HIV CURE-RELATED CLINICAL RESEARCH WORKSHOP

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accelerate decay • activation agents • allogeneic bone marrow transplantation • analytic treatment interruption anatomical compartments • animal models • art intensification • astrocytes • baboon bone-marrow xenotransplant bcl-2-transduced cell model • benefit/risk balance • biobanks • blood cell ablation • ccr5-delta-32 coreceptor cd3 antibody • cd4 reservoirs • cell exhaustion • central nervous system tissues • chemotherapy • culture assays dendritic cells • disulfiram • dna 2-long terminal repeat circles • equipoise • eradication • first-in-class functional cure • gene expression • gene therapy • genital tissues • graft-vs.-host disease • gut biopsies hematopoietic stem cells • high-throughput cell-based assays • histone deacetylase inhibitors • hiv-rad 5 vaccine homeostatic proliferation • host-cell transcription factors • humanized mice • immune activation • immune boosting immunosenescence • inflammatory markers • informed consent • inhibitory quotient • institutional review boards intellectual property • interleukin-2 • interleukin-7 • latent reservoirs • low-level blips • lymphoid tissues macrophages • modified cd4 t-cells • monoclonal antibodies • monocytes • nonhuman primate models pd-1 expression • pedigreed samples • peripheral blood • persistent viremia • phytohaemagglutinin activation prioritized cell models • progenitor cells • proliferation • proof-of-concept • proprietary compounds purging reservoirs • quality assurance parameters • real-time reverse transcriptase-initiated pcr assay regulatory roadblocks • relevant endpoints • replication competence • reservoir depletion • residual virus resting cd4 cells • single-copy plasma assays • siv/macaque system • small molecules stem cell engraftment • stochastic variation • suberoylanilide hydroxamic acid • surrogate marker therapeutic vaccine • tissue assays • trafficking • tropism switching • unintegrated dna • validate preclinical models valproic acid • viral replication • viral suppression • vorinostat • zinc finger nuclease • zoonotic pathogens

HIV **CURE**-RELATED CLINICAL RESEARCH WORKSHOP

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Baltimore, MD

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AIDS Policy Project

amfAR 25 yrs MAKING AIDS HISTORY

PROJECT INFORM

TAG Treatment Action Group

EXECUTIVE SUMMARY

A cure for HIV will be an essential part of ending the pandemic.

In the past three years, increasing scientific momentum has been evident in research aimed at curing HIV infection (Lehrman 2005; Richman 2009; Trono 2010; Palmer 2011). The remarkable case of "Berlin Patient" Timothy Brown—an HIV-positive American diagnosed with leukemia who appears to have been cured of HIV infection (Hütter 2009; Allers 2011; Hütter 2011)—has contributed to reinvigorating the scientific community to investigate the possibility of discovering and developing a safe, effective, feasible, and scalable HIV cure (Lewin 2011a, 2011b).

Among the signs of progress, researchers have contributed new insights into where and why HIV persists in the body even when powerful antiretroviral therapy has all but shut it down. Ultrasensitive tests can detect the virus at the level of a single copy of RNA. The first controlled trials of a class of drugs called histone deacetylase (HDAC) inhibitors that may roust HIV from its hiding places are underway, and other types of treatments designed to teach the immune system to either clear or control the virus on its own have been initiated. The National Institutes of Health (NIH) is now funding cure-related research specifically through three consortia funded by grants named after long-time AIDS activist Martin Delaney.

Now that a cure has been proved to be possible, the challenge has moved from encouraging researchers to take up cure-oriented studies to figuring out how to design and conduct those studies. What's more, given that such trials are likely to confer risks to the HIV-positive people who participate in them, researchers, regulators, and activists must come together to ensure not only that participants are kept safe, but also that research can move forward quickly and confidently, even if the first trials do not produce positive results.

To address these objectives, four HIV research advocacy organizations—the AIDS Policy Project, the Foundation for AIDS Research (amfAR), Project Inform, and the Treatment Action Group (TAG)—convened a meeting in April 2011 bringing together academic researchers, government scientists, regulators, and community advocates to discuss the state of the field and to identify action steps that can be taken to both sustain and hasten the progress of cure-related research.

Some critical questions remain unanswered:

- If HIV eradication is the goal, how can this be proved when the best currently available tests may still miss the tiny residual amount of the virus that can bring the infection roaring back to life when antiretroviral drugs are withdrawn?

- If treatment interruptions are necessary, how can they be conducted safely in research participants when prevailing data suggest that even relatively short treatment interruptions can be harmful for some?

- If immune control of the virus is the objective, what kinds of changes in the immune system and inflammatory markers will tell us we are on the right track? and

- If early trials require participants to take greater risks with little hope of gain, how can we ensure that studies are ethical and guarantee that those taking the risks are fully informed?

The four conference organizers have issued a report laying out the latest thinking on these core questions, the key obstacles in front of us, and a series of next steps proposed by conference attendees to address those challenges.

The work ahead will require new resources and new levels of cooperation and collaboration—among scientists, and among researchers, government agencies, activists, and people with HIV. Workshop cosponsors and participants have all committed to transforming the ideas generated at the conference from words on paper into concrete actions.

INTRODUCTION

A cure for HIV has become a subject of intensive interest in recent years.

Antiretroviral therapy (ART) has dramatically reduced morbidity and extended survival, but people with HIV still do not have a normal life expectancy and are prone to long-term drug toxicities and the ravages of persistent immune activation and inflammation (Deeks 2011).

The remarkable case of the Berlin Patient—a man who has no evidence of residual HIV four years after undergoing two bone marrow transplants from a CCR5-delta-32 homozygous donor—offers proof-of-concept that rendering immune cells resistant to infection might achieve at least a functional if not a sterilizing cure (Allers 2011).

