His lab has evidence that the cellular receptor CD30 may be a candidate "biomarker" and that rising CD30 levels may be a harbinger of a viral load rebound in people experiencing a transient period of remission after HIV treatment interruption.[v] That could turn into a future diagnostic tool to help individuals assess the risk of a treatment interruption. "We hope to apply our know-how and look in more depth for these markers in the trial," Henrich says.


SATISH PILLAI

‘While the big goal is remission, the **development of these new technologies is also an important outcome** of such studies.’
—HIV LABORATORY EXPERT **SATISH PILLAI**

**What about the big** paradigm shift we’re after: long-term immune control of HIV? How do we elicit the exact immune defenses that will stop HIV, and restore lost or missing immune strength in individuals with chronic versus acute HIV infection? While so much of our long fight against HIV has focused on developing antiviral drugs, the new frontier is the immune system: how to harness nature’s power. Can we identify the right mix of immune responses we need to prevent HIV from rebounding?

In the SCOPE cohort, studies of elite controllers have given us some clues about what’s needed: CD8 T cells (CTLs) can target the virus (called “HIV-specific”) and help suppress HIV replication. The Barouch monkey study that combined a therapeutic vaccine with a TLR7 agonist found that specific T cell responses to the HIV proteins Gag and Env were associated with control of viral rebound.

In the trial, Gladstone’s Rutishauser will be responsible for analyzing HIV-specific T cell responses. Like Pillai, she’s optimistic about what the study may teach us—even though we don’t know exactly what type of immune response may predict success. “I think we can come close to understanding whether a robust immune response has been elicited,” says Rutishauser, “and now we can do that so much better than we could even five years ago given the immunologic tools that we have.” She’s busy testing a new flow cytometry tool called mass cytometry that can analyze a dizzying array of 40 different possible T cell functions simultaneously.

She’s also hoping to apply insights from elite controllers: “All the knowledge that we’re getting about what constitutes a good T cell in natural controllers can inform that really well, in terms of being able to say, ‘Are these CD8 T cells similar to that or not?’” she explains. Right now, she stresses, much more needs to be learned about what’s happening with T cell responses in tissues, and how the desired immune responses might be directed to where they’re most needed.

The study team is also eyeing the potential of natural killer (NK) cells to play a part in remission. Lab studies show that NK cells have the potential to bind to HIV-infected T cells in the reservoir, flagging them for destruction. This mechanism is called antibody-dependent cellular cytotoxicity (ADCC).

Pillai also plans to assess immune system pathways likely to be affected by the TLR9 agonist, particularly the induction of interferon, an immune system protein with antiviral properties. Meanwhile, Pillai’s colleague Konstantinos Georgiou will probe “host restriction factors”—enzymes produced within cells that aren’t traditionally considered part of the immune system but have HIV-suppressing capacity. The best-known example of such an enzyme is the tongue-twister, APOBEC3G (see “The Mapmaker” on page 20).

Pillai is also hoping that some cases of prolonged control of HIV viral load will be observed in the trial, because of the opportunities that it will open up. “I’m really crossing my fingers,” he says, “If we do, the tools that Konstantinos and our whole tech crew are working on will really help us zero in on the particular immune mechanisms that were primed to allow for that extended control. That should give us a whole new generation of ways to manipulate the immune system to have that effect.” While the big goal is remission, the development of these new technologies is also an important outcome of such studies.

**Midmorning. Back at** Ward 86. SCOPE’s clinical research coordinator Becky Hoh and several members of the research staff are huddled in conversation, reviewing a tightly scripted schedule of the day’s appointments. The schedule is always a moving target; flexibility is essential. Usually by 9 a.m., people have cancelled, changed, or asked to drop in. When that happens, the SCOPE team has to notify labs or scientists who may be waiting to receive fresh samples, or a visit from a participant being referred for an outside field procedure. A large clinical trial demands a high degree of choreography to run smoothly: people need to know their roles and when they are needed to show up, including the volunteers. That’s where Hoh gets high marks from her colleagues and boss Deeks: she is well organized, calm, highly experienced, and, most important of all, she’s a people person—she loves her patients.

“A lot of it is coordination, logistics, communications, asking patients, and making sure expectations are met,” says Hoh, laying out the day-to-day demands of managing the SCOPE cohort and myriad studies. While Pillai dreams about biomarkers and how to map the molecular world inside the bodies of participants in the study, Hoh and her staff focus on the emotional side of their lives: what it takes to support them, how to balance the hope that naturally comes with such a trial against the fatigue and discomfort that may follow a lymph node FNA or a two-hour leuko pak session.

“We definitely want to make sure that folks have an idea of what they are going to do here,” explains Hoh. “We never want people to show up and not know what is going to happen that day, what they need to prepare for a visit. If it’s a procedure like a colonoscopy, we’ve already been in touch with them two or three days beforehand to say, ‘Hey, we would you like to have everything ready. Is there a special diet that you follow? Do you have the instructions you need?’”

