EXECUTIVE SUMMARY

A cure for HIV will be essential to ending the AIDS pandemic, but science that is focused directly on a cure is still in early stages and will likely require the support of multiple stakeholders to proceed at the fastest pace. A day before the opening of the 19th Conference on Retroviruses and Opportunistic Infections (CROI), held in Seattle from March 5 through 8, 2012, 58 participants—including representatives from the U.S. Food and Drug Administration (FDA), members from the International AIDS Society (IAS), as well as academic and industry researchers and activists from the United States and Europe—viewed presentations by leading HIV researchers and companies working on HIV cure research. The goal of the meeting was to describe the current state of cure research and identify barriers to moving such research forward swiftly and smoothly.

In the past four years, we have seen signs of increasing scientific momentum and funding directed toward curing HIV infection. The remarkable case of “Berlin Patient” Timothy Brown—a man who all signs suggest has been cured of HIV—has catalyzed and expanded what was once a small and somewhat fragmented effort to understand how HIV persists despite effective antiretroviral (ARV) therapy and to explore mechanisms to eliminate the hidden pool of virus in people on ARV treatment (a sterilizing cure) or to enable the immune system to control HIV without the need for ARVs (a functional cure). This momentum has been greatly enhanced by the NIH-funded Martin Delaney Collaboratory projects, partnerships between academia and industry focused on the possibility of discovering and developing a safe, effective, feasible, and scalable HIV cure.

Among recent signs of progress, researchers have contributed new insights into where and why HIV persists despite potent ARV therapy. Ultrasensitive tests can detect the virus at the level of a single copy of RNA. Such tests will be central to testing theories and treatments aimed at viral eradication. The first controlled trials of drugs to activate latent cells, such as histone deacetylase (HDAC) inhibitors, are yielding promising signals, and other types of treatments designed to teach the immune system to either clear or control the virus on its own have been initiated. Despite significant progress, key questions remain unanswered:

- In what types of cells and anatomic compartments does HIV persist and what are the best methods for measuring the latent virus in these reservoirs?
- How is the virus able to replenish these reservoirs during fully suppressive ARV therapy?
• Is modern ARV therapy actually fully suppressing viral replication?
• What is the role of the immune system in HIV persistence?
• What forms of immunologic HIV control can we enhance safely?
• What are “reasonable” risks for the HIV-positive individuals who will be participating in early and potentially dangerous cure studies and how can we best protect those individuals?

To address these questions, three HIV research advocacy organizations—the AIDS Treatment Activists Coalition (ATAC), Project Inform and the Treatment Action Group (TAG)—asked a handful of leading industry and academic researchers to describe their current projects, to outline the obstacles and facilitators to cure research and to offer suggestions for the kinds of activities that community advocates might undertake to overcome current obstacles. We have provided herein brief synopses of each presentation followed by an outline of areas identified by the workshop speakers and participants for further exploration, development and incorporation into a cure advocacy agenda.
The AIDS Clinical Trials Group (ACTG): Clinical Trial Development

Dan Kuritzkes, MD, ACTG Principal Investigator, and Chair, ACTG Executive Committee, provided an overview of ACTG cure-oriented research. The ACTG has formed a Cure Transformational Science Group, which is guided by researchers inside and outside the ACTG network. Kuritzkes framed important questions for the field and for future ACTG studies:

- Can reservoirs be identified and measured?
- Can the residual virus production below the limit of detection by routine clinical assays be suppressed by intensification of ARVs?
- Do latent reservoirs decay?
- Can strategies that activate latent cells reduce the reservoir?
- Can a combined approach using different interventions lead to control of viral replication without ARV drugs?

ACTG has ongoing cohort studies of low viral replication during ARV therapy and decay of HIV reservoirs in different patient groups as well as several studies examining viral dynamics under different therapeutic interventions, including optimized ARVs, Anti-PD1-Antibody and HDAC inhibitors. Kuritzkes noted that because proving eradication or immune control will necessitate individuals going off treatment for a set time (called analytical treatment interruptions or ATIs), we must define when and how to proceed with ATIs in the safest manner. The risk/benefit balance is not always clear, since all new cure therapies must compete with the well-established efficacy of current ART, which is generally well tolerated and harbors usually only minor or infrequent risks of adverse events.

Testing New Compounds

Romas Geleziunas, PhD, Director of Clinical Virology at Gilead Sciences, gave an overview of Gilead’s research focusing on the activation of HIV gene expression in latently infected cells. Getting latently infected cells to express their HIV genes is a first critical step toward eradication. Geleziunas said that the mechanism of HIV latency still needs to be understood more fully and new drugs need to be discovered that play a role in or that can interfere with this process.