A variety of approaches are under study as potential cures for HIV, including zinc finger nuclease gene therapy to alter CD4 T-cells or hematopoietic stem cells, immune-based therapies, and agents that interfere with HIV latency to flush the virus out of resting memory CD4 cells and other cellular and anatomic reservoirs.

A number of barriers prevent this research from moving forward as rapidly as scientists and advocates think is necessary. These include scientific questions about how to measure the size of the latently infected reservoir and monitor its response to therapy, clinical trial design issues, and concerns about how to proceed with ethical clinical trials of potentially risky therapies that also offer the prospect of high reward, especially in people who are doing well on current antiretroviral treatment.

On 20–21 April, 2011, more than 50 leading public- and private sector HIV researchers, AIDS treatment advocates, and U.S. government officials convened in Baltimore, Maryland, to discuss challenges in the area of HIV cure-related research and strategies to overcome them.

The meeting, sponsored by the AIDS Policy Project, amfAR, Project Inform, and TAG, featured an overview of HIV latency, persistence, and eradication research; lessons from past clinical trials; a review of current or impending trials; and a full discussion of issues including trial design, appropriate markers and endpoints, and development of better assays.

Participants heard a presentation on the ethics of clinical trials and discussed the federal regulatory process and how best to engage the several branches of the U.S. Food and Drug Administration (FDA)—including the Antiviral Division in the Center for Drug Evaluation and Research (CDER), as well as the cellular and gene therapy, tissue, vaccine, and transplant divisions in the Center for Biologics Evaluation and Research (CBER)—in a coordinated and collaborative way to work together to ensure that cure-related clinical trials proceed expeditiously, ethically, and safely.

"This is a critical time in the epidemic when it's really possible that in next ten years we may have a cure," said TAG's Mark Harrington. "We are either at end of the first 30 years of a 50-year struggle, or we're at the beginning of an endless pandemic that we will never be able to solve."

Daria Hazuda from Merck presented an overview of mechanisms of HIV persistence. Robert Siliciano's group at Johns Hopkins and others have shown that the virus is able to maintain latency in long-lived resting CD4 T-cells and possibly in other types of immune cells (Wong 1997; Finzi 1997; Chun 1997).

While this cellular reservoir decays slowly over many years, it has never been fully eliminated, leading to the supposition that HIV infection may be incurable, at least via combination antiretroviral therapy alone. Later research indicated that latent reservoirs are continually replenished, at least in part, when latently infected resting CD4 T-cells intermittently divide in a self-renewal process referred to as homeostatic proliferation (Chomont 2009). Development of single-copy assays for the detection of very low levels of HIV RNA revealed persistent viremia even in patients on the most potent antiretroviral drugs (Palmer 2003; Palmer 2008).

ART intensification with raltegravir and other newer antiretroviral agents does not eliminate persistent low-level plasma viremia that is below the limit of detection of commercially available assays (<50 copies/mL) but can be picked up using ultrasensitive tests (which can detect as few as 0.1 copies). But Hazuda noted that the story is complicated, given unexplained and inconsistent findings such as unintegrated DNA (2-LTR circles), which, in one raltegravir intensification study, appeared to rise transiently in tandem with a reduction in immune activation (Buzón 2010); ART intensification has also been reported to reduce measures of viral replication and immune activation in the gut (Yukl 2010). And we may not yet fully understand the pharmacology of current antiretroviral agents, especially their distribution and activity in various body compartments.

David Margolis from the University of North Carolina at Chapel Hill and others have shed light on mechanisms that maintain HIV latency and developed methods that may induce latent virus to replicate. Induction of viral replication can be accomplished by directly activating cells that harbor HIV or by disabling mechanisms that keep them inactive. Recent drug discovery research has focused on molecules that trigger HIV gene expression—such as histone deacetylase (HDAC) inhibitors—and agents that alter host-cell transcription factors.

Hazuda concluded that the known mechanisms of HIV persistence are not mutually exclusive and are probably interrelated. This suggests that an effective cure strategy will likely require a multipronged approach, potentially including ART intensification, induction of HIV gene expression, and immune-modulating therapy. (For a later iteration of Hazuda's overview, see Hazuda 2011.)

Tae-Wook Chun from the National Institute of Allergy and Infectious Diseases (NIAID) then discussed lessons from past clinical research including ART add-on intensification, generalized T-cell activation with CD3 antibody and interleukin 2 (IL-2), and early HDAC inhibitors such as valproic acid. These initial exploratory efforts were ultimately stymied by lack of efficacy and, in the case of generalized T-cell activation, severe and life-threatening toxicity (Archin 2010; Kulkosky 2002; Prins 1999).

Chun's group is conducting ongoing research on HIV patients who started potent combination ART during early infection. While some participants have achieved profound viral suppression, none have succeeded in eradicating HIV, which always returns after ART is discontinued (Chun 2010).

Achieving a broad-based cure for HIV "will likely remain a daunting challenge for the foreseeable future," Chun concluded. Even if the viral reservoir is dramatically reduced, it remains to be seen if

a functional cure is feasible because we do not know whether the immune system can maintain viral suppression for a prolonged period. "We may need to think about ways to boost the immune system," he suggested.

CURRENT RESEARCH

A panel of researchers from academia and industry presented an overview of cure-related clinical research and a summary of several studies currently underway, focusing on criteria for advancing novel approaches into human trials.

Gene Therapy

Ellen Feigal from the California Institute of Regenerative Medicine discussed HIV-related research funded by CIRM, which was formed in the wake of a 2004 state ballot initiative to provide $3 million to support stem-cell research.

CIRM is funding a collaborative effort led by John Zaia at the Beckman Research Institute of City of Hope using zinc finger nuclease technology to render hematopoietic stem cells (HSCs) resistant to HIV infection.