“It’s amazing how many people are still in SCOPE,” says Hoh, who started at Ward 86 in the 90s (see “Doctor Steven Deeks” on page 18), “but certainly some go away and come back. You never know when you are talking to somebody about a study that may take a year to complete, what is going to happen in that time: there may be health changes, relationships change, a lot happens. But I have to say, for all of us working on the team, that working with patients is the best part of the job... the relationships you build. You are hearing their stories and you are working with people who are generous and want to contribute.”

**Two words come up over** and over again in conversations with both staff and clients in the SCOPE cohort: trust and inspiration. “I do trust them; they have taken such good care of me,” Malone says. “I feel inspired to be here.” Study coordinator Hoh agrees: “We feel a great degree of trust and respect for our patients. They inspire us to do our best. We always learn from them.”

That trust begins with a tool that serves continually as the reference point and ethical compass for all parties in a trial: the informed consent form and process. Hoh and her colleagues get ahold of the draft informed consent early on, even before an outside Institutional Review Board or the patient Community Advisory Board, or CAB. All review parties are tasked to make sure the protocol conforms to ethical and best practice standards. They look closely at inclusion and exclusion criteria, what will be asked of volunteers, the benefit vs. possible risks. All of the SCOPE team have clinical research backgrounds.

For this study, the CAB co-chairs are two longtime HIV activists who have sat on clinical trials over the years: Jeff Taylor, who's been HIV-positive for 35 years, and Lynda Dee, who's been doing HIV advocacy for 33 years (see "The Community Watchdog" on page 21). Both are outspoken, intelligent activists who can hold their own with researchers when it comes to deep geek science.

CAB members see themselves as having two key roles in such studies: the first is as community watchdogs to ensure the safety and participation of volunteers; the second, to do outreach and educate the larger and local HIV community about the study. Throughout a long trial, they solicit the community's views and concerns, and bring that feedback to the investigators. The UCSF study is among the first human remission studies to get rolling, but similar studies are ongoing or planned elsewhere, including globally. What happens in SCOPE will inform other sites, and vice versa.

At the moment, the main thing that preoccupies Dee and her colleagues is the part about stopping therapy, known as an "analytical treatment interruption," or ATI, in CAB-slang. "Everybody's doing them," says Dee referring to remission studies, "and they're doing them with very capricious sorts of metrics just like we did in the beginning of antiretroviral trials. But in those days, you know, people were beating the doors down because they were dying." She wants to move with caution: "I think the biggest ethical issue we face are these ATIs, and we have to be really, really sure that they [are as] safe as they can be—especially these initial ones going right from monkeys into people." She'd like to see inclusion/exclusion criteria be a little—she searches for the words—"more safe, less risky; let's put it that way."

Dee has made it her personal mission to ensure the CAB has diversity, and she's invested in helping mentor less-experienced CAB members who are new to cure trials. "It's not been easy to get a diverse group," admits Dee, a Baltimore resident who enjoys a good challenge. "But it's a really good little group and we're devoted to making sure women and people of color are included."

Dee and Taylor have known Deeks and other co-investigators for years; when they speak, they're listened to. They want the same to be true of their newer CAB colleagues. "They know me; they know that I do what I say I'm going to do," Dee says about the other parties in the study—including the FDA. "They always say I keep them honest," she laughs. "So I think that's my role anywhere in this activism."

Right now, that honesty means she's not holding back about her concern that more effort may be needed to make sure women and folks of color are recruited. After years of HIV activism, she's well aware that fear, misinformation, and denialism about HIV may pose hurdles to participation for some members of vulnerable communities. She cites the infamous Tuskegee experiments in which African Americans were allowed to get sick in the ostensible name of scientific progress. Given historic racism, and exclusion from research, she is attuned to the need for research studies to make community education and outreach a priority.

**At last year's amfAR cure conference,** two SCOPE members shared the stage with researchers: Clark Hawley and Luis Canales. The duo represent the newest poster boys for HIV remission (see "Double Take" on page 16). Both men had enrolled into a PrEP demonstration project in San Francisco, but were found to have acquired HIV during a short window of time between undergoing screening tests and being prescribed their first dose of Truvada PrEP. As soon as HIV infection was confirmed by PCR viral load test, they were switched to combination HIV treatment regimens—an estimated 17 days after infection in Hawley's case, 24 days for Canales. Hawley is believed to be the most rapid case of adult treatment initiation ever documented, with Canales not far behind.

Both men were then enrolled in SCOPE, where researchers closely tracked their status. For over two years, no sign of HIV could be found in their blood or body tissue. Were they now cured?

To find out, Hawley stopped taking his HIV drugs

'...working with patients is the best part of the job.'

**BECKY HOH**, SCOPE CLINICAL RESEARCH COORDINATOR

and remained undetectable for over seven months until HIV reappeared. Meanwhile, researchers found evidence of HIV in Canales' cells when they were put into mice with humanized immune systems. In both cases, early treatment reset the clock, limiting HIV's spread. The duo represents a small number of individuals who, via early interventions, may achieve remission more easily than those with chronic infection. The smaller arm of the new study may tell us more.

