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tagline

TAG
Treatment Action Group

THE DOMESTIC ISSUE

NEWS ON THE FIGHT TO END HIV/AIDS, VIRAL HEPATITIS, AND TUBERCULOSIS

Rising to the Domestic Challenge

By Mark Harrington

> In death one can't be vocal or witness time and motion and physical events with breath,
> one can't make change. Abstract ideas of energy dispersing, some ethical ocean crawls
> through a funnel of stars, outlines of the body, energy in the shape of a body,
> a vehicle then extending losing boundaries separating expanding into everything. Into nothingness.
> It's just I can't paint. I can't loosen this gesture if I'm dead.
>
> —David Wojnarowicz, *In the Shadow of the American Dream*

The past decade has brought astonishing developments in HIV disease management: antiretroviral therapy options that are safer, more effective, and easier to take than their predecessors; evidence that HIV treatment can substantially reduce the risk of transmitting the virus; rapid assays to detect HIV within days of infection; and the approval of preexposure prophylaxis (PrEP) to minimize the risk of infection among those at risk. Yet the U.S. epidemic continues unabated. Roughly 50,000 U.S. residents are newly infected every year (with a recent 22 percent increase among young gay and bisexual men). Of all U.S. residents living with HIV, one in five is unaware of having been infected; only one in four has an undetectable viral load; and less than half are in continuous care.

We are at a stalemate. This issue of *TAGline* underscores TAG's commitment to ending AIDS in the United States and realizing the goals of the National HIV/AIDS Strategy.

Scott Morgan discusses how the president's recently announced HIV Care Continuum Initiative represents a victory for advocates, while **Tim Horn** writes about the need for an implementation science agenda designed to improve engagement in care. **Coco Jervis** describes encouraging progress—spurred by activists—to develop a comprehensive plan to end AIDS in New York State. And **Jim Eigo** and **James Krellenstein** of ACT UP/NY review the tremendous advocacy work under way to force New York City's health department to ramp up HIV prevention and testing efforts.

Also in this issue is **Richard Jefferys**'s clear-eyed synopsis of the ethical considerations surrounding essential cure-related research.

Advocacy for sound domestic health care policy must also extend to tuberculosis (TB). As Jervis and **Lindsay McKenna** explain in separate articles, political apathy, dwindling federal and state resources, and an uptick in domestic drug shortages have already caused public health crises, and, without bold strategies quickly put into place, may lead to a resurgence of this deadly and costly disease.

There are challenges ahead, including this country's hepatitis C epidemic. Upcoming issues of *TAGline* will cover the advancement of direct-acting antivirals, which are bringing us closer to the day when hepatitis C can be cured with all-oral, interferon-free treatment regimens.

Fortunately, the opportunities to end the HIV, TB, and hepatitis C epidemics in the United States have never been greater. •

IN THIS ISSUE

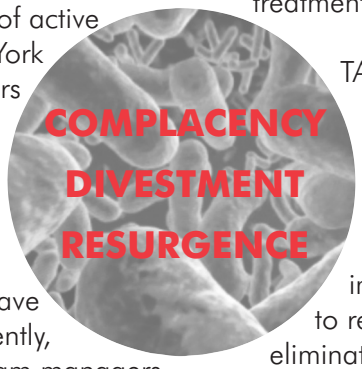
U.S. TB Control: From **Confidence** to Crisis

Funding cuts and shifting budgetary priorities threaten tuberculosis gains

By Coco Jervis

The United States is losing ground in its fight against the tuberculosis (TB) epidemic within its own borders. Sequestration and shifting priorities of Congress and the Obama administration have led to a waning of political support and resources for domestic and global TB programs. More than 10,000 people are diagnosed with active TB disease every year in the United States, and an estimated nine to 14 million American residents are currently living with latent TB infection. Perceived low prevalence, coupled with a lack of political vigilance and declining federal and state resources for TB control and elimination, has set the stage for a dangerous and costly resurgence of domestic TB.

Complacency, divestment, and resurgence are a recurring pattern. Funding for TB control and elimination efforts declined precipitously throughout the 1970s and early 1980s, leading to a deadly explosion of active and drug-resistant TB—particularly in New York City—in the early 1990s. More than 20 years later, funding for our domestic TB response has been further slashed due to shifting priorities and sequestration-related cuts. As a result, the prevention and control infrastructure on state and local levels has fallen into neglect, setting the stage for a grave and costly domestic resurgence of TB. Currently, many resource-strapped domestic TB program managers struggle to provide basic diagnostic, treatment, contact-tracing, and ancillary services to patients.



Treatment of active, drug-sensitive TB in the United States can cost between $11,000 and $27,000 per patient; treatment for multidrug-resistant TB costs taxpayers upwards of $500,000 per patient. Compounding these exorbitant costs, many TB programs have recently experienced difficulty accessing drugs to treat latent and active TB either because of nationwide shortages (see page 4) or because the necessary drugs are too expensive. The strain on state and local TB programs will undoubtedly heighten with the rollout of health care reform and the influx of new insured and uninsured TB patients that will be in need of care.

Sequestration is devastating our domestic TB research progress as well. The Centers for Disease Control and Prevention's (CDC's) Division of TB Elimination (DTBE) has been forced to make some difficult funding cuts to its Tuberculosis Trials Consortium (TBTC), the leading TB clinical research collaborative in the world. Despite its already negligible budget, the TBTC has conducted critical research that could spur the development of shorter, better-tolerated treatment strategies for curing and preventing the spread of TB. The TBTC has pioneered clinical research that has led to shortening active, drug-sensitive TB treatment from six months to just three or four months. A shorter, safer, better-tolerated regimen would be transformative. Shaving even two months off TB's long treatment course would mean one-third fewer patients on treatment at any given time, saving millions in treatment costs each year in the United States alone. But sequestration-related cuts are jeopardizing the launch of important late-stage clinical research for a new treatment regimen.

TAG has been aggressive in its response to these cuts. In July, TAG launched the Save the TBTC campaign aimed at mobilizing the domestic TB research and activist community to reach out to their members of congress to educate them about the importance of the TBTC's work and the need to reinvest in the DTBE's TB control and elimination activities. TAG is also working in coalition to reintroduce an ambitious Comprehensive TB Elimination Act that is sunsetting this year. TAG has also been working closely with the congressional TB Elimination Caucus, the CDC, and the FDA to address the ongoing TB drug shortage crisis.

Reaching zero TB deaths, zero new infections, and zero suffering and stigma in the United States is achievable with political will and a sustained commitment of resources to our TB control programs. Additionally, in order to achieve total TB elimination, both here and abroad, it will be necessary to accelerate the research and development of new diagnostics, drugs, prevention, and treatment, and to improve strategies to reach underserved populations. We must remain vigilant in our advocacy in order to ensure that TB remains in the spotlight. •

An Obligatory Overhaul to Address Domestic TB Drug Shortages

Bold strategies are required to remedy frequent stock-outs and supply interruptions

By Lindsay McKenna

Drug shortages, especially of tuberculosis (TB) drugs, have become increasingly common in the United States. Over the past year alone, the U.S. Centers for Disease Control and Prevention (CDC) has reported shortages (also referred to as stock-outs or supply interruptions) of various TB products including second-line injectables (capreomycin and amikacin), required to fight drug-resistant TB (DR-TB), and tubersol and aplisol, important products for TB diagnosis.

There have also been shortages of isoniazid, one of the most powerful drugs to fight both drug-sensitive TB (DS-TB) and latent TB infection (LTBI); such shortages led to rationing in some U.S. regions. "That put me in a really uncomfortable position as a providing physician, but also as the health official telling doctors they had to pick and choose who gets isoniazid and who doesn't," explains Charity Thoman, MD, MPH, deputy director of the Santa Barbara County Public Health Department, which began rationing its supply of isoniazid in January. "For me, that created an ethical dilemma, because that's not what you sign up to do as a doctor. We should be providing treatment for all our patients."