Gilead is looking at several approaches including HDAC inhibitors and immune modulators. Gilead has indentified three HDAC inhibitors from its collection that activate latent HIV and has also screened nearly 500,000 compounds in search of novel chemical classes that activate expression of latent HIV. Some of these compounds are broad inhibitors of cellular kinases and the company is interested in better understanding how these compounds activate HIV. Gilead also has a toll-like receptor (TLR)-7 agonist in clinical testing in patients with HBV infection and it is interested in determining whether
such compounds can also contribute to eliminating infected cells expressing re-activated HIV.

Gilead, along with Merck, has been one of the most openly collaborative companies with academia in its cure research endeavors.

**Gene Therapy**

Dale Ando, MD, Vice President of Therapeutic Development and Chief Medical Officer at Sangamo BioSciences, presented the company’s approach to knocking out the CCR5-receptor gene with a technology called zinc finger nucleases (ZFNs). ZFNs can be used to render CD4 cells and stem cells immune to infection by most strains of HIV (either by targeting the CD4 cells directly or modifying the stem cells that give rise to them). Trials using ZFN-manipulated CD4 cells have been encouraging. These cells persist, though at relatively low levels. It appears that one patient who naturally carried a mutation making his own CD4s less able to produce functional CCR5 co-receptors might have, after ZFN treatment, gained the ability to control HIV without ARV therapy. Further trials of the technology are proceeding while the company seeks new methods to streamline and lower the cost of modifying cells.

**Therapeutic Vaccines**

Researchers in the laboratory of Robert Siliciano, MD, PhD, at Johns Hopkins University, published a paper that coincided with the cure workshop indicating that therapeutic vaccines may be a necessary component of a successful eradication strategy. This paper made a presentation by Vidar Wendel-Hansen, PhD, Chief Medical Officer from Bionor Pharma ASA, very timely on his company’s therapeutic vaccine approach targeting the virus’s p24 protein.

In the company’s therapeutic vaccine studies four primary and two booster immunizations of the Vacc-4x p24 vaccine together with granulocyte macrophage colony stimulating factor (GM-CSF) resulted in sustained immune responses to p24, and in a subset of patients lowered the viral set point (0.44 log compared to the placebo group) during a carefully monitored treatment interruption. Bionor is going to explore combining Vacc-4x with the immune modulator lenalidomide or a new product, dubbed Vacc-C5, which stimulates antibodies to the C5 region of the gp120 portion of HIV’s envelope proteins. Wendel-Hansen indicated that the primary rate-limiting factor to therapeutic vaccine research is lack of funding for sustained discovery programs and larger scale clinical trials and that all biotechnology companies struggle with this hurdle.

**Stem Cell Research After the Berlin Patient**

John Zaia, MD, from Beckmann Research Institute at City of Hope, gave an overview of the state of stem cell research. He noted that it is not entirely clear which factors were most important in clearing the virus in Timothy Brown, the Berlin patient who has apparently cleared HIV. Though Brown was given HIV-resistant stem cells on two occasions, he also endured other procedures and conditions that likely contributed to viral
clearance. These included two rounds of intensive chemotherapy to wipe out most of his existing immune system as well as the fact that Brown’s new donor stem cells resulted in a graft-vs-host process, which likely ensured that any remaining cells capable of being infected with HIV were eliminated.

Zaia noted that the scarcity of available HIV-resistant stem cell donors, along with other factors mean it could be 20 to 25 years before stem cells can be used to cure HIV. Thus, it is very important not to oversell this approach. There has been no second Berlin Patient because of difficulty in finding a matching allogeneic donor with a CCR5 deletion. Zaia is working on a new hypothesis using stored cord blood donations, which may prove easier than relying on stem cell banks. He is also actively engaged in collaborations with other researchers to look at methods, such as Sangamo’s ZFN technology, to manipulate a person’s own stem cells.

**Improving Immune Responses**

Pablo Tebas, MD, University of Pennsylvania, gave an overview of his work to enhance the ability of CD8 killer T cells to recognize and destroy HIV-infected T cells. A study is moving forward to test the ability of the immune systems of those with the modified NK cells to control the virus in the absence of ARV therapy. These studies will include a 16-week treatment interruption.

Tebas also reported on the HIV-fighting potential of an existing broad spectrum antiviral chemokine called interferon alpha. A pegylated version of interferon alpha is currently part of the standard of care regimen against hepatitis C virus (HCV). Tebas reported on a study where people with HIV on ARVs also took pegylated interferon for five weeks, then stopped their ARVs but continued on just interferon. In this study, 45 percent of patients (9 out of 20) were able to maintain a viral load under 400 copies for the 24 weeks they remained off ARVs. These data were presented the following week at CROI (www.retroconference.org/2012b/Abstracts/43948.htm).