Both men are familiar figures at Ward 86 and the inpatient Ward 5B, where Deeks is now building a new cohort of "exceptional controllers"—a subset of elite controllers who show evidence of HIV but have functional immune systems, and no signs of residual inflammation—a hallmark of chronic HIV infection. Right now SCOPE has four such individuals. "They are probably the people we need to base our cure work on," says Deeks. "Some people have less than50 copies of HIV, and others are essentially so close to being cured that they in fact might meet some definition of a cure." That said, his heart is with the vast majority of individuals like Malone, living for years with HIV, who dream of remission, never mind a cure. Deeks hasn't forgotten the early days at Ward 86, either.

**A week after the CROI 2018 conference,** Deeks has run into a snag. He's not going to be able to get the potent antibodies in time for the start of the trial. The manufacturing of the novel antibodies is difficult and very costly, a painstaking process. There's not much supply of these agents out there. The trial design will thus have to be tweaked; the antibody given in year two. "I think we should still be okay," says Deeks. "It's not a deal breaker." Luckily, the hiccup has come before final FDA approval. "We're still on track," he sums up. "So far, so good." PA

**FOOTNOTES**

i ucsf.edu/news/2011/06/9971/thirty-years-aids-timeline-epidemic

ii janssen.com/new-therapeutic-vaccine-approach-non-human-primates-shows-potential-functional-cure-hiv-1

iii science.sciencemag.org/content/early/2017/09/19/science.aan8630.full

iv niaid.nih.gov/news-events/broadly-neutralizing-antibody-treatment-may-target-viral-reservoir-monkeys?utm_campaign=+31404473&utm_content=&utm_medium=email&utm_source=govdelivery&utm_term=

v journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006856 Hogan LE, Vasquez J, Hobbs KS, Hanhauser E, Aguilar-Rodriguez B, Hussien R, *et al.* (2018) Increased HIV-1 transcriptional activity and infectious burden in peripheral bloodand gut-associated CD4+ T cells expressing CD30. PLoS Pathog 14(2): e1006856. doi.org/10.1371/journal.ppat.1006856

# FANTASTIC JOURNEY

**HIV begins the journey into its hiding places** in tissue reservoirs from the first hours of its entry into the body. In sexual transmission—vaginal or anal—sentinel immune cells found in the mucosa lining the reproductive tract or colon immediately recognize the presence of the virus and raise the alarm.

CD4 T cells are among the first responders to an infectious invasion, and act like the quarterback on a football team, coordinating both offense and defense by instructing other elements of the immune system to control or repel the invader. But because HIV preferentially targets CD4 T cells for infection, the virus essentially exploits the normal workings of the immune system for its own benefit.

HIV fuses with surface proteins on a CD4 T cell, slips inside, and integrates itself, or hijacks, the cell's genes. The infected T cell spews out millions of HIV copies while other immune cells—CD8 T cells and cytotoxic T lymphocytes (CTLs), known as killer cells—attack back.

Right away HIV particles are ferried along the body's immune highway, lymph, to the lymph nodes. More warring takes place there, as the immune system marshals its army of immune cell soldiers—more CD4 and CD8 T cells, and antibody-producing B cells—that rapidly divide and multiply in number. All this activity contributes to the telltale swollen lymph nodes and flu-like symptoms that mark acute HIV infection.

The immune army is typically able to bring HIV replication under some degree of control, and the big initial spike of viral load drops. If HIV drugs are introduced, they quickly block virus replication by inhibiting multiple steps of HIV's lifecycle, preventing further spread. Many of the HIV-infected CD4 T cells die rapidly, either directly, due to effects of the virus, or indirectly, via programmed cell death. But a subset of the infected T cells return to a deactivated, resting "*memory*" state, and they form a latent viral reservoir.

The HIV reservoir is thus established almost right away, and typically grows in size the longer an individual remains untreated. The faster someone goes on therapy, the smaller their HIV reservoir, and—here's where the new studies come in—the greater their chance of reducing, controlling, and perhaps one day seeing HIV eradicated from its last hiding places.

Memory CD4 T cells are designed to be long-lived, with the ability to recognize a previously seen invader. Once inside resting T cells, the virus's genetic code (or genome), called a provirus, remains trapped and essentially dormant, stuck inside the cell's genome. Cure studies have shown some proviruses can restart viral replication should the host cell become reactivated, and HIV drugs are withdrawn. (See "Where HIV Hides: The Reservoir" on page 15.)

Now comes the good news: studies also show the vast majority of proviruses in the reservoir are defective and can't reproduce. Scientists refer to them as "junky" or "zombie" HIV. At Johns Hopkins School of Medicine, Robert Siliciano, a pioneer of HIV latency, estimates that only 12 percent of the reservoir contains "replication-competent," or infectious, HIV provirus. So that's the real target of cure interventions. "Defective proviruses can never give rise to a new infection; the defects are so severe," Siliciano explained in a recent interview.