"...as the health official telling doctors they had to pick and choose who gets isoniazid and who doesn't, for me, that created an ethical dilemma, because that's not what you sign up to do as a doctor. We should be providing treatment for all our patients."

Domestic TB drug shortages are a recurring issue, and existing stopgap measures are inadequate, threatening the United States' status as a model for TB elimination. Over the last decade, U.S. TB drug shortages have tripled. In addition to the aforementioned drugs, the CDC has reported interrupted supplies of injectable rifampin, fixed-dose combinations of isoniazid and rifampin (used to treat and reduce the pill burden for DS-TB and LTBI patients), rifabutin (commonly used to treat TB in HIV-coinfected patients), ethambutol (one of four drugs that make up first-line therapy), and ethionamide, streptomycin, and cycloserine, which are used to treat DR-TB.

To add insult to injury, it is not unprecedented for manufacturers to take advantage of ongoing shortages to increase prices. In 2007, when Akorn took over manufacturing of capreomycin, the price for a one-gram vial increased thirtyfold from US$11.71 to US$300. During the isoniazid shortage earlier this year, pharmacies reported that the price of a 30-pill batch of 100 mg tablets would increase from US$35.51 to US$1,309.94—a 3,589 percent price increase. Fortunately, after much vocal protest and the promise of public shaming, isoniazid manufacturers did not follow through. But even small price increases from preestablished levels can devastate state programs working within cash-strapped budgets.

Though President Obama issued an executive order in 2011 directing the U.S. Food and Drug Administration (FDA) to notify the Justice Department of suspicious pricing, the FDA states that pricing issues are outside of its purview. Nonetheless, the FDA needs to take accountability for and address drug pricing, and work with the Justice Department to reprimand all manufacturers who increase prices during ongoing and future drug shortages.

The effects of drug shortages are burdensome to TB programs and patients: they consume program staff time, cause patients to miss doses (which can lead to the development of drug-resistance), force patients to switch to inferior regimens, and require the use of more expensive drugs. Drug shortages are also problematic for research programs. If study drugs are not purchased up front for use in clinical trials, shortages can result in research interruptions and delays, which have the potential to threaten the validity of study results. The negative impact of shortages is compounded by a lack of effective communication to TB program managers, researchers, and care providers.

Although shortages are reportable to the FDA under Title X of the 2012 FDA Safety and Innovation Act (FDASIA), this legislation is weak, and passive at best. If a manufacturer fails to report an impending drug shortage, its punishment is an FDA-issued noncompliance letter, which is made available to the public. The FDA does not work closely with the CDC to communicate shortages systematically and effectively to those who are actually responsible for treating patients, or to gather information from providers and pharmacists to determine if there are local supply issues.

Figure 1. A Recent History of TB Drug Shortages

TB Product	Suppliers	Reason(s) for Shortage (2011–2013)
Isoniazid	Teva, West-Ward (VersaPharm), Sandoz	Lack of raw materials; manufacturing discontinuation; other
Ethambutol	Teva, West-Ward (VersaPharm), Lupin	Manufacturing discontinuation
Injectable rifampin	Bedford, Pfizer, West-Ward (VersaPharm)	Increased demand outpacing supply; other
Capreomycin	Akorn	Manufacturing problems; lack of raw materials; sole-source U.S. manufacturer
Amikacin	Teva, Bedford (discontinuing production)	Manufacturing problems; lack of raw materials; increased demand outpacing supply
Streptomycin	X-GEN	Increased demand outpacing supply
Kanamycin	APP Pharmaceuticals	No longer produced in the United States
Since 2005, the CDC has also received reports of difficulty obtaining isonarif, rifamate, rufabutin, ethionamide, and cycloserine.		

One way to improve close collaboration between the CDC, the FDA, providers, and pharmacists, and to prevent programs and patients from suffering the effects of shortages, is for the CDC to establish a central emergency stockpile of TB drugs at the U.S. Department of Health and Human Services Supply Center. Programs can then draw from the emergency stockpile during shortages. Additionally, government resources and capacity for preventing and monitoring shortages must be increased, and interagency coordination and communication must be improved. Manufacturers should inform the FDA of impending shortages or plans to withdraw products much earlier, and the FDA should vigorously enforce Title X of the FDASIA.

According to manufacturers, there are several causes of drug shortages [see figure 1]. But the underlying issue is the small number of manufacturers producing FDA-approved TB drugs and active pharmaceutical ingredients (APIs). Capreomycin and amikacin each has a sole manufacturer with FDA approval. This leaves programs reliant on one manufacturer, who can exit the TB space at any time without repercussion. This lack of manufacturing diversity is partially due to the fact that most TB drugs are older and off-patent, so the TB market—especially the small number of cases of DR-TB—is not viewed to be profitable for manufacturers, and few of them are willing to take on the expense and challenge of seeking FDA approval.

To make matters worse, starting in October 2013, the FDA will increase application fees for manufacturers seeking approval to make generic drugs, potentially further discouraging manufacturers from entering this already neglected space. The FDA should exempt TB drugs from these fee increases and provide incentives (such as tax credits) to diversify TB product manufacturers. Making TB an attractive market is of particular importance, as the FDA has no authority to mandate manufacturers to make drugs or to continue to produce older products, even if they are medically necessary and relevant to public health.

Alternatively, if the FDA were to accept approval from other Stringent Regulatory Authorities (SRAs) or the World Health Organization Prequalification of Medicines Programme, programs would be able to procure capreomycin and amikacin, for example, from additional manufacturers (Vianex and Cipla, respectively), even if only during domestic shortages. In addition, programs would be able to procure drugs through the Global Drug Facility, housed in the Stop TB Partnership and mandated to ensure uninterrupted access by national TB programs to high-quality TB drugs.

Barring FDA acceptance of WHO prequalified drugs, the United States could create a parallel national centralized TB drug system that would allow for pooled procurement and more efficient ordering than the current fragmented system in which each program procures independently. It would also monitor supply to prevent shortages or detect them early, and to coordinate distribution in times of shortages. A centralized TB drug procurement and distribution system could be modeled after the CDC's Vaccines for Children Program or Texas's centralized drug procurement program. However, establishing a new system would be quite resource-intensive—an important consideration given the current fiscal crisis.

TB drug shortages are a public health emergency that should not be left to market forces for resolution. "I understand there are a lot of challenges for the Obama administration to tackle right now," Thoman told *TAGline*. "I know there are bigger fish to fry, but I would like to see another presidential executive order directed at the drug shortage. Either the FDA needs to step up and actually figure out how to solve the drug shortage, or another entity should be put in charge." •

A Commitment to the HIV Continuum of Care

President Obama orders multiagency cooperation to achieve National HIV/AIDS Strategy goals, but without required funding commitment

By Scott Morgan

If the United States is to effectively move toward the 2015 goals outlined in the National HIV/AIDS Strategy (NHAS) through the scale-up of evidence-based strategies and practices intended to maximize engagement in care and treatment outcomes, tighter collaboration between various federal agencies will be required. A critical step to accomplish this was made on July 15, when President Obama issued an executive order establishing the HIV Care Continuum Initiative, which mandates the creation of a working group that crosses federal agencies to work toward these goals.

An accompanying White House fact sheet further underscored the administration's commitment to building capacity for community-based organizations and health departments, along with improvements in prevention and treatment integration across the HIV continuum of care, which begins with only 80 percent of those with HIV being aware of their status and ends with only one in four being effectively treated with antiretroviral therapy.

TAG issued recommendations in an action plan to revitalize the NHAS in April of this year (treatmentactiongroup.org/hiv/nhas), and it is heartening to see that many of those recommendations are reflected in the HIV Care Continuum Initiative and its associated efforts. Of concern, however, is the specified funding commitment, which falls considerably short of what's needed to achieve NHAS goals, at least by 2015.