Paula Cannon and colleagues at the University of Southern California demonstrated that a zinc finger technique developed by Sangamo BioSciences can disrupt the gene that encodes the CCR5 coreceptor in human HSCs. Altered cells engrafted into humanized mice gave rise to a lineage of immune cells that lack the coreceptor, thereby preventing HIV entry. Mice that received altered HSCs had significantly lower HIV viral load and better CD4 T-cell preservation than did the control mice (Holt 2010).

Zaia's group is testing this procedure in HIV patients who require stem cell transplants to treat lymphoma—an effort to replicate the Berlin Patient phenomenon without the need for naturally resistant donor cells. The first participants will receive a small number of modified cells, and researchers are increasing the percentage as safety is demonstrated.

Zaia explained that high-risk blood cell ablation to "make room" for modified HSCs can be done in patients who require bone marrow transplants due to an immediately life-threatening condition, but it raises ethical issues with HIV-positive people who are doing well on ART.

Carl June from the University of Pennsylvania described ongoing trials using the same zinc finger nuclease technology to modify CD4 T-cells; Jay Lalezari at Quest Clinical Research and Ronald Mitsuyasu at UCLA are conducting parallel trials in California. Altering CD4 cells rather than HSCs may generate fewer modified cells in vivo, but it is also safer and does not require ablation.

As described at the 2011 Conference on Retroviruses and Opportunistic Infections, participants treated with modified CD4 T-cells (SB-728-T) experienced significant and sustained CD4 cell gains lasting up to 18 months so far. Gut biopsies showed that modified T-cells exhibited normal trafficking and proliferation, and their increasing percentage suggests they have a survival advantage over unaltered cells. The procedure is well-tolerated, and there has been no evidence of HIV tropism switching (Lalezari 2011).

The East Coast trial protocol included ART interruption, with the first patient exhibiting delayed viral rebound. Researchers are now enrolling additional participants including ART-naive people, those experiencing virological treatment failure, and those with discordant response. June is also seeking HIV-positive individuals with cancer who require chemotherapy.

Activating Agents

Romas Geleziunas from Gilead Sciences discussed the testing of agents to activate latent HIV in resting cells. We do not yet know how to determine the activity of such agents, or even how to accurately quantify the reservoir. There are currently no standard measures—akin to EC50 or inhibitory quotient for antiretrovirals—to reliably assess the activity of activating agents. There are also unanswered questions about how to select appropriate doses and what constitutes proof of efficacy in animal studies.

Researchers need high-throughput cell-based assays to efficiently test large numbers of candidate compounds. Margolis, Siliciano, and others have developed sensitive assays to evaluate HIV activators in the laboratory, but current tests do not always give consistent results. Nevertheless, screening of compounds using available tests has identified several promising agents for further exploration.

Margolis explained some of the mechanisms of activating latent HIV. HDAC inhibitors—so far the most widely studied agents—work by "derepressing" viral gene expression. Different classes of HDAC inhibitors have varying efficacy against HIV. Valproic acid and vorinostat (SAHA) both demonstrated low-level activity, but researchers are now evaluating related drugs that are more potent and specific.

Compound screening by Siliciano's group revealed that disulfiram (Antabuse, used to manage alcoholism) can reverse HIV latency by a mechanism that is not yet understood (Xing 2011). Steven Deeks from the University of California at San Francisco (UCSF) described a small ongoing proof-of-concept study of disulfiram to accelerate decay of the HIV reservoir in patients on ART.

Most experts predict that a single strategy for curing HIV will not be sufficient. Rob Murphy from Northwestern University presented an overview of the Eramune trials, which will start with ART intensification followed by addition of interleukin-7 or a therapeutic vaccine. A major issue facing the field now is how best to study and evaluate multiple interventions used in combination.

Risk versus Benefit

Disulfiram is an example of a drug that has been available for many years and has no significant safety issues. But research on HDAC inhibitors and other small molecules has run into the same issue as the more intensive gene therapy approach: how much risk is acceptable when studying novel therapies in people who are doing well on ART?

Drug discovery for HIV activators is "really at the very beginning," said Margolis. Our current understanding of the appropriate pharmacokinetic parameters for HIV drugs comes from work on antiretrovirals, and the paradigm may be different when trying to activate latent virus. It may be feasible to use high or even toxic doses for a short period, as is done with cancer chemotherapy. HIV researchers "could use interdisciplinary help" to explore approaches more familiar in other areas, he added.

Deeks posed the question of how to balance the risks and rewards of potentially curative interventions. For example, agents that block PD-1, which contributes to CD4 cell exhaustion, may have the potential to cause inflammatory reactions and other serious side effects—but the benefits in terms of reservoir depletion and enhancement of HIV-specific immune responses could also be substantial.

These types of cure-related studies will require participants who understand that risks may be greater than benefits for an individual, but need to allow for considering global as well as individual benefit, Deeks suggested.

Workshop participants discussed issues of informed consent, compensation, incentives, and the potential for coercion in clinical trials. Study participants may take time off work, travel, and undergo considerable discomfort and inconvenience, so many people think monetary compensation is reasonable. But there was concern that payment might distort consent or even imply coercion, especially for low-income people. Studies involving multiple compensated procedures may provide sums substantial enough to override true equipoise and patient autonomy, potentially making it more difficult for some people to decline participation.

Patient and community education is a key issue. Activist and treatment educator David Evans noted that cure-related research is complex and may be difficult to explain, asking, "Is the current consent process as robust as it needs to be, especially for people with lower health literacy?"

Informed consent documents are long and complicated and few people read them in full. "Consent forms are worse than the fine print on insurance forms," said Douglas Richman from the University of California at San Diego. "Informed consent documents are no longer ethical, they're for the benefit of lawyers."