**Assessing Community Tolerance for Risk**

Early proof-of-concept studies of new cure-oriented interventions have a very low likelihood of producing lasting benefit for the HIV-positive men and women who volunteer for them, yet may subject those men and women to significant and unknown risks. Central to discussions of the ethical considerations regarding this type of research is the willingness of individuals to participate for purely altruistic reasons and our ability to understand people’s motivation to engage in the research process.

David Evans, the Director of Research Advocacy for Project Inform, and Houston activist Nelson Vergel presented data from a 2,100 person online survey to help understand the risk tolerance of potential HIV-positive study participants. Though the online nature of the survey made it difficult to be certain that the respondents fully understood the risk being described, greater than 40 percent stated they would be willing
or very willing to participate in studies that would confer a low chance of personal benefit and present the possibility of at least a moderate chance of harm, provided that the study would advance the field of cure research. The survey also found that older participants, those less knowledgeable about HIV, those with higher incomes and those with higher CD4s were less likely to participate.

The ability of social media to identify such a large pool of potential study participants in such a short period of time is also significant. It speaks to the ability of such methods to assist in accruing patients for future cure research studies.

**Martin Delaney Collaboratory Projects**

Steven Deeks, MD, University of California in San Francisco, started the presentation of the three collaboratory projects by saying that research needs to have real clinical meaning to patients. Martin Delaney—a founder of the HIV activist movement who died in 2009, and the person after whom the who the National Institutes of Health (NIH) collaboratory project is named—was a strong proponent of translational research and a tireless advocate for the possibility of a cure for HIV.

Deeks provided additional insight into the mechanisms of viral persistence of HIV. He described these mechanisms in further detail and also provided ideas about how to overcome them, e.g. antibodies against PD1 to reverse latency. PD1 might be the best correlate of the size of the HIV reservoir. Deeks also recounted that one of the key areas of research integration within the three collaboratory projects is in characterizing the HIV reservoirs. Nevertheless, consensus on how to measure reservoirs remains an important question that has yet to be fully answered.

Keith Jerome, MD, PhD, and Hans-Peter Kiem, MD, from the Fred Hutchinson Cancer Center in Seattle next described their efforts to eliminate existing HIV reservoirs, which also uses ZFNs. In one approach, ZFNs will be used to disrupt the CCR5 gene in stem cells, allowing the immune system to regenerate with HIV-resistant cells. Another method uses homing endonucleases that recognize HIV-specific areas in the human genome and cuts the DNA at these sites. The cuts will be recognized by the cell’s repair system causing gaps within the HIV’s DNA. This leads to nonsense viral sequences that don’t produce active HIV virus anymore. Their work was presented the following week at CROI (www.retroconference.org/2012b/Abstracts/45100.htm)

David Margolis, MD, from the University of North Carolina in Chapel Hill, provided some thoughts on obstacles for cure research. In his view, the most important factor in community advocacy should not simply request more funding, but to compel academic and industry leaders to take risks, insist upon greater collaboration between stakeholders and respectfully push against the limitations of the system. He challenged the group with the notion that whether the cure is sterilizing or functional may not be the real question at this time. Resulting cure research with simply must be better than what we currently have at our disposal. Margolis also presented his successful work to reactivate the latent HIV reservoir with the HDAC inhibitor vorinostat at CROI (www.retroconference.org/2012b/Abstracts/45315.htm).
DISCUSSION

The prevailing view of all the speakers was that we must not raise premature and unrealistic hopes of a cure for HIV either in people who volunteer their bodies for cure research, or in the wider community of people with HIV and their allies. Critical early steps have been identified, but we need many more successes in analytics, basic science and translational research—in both animals and people—before the cure will be within our grasp. Nevertheless, the following themes became clear throughout the day-long series of presentations that may be fertile ground for community advocacy strategies.

**Funding:** We need to ascertain how much money globally is being allocated to cure research. While the NIH is coding research as HIV cure research, we have not fully elucidated the current NIH investment. Significantly more funding will be needed to make a cure a reality. That said, cure research will likely take many years, sustaining multiple failures and dead ends. Thus, it is abundantly clear to many experts that current funding levels are not sufficient to move both basic and translational projects forward at an optimal pace.

It is also clear that there is insufficient funding for either academic or industry projects that will help build the infrastructure of people, labs and concepts necessary to maintain progress beyond the typical two- to three-year investments of standard research funding cycles. As one researcher mentioned, the road to success is often long and littered with failure and it is often stamina as much as brilliance that achieves victory. We need funding that rewards stamina in cure research, not just easy wins. This is especially true for small biotech companies with promising technologies.