The HIV Continuum of Care Initiative

The Office of National AIDS Policy (ONAP) will oversee the initiative set forth by the president's executive order; the ONAP Director will co-chair the working group with the secretary of health and human services (or her designate). Federal agencies participating in the initiative include the Department of Justice (DOJ), the Department of Labor (DOL), the Department of Health and Human Services (HHS), the Department of Housing and Urban Development (HUD), the Department of Veterans Affairs (VA), the Office of Management and Budget (OMB), and other agencies appointed by the co-chairs. The Presidential Advisory Council on HIV/AIDS (PACHA) will be consulted "as appropriate."

The working group's task is to gather information from these agencies on how to improve HIV testing, treatment, and care; to review potential research that can reduce gaps across the continuum; and to obtain input from affected communities and stakeholders that may improve outcomes. It is also intended to identify barriers and obstacles that particularly affect high-risk populations, devise ways to overcome the barriers, and better align efforts across federal agencies to move more rapidly toward the goals of the NHAS.

In a related effort, HHS will launch a new demonstration project, Integrating HIV Prevention and Care Services to Improve HIV Outcomes in Areas of High Unmet Need, designed to provide integrated prevention, treatment, and care throughout the treatment cascade. Another project aims to enhance the services and capacity of health care settings, revamp systems and procedures, institute better practices to identify those with the virus, and link clients to care so they can achieve and maintain an undetectable viral load.

Another demonstration project being mounted by the Centers for Disease Control and Prevention (CDC) is the Capacity Building Assistance for High Impact Prevention, which will run through March 2019 and will address gaps all across the continuum by providing information, training, and technical assistance for health departments, community-based organizations, health care organization, and capacity-building assistance/resource centers.

Advocacy Priorities

The HIV Care Continuum Initiative and its related programs accord with with many of TAG's recommendations in our April 2013 *Revitalizing the U.S. National HIV/AIDS Strategy Action Plan*, produced following a December 2012 meeting with advocates, service providers and researchers to review the current state of the national HIV response.

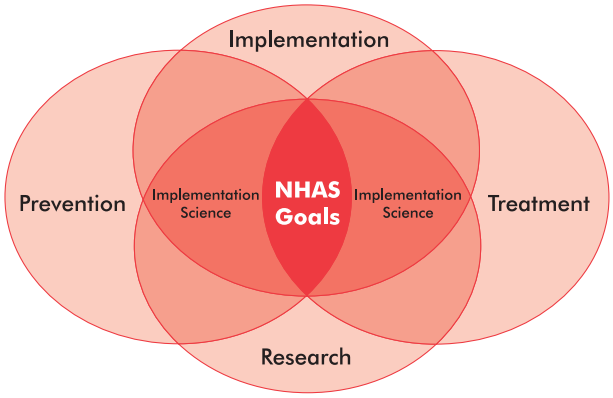
In particular, TAG recommended that ONAP coordinate the efforts of numerous federal agencies—the root of the Continuum Initiative—though we specifically note the importance of collaboration on the development of

an implementation science research agenda. This agenda would guide the scale-up of evidence-based interventions to improve prevention, care, and treatment outcomes in populations facing important structural, behavioral, and cultural barriers to uptake (see page 8).

TAG also recommended that the Affordable Care Act (ACA) and Medicaid expansion be implemented efficiently, as the systems through which people with HIV currently receive prevention, care, and treatment are going to go through many changes—a potentially turbulent process at first. This recommendation ties to the CDC's capacity-building prevention project, which will ensure that community-based and health care organizations have the skills and information to better achieve the goals of the NHAS throughout the ACA transition.

A significant recommendation coming out of TAG's report is to reallocate investments in HIV prevention and care for better results, using an investment framework that targets those most in need and where limited resources will do the most good. The HHS demonstration project has the potential to shed light on where investments are most needed, thereby improving outcomes across the HIV care continuum in areas of high unmet need.

Whether we are talking about TAG's recommendations or the executive order, community mobilization and activism will be critical, both in terms of working toward revitalizing the NHAS and ensuring that accurate and complete information is fed back to the working group so that needs, priorities, obstacles, and community perspective are given full consideration.



Toward the Goals of the National HIV/AIDS Strategy (NHAS)
The HIV Care Continuum Initiative, with its mandate for collaboration between various federal agencies to achieve the targets of the NHAS, will require the implementation of research-validated treatment and prevention strategies. This will require a commitment to a implementation science agenda to ensure adequate translation and evaluation of essential services in key populations and areas.

The Question of Funding

Significant new financial resources must be mobilized and invested to reduce new infections, eliminate health disparities, and improve health outcomes for people with HIV.

In a 2012 article, David Holtgrave, PhD, of the Johns Hopkins Bloomberg School of Public Health estimated that an additional $15.2 billion is required to reach some of the modest prevention and treatment targets set forth in the NHAS. However, the window of opportunity is rapidly closing, and there are no indications from the administration that these resources will be forthcoming. In fact, the proposed 2014 domestic HIV budget request is for $23.2 billion, a less than $2 billion increase from 2012.

A reevaluation of the original timeline is inevitable. At the same time, it will be critical to reevaluate the discrete targets within the goals of the NHAS. As Dr. Holtgrave recently pointed out in an August *AIDS and Behavior* commentary, "we propose bold yet achievable quantitative 2020 goals based on previously published economic and mathematical modeling analyses."

As 2014 appears on the horizon, it is becoming clearer that the 2015 NHAS goals will remain out of reach. This administration must not simply kick the can down the road toward 2020, but rather engage fully in critical analysis and novel thought to formulate and achieve NHAS goals, relying on scientific evidence to drive sufficient funding.

The Obama administration's commitment to making the NHAS more ambitious is in line with the latest science, with the opportunities provided by the Affordable Care Act, and with the U.S. activist community's interest in ending the AIDS pandemic. The new Continuum of Care Initiative as laid out in the July 15 executive order is commendable on many levels, and there is reason to hope that investments in the demonstration projects outlined in the order will yield new evidence and insights that will not only propel the NHAS forward, but provide a basis from which to mobilize the required resources to end AIDS in the United States. •

Engagement in Care: A Final Frontier of HIV Medicine

Getting more HIV-positive people linked to and retained in care requires innovation and research

By Tim Horn

Viral-load suppression remains the holy grail of HIV care. Its associations with AIDS-free survival and a profound reduction in transmission risk are well established. To maximize the odds of getting viral load undetectable and keeping it there, numerous safe, effective, and miraculously simplified HIV drugs and fixed-dose combinations have been developed and approved. But there's a problem: far too many people living with HIV in the United States—and elsewhere around the world—aren't accessing the care they need to benefit from the personal and public health benefits of antiretroviral therapy.

The good news is that roughly 75 percent of HIV-positive people who are engaged continuously in care have suppressed virus. The bad news is that this accounts for only one in four of all people with HIV residing in this country. According to the U.S. Centers for Disease Control and Prevention (CDC) HIV continuum of care—also known as the treatment cascade—only 62 percent of people living with HIV have been linked to a care provider, and an abysmal 37 percent are engaged in regular care—the initial steps required to get HIV-positive people on treatment.

Not surprisingly, cascade outcomes differ according to the population analyzed. According to the CDC, 62 percent of African Americans living with HIV, compared with 71 percent of whites, have been successfully linked to care. And whereas several states and municipalities have reported linkage and retention estimates that are below those of national cascade averages, others are reporting more encouraging outcomes. Massachusetts is a prime example: of those who have been diagnosed, roughly 99 percent are in care, and 71 percent have current or sustained viral-load suppression.

Interventions to the Fore

Barriers to care, which are myriad and overlapping, have been well characterized in the literature. Largely missing are data supporting successful approaches that can be scaled up to overcome these barriers. Whereas we have hundreds of clinical trials and other prospective studies to determine which HIV treatment regimens to use in particular circumstances, the evidence base needed to inform engagement-in-care practices and policies is limited at best.