Research Ethics

Expanding on the same theme, medical ethicist Bernard Lo from UCSF gave a comprehensive presentation on ethical issues surrounding medical research, focusing on three questions:

- What benefit/risk balance is acceptable?
- Who decides what risk is acceptable?
- How should informed and voluntary consent be obtained?

There are precedents for studying high-risk interventions that could lead to a cure, Lo explained. Kidneys transplants, for example, were considered extremely radical in the early 1960s.

In 1995, AIDS activist Jeff Getty underwent a controversial baboon bone marrow transplant on the hypothesis that the baboon's immune cells would be resistant to HIV infection. That case aroused concern not only about risk to Getty himself, but also the possibility of zoonotic pathogens that could endanger others. The transplant was not expected to lead to a cure, but Getty was well-informed about the potential risks and (probable lack of) benefits (Michaels 2004). Lo raised the issue of benefit to the individual versus the wider community, and asked how much risk is acceptable for altruistic reasons. Kidney donors, for example, face considerable risk of discomfort and more serious harm, but the benefit accrues to others.

Federal regulations require that risks must be "reasonable" when weighed against expected benefit to the study subject and knowledge gained, and risk must be minimized to the extent possible. But the U.S. clinical trials process has been influenced by activists, and attitudes have shifted over the years from "unless there are clear benefits, don't do it" to "if it's a toss-up, why not do it?"

Lo emphasized that studies with negative outcomes also provide a benefit by showing that an approach does not work, thus sparing future patients and allowing resources to be devoted to more promising efforts.

Research risks can be minimized by selecting appropriate subjects, planning for unexpected adverse outcomes, and educating prospective participants about drawbacks. People should have access to medical care and basic necessities so they do not feel the need to join a trial to obtain them; however, concerns about coercion should not deprive disadvantaged groups of potentially beneficial therapies.

Discussing this presentation, Stephen LeBlanc of the AIDS Policy Project suggested that researchers should tell people if research is aimed at finding a cure, as this reinforces altruism. But Margolis countered that speaking about a cure "engenders irrational hope."

Lo concluded by emphasizing that individuals have varying attitudes towards risk, underscoring an issue treatment activist Matt Sharp brought up in his introduction to the workshop.

Speaking of his participation in Lalezari's zinc finger gene therapy study, Sharp said, "It won't provide me with a cure, but it significantly increased my T-cells out to six months, which I never imagined I would achieve with ART. I would not be alive today had I not taken risks."

Regulatory Roadblocks?

Researchers may be eager to conduct HIV cure-related studies, and patients may be lining up to join them, but the FDA imposes limitations intended to protect participants. Margolis, for example, has had difficulty getting approval for a trial of vorinostat in people doing well on ART.

Carol Weiss from the FDA's Center for Biologics Evaluation and Research (CBER) said there are "a lot of misconceptions about the way we work," but she had not heard of any major roadblocks from a regulatory point of view at the workshop. "People say 'FDA would never allow that,' but it's not generally true," she added. The agency has allowed treatment interruption in therapeutic vaccine studies, for example.

In phase I trials, Weiss explained, the FDA's focus is avoiding undue risk to patients; discussion of a specific product's risk-benefit ratio comes later. First-in-class agents are likely to face more scrutiny. "If something is potentially high-risk, we want to start small and stagger patients," she said; the exact elements of an appropriate study design can be points for discussion and negotiation.

Harrington recalled that treatment activists worked with FDA and the ACTG in some contentious meetings to agree on surrogate marker data for antiretroviral drug trials. The FDA was willing to accept CD4 cell changes—"a pretty poor marker"—which gave pharmaceutical companies a way to move forward with drug development. "A virtuous cycle was initiated when all groups began talking with each other," he said. This, combined with the FDA's accelerated approval process, shortened approval times and decreased study sizes for registrational trials of new antiretroviral drugs,

bringing more sponsors into the field and speeding the development of highly active antiretroviral therapy (HAART).

Knowing What We Don't Know

Alan Landay from Rush University Medical Center addressed the selection of appropriate measures or relevant markers for interventions including ART intensification, purging HIV reservoirs, and gene therapy. When assessing HIV eradication, where should we look for residual virus? What are the most important sites for gut biopsies? What about the central nervous system, lymph nodes, and spleen? (For a concise review of HIV reservoir assay issues, see Wong 2011.)

In the absence of eradication, what might count as a functional cure? Can we measure improved CD4, CD8, and other immune-cell responses? What about reversal of persistent immune activation and inflammation? Can we achieve "success" even if some virus persists?

The need for better assays was a recurrent theme of the meeting. "We need to know some very basic stuff we don't know," such as where most CD4 cells reside, said Joseph McCune from UCSF. "Obviously we're not going to biopsy every organ in every patient…What is representative?"

"The [HIV] reservoir is like an iceberg and now we're only capable of measuring the very tip," Richman concurred.

Deeks suggested that focusing on single-copy plasma assays has detracted from necessary work on tissue assays, but Richman countered that sensitive plasma assays are useful for detecting low-level blips of released virus to show if a purging therapy is working.

Some participants lamented the proliferation of assays that do not provide comparable results, but Una O'Doherty from the University of Pennsylvania suggested that different laboratories might specialize in particular measurement techniques and collaborate so that each does not have to develop expertise in so many areas.

McCune expressed concern that we might throw out drugs that work well due to inadequate or poor measurements. The opposite concern is that we might continue to pursue approaches that do not work. Feigal stressed the importance of sharing information so researchers can avoid "going down blind alleys"—an issue with implications for pharmaceutical industry competition and intellectual property concerns.