**Monkey Models:** We have made much progress in our efforts to breed mice with human immune systems, but we have yet to develop an animal model that perfectly replicates the course of HIV infection in humans. Primate models using various strains of simian immunodeficiency virus (SIV) have made great strides, but still fall short, especially when trying to test theories and therapies related to HIV latency. More resources are desperately needed in this area of high cost, but also of exceptionally high potential. Obtaining ARV treatments for monkey studies was also flagged as a potential problem: some manufacturers are consistently cooperative and happy to provide free supplies for this research, while others have been reluctant.

**Tests to Assess Latency and Reservoirs:** Currently, researchers are relying on several methods to assess whether reservoirs of latently infected T cells have been perturbed and if so, by how much. Establishing a standard model, or set of accepted assays, will be critical to evaluating early intervention studies. As one advocate commented at a session devoted to cure research at CROI, “If we are going to ask people to put their bodies on the line for cure research purely for altruistic purposes, we must ensure that those studies are designed to answer key scientific questions in an acceptable manner.”
Risk vs. Benefit: Some cure research may be quite risky, with little chance of benefit for the people who are putting their bodies and lives on the line as guinea pigs. How much risk is too much? Where should we draw the line? How can we ensure that when people volunteer for studies they really understand the potential risks and consequences? It is unethical for us to move forward with vital early stage human studies without satisfactory answers to these questions. Developing guidelines for determining when potentially risky treatment interruptions are appropriate is a critical next step. Such guidelines require not only scientific rationales and justifications, but also community input. A community advisory board for the Martin Delany Collaboratory projects was suggested as essential in ensuring ethical, patient-oriented studies.

Coordination: Many currently feel that cure-oriented research, particularly related research being conducted in other fields outside HIV, is uncoordinated and fragmented. This hinders our ability to move forward as quickly as possible. In recent months, a number of important initial collaborations among various academic and industry partners has emerged. Moreover, both academic and industry researchers expressed a profound willingness to come together both to attend this meeting and future research projects. That said, we have heard in previous years that coordination that is too centralized and too focused could hinder more innovative approaches and become overly bureaucratic. What is the appropriate level of collaboration and coordination for cure research, and how can community advocacy influence this process?
Moisés Agosto-Rosario, NMAC
Dale Ando, Sangamo BioSciences
Michael Arnold, Legacy Project
Jeffrey Bartlett, Calimmune
Jeanne Bergman, IAVI, ATAC
Jeff Berry, TPAN, ATAC
Wilson Bryan, FDA, CBER
Gus Cairns, EATG
Rob Camp, ATAC
Maria Carroll, Calimmune
Lei Chou, TAG
Simon Collins, i-Base, EATG
Giulio Maria Corbelli, ECAB
Ray Corrin, Health Canada
Lynda Dee, AAB, ATAC
Steve Deeks, UCSF
Michael Dorosh, ATAC, ACTG CSS
David Evans, PI, ATAC
Kevin Fisher, AVAC, ATAC
Romas Geleziunas, Gilead Sciences
Dennis Grasela, Bristol-Myers Squibb
George Hanna, Bristol-Myers Squibb
David Haerry, EATG
Changting Haudenschild, Medical Team Leader, CBER
Ying Huang, FDA, CBER
Mark Hubbard, Tennessee Association of People With AIDS
Damon Humes, Legacy Project
Richard Jefferys, TAG
Keith Jerome, Fred Hutchinson Cancer Research Center
Bernard Kadasia, IAS
Hans-Peter Kiem, Fred Hutchinson Cancer Research Center
Dan Kuritzkes, ACTG
Jay Lalezari, Quest Medical
Stephen LeBlanc, AIDS Policy Project
Jules Levin, NATAP
Kendall Marcus, FDA, CDER
David Margolis, University of North Carolina
Veronica Miller, Forum for Collaborative HIV Research
Bob Munk, AIDSInfonet
Jeff Murray, FDA, CDER
Heidi Nass, ATAC
Geoff Nichol, Sangamo BioSciences
Marie-Capucine Penicaud, IAS
Matt Sharp, ATAC
Jeff Schouten, HANC
Jeff Sheehy, CIRM governing board member
Birger Sorenson, Bionor Pharma
Siegfried Schwarze, EATG
Winson Tang, Sangamo BioSciences
Jeff Taylor, ATAC
Pablo Tebas, University of Pennsylvania
Nelson Vergel, PoWeR, ATAC
Alain Volny Anne, ECAB
Vidar Wendel-Hansen, Bionor Pharma
Celia Whitten, FDA, CBER
Wakefield, Steven HVTN, Legacy Project
Shelley Wang, Sangamo BioSciences
John Zaia, City of Hope