This is not to say that interventions do not exist. In fact, numerous clinics and organizations have, for decades, been employing tactics to get people tested, into care, and retained in care. When it comes to engagement-in-care strategies, real-world experience far exceeds the science. But where there is a dearth of evidence-based practice, there may be much to be learned from practice-based evidence.

Among the interventions that have been shown to be effective, albeit in limited and often informal studies, are: strengths- and empowerment-based linkage case management (the only engagement-in-care intervention evaluated in a randomized, controlled clinical trial to date); medical case management, with a focus on helping patients get critical ancillary services providing food security, transportation, and housing; intensive outreach; reengagement case management; and systems navigation, an intervention that employs peers or paraprofessionals to help clients identify barriers and available services.

Another intervention being evaluated involves financial and nonmonetary incentives for patients who remain in care and on course toward positive health outcomes. Red-carpet entry programs, whereby newly diagnosed individuals are swiftly and supportively brought into care, are also being explored, as are recapture programs, whereby electronic medical record data are synced with surveillance data to identify individuals who have fallen out of care.

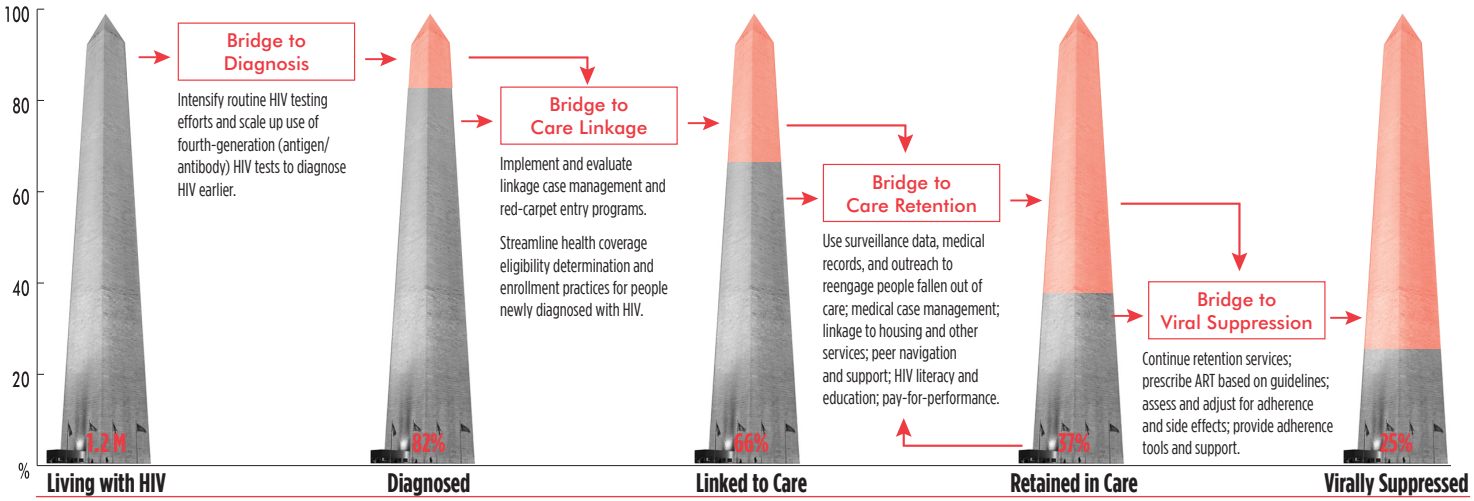
Evaluation and Translation

The scale-up and adoption of these and other practices, particularly those that have the potential to work in different populations and geographies across the continuum of care, require multidisciplinary research. Not only is this needed to better understand how to support the engagement needs of those who have not yet been successfully retained in care, but it is also necessary to minimize the risk of attrition among those currently relying on these services.

Expanding the evidence base, notably controlled clinical trials evaluating the efficacy of innovative approaches and prospective cohorts to further validate the outcomes and cost-effectiveness of established

Bridging the Gaps in the Continuum of Care

According to CDC estimates, only 37 percent of people living with HIV are engaged in care, thereby minimizing rates of viral suppression in the United States (gray). Ongoing research, implementation, and evaluation of strategies to successfully link, retain, and reengage people in care are critical to improving outcomes across the continuum (red).



interventions, is essential, particularly if we're to fully establish best practices to overcome barriers to care. Such research, however, isn't cheap, and linkage/retention intervention protocols will require financial commitments from the National Institutes of Health.

Interventions also need to be scaled up. To ensure effectiveness, we need to determine in which settings interventions may be necessary, the motivators and barriers associated with their uptake, and ways to tailor the interventions while maintaining fidelity to their proven methodology. It is here that we can deploy implementation science, a rapidly evolving field of research, to determine how best to translate proven interventions into clinical practice and further validate their role in improving all aspects of the continuum of care.

Implementation science begins with the understanding that "top-down" clinical trial efficacy does not necessarily translate into effectiveness and efficiency in the real world, in large part due to social, behavioral, cultural, and service-delivery factors that exist outside of the research setting. The "bottom-up" approach to implementation science involves collaboration between service providers and people living with HIV to answer critical questions about effective translation of proven innovations—a number of study frameworks, characteristics, and methods are described in the literature—while at the same time yielding scientifically validated implementation strategies and outcomes measurements that can be disseminated and replicated elsewhere.

The President's Emergency Plan for AIDS Relief (PEPFAR), which was initially concerned with reducing AIDS-associated morbidity and mortality as quickly as possible in lower-income countries and did not at the outset include research, now supports implementation science to ensure that evidence-based engagement, prevention, and treatment strategies are evaluated and translated into sustainable, locally owned practices.

It's now time to develop and implement a domestic implementation science research agenda. This will require the Office of National AIDS Policy to coordinate the resources and capabilities of many U.S. Department of Health and Human Services agencies, along with critical input from state health departments, health and social service providers, activists, and people living with HIV. Encouragingly, this cross-agency collaboration has already been put into play, with President Obama's July executive order for an HIV Care Continuum Initiative (see page 6).

To achieve the HIV disease management goals of the National HIV/AIDS Strategy as we prepare for a substantial shift in the U.S. health care delivery framework, a nationwide push is needed for the necessary evidence-based research and science-driven implementation to maximize engagement in care. We've made tremendous progress in our ability to safely and effectively treat HIV over the past 25 years. We now need to ensure that its lifesaving and transmission-preventing potential isn't limited to only 25 percent of people living with HIV.

With thanks to Michael Mugavero, MD, of the University of Alabama for his review and insight. •

Toward a Plan to End AIDS in New York State

A coalition of community groups push to end AIDS at the epicenter of the U.S. epidemic

Beginning in January 2013, a coalition of New York HIV/AIDS leaders came together to begin a series of discussions to reenvision the state's HIV/AIDS response. The goal was to encourage the state government to develop a New York State plan to end AIDS, applying the latest science, and building on implementation of the Affordable Care Act (ACA).

This initiative, organized by TAG and Housing Works and hosted by Wafaa El-Sadr, MD, MPH, at Columbia University's Mailman School of Public Health, draws on the most recent science indicating that widespread HIV treatment can reduce new infections, and on the imminent implementation of health care reform through the ACA and Medicaid expansion. In October 2013, New York State will launch its state insurance exchange, while the federal government will begin to enforce the individual health mandate in 2014.

New York State remains the epicenter of the nation's HIV epidemic. According to the state AIDS Institute, presenting at the second Housing Works and TAG meeting at Columbia in May 2013, new infections have dropped 36 percent since 2007. New infections in New York State dropped from 10 percent of the national level in 2007 to seven percent in 2010; yet it still has the largest number of people living with HIV/AIDS of any state. According to 2010 estimates, 156,000 people were living with HIV/AIDS in New York; at least 28,000 of them were unaware of their status; and only 37 percent had undetectable viral loads.