Turning to animal models, Paul Luciw explained that animal studies offer the opportunity for more intensive and invasive analysis of reservoir sites, as well as the ability to learn about mechanisms of action of compounds too toxic for human use. Luciw noted, however, that while he works with the SIV/macaque system, there is as yet no consensus on how best to use it to model cure-related therapeutic strategies. McCune also pointed out that humanized mice cannot say anything about a cure, because they cannot be kept alive long enough to model the impact of long-term ART.

Richman and Deeks each invoked the history of ART development to reach opposing pessimistic and optimistic conclusions. "Even when we knew the targets for inhibiting HIV replication, we could not develop effective ART in ten years," Richman said. But with cure research, no one knows the targets. We are not sure we know all the reservoirs, and our ability to measure the compartments we do know

about is inadequate. Our assays are not very precise, and many agents will not produce enough of an effect to measure.

But Deeks recalled that when the first antiretrovirals were developed, we did not have good ways to measure viral load. Researchers could not measure precisely how AZT worked. Who would have guessed that we would be able effectively suppress the virus by combining three drugs, none of which worked well by themselves? "When you perturb a system in a controlled way you learn things, and it's not always clear in advance what we'll learn," said Deeks.

Clinical Trial Issues

In a wide-ranging discussion of issues related to clinical trials, workshop participants touched on a number of aspects including study design, protocols, patient populations, assays, and endpoints.

Pablo Tebas from the University of Pennsylvania focused on structured or analytic treatment interruption (ATI), which—unless an alternative method is developed—will ultimately be needed to show whether an approach controls HIV once the antiretroviral safety net is removed—the determinant of a functional cure.

The SMART trial showed that patients who interrupted treatment had more AIDS-related and non-AIDS clinical events, but the overall event rate was very low, and there was little difference during the first few months (SMART Study Group 2006). This suggests, Tebas proposed, that ATI with careful monitoring and prompt resumption of therapy if needed may not be too dangerous in the short term.

Landay noted, however, that inflammation peaks early after ATI, suggesting that changes in inflammatory markers might be another indication for restarting therapy. Simon Collins from HIV i-Base added that some individuals have additional risk factors—from cocaine use to cardiovascular disease—that may make them inappropriate candidates for treatment interruption.

Treatment educator Nelson Vergel stated that treatment interruption can be a major motivator for joining a clinical study. Just the thought of getting off meds for a few months is attractive to many people, even if it comes with some risk.

Richard Ambinder from Johns Hopkins followed with a discussion of allogeneic bone marrow transplantation and recent advances in the field. The national bone marrow donor registry includes nine million donors, he explained, suggesting it may be possible to find suitable CCR5-delta-32 donors for most Caucasians (the population with the highest frequency of the mutation). Engraftment of donor stem cells can now be achieved without complete ablation, and lifelong immunotherapy to prevent graft-vs.-host disease may not be necessary. Ambinder's participation underlined the importance of cross-disciplinary collaboration with researchers outside the HIV field.

Deeks then discussed differences between immunologic responders and nonresponders on ART, including variations in T-cell subsets and PD-1 expression. These groups are "very distinct, almost like treated versus untreated," he said; elite controllers who maintain undetectable viral load without ART are also different. We may need to study these groups separately when evaluating cure-related approaches, he recommended.

CHALLENGES AND RECOMMENDATIONS

On the second day of the workshop, participants split up into smaller breakout groups to discuss four aspects of cure-related research in more depth:

- Assays and new technologies
- Criteria for advancing new approaches into clinical trials
- Clinical trial design
- Recruitment and informed consent

Each group subsequently reported back to the full meeting on their discussions and recommendations.

Assays and New Technologies

The group noted that while ATI is the acknowledged "gold standard" for assessing any potentially curative intervention, before that point there are many types of assays that can be employed, with varying levels of ease, speed, and complexity. Currently, scientists in the field tend to have their own way of doing things, and there is no consensus about which approach—if any—is optimal. With regard to measuring HIV in body compartments, for example, blood is easy, but others sites that are more difficult to access are probably of greater importance.

Recommendations: Assays and New Technologies

- A rigorous comparison of the multiple available assays is needed in order to prioritize and standardize the best approaches; ideally this would be performed by several independent research groups using pedigreed samples.

- Quality control and quality assurance parameters should be developed to ensure that assay data from different trials can be compared with confidence.

- A tissue and blood repository for samples from cure-related clinical trials should be established.

Rowena Johnston indicated that amfAR is interested in supporting work on assays. Kate Krauss of the AIDS Policy Project emphasized that the speed at which this work proceeds determines the speed at which the entire field can move forward.

Criteria for Advancing into Clinical Trials

The group highlighted the need to better understand which cell models should be prioritized and which animal models are most appropriate. It was noted that the ideal system for preclinical evaluation may vary for virus-activating, virus-killing, and immune-modulating approaches. Cell lines were generally considered less useful than primary cell models for studying viral latency, due to their artificial nature and the likelihood that they do not accurately reflect the behavior of the virus in vivo.

Participants suggested that it would be helpful to have a consistent approach to assessing candidate compounds using several different assays, looking for potentially informative similarities and differences in how the compounds perform in each assay. However, it was stressed that there are currently no clear criteria for deciding whether a compound has sufficient activity to be worth pursuing. Disulfiram was cited as an example of a compound that has shown inconsistent activity in different laboratory assays, but is undergoing clinical evaluation due to its excellent safety profile.

In terms of animal models for studying HIV latency, there is no single model that is universally considered ideal. Humanized mice are viewed as problematic in this context due to their short life spans and low blood volume. There are several nonhuman primate models with different strengths and limitations. The group suggested that it would be premature to require that all candidates go through nonhuman primate testing at this time, but it should be encouraged when appropriate.