That still leaves a major threat. **Even a single infectious provirus poses a theoretical risk of reigniting an infection.** "I think we're far from getting rid of the 12 percent," Siliciano added.

His opinion is shaped by a surprising discovery he made last year that was published in *Cell* and has shifted long-held views of the reservoir. He found resting memory T cells in tissue sites aren't totally dormant: they slowly spread via cell division. Using a new PCR technology, he identified daughter T cells with copycat HIV proviruses intact. While the size of the HIV reservoir declines in most people once they start HIV drugs, other cells are slowly proliferating. "The 12 percent represents a steady state," Siliciano explains.

—**ACD & RJ**

ISTOCKPHOTO

WHERE HIV HIDES

# THE RESERVOIR

**While the HIV reservoir has yet to be fully mapped, we know HIV targets key immune cells of the body. The cells travel along an inner body highway of lymphatic vessels the size of capillaries that flow next to the bloodstream and are found in lymph, a clear fluid that bathes body tissues and must be drained. The lymph gets dumped back into the bloodstream. That's how B and T cells move between the blood and tissue; as HIV infects T cells, the virus is transported into tissue sites throughout the body.**

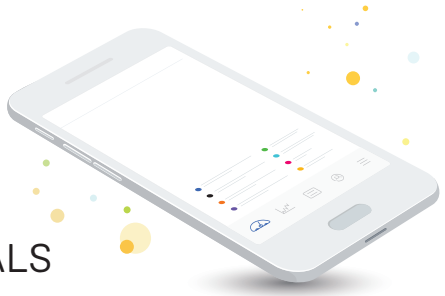
A small percentage of these activated T cells will later revert to a resting state to become "memory" T cells that harbor particles of HIV and make up the HIV reservoir. Rather than a single site, the HIV reservoir exists in tissue throughout the body.

Today we know that the bulk of HIV viral particles in the reservoir are actually fragments that can't reproduce; a small fraction are "replication competent," or infectious. So we're actually targeting a very small percentage of an already small dormant HIV pool. That doesn't make it any easier to find the latent HIV particles because the hiding places are all over the body.

The lymphoid system is made up of three main cell types found in lymphoid organs: Lymphocyte (B and T cells), epithelial, and stromal cells. Other cells in tissue include bone-marrow derived macrophages and antigen-presenting cells.

In the body, lymphoid organs serve a front-line role in fighting infection. They are a pit stop for immune cells to stop, trap, and kill invading and disease-causing organisms. Normally, circulating T cells return to the blood from the lymph nodes within a few hours.

Other primary lymphoid organs are fetal bone marrow and the liver that produce B cells, and the thymus, which produces T cells. Secondary lymph organs include the spleen, adult bone marrow, and gut- and mucosal-associated lymphoid tissue (GALT and MALT) that line many organs, including the Peyer's Patches of the small intestine, digestive tract, colon, appendix, tonsils, adenoids, retinas, and the testes and male genital tracts. The brain, fed by blood and cerebrospinal fluid, is considered a special sanctuary site that is protected by a thick "blood-brain" barrier. Some HIV drugs can cross that barrier better than others. But the brain is an HIV reservoir site. —**ACD**



# COMMUNITY RESOURCES— HIV REMISSION AND CURE TRIALS

THE FOLLOWING are some community resources for individuals who'd like to learn more or participate in HIV remission cure and other clinical research studies, join a Community Advisory Board, and find out where new studies may be happening. The CUREiculum is currently housed at AVAC and was developed with lots of community input; it's a good tool for learning the basics and teaching others, with print and visual modules. Jump in!

**amfAR**
amfar.org/research

**CUREiculum**
avac.org/cureiculum

**defeatHIV Social Media**
TWITTER HANDLE: @defeathiv
FACEBOOK: facebook.com/defeatHIVseattle

**HIV/AIDS Cure Research Glossary & Resource Guide**
projectinform.org/pdf/HIVCureGlossary.pdf

**HIV Cure – National Association of People with HIV Australia**
hivcure.com.au

**POSITIVELY AWARE Winter 2017 Issue: HIV Cure Research**
positivelyaware.com/issues/winter-issue-2017

**SearcHIV: Social and Ethical Aspects of Research on Curing HIV**
searchiv.web.unc.edu

**Treatment Action Group Research Toward a Cure Clinical Trials Listing**
treatmentactiongroup.org/cure/trials

THE MARTIN DELANEY COLLABORATORIES:

**BEAT-HIV: Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy**
beat-hiv.org

**BELIEVE: Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication**
smhs.gwu.edu/believe/our-research

**Combined Immunologic Approaches to Cure HIV-1**
cvvr.hms.harvard.edu

**Delaney AIDS Research Enterprise to Cure HIV (DARE)**
ucsfdare.wixsite.com/dare

**Delaney Cell and Genome Engineering Initiative (defeatHIV)**
defeathiv.org

**The Collaboratory of AIDS Researchers for Eradication (CARE)**
delaneycare.org

THE NEW POSTER BOYS

# DOUBLE TAKE

BY **ANNE-CHRISTINE D'ADESKY**

**What does it feel like to be told you're a symbol** of the world's hope for stopping HIV? That your unusual case could be like the Berlin Patient—the only person ever cured of HIV—or the next best thing: remission? That in your case, super early HIV treatment has limited HIV's ability to gain a foothold in your body. Your case is so unique and inconclusive that scientists urge you to let them probe your body to look for the virus. The answer comes seven months after you finally stop therapy, two years after starting it. You aren't cured, but you were nearly cured and you're now the newest poster child for HIV remission.