While the overall HIV incidence in the state has been decreasing, the rate of new HIV infections among men who have sex with men (MSM) and young MSM of color continues to rise disproportionately. Wide disparities along the continuum of care—including rates of diagnosis, linkage to care, retention in care, and undetectable viral-load rates—also continue to persist among underserved groups. Transgender people, women, youth, people of color, low income and homeless individuals, people who inject drugs, immigrants, and the formerly incarcerated are less likely to be engaged in care.

The rollout of the ACA in January 2014 is anticipated to cause massive shifts in the publicly funded health care delivery models for people with HIV in the state. For those who don't have employment-based insurance, people previously barred from private insurance due to preexisting conditions can now access care through the NYS Health Benefits Exchange. While "navigators" are undergoing training to help people evaluate and choose a plan that meet all of their health care needs, with different levels of premiums, deductibles, and covered services, the process will be challenging. In Manhattan alone, there are nine individual plans and three small business plans. Individuals with incomes between 133 and 400 percent of the federal poverty level will receive subsidies and out-of-pocket support provided by the ACA.

People receiving care through Ryan White CARE Act–funded programs will likely be moved to either the expanded Medicaid, or transition to an Exchange plan with their premiums and deductibles covered by the AIDS Drug Assistance Program (ADAP), depending on their income. Ryan White programs will also be needed to provide support services such as case management, food, legal and linguistic services, housing, transportation, and psychosocial support programs required to keep people engaged in care and adherent to treatment.

Access, retention-in-care, and disparity issues were among the recurring themes raised during the TAG and Housing Works consultations in January and May of this year. Prominent New York City and State AIDS advocates, service providers, public health officials, and researchers came together to discuss where policy and funding gaps persist in our local and statewide HIV/AIDS response and how these gaps can be addressed using existing Ryan White program funding and new investments made in compliance with the state's implementation of health care reform.

Overarching themes of the community consultations were improving the continuum of care in New York State by reallocating funding to better target those at greatest risk and refocusing on evidenced-based, high-priority interventions, especially treatment and prevention scale-up. Consultation participants discussed some of the innovative testing and linkage-to-care strategies already being used in some parts of New York City—the Bronx

NYS: Continuum of Care, 2010

156,287 residents estimated to be living with HIV

54% of residents with any HIV care during year

47% of residents with continuous care during year

37% virally suppressed at test closest to midyear

Knows campaign, for example, which surpassed targets initially set for the program—and explored innovative mechanisms for improving early antiretroviral therapy (ART) initiation; increasing the rates of ART utilization; addressing clinical care engagement challenges, notably persistent racial, ethnic, and age-related disparities; and maximizing common-sense HIV prevention services (e.g., greater access to free condoms and housing) for those at greatest risk.

Consultation panelists provided nuanced overviews of the challenges and successes of the San Francisco and Massachusetts community models, wherein reductions in HIV incidence were achieved over the past couple of years by scaling up a number of key evidence-based strategies for success, such as universal access to, and expanded utilization of, health care. Examples include health care provided in ways that are respectful of the needs of affected populations, investment in support for critical ancillary services (e.g., housing, nutrition, transportation, mental health, and supportive environments), and close and intensive communication among public health authorities, researchers, providers, and the HIV community.

Guaranteed universal access to lifesaving medications, treatment, and HIV prevention education will be essential for the health and quality of life of all New Yorkers. Advocates and service providers have long recognized the importance of regular, routine, accessible, and affordable care and services as a means of preventing transmission for those at risk of contracting HIV and for slowing the progression of HIV to AIDS.

In August 2013, Housing Works, TAG, and a coalition of community groups submitted a working paper to New York State's deputy secretary of health, describing five key elements of a plan to end AIDS in the state; the working paper is now under review (an early draft can be accessed at: treatmentactiongroup.org/policy/NYS-end-aids). It is hoped that during his 2014 State of the State address Governor Cuomo will fully recognize the need for a plan to end AIDS, and that he will announce the formation of a commission to implement this plan.

New York State, where, along with California, the epidemic first emerged in the United States, now has the chance to become one of the first states to commit to ending the pandemic. •

HIV Prevention Is the Surest Way to Fight AIDS

ACT UP/NY demands Department of Health accountability at the epicenter of the U.S. epidemic and commits to reinvigorate the national prevention agenda

By Jim Eigo and James Krellenstein, ACT UP/NY

Before Hillary Clinton stepped down as secretary of state, she presided over the official November 29, 2012, release of *PEPFAR Blueprint: Creating an AIDS-Free Generation*. With a trumpeter on the inside front cover, the 64-page document declared that the world was about to enter the third and final phase of the war against HIV infection. After AIDS as a full-scale plague, and AIDS as a manageable disease, we now had within our sights the elimination of symptomatic HIV. Twenty days later, however, another arm of the U.S. government released another document. Some news it contained struck a discordant note with Secretary Clinton's battle cry. After reading it, many wondered if we hadn't somehow traveled back to the dark early years of the epidemic.

An HIV Prevention Emergency

According to U.S. Centers for Disease Control and Prevention (CDC) incidence estimates released on December 19, men who have sex with men (MSM; a category that includes transgender women), comprising less than two percent of the population, accounted for 66 percent of the 47,600 new HIV infections in 2010. Between 2008 and 2010, new infections rose 12 percent for all MSM and 22 percent for young MSM. Some subpopulations were at substantially higher risk: an African American man who had sex with men was six times likelier to acquire HIV infection than his white counterpart.

Spurred by news of the sharp upward trend of new infections, a core of grassroots activists of differing ages, sexes, orientations, colors, and serostatus began working on prevention issues for ACT UP/NY—they include the authors. Though the CDC numbers told of a prevention emergency, few in New York's gay communities—from the rank-and-file to the top echelons of Gay, Inc.—seemed to realize what was going on. HIV was something that the community had taken care of back around 1997, wasn't it? Effective antiretroviral therapy (ART) has made HIV manageable for most who have access to the drugs. For many younger men, AIDS was a disease—and a political cause—of the 1980s.

The authors, James Krellenstein (left) and Jim Eigo, at an August 15 demonstration at the New York City Department of Health and Mental Hygiene, where ACT UP/NY and allies protested recent funding cuts to the City's postexposure prophylaxis (PEP) program, a lack of awareness campaigns and availability of HIV-prevention drugs PEP and preexposure prophylaxis (PrEP), and faulty, misleading data—all factors contributing to what ACT UP deems the "second wave" of HIV/AIDS. Photo credit: Ben Shepard.

Yet the successful treatment of HIV requires that strong drugs be taken over a lifetime. And those most likely to become infected—young, queer, and of color—are among the least likely to receive care, or even to know they're infected.

HIV prevention—avoiding infection in the first place—is still the surest way to fight AIDS. Yet gay men's perceptions and personal practice of HIV prevention are wildly inconsistent. Studies find that gay men use condoms—still the most effective way to prevent the sexual transmission of HIV—less than half the time they practice anal sex; a recent study cites this as the major factor in the rise of new HIV infections among MSM. Without the support of the HIV prevention establishment or official safer-sex guidelines, gay men have long practiced risk-reduction techniques like serosorting (positives have anal sex with positives; negatives with negatives) and seropositioning (only negative guys top), but often erratically and with mixed results. Moreover, well-regarded studies led by Beryl Koblin, PhD, and

Nancy Padian, PhD, have found no evidence to support the efficacy of behavior-based prevention efforts—mostly variations on the early epidemic's condom-based safer-sex workshops. So in recent years the AIDS world has turned toward pharmaceutical prevention.

The most important pharmaceutical prevention has been treatment as prevention (TasP). When treated with ART, people living with HIV can achieve and sustain an undetectable viral load—and are unlikely to pass on the virus. Yet 15 years after the introduction of effective ART, only a quarter of U.S. residents living with HIV have achieved sustained undetectability. Clearly, treating individuals who have HIV infection helps them and the community. But in the real world, many thousands of HIV infections will occur before treatment alone puts an end to HIV transmission.