Recommendations: Criteria for Advancing into Clinical Trials

- Test candidate compounds with diverse mechanisms of action using 5–7 different assays in 6–7 different academic laboratories.
- Share candidate compounds.
- Share data in order to focus and enhance future studies.
- Store relevant specimens in biobanks so that they can be tested prospectively and retrospectively.
- Develop an iterative model to test activity of potential candidates using exploratory biological specimens collected in human clinical trials and prioritized assays.
- Address intellectual property issues to allow proprietary compounds or molecules (e.g., monoclonal antibodies) to be shared among multiple laboratories for testing).

Trial Design/Analytic Treatment Interruptions

The group consensus was that while each cure strategy (small molecules, gene therapy, etc.) may require a different type of trial design, eventually all would likely need to be evaluated in the context of an analytic treatment interruption. Suggested criteria to be considered in the design of ATI trials included CD4 cell count, CD4 nadir, history of clinical disease, time to viral suppression, HLA haplotype, inflammatory markers, and remaining viable regimens. It was recommended that people with cardiovascular, renal, or neurological risk factors be excluded from early ATI studies. In terms of the timing of treatment interruption and resumption of ART, it was felt that this should ideally be response-guided; patients should not necessarily be required to restart ART at a set time point.

Recommendations: Trial Design/Analytic Treatment Interruptions

- Animal and preclinical data should demonstrate an effect on relevant endpoints (e.g., viral load, set point, survival, etc.).

- Prior to an ATI trial, a decrease in at least one viral reservoir should be documented in a pre-ATI study.

- At least two reservoirs should be studied in any trial.

- Study sponsors should assure appropriate monitoring for side effects, drug resistance, long-term efficacy, etc.

- Long-term follow-up of study participants should be provided for.

- The pharmacokinetics of antiretroviral drugs that are interrupted need to be taken into consideration in any ATI study. For instance, NNRTIs may have to be switched to PIs or other ARV drug classes prior to an ATI.

Recruitment and Informed Consent

Group discussions highlighted the concern that clinical trial oversight structures now in place are more geared toward protecting institutions than trial participants, and that different bodies are making different—perhaps incorrect—assumptions about what people with HIV know and want. Priorities identified by the group included the need to address who should be included in or excluded from trials and who is appropriate for ATI, as well as issues regarding the possible coercive implications of financial compensation for trial participation if people have limited economic means. The question whether researchers are taking advantage of the opportunity to work with activists to facilitate the recruitment and informed-consent process was also raised.

Recommendations: Recruitment and Informed Consent

- Convene a meeting among CBER, CDER, researchers, research sponsors (NIH, industry), and activists to improve communication, increase the expertise of the FDA on HIV-related issues, and increase knowledge among researchers about key FDA concerns, policies, and standards.

- Convene a meeting with the NIAID Division of AIDS (DAIDS), investigators, IRB chairs, and the community to discuss problems with IRB standards, informed consent processes, and issues related to compensation and other ethical considerations.

- Work with medical ethicists to research how people with HIV view risk with regard to varying clinical trial designs as well as issues related to consent and compensation.

- Improve communication between researchers and activists on emerging data and proposed trial designs (e.g., ATIs).

- Work with experts in health literacy and education to develop videos, fact sheets, and other educational materials about the clinical trials process and its related risks and benefits.

MOVING FORWARD

During the final workshop, session participants discussed steps for moving forward. Diana Finzi from DAIDS acknowledged that since we are at the limit of detection of current testing methods, we have had to make progress at that edge. In this respect, HIV eradication is similar to cancer: you can take out the tumor, but do you succeed if you don't take out every last malignant cell?

"Clinical trials are like a lottery," Finzi noted. "Everyone contributes a little bit, but the payoff only goes to a few." She suggested that the best way to proceed is a divide-and-conquer approach, with everyone working in their areas of strength. We do not need to do everything in large groups with all stakeholders, she added; much can be accomplished by smaller groups, and community input is helpful at all levels.

Harrington emphasized that we need to work together. Over the past few years, amfAR started its research consortium on HIV eradication (ARCHE), the Berlin Patient sparked renewed hope, the NIH and subsequently the ACTG changed their priorities to make cure research more prominent, and the International AIDS Society (IAS) undertook the development of a collaborative global scientific strategy "Towards an HIV Cure." "There has been great progress over four years and more consensus than expected," he concluded.

Harrington and other advocates stressed the need for more funding and support for HIV cure-related research, pointing out that medical advances and improvements in the clinical trials process will also benefit people with other diseases, as has been the case throughout the AIDS epidemic.

AFTERWORD

Since the workshop took place in April 2011, a number of important developments have occurred in the HIV cure research field. The NIH announced the award of three grants under the Martin Delaney Collaboratory, expanding both the size and amount of funding allocated to the project. The amfAR ARCHE program also announced several new awards. At the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Rome in July 2011, there was an unprecedented number of cure-focused sessions and talks. The conference also served as a platform to launch the Rome Statement for an HIV Cure, calling for an acceleration of HIV cure research.

Further reading:

NIH Funds New Research Toward an HIV Cure – Five-Year Grants Total $14 Million in First Year. http://www.niaid.nih.gov/news/newsreleases/2011/Pages/DelaneyCollab.aspx.

Martin Delaney Collaboratory. http://martindelaneycollaboratory.org/.

amfAR Consortium Helps Lead Efforts for HIV/AIDS Cure – Second Year of Grants Builds on Momentum. http://www.amfar.org/lab/article.aspx?id=9935.

International AIDS Society "Towards an HIV Cure" Global Scientific Strategy. http://www.iasociety.org/Default.aspx?pageId=349.

Towards an HIV Cure: New Strategies for an Old Challenge, 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. http://pag.ias2011.org/session.aspx?s=15.

Rome Statement for an HIV Cure. http://www.iasociety.org/Default.aspx?pageId=584.