Call it *Mr. Toad's Wild Ride*, or, better, *Alice in Wonderland*'s fall through the looking glass. For Clark Hawley, 55, the past three years have definitely been wild, but also positive—a renewed chance to make a difference in an epidemic that killed many of his gay male friends in the '80s and '90s. It's been an equally long, strange trip for Luis Canales, 31, who felt a bit less special when he later learned about Hawley. The duo are among the earliest adult cases of treatment to date.

Both men describe the surreal experience of living in limbo for years—uncertain if they still harbored HIV or not. Hawley now knows; Canales hasn't elected to go off meds to find out for sure. But they've both become ambassadors for HIV clinical research, putting their bodies on the line for answers.

"I would never have put as one of my goals in life to become the poster boy for HIV research," says Hawley. "But nobody else could do this; Luis (Canales) came after me." He adds, "It was my responsibility."

The two men were highlighted guests at last year's amfAR HIV Cure Summit, where they met each other for the first time. Both are active participants in SCOPE studies.

**Hawley looks like a typical** middle-aged denizen of the Castro, his style a bit preppy. At the summit, he wore a loose dark jacket over a checked flannel shirt pinned with a large red ribbon. He's a sweet man, friendly and chatty. He's also a former married, ex-straight dad of two sons, aged 20 and 22, who came out later in life, then fell into a spiral of meth addiction. He had so many partners for so long that he doesn't understand how HIV had spared him. He got tested for HIV every six months but went off the rails with meth. In recovery, he enrolled in a PrEP demonstration project in San Francisco, ready to commit to a single pill a day to ward off HIV.

He's gotten used to the media spotlight. He's also grateful for the opportunity to contribute. "**I worry that no one is talking about AIDS anymore**," he says, "but the epidemic is still here." Being back at Ward 86, the early epicenter, grounds him in his own history; here, everyone is still in the fight; he's not an artifact of a fading gay epidemic.

"How could I not want to help find a cure?" asks Hawley rhetorically. "I'm obviously lucky; my case is rare. I feel a sense of duty to my community to participate." If anything, he's come to believe he's here for a reason. "I mean, I was so promiscuous," he says, shaking his head. "Why didn't I get HIV back then? Well, now I have an answer."

The minute he walks into Ward 86, he feels welcomed, needed, appreciated, he says. "Being here, you learn a lot about what's being done. I've gotten really educated; honestly, it's very inspiring."

At the same time, it's not always easy to be a rare specimen. Hawley became infected with HIV during a short time period between screening for the PrEP project and being prescribed his first dose of Truvada. HIV infection was diagnosed via a viral load test; he was caught so soon after acquisition that his HIV antibody test results were negative. Truvada was quickly switched to a four-drug HIV treatment combination, an estimated 17 days after infection had occurred. Deeks hoped that treatment had been started early enough to prevent HIV from seeding an infection. "We got close; we may have been off by a day or two," says Deeks of the case. "He's as close to a cure as you can get."

Hawley's case is more than that: it's hard proof that, even with immediate treatment, we can't stop HIV but we can radically alter its course. How radically? What might be possible now that we add novel drugs to flush out the HIV reservoir and boost immune responses? The new trial aims to find out.

FROM LEFT: **CLARK HAWLEY** AND **LUIS CANALES**

PHOTOS: JUNO ROSENHAUS

**At 31, Canales represents** a stark contrast to Hawley, Mr. Gay Everyman. A performer and dancer, Canales is used to making an entrance—and a statement. He captured the stage at the amfAR summit in a bold red-, yellow-, and peach-colored dress paired with his knee-high red leather lace-up boots—a modern drag Dr. Frank N. Furter from *The Rocky Horror Picture Show*. He completed his dramatic outfit with a white surgical mask that bore a drawing of a big toothy mouth lined with red lipstick.

"I didn't want to look too normal," Canales says, half-jokingly. He's an artist, and he says, a freak. That's a positive label; he cultivates an art and gender outlaw persona—a rad drag HIV activist.