Some prevention drugs target people who are HIV-negative but at risk. Postexposure prophylaxis (PEP), a 28-day course of antiretroviral drugs, can prevent HIV infection after a potential exposure to the virus. It has long been available to health care workers after potential exposure to HIV on the job. In 2005, the CDC released guidelines for nonoccupational PEP—potential exposures where a condom malfunctions or hasn't been used, or from sharing a needle. Eight years later, ACT UP found that few members of the community know what PEP is. Preexposure prophylaxis (PrEP), a daily dose of antiretroviral drugs, can prevent HIV infection in people at risk for repeated exposure to the virus, most often due to condomless sex. More than a year after the U.S. Food and Drug Administration (FDA) approved Truvada (a fixed-dose, two-drug combination) for PrEP, ACT UP found that few members of the community know what PrEP is.

Derelict of Health

This is the prevention landscape ACT UP found in spring 2013. We had to convince queer communities of an HIV prevention emergency. Our first fact sheets warned, "More than 1 in 2 young gay men will be HIV-positive before they are 50—unless we act now." Community health care providers were telling us that younger patients had a fuzzy understanding of the specifics of sexual risk. ACT UP's *FCK SMRTR*, a smarter-sex toolkit produced for New York's annual gay pride march, provided basic information on the range of prevention tools and strategies available in 2013. It asked gay men to consider their level of risk ("Sucking dick has very low risk") and to realize that some popular prevention strategies are only sometimes effective ("Knowing your partner's HIV status only reduces risk if you REALLY know it"). In sex education workshops and community forums that ACT UP has planned for the fall, we hope to extend prevention into a wider discussion about community health and pleasure and reengage the spirit of self-empowerment that infused the first generation of safer sex.

People make sex decisions within a political context. New York's mayor, Michael Bloomberg, has put his personal stamp on campaigns against guns, cigarettes, and big soft drinks. But HIV prevention has been neglected for years. The city spends little of its own money on prevention—1.2% of its proposed overall disease prevention budget for 2014. When the CDC cuts prevention funding to the city, the city cuts programs. In what has become a yearly ritual, New York City's Department of Health and Mental Hygiene (DOHMH) tries to reduce or eliminate prevention grants to local AIDS groups by as much as 50 percent, and the city council fights to restore them. With the money it spends, the city has favored uninspired condom distribution programs and dated workshops not markedly different from those that have failed before.

The DOHMH has not directed prevention funding toward people at highest risk. In the last year for which there are figures, 2009, only five percent of the city's nonclinical HIV tests targeted MSM—who constitute more than half of the new HIV cases in the city. The DOHMH has officially pronounced that 14 percent of the city's HIV-positive MSM are unaware of their serostatus. But this figure comes from two months of testing the blood of everyone who passed through a single emergency room in the Bronx—without any way of knowing which were MSM. At the same time, the DOHMH has conducted the local component of the 2011 National HIV Behavioral Surveillance (NHBS) study, funded and designed by the CDC, which estimates that 40 percent of the city's HIV-positive MSM didn't know they'd been infected. Not having reliable numbers makes it harder to direct prevention efforts.

The city's record on pharmaceutical prevention has been spotty. When ACT UP asked the city to target New

Yorkers at risk with a PrEP awareness campaign, the DOHMH told us the city was afraid its non-emergency 311 hotline would be swamped with PrEP requests and that there were not enough PrEP-savvy practitioners in the city to whom to refer people.

When ACT UP asked the city to target New Yorkers at risk with a PEP awareness campaign, the DOHMH said such a campaign would not be cost-effective. ACT UP countered that candidates for PEP are at the frontline of risk: getting them into care would repay the effort. The group decided to do a PEP sticker campaign of its own, with contact information for city-subsidized facilities that provide PEP drugs to the uninsured. But the DOHMH informed ACT UP that programs at four of six subsidized facilities were not really under way, and all six were afraid of running out of subsidized drugs if demand were too great. The DOHMH suggested that ACT UP's stickers should instead refer New Yorkers to the 311 hotline. But PEP drugs have to be started as soon after exposure to HIV as possible, and PEP information that 311 now dispenses varies wildly from call to call. The city recently eliminated PEP funds to facilities beyond the six they subsidize, even as the cost for PEP drugs is rising due to recent changes in the state's guidelines. ACT UP has also documented major PEP-related mistakes—from outright refusal to day-long delays—at several New York City medical facilities, among them the most esteemed. Clearly, training the city's practitioners about HIV prevention drugs will require more than an ACT UP sticker.

WHAT'S THE 311?

PEP drugs have to be started as soon after exposure to HIV as possible, but PEP information that 311 now dispenses varies wildly from call to call.

Charging the DOHMH with neglect, ACT UP demonstrated outside the department's Long Island City headquarters in August and demanded that the department

- fund essential HIV prevention services, even when federal funding is cut;
- gather the data needed to target New York's at-risk communities for prevention efforts;
- educate the public and medical practitioners about HIV prevention drugs, find and extend care to New Yorkers who could benefit from those drugs, and fund those drugs when people who are uninsured have no alternatives; and
- work with communities at risk for HIV to develop sex-positive, queer-friendly HIV prevention programs that use today's full range of prevention strategies and tools, building on the early success of safer-sex programs while moving beyond them.

Acting Locally, Thinking Nationally

ACT UP's local campaigns on HIV prevention revealed problems and gaps that require data collection and research at the federal level. The bedrock of prevention is HIV testing that's accurate and sensitive to early infection. Undiagnosed MSM, most in early infection, account for 82 percent of new infections, according to a recent study. The recently approved fourth-generation Alere Determine rapid HIV test detects p24 antigen as well as antibodies to document infection much earlier than previous generations. The speedy, universal implementation of this test—and more sensitive tests in the research pipeline—will maximize the likelihood of early detection of HIV infection. A recent study using fourth-generation testing reported that 32.4% of HIV infections diagnosed would not have been detected with earlier, less-sensitive testing.

Fast-tracking research on HIV infection recency– and new-incidence estimation procedures will aid in gathering more complete, accurate numbers. The annual NHBS study, the source of much of what we know about HIV and at-risk populations, would tell us more if the sample size increased. Real-time PCR sampling of NHBS subjects could determine the incidence of acute infection in those who report an unknown serostatus, and their viral load as well, helping to determine the "community viral load." NHBS serosurveys need to ensure that participants who say they are unaware of their infection are not simply reluctant to share personal information. Looking for antiretroviral drugs in the blood of persons of unknown serostatus is one possible way. We also need research into possible correlates of HIV infection in subpopulations at the highest risk for HIV, and studying factors that are behavioral (like differences in sexual networks) and biomedical (like incidence of untreated sexually transmitted infections).

We need implementation science to support the scale-up of HIV prevention weapons we already have, as

well as a robust research and development pipeline for new biomedical interventions. In the age of PrEP, the development of antiretroviral drugs in long-acting formulations for HIV treatment should be accompanied by their parallel development as prophylaxis. We need to increase research into microbicides (rectal as well as vaginal, in multiple modes of delivery) and into alternatives to the current condom for barrier protection, including but not restricted to new kinds of condoms. In addition, we need research to confirm that these alternatives work effectively for anal as well vaginal sex; if they don't, we need to develop alternatives that do.

We need to know more about HIV transmission biology. We need to know to what extent viral suppression translates into lower risk of HIV transmission during anal sex among MSM; only two percent of the serodiscordant couples in the much-cited HPTN 052 study that established the benefits of treatment as prevention were same-sex (male) couples. Easy, available assays to detect the presence of HIV in the semen of virally suppressed patients might eliminate the need for some of that research. To help us evaluate when and for whom PrEP is a good prevention choice, we'll need to monitor for transmission of drug-resistant HIV among patients who've received antiretrovirals prophylactically, and understand the barriers to adherence to PrEP medications in the real world. Will a successful vaccine against HIV be the ultimate prevention technology? Its development will depend on expanding basic and applied research into a truly effective immune response to HIV.