APPENDIX A: BREAKOUT GROUP RECOMMENDATIONS

Group 1. Assays/New Technologies

Group leaders: Diana Finzi, Nicolas Chomont

The current gold standard endpoint for cure-related research is an analytic treatment interruption (ATI), which allows the timing and magnitude of the viral rebound to be studied.

There are a number of virological assays that might be used to measure the impact of an intervention before, during, and after an ATI, each measuring a different virus intermediate, listed below in approximate order of quality, quantity, difficulty, reproducibility, sensitivity, and scalability:

- total HIV DNA
- 2-LTR (2-long terminal repeat circles)
- cell-associated HIV RNA
- single copy assays (SCAs)
- culture assays

The significant problem for all assays is that the amount of virus being measured is at the limit of detection, and it is difficult to establish a narrow enough dynamic range to be able to reliably track changes in the size of the reservoir or in the dynamics of viral replication; given current assay limitations, it may be difficult to distinguish signal (therapy-induced reduction in reservoir size) from noise (stochastic variation in measurement output).

Different cell types and anatomical compartments are also key variables in HIV eradication–related research. Cell types of interest would include CD4 T cells, hematopoetic stem cells, monocytes and macrophages, astrocytes, and several kinds of dendritic cells. Typically, cells are taken from peripheral blood, but more relevant sites might include the gut, central nervous system, and lymphoid, genital, and solid tissues, some of which are by definition less accessible to measurement. The site of sampling affects the denominator for assessing the relative amount of virus present; blood is easier to sample than tissues, but it may be less informative.

Recommendations: Assays/New Technologies

- A rigorous comparison of the multiple available assays is needed in order to prioritize and standardize the best approaches; ideally this would be performed by several independent research groups using pedigreed samples.

- Quality control and quality assurance parameters should be developed to ensure that assay data from different trials can be compared with confidence.

- A tissue and blood repository for samples from cure-related clinical trials should be established.

Group 2. Criteria for Advancing Approaches into Clinical Trials

Group leaders: Ellen Feigal, Romas Geleziunas

It is difficult to establish clear criteria for advancing innovative cure-related therapeutic interventions into clinical trials given the broad range of approaches used by different laboratories. There is a need to validate preclinical models and assays and encourage consistency. It would be helpful to focus on a test set of candidate compounds that are mechanistically diverse in order to assess the ability of different assays and systems to measure their activity, but demanding consistent approaches prematurely in a growing field could preemptively block out innovative, high-risk approaches that may be needed for ultimate success. However, full validation of laboratory measures cannot occur until an agent is shown to be active in the clinical setting.

Proof-of-concept studies may be needed when assay results are inconsistent (e.g., disulfiram shows activity in stimulating latent HIV in some systems but not others). Primary cell models are likely to be more relevant than cell lines, and their use should be encouraged. However, it is still unclear what percentage of latently infected cells should respond to a compound in order to justify moving to a clinical trial. Currently, the positive controls used for comparison are also very blunt instruments that cause mass activation of cells (e.g., PHA), and attention should be paid to developing less crude approaches.

Safety issues are critical, but dependent on mechanism of action; new chemical entities may well face a longer path toward the clinic than known compounds.

There is as yet no optimal animal-model system to use for preclinical evaluation. Humanized mice have too short a lifespan and insufficient blood volume to be useful. There are many different nonhuman primate (NHP) models, each with strengths and limitations. No single NHP model has established itself as a clear benchmark for assessing cure-related strategies. Until there is greater consensus on this issue, use of NHP models should be encouraged but is not an absolute requirement.

Recommendations: Criteria for Advancing into Clinical Trials

- Test candidate compounds with diverse mechanisms of action using 5–7 different assays in 6–7 different academic laboratories.
- Share candidate compounds.
- Share data in order to focus and enhance future studies.
- Store relevant specimens in biobanks so that they can be tested prospectively and retrospectively.
- Develop an iterative model to test activity of potential candidates using exploratory biological specimens collected in human clinical trials and prioritized assays.
- Address intellectual property issues to allow proprietary compounds or molecules (e.g., monoclonal antibodies) to be shared among multiple laboratories for testing).

Group 3. Trial Designs/Analytic Treatment Interruption

Group leaders: Rob Murphy, John Zaia

Any approach should be two-pronged, with a pre-ATI and ATI strategy. The exact approach would have to be customized and designed based on the type of therapy, such as 1) cell-based, 2) immunologic, and 3) small molecule/drug therapy. Prior to proceeding to an ATI study, some effect on the reservoir or immune system should be documented in at least one of the pre-ATI studies.

Regarding ATI parameters and inclusion/exclusion criteria for these trials, at least nine criteria should be taken into consideration:

1. Current CD4 cell count (>350?, >500?)
2. CD4 nadir (none, >200?, >350?)
3. Prior clinical disease state (asymptomatic, CDC stages I/II vs. III/IV, etc.)
4. Time with optimal viral suppression
5. HLA haplotype
6. Inflammatory marker status
7. History or risk of cardiovascular, renal, and/or neurologic disease
8. Number of ART regimens remaining and available to the patient
9. Current treatment guidelines

The priorities for the endpoints of an ATI trial would include the following: time to viremia, CD4 count decline (50% drop, return to baseline, below a certain level such as 200 or 350), and in certain cases, posttreatment viral set point.

<u>Recommendations: Trial Design/Analytic Treatment Interruptions</u>

- Animal and preclinical data should demonstrate an effect on relevant endpoints (e.g., viral load, set point, survival, etc.).
- Prior to an ATI trial, a decrease in at least one viral reservoir should be documented in a pre-ATI study.
- At least two reservoirs should be studied in any trial.
- Study sponsors should assure appropriate monitoring for side effects, drug resistance, long-term efficacy, etc.
- Long-term follow-up of study participants should be provided for.
- The pharmacokinetics of antiretroviral drugs that are interrupted need to be taken into consideration in any ATI study. For instance, NNRTIs may have to be switched to PIs or other ARV drug classes prior to an ATI.