Canales is a member of the post-protease generation, a cisgender gay man who's known a very different world: PrEP, U=U; a new era in which HIV is touted as a manageable disease. Although he knew about HIV, it's all been a steep scientific learning curve. He also entered the PrEP demonstration project and, like Hawley, was found to have acquired HIV in the time between undergoing screening tests and starting Truvada. Canales was switched to ART on day 12 of Truvada dosing (an estimated 24 days post-infection), after the virus was detected via PCR, while his antibody test results remained negative. He was in the first stages of seroconversion.

"At first I thought it was cool; the way they presented everything," Canales says about being told his was a unique case. "But for a while I was just being dissected, injected, my body parts looked at...so it was a lot of physical pain and emotional pain and not being able to fucking get any straight answers for about two years."

For a long time, he also thought his was the only case of its kind because SCOPE confidentiality rules limit disclosure about participants. His first two years of HIV limbo were marked by anxiety, stress, and fear. "I mostly felt lost," he says. He credits the SCOPE team, and especially Becky Hoh, for a lot of hand-holding. "They were very supportive. Becky is my girl," he declares.

But the reception outside SCOPE was less kind. "Before the scientists thought they really knew what was going on, and that I might be cured, I would try to tell people about it," Canales explains. "They either believed me or thought I was lying." That got worse after the *Bay Area Reporter* wrote up his case. "People thought I was just trying to capitalize on some made-up thing," he says. "It was like, 'Oh, this crazy, wacky off-the-wall, avant-garde performance artist in fucking drag clothes is making up this fantastic story, and he's trying to pull a fast one on us.' I was publicly called a liar." That changed when PBS ran a segment about his story. Now, he couldn't care less about the skeptics.

His entry into research has also helped counter a deep regret at contracting HIV. "I knew about HIV, but I let my guard down," he says, still angry with himself. "I was engaging in risky sex; I obviously wasn't making good choices healthwise. So when they told me my situation had the potential to find answers and stuff—honestly that's really great."

Did he feel he had a choice to participate? "**I do it because it's the right thing to do**," he adds, echoing Hawley's sense of ethical obligation. Then he jokes: "Honestly it felt kinda like *Star Wars*"—a reference to Luke Skywalker and the battle to save humanity.

Still, the experience hasn't been a picnic. In a two-week period he endured five major procedures, including a lymph node biopsy. He described the operation as "searing pressure" on his skin. Yes, he's a drama queen, but it's been tough. He doesn't look forward to the leukopheresis blood hookups either. "So fun," he jokes, meaning—*Not*.

Yet he's emerged with a deepening sense of mission, too. A newly-minted AIDS activist, he joined his first CAB a year ago and is learning fast. "I want to be a part of that 'cuz I have this perspective that no one else has, but at same time, I'm trying to find my footing," he says, "and how I can play an important role in that." He even sought out Timothy Ray Brown to learn more from the Berlin Patient's journey. "His celebrity dwarfs me," laughed Canales.

Looking ahead, Canales says, "I want to do a good job, so how do I get there? That's been my process." That's also what prompted him, at the eleventh hour, to ask his drag artist friend, Hollow Eve, to cook up a spectacular outfit for his public coming out at the amfAR summit. If he's going to represent, then he plans to *represent*. His battle cry: "Go Bold." PA


THE TEAM PLAYER

# STEVEN

**At 55, Steven Deeks** is definitely a Big Man On Campus at San Francisco General Hospital, where he's been prowling the halls since 1990. His resume is a hefty 77 pages, chock-full of accomplishments and publications in the HIV field. So it's a bit surprising to find him sitting inside a rather small, minimalist office at Ward 86 on a March morning, not a fancy director's one. It's got a small desk, basic chair, his laptop, some filing cabinet space—not much more. It's devoid of many personal touches, or many framed certificates that his illustrious career might warrant. That's exactly how Deeks would like it, it seems.

Sure, he's a big guy in the HIV world, but he's a regular Joe, a bit shy in person, and friendly, quite curious about others. He actively seeks the media spotlight not for himself per se; rather, for his work, his projects, his patients, and his current HIV goal—working toward a cure. While he's known as a talented and innovative researcher, a brilliant solo act on his own, Deeks likes to shine as a team player, hub, cheerleader, and co-captain of the big ship SCOPE at Ward 86.

"I like collaborating with others; that's where I find the

PHOTO: JUNO ROSENHAUS

# DEEKS, MD

magic," Deeks admits. "The more brains, the better," he adds, smiling. He likes to be surrounded, likes bouncing ideas off others, likes "the concept of Team Science," as he puts it. "I've never been a person who liked to build empires or just did the same thing over and over again," Deeks explains. "I prefer to build a program that is quite plastic and can change direction very quickly to find those opportunities."

He might also be talking about himself: a bright self-starter who learned to overcome early challenges in his family life, one who's learned to prize flexibility and the ability to take lessons from the hard knocks, and most of all, to stay the course while strategically tacking. Right now, he's bringing that approach to his biggest career challenge yet: the planned HIV remission trial others jokingly nickname "Jaws," it's so ambitious.