Prevention as Treatment

When the Affordable Care Act goes into full effect, the notion of prevention will have statutory standing for the first time. Local and federal agencies must seize the opportunity, coordinate efforts, and mobilize around HIV prevention. We need to fund a full prevention agenda: easy and accurate HIV testing, sex-friendly behavioral programs, prophylactic drugs and a practitioner's network schooled in their use, innovative prevention research, and quick implementation of results—all within a larger framework of comprehensive primary care that addresses the various health needs of MSM. To spare the current and future generations of men the infection that badly wounded the last one, the HIV cascade of care—which focuses now on the testing, linkage, retention in care, and treatment of people living with HIV—will have to extend across the great serodivide and reconceive prevention as treatment, as ongoing care for people who are HIV-negative and at risk, arming them with skills and all the tools available, pharmaceutical and other, to maintain their health. •

Design by Bacilio Mendez II, ACT UP/DAWG (the Digital Activism Working Group)

TAG's Commitment to HIV Prevention

By Tim Horn

Though the number of new HIV infections in the United States is down from its peak in the 1980s, incidence has refused to budge below its decade-long average: roughly 50,000 American residents are infected with the virus every year. While advocacy is making significant progress in terms of scaling up HIV testing, engagement-in-care and treatment for people living with the virus—all stages of the HIV care continuum that can help prevent ongoing transmission of HIV—little has been done to see key prevention goals of the National HIV/AIDS Strategy implemented and achieved.

TAG, in close collaboration with activists, national and community-based organizations, researchers, and federal and state government agency heads, is gearing up to develop and advance the research and policy advocacy necessary to **lower the annual number of new infections by at least 25 percent**. To help us achieve this, two stellar activists, Jeremiah Johnson and Kenyon Farrow, have joined TAG and will play essential roles as we recommit ourselves to minimizing the risks of HIV, particularly in the hardest-hit populations and areas. Johnson will serve as TAG's first HIV Prevention Research and Policy Coordinator and Farrow as the organization's new U.S. and Global Health Policy Director.

Attention to the burgeoning epidemic among men who have sex with men (MSM) and transgender women will be essential. Despite comprising just four percent of the U.S. population, MSM accounted for 63 percent of estimated new HIV infections in the country and 78 percent of infections among all newly infected men in 2010. What's more, from 2008 to 2010, new HIV infections increased an astonishing 22 percent among MSM between 13 and 24 years of age. As for transgender women, a 2008 analysis of four studies documented an HIV prevalence of nearly 28 percent, with one of the studies noting that 73 percent of transgender women who tested positive were unaware of their HIV status.

One advocacy priority will be a push, on federal and state levels, to use twenty-first-century surveillance tools, including the scale-up of fourth-generation HIV antigen/antibody assays that allow for diagnosis within days of infection and can distinguish between acute and chronic HIV. Another will be the enlargement of cohorts used as part of the National HIV Behavioral Surveillance study to evaluate trends in incidence.

TAG will be working to develop national, regional, and systems-specific continuums of disease prevention. Our efforts to maximize the engagement of people living with HIV in continuous care must be matched by implementation strategies and science to link and retain those who test HIV-negative—particularly those who are at high risk of being exposed to the virus—in primary care and community programs equipped to provide comprehensive preventive services. These would include high-quality HIV-, reproductive health–, and sexual health education; nonoccupational postexposure prophylaxis (PEP); preexposure prophylaxis (PrEP); as well as screening and treatment for substance use, depression, mental health issues, trauma, and violence.

Even with massive efforts to increase rates of HIV diagnosis, engagement in care, and undetectable viral load among U.S. residents living with the virus, it will still take several years for treatment-as-prevention to substantially reduce HIV incidence. We cannot sit by and wait for this to occur. Rather, we must revitalize the U.S. commitment to high-quality, evidence-based HIV prevention in tandem with strategies to maximize HIV care and treatment.

Emerging Regulatory Issues in HIV Cure Research

The science of discovery comes with ethical challenges in human clinical trials

By Richard Jefferys

Over the past several years, there has been a welcome invigoration of the research effort to cure HIV infection. The mainstream media has picked up on this development, and stories about putative or possible cures are appearing more frequently than in the past. Contrary to the impression conveyed by some of these stories, a cure is not likely to announce itself by leaping from a scientist's test tube waving a flag of victory. To prove their worth, potential curative strategies—whether based on a single approach or a combination—will need to be evaluated in human trials.

The conduct of clinical trials related to HIV cure research raises new issues that multiple stakeholders—regulatory agencies, scientists, biotech and pharmaceutical companies, HIV-positive people, activists, community advisory boards, and institutional review boards—are now beginning to discuss and address. In 2011, TAG along with the AIDS Policy Project, amfAR, and Project Inform sponsored the first workshop on the topic (report available at: treatmentactiongroup.org/cure). More recently, on June 14 of this year, the U.S. Food and Drug Administration (FDA) hosted a one-day public event that sought community input on the regulation of HIV cure research. Webcasts, slide presentations, and a full transcript are available (search "cure research" at fda.org).

Comprehending Risks and Benefits

At this early exploratory stage, the overarching concern involves the risk/benefit calculus of participation in clinical trials. In most cases, there will be risks but little or no possibility of benefit to an individual participant; rather, results from trials will inform and advance the scientific pursuit of a cure. There is universal agreement that this will need to be explained carefully in both educational efforts and the informed consent documents that trial participants are required to read and sign.

Discussions about informed consent in the context of HIV cure research dovetail with wider interest in evaluating how useful and understandable the process is for trial participants. This is a burgeoning area of academic investigation, partly due to concerns that informed consent has become more about protecting against legal liability than providing clear information to individuals joining a trial. Recently published findings on the topic are consistent with the idea that comprehension of informed consent is often far from optimal, and educational interventions and computer-based processes are being assessed as possible solutions. A study by researchers at the HIV INSIGHT network has also suggested that informed consent could be improved by making it an ongoing process throughout a trial, rather than a one-off procedure at the start.

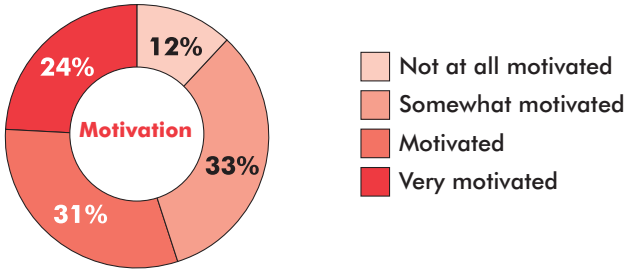
Another potential issue is that the term *cure research* can lead to a problem known as therapeutic misconception—the desire to be cured might trump cautions pertaining to risk and lack of benefit. In addition to suggesting that informed consent documents be made accessible and easy to understand, those involved in the FDA meeting also endorsed the idea of evaluating how potential trial participants have interpreted the information provided to them before permitting enrollment.

In the absence of any chance of immediate benefit, altruism and the desire to contribute to the search for a cure can still be powerful motivating factors. In a survey of over 2,100 people with HIV that was conducted by David Evans from Project Inform and Nelson Vergel from the Program for Wellness Restoration, over half the respondents (55%) reported that the possibility of benefiting others would motivate them to join a trial even if there were some potential risks. A separate question asked about willingness to participate in studies that might advance the science but offer little prospect of individual benefit; 45 percent responded that they would be either willing or very willing. Additional surveys are now being planned under the aegis of the International AIDS Society's Towards an HIV Cure initiative.