Group 4. Recruitment and Informed Consent

Group leaders: David Evans, Bernard Lo

The group agreed on several key factors that could become barriers to cure-oriented research's proceeding as quickly as we would prefer. These factors include:

- Uncertainty about the criteria by which the FDA's Center for Biologics Evaluation and Research (CBER) will be evaluating proposed studies for safety concerns;
- Varying standards and expertise of institutional review boards (IRBs) with regard to cure-oriented research specifically, and HIV research more broadly;
- Inferior informed consent processes and document standards that neither fully inform nor protect prospective study participants;
- Unanswered questions about how best to identify the proper participants for a given trial beyond their clinical characteristics (e.g., economic status, baseline health literacy, etc.) and how recruitment and compensation may need to vary based on these additional factors; and
- Fragmented relationships among researchers, health care providers, local regulatory bodies, and research advocates.

Breakout group participants were concerned that researchers and activists do not have an established history of working with CBER as they do with CDER. This means that CBER processes can be opaque and difficult to interpret. Given the fact that proposed research protocols may be reviewed by differing branches of CBER, which may not have an extensive history of working on HIV trials, there was further concern that trials could be unnecessarily modified or rejected. As well, there seems to be a lack of proactive guidance available from CBER to allow researchers to anticipate potential roadblocks to proposed clinical trials, nor are there mechanisms or established relationships between the community and CBER staff to ensure that input from the community is considered by the agency.

Another key concern was that the informed consent process has devolved from an honest effort to ensure that every research participant is sufficiently knowledgeable about a proposed trial to allow them to make an informed choice about participation, to a process that is largely concerned with protecting the interests of the academic institution overseeing the research, particularly in terms of legal liability. Great strides have been made in improving the consent process, yet many HIV trials have not adopted these new methods, and IRB standards can vary considerably around the country.

Beyond issues related to the consent process, there was concern about how to ensure that trials are ethical in terms of compensation for time and hardship associated with a study. By their very nature, some studies require significant sacrifices on the part of participants in terms of time, travel, and discomfort. For this reason, compensation in some trials can be considerable and could be viewed by some as potentially coercive. Participants agreed that further exploration of these issues is needed.

Lastly, there was concern on the part of community activists that researchers and regulators are not utilizing the expertise and knowledge of people living with HIV to make decisions about trial design and the research recruitment and consent processes.

To overcome these barriers, the group identified the following action items:

Recommendations: Recruitment and Informed Consent

- Convene a meeting among CBER, CDER, researchers, research sponsors (NIH, industry), and activists to improve communication, increase the expertise of the FDA on HIV-related issues, and increase knowledge among researchers about key FDA concerns, policies, and standards.

- Convene a meeting with DAIDS, investigators, IRB chairs, and the community to discuss problems with IRB standards, informed consent processes, and issues related to compensation and other ethical considerations.

- Work with medical ethicists to research how people with HIV view risk with regard to varying clinical trial designs as well as issues related to consent and compensation.

- Improve communication between researchers and activists on emerging data and proposed trial designs (e.g., ATIs).

- Work with experts in health literacy and education to develop videos, fact sheets, and other educational materials about the clinical trials process and its related risks and benefits.

APPENDIX B: WORKSHOP AGENDA

AIDS Policy Project, amfAR, Project Inform, Treatment Action Group
Cure-Related Clinical Research Workshop

Wednesday, 20 April

9:00–9:20 Welcome and introductions – Matt Sharp, Dana Van Gorder, Mark Harrington on behalf of the conveners

9:20–9:40 Overview on mechanisms of persistence – Daria Hazuda, Merck

9:40–10:00 Lessons from past clinical research – Tae-Wook Chun, NIAID

10:00–12:00 Current or imminent trials, criteria for advancing into humans – Panel

Moderator: Ellen Feigal, the California Institute of Regenerative Medicine

Romas Geleziunas, Gilead (overview)

Rob Murphy, Northwestern University – Immunomodulation with IL-7 and HIV-rAd 5 vaccine and its effect on the viral reservoir: the ERAMUNE trials

Carl June, U Penn (Sangamo CCR5-deletion cellular therapy)

David Margolis, University of North Carolina (SAHA, HDACs)

John Zaia, City of Hope (stem cell gene modification)

Steve Deeks, UCSF (ACTG, disulfiram)

12:00–1:00 Lunch break

1:00–3:00 Clinical trial issues (trial designs including analytic treatment interruption, ablation, trial populations, virological assays, endpoints) – Panel

Moderator: Sarah Read, Division of AIDS

Alan Landay, Rush University

Rich Ambinder, Johns Hopkins

Daria Hazuda, Merck

Pablo Tebas, U Penn

Steve Deeks, UCSF

3:00–3:15 Coffee break

3:15–5:00 Current regulatory environment discussion – What issues arise & how should they best be addressed?

Moderator: Mark Harrington, TAG

5:00–5:15 Update on the IAS Towards an HIV Cure Initiative – Shirin Heidari, IAS

Thursday, 21 April

9:00–9:25 Ethics – Bernard Lo, UCSF

9:25–10:00 Discussion

Moderator: Stephen LeBlanc, AIDS Policy Project

10:00–11:20 Breakout discussion sessions:

- Assays/new technologies
- Trial designs
- Criteria for advancing approaches into clinical trials
- Recruitment & informed consent

11:20–11:30 Coffee break

11:30–12:30 Report-backs

12:30–1:30 Working lunch discussion (including resources)

Moderator: Diana Finzi, NIAID

1:30–2:00 Wrap-up, acknowledgements, next steps

APPENDIX C: LIST OF PARTICIPANTS

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20–21 April, 2011

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