"I think the values that have dominated my career trajectory have been this drive—this work ethic—and the sense that anything you wanted to do you had to go and get; nothing was going to be handed to you," explains Deeks, when asked to look back on his career path. He learned personal drive from his parents and the chronic adversity his family faced, along with two other family values: loyalty and honesty. "There was no tolerance for dishonesty in our household," he recalls. "And the thing I grew to admire about my parents was loyalty to the family, despite all this chaos and all this drama—there was never any question of loyalty to the kids." He has one younger brother.

Today, that drive and his loyalty apply to his work with the SCOPE cohort, his longtime professional home and family. Here, he's a dedicated mentor and teacher to younger staff, and a trusted, beloved physician to patients. "It's all a group effort," he says of his team. "We have a lot of great people here."

Deeks was born in Trenton, New Jersey, a city that takes pride in its manufacturing, working-class roots. A sign has long dangled under a bridge over the Delaware River, welcoming visitors: "Trenton Makes, The World Takes," it declares. Deeks didn't stay there long; his family moved south to Fort Dix, where he grew up in a trailer park. He's open about how poor his family was for years and his father's chronic battles with alcohol dependency. Today, Deeks is known as a compassionate doctor, one sensitive to the needs of clients living on the social and economic margins.

"It was a challenging time," he says candidly of his childhood. "We bounced around a fair amount at one point in time." But he wants to correct any sense of deprivation: "Although I think my parents struggled, I had a loving family," he stresses. "We had all we needed and we went to public schools."

His father was a baker —"an extremely bright, very charismatic, hard-working guy," he notes. His mother is a nurse; he may have gotten his compassionate streak from her. In the family, things went south when his father's house burnt down. The elder Deeks reinvented himself as an AT&T salesman in Southern California, one good at his job.

By then Deeks had found his refuge in school, where he overcame a budding reputation as a third grade troublemaker to become a steady A student, usually the top of his class. "I was pretty into the math and sciences," he says. After high school, he went to the University of California at Berkeley to study pre-med, a tough program where he thrived. He arrived at San Francisco General for his first residency in internal medicine in 1990. By then AIDS had reshaped the city and the hospital; it quickly reshaped his life, too. Along the way, Deeks also became a cross-country runner, and likes to bike.

He enjoys solving problems—and wants to relieve suffering. "What I like to do is identify two major disciplines and insert myself at the barrier of those disciplines, because that is where all the chaos and drama and innovation occurs," he explains. He likes the idea of out of the box thinking. But he's no cowboy, he insists. He believes in scientific rigor. His fondness for collaboration and "translational research" have shaped SCOPE and its expanding cure program.

"A true cohort is when you identify certain individuals and you enroll them in a study and follow them all the time," Deeks says of the long-running SCOPE HIV observational study. "We didn't do that," he states. "We didn't necessarily want to give people what we thought they needed, but we gave them what they wanted," he explains. With SCOPE, he says, "We began to realize there was all this wealth of data that had been generated, which is actionable. **We began to work with our colleagues to take their ideas into the clinic.**" Here, what's actionable is finding the right question to ask, then designing the experiment so it can be tested in a lab before trying it in his patients.

Deeks was among the first to help push HIV cure research forward and he continues to believe it's a worthy goal. After all, we have a living example, the Berlin Patient. But he's focused on remission as the next actionable step and is applying new insights from immunotherapy cancer studies. "There are all these new studies where, if you tickle these particular [immune] pathways, the host response is improved, both for chronic infection and malignant cells," Deeks explains.

While no one can predict if the trial will produce a hoped-for breakthrough of remission, Deeks views it as a win-win either way. "We're going to learn a lot in doing the study that will help us advance our understanding of the reservoir," he says, summing up. "I wouldn't be here, doing what I do, if I didn't believe we have a chance of achieving remission. Whatever happens here, we're poised to make some real strides." —**ACD**


THE MAPMAKER

# SATISH PILLAI

**Satish Pillai almost missed his calling** in HIV science, and still feels drawn to a second, deep love—music, with a third passion, math, just behind. At 44, he's a self-professed geek, born in Boston, retaining fond memories of having been a young hippie kid in high school who followed the Grateful Dead around before moving on to hardcore punk and later, fusion blues. It may seem an odd route to HIV cure research, but for Pillai, music's the ticket: "It's a controlled experiment," he explains, only half joking. "When I'm playing a lot of music I think a lot more clearly; I'm more energized and directed scientifically."

He also loves collaborating and riffing ideas with others, something he does playing jazz, and now, as part of a big stakeholder group planning the SCOPE remission trial. Lately, he's been delving into the cancer world, borrowing ideas from oncologists battling tumors. "I would say the genetic analysis of cancer can be directly applied to HIV," he says. "When I think of the HIV cure field, I think the cancer immunotherapy world is really being swallowed into the HIV cure field."

Pillai credits his Indian-American family for his path to the lab. "Both of my parents were kind of nerds," he says right off the bat. "My mother is a math geek and my dad is a clinical biochemist." Pillai worked in his father's lab in the summer. "That's where I cut my teeth in terms of being in a lab," he explains. He has one sibling, and is married, with two children.

While the cure field has advanced in recent years, Pillai feels we're still standing in a new doorway. His job in the SCOPE trial is to test new strategies to map and target the reservoir. "One thing we hope to achieve is to get more information on the pockets of where HIV actually resides," he explains. That's where things remain challenging. "We don't understand clearance in the reservoirs—it's that simple," Pillai states, mincing no words. "I've heard people say things to the contrary that I find concerning, but to me we are still in the trenches. It's very early days, and we are not in the technological or scaling up era."

Right now, he's eyeing the first rungs of the ladder to advance our knowledge. **"The most basic question that we need to answer to cure HIV is, 'How do you kill cells infected with HIV?' And we do not know,"** says Pillai, adding quickly, "I mean, we are starting to get more and more clues about how cells that are infected die and how we push them in that direction, and they can die a little quicker, but we barely know anything about the process."

Despite the gaps, he's confident we're on the right path—*jazzed* might be a better word for a fusion blues guy. "I'm actually very optimistic that we will see some evidence of spontaneous control after the rebound period," he says of the coming SCOPE trial. "I'm really crossing my fingers." —**ACD**

PHOTO: JUNO ROSENHAUS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THE COMMUNITY WATCHDOG

# LYNDA DEE

**It's hard to miss Lynda Dee** at an HIV conference: her unique voice will guide you like a GPS tracker. She's the first to admit she's got a big personality and talks like a brash Italian New Yorker, though she hails from East Baltimore—land of John Waters and ultimate diva Divine. Her voice is often being directed at researchers, or Big Pharma corporate reps, or fellow HIV activists as she lets loose about her concerns related to HIV research. She's a spitfire, always has been, and clinical trial activism has proved an ideal battleground for her lifelong desire to, as she often puts it, make things right for her people. These days, her people include those who will be recruited to join the planned remission trial at SCOPE.

Dee now serves as a co-chair for the Community Advisory Board of the amfAR Institute for HIV Cure Research at UCSF, sponsor of the planned remission trial (see main story). By now, she's been on dozens of CABs since her start in AIDS activism in the late '80s. She's OG—a member of a vanguard of community activists who began pushing their way into drug company, government, and scientific meetings, demanding a seat at the table to help shape the HIV research agenda.

"I was an activist my whole life, from the Vietnam War," Dee says, reflecting on her watchdog journey. "I was a recovering heroin addict, but still a real party girl when I met all of my gay friends," Dee admits, a blunt truth-teller. "They took me away from the mean heroin streets. They really saved me and took care of me; I mean they probably kept me from dying and I mean that literally. I loved those boys and thought they would always be with me," she adds.

"I started college and later law school and became a criminal lawyer because I wanted to be a Fourth Amendment girl, you know, and get everybody off the hook from lying cops," she jokes. Turns out her skills have been very useful to the HIV movement.

Dee, who is heterosexual, fell into hell and heaven at the same time. She partied up and down the east coast with her gay friends and eventually moved to New York. Soon she watched helplessly as many of her friends fell sick and died of "the most horrible diseases you can ever imagine," she says.

Her grief—and fury about government inaction around the lack of lifesaving drugs—pushed her into trials activism. "**I figured if they can put a man on the moon, if they spent enough money on this [HIV], there was no reason we couldn't beat this.** I'm a big control freak, so I figured I could be very helpful in pushing our way in and being able to change things," she explains. "I had even more motivation to be involved in the fight against AIDS when my husband was diagnosed with AIDS in 1986. He died from AIDS complications in 1987."

Dee attributes being the screamer she is today to her parents. "My family was nuts," she says, smiling. "My mother's from Italy; she is exactly where I get my fight from: she's fierce and makes me look touchy-feely." She joined her first CAB at the Johns Hopkins AIDS Service and has been involved in many advisory bodies in the years since. An activist pal, Jeff Sheehy, invited her to join the amfAR Institute for HIV Cure Research. She brought along Jeff Taylor when Sheehy had to drop out.

From there, she's made it a personal mission to diversify the group, well aware of the historic underrepresentation of women and communities of color in HIV clinical trials. "It's important for me to get some diverse people on, because I feel we've made so many mistakes in the past. We have a chance to do it right now." That includes outreach to HIV-positive women's groups and trans communities. She organizes one CAB business call a month, alternating with a scientific webinar for newer members to get up to speed on cure science. Once a month, she also organizes an HIV education session in Baltimore for community groups and has invited cure scientists to discuss the pipeline.

"They were enthralled," says Dee of the community audience. "They're all African Americans, MSM [men who have sex with men], and transgender women. They were so into it." She hopes a planned forum for positive women in Oakland in May will spur local interest in joining new cure trials and CABs too.

Looking ahead, she's closely eyeing the trial's safety issues, but admits to feeling hopeful, too. "I think we might have some long-term remissions; I hope we can get to that point," she says. —**ACD & RJ**


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