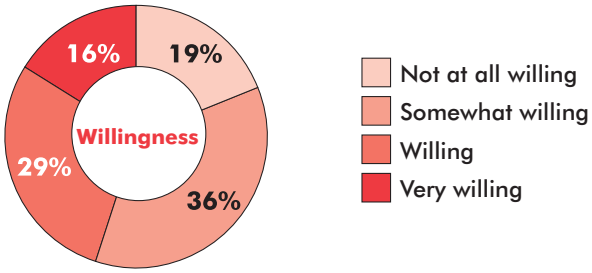
Current Examples

Recent and ongoing clinical trials provide examples of the uncertainties and risks that can be associated with cure-related research. A leading approach for awakening the latent HIV that persists despite ART is the administration of anticancer drugs called HDAC inhibitors. Although several HDAC inhibitors are FDA-approved for the treatment of cancers, they have many

Assuming that entering a study might pose health problems and other risks, how much would the chance to benefit others by participating in the study motivate you to join the study?



Assuming that entering a study might pose health problems and other risks, if you were aware that you would probably not benefit from a new drug or procedure but that your participation might advance the field of HIV research, how willing would you be to participate?



An online community survey of over 2,100 HIV-positive respondents conducted in late 2011 and early 2012 (83% were male, 73% were white, 65% were over 40 years of age, 94% were on ART, and 35% had previously participated in a clinical trial) indicated a high level of altruism regarding early-stage HIV cure research.

Adapted from: Evans D. Ethics and informed consent in cure research (Session SUSA28). Paper presented at: workshop, "Towards an HIV Cure": 19th International AIDS Conference; 2012 July 22–27; Washington, D.C.

potential side effects and in some cases score positive in the Ames test (which measures the ability of a drug to cause mutations that might increase the risk of cancers). Three clinical trials assessing the impact of HDAC inhibitors on HIV latency have been conducted to date, fortunately without any serious safety issues emerging. The research has demonstrated that the drugs may be able to activate latent HIV, at least in some infected cells, but no reduction in the overall size of the HIV reservoir has been documented among participants.

The use of ART interruptions in cure-related research offers another example of the potential risks associated with trial participation. Although short-term interruptions were once thought to be relatively benign as long as CD4 T-cell counts did not fall to levels associated with the development of opportunistic infections, the SMART trial showed that viral-load rebound after ART cessation increases levels of inflammation, which is known to pose health risks. In the SMART trial population (in which individuals in one group interrupted ART when their CD4 T-cell counts rose above 350/mm^3, then restarted if they fell below 250/mm^3), this was associated with significant increase in the risk of illness and death compared with the group that received continuous ART.

As a result of the data from SMART, HIV treatment guidelines explicitly caution against ART interruptions. But if an experimental intervention aims to induce control of HIV off ART (or even to eliminate the virus), the only way of assessing effectiveness is to stop treatment. One proposed approach is to monitor trial participants for viral-load rebound frequently, and restart ART as soon as HIV becomes detectable; this is almost certainly the best way of preventing the virus from provoking high levels of inflammation, but there still could be other concerns such as increasing the size of the HIV reservoir. More controversial—and even less consistent with the current standard of care—are study designs that involve longer-term interruptions or require participants to have stopped ART prior to enrollment. These types of trials are far more likely to increase the risk of inflammation-related morbidity and mortality, and as yet there is no consensus about the acceptable guidelines for trials involving ART interruption.

Thinking of the Children

Adults with HIV infection are not the only population being considered in cure research, and ethical and informed consent issues for studies involving infants and

children are even more complex. Currently, a protocol is being developed that intends to investigate whether an apparent cure of HIV in an infant in Mississippi can be repeated. The goal is to identify 20 to 30 infants born to HIV-positive mothers who did not receive ART to prevent mother-to-child transmission, and administer a three-drug therapeutic regimen within 48 hours of birth (instead of the standard two-drug prophylactic approach) until HIV diagnosis is established by testing, which usually takes around seven days. Treatment will then be continued for around three years in infants confirmed to be infected; at that point, if HIV can no longer be detected, ART will be interrupted to assess whether a cure has been achieved. Among the many issues involved will be the incremental increase in risk of side effects that may accompany the use of a three-drug treatment versus a two-drug prophylactic regimen in infants who turn out to be uninfected, and the need to fully explain and discuss the trial with the mothers prior to seeking informed consent (in a situation where time will be limited).

Endpoint Uncertainties

In addition to risks and benefits, another challenge for the regulation of cure research is the selection of appropriate endpoints (the means of measuring the success or failure of an approach). One possible endpoint is the previously cited example of assessing whether viral load rebounds after ART interruption. But for interventions designed to reduce the size of HIV reservoirs, selecting an appropriate endpoint is more challenging due to the difficulties of reliably documenting changes in levels of HIV that are extremely low to begin with. Although a variety of tests for trace amounts of HIV are available, their reliability and comparability is only starting to be assessed, and as yet there is no universally accepted standard technique.

Conclusion

As the HIV cure research effort continues to gain momentum, regulatory and ethical issues will need to be a continuing subject of discussion among all stakeholders. The FDA has expressed a commitment to ongoing engagement on the subject, and a broader dialogue convened by the Forum for Collaborative HIV Research is due to get under way soon. Community advocates and HIV-positive people have an essential role to play in decisions around appropriate risk/benefit, and informed consent and ethics in HIV cure research, and community engagement in discussions around regulatory issues needs to be ongoing. •

Stem Cell Transplantation for People with HIV and Cancers

The first well-documented HIV cure occurred in a now famous individual named Timothy Brown, and resulted from stem cell transplants (SCTs) that were required to treat concomitant acute myeloid leukemia. Two additional possible HIV cures have been reported more recently, also involving SCTs that were administered due to cancer diagnoses (although, unlike Brown, these individuals did not receive transplants from a donor possessing the CCR5-Δ32 mutation that prevents most types of HIV from entering cells).

Understandably, there is a great deal of interest in trying to achieve similar outcomes in other HIV-positive people with cancer who require SCTs, but it's important to note that there can be regulatory issues associated with these procedures. In some cases, individual approval from the FDA is required, depending on the source of the stem cells (which can be obtained from adults or umbilical cord blood units stored for this purpose) and whether the stem cell source has the CCR5-Δ32 mutation.

As with other types of transplants, a key variable in these procedures is the degree of genetic matching between the stem cell donor and recipient; a poor match typically increases the risk of the transplant's being rejected and the potentially lethal condition graft-versus-host disease (GVHD). So far, two cases in which people with HIV and cancer received cord blood stem cells from donors with the CCR5-Δ32 mutation have been publicly described: in one case the individual died due to the underlying cancer, and in the other case death occurred due to the development of severe GVHD.

As with other regulatory issues pertaining to cure research, there is a need for a broader public discussion among stakeholders—in this case including experts in stem cell transplantation—about the appropriate guidelines for using this approach to try to cure HIV.

SAVE THE DATE

2013 Research in Action Awards

TAG's annual Research in Action Awards (RIAA) event honors activists, scientists, philanthropists, and creative artists who have made extraordinary contributions to the fight against AIDS. Resources raised at RIAA provide vital support for TAG's programs throughout the year, and enable us to honor champions in the fight to end AIDS.

This year's award recipients are CNN's **Anderson Cooper**, Academy Award–winning actress and human rights activist **Olympia Dukakis**, and pioneering community-based AIDS researcher and physician **Joseph A. Sonnabend**.

This year's awards will be held on **Sunday, December 15, 2013**, at 404, located at 404 Tenth Avenue in Chelsea (New York City). Our hosts will be **Jenna Wolfe**, anchor of NBC's *Weekend Today*, and **Meredith Vieira**, host of *Dateline NBC* and *Who Wants to Be a Millionaire*, as well as former anchor of NBC's *Today* and former host of ABC's *The View*.

Gold and Silver level sponsors for this year's RIAA will receive a framed cibachrome photograph by acclaimed artist **Nan Goldin**.

For more information, go to: www.treatmentactiongroup.org/riaa.

SUPPORT TAG

Supporting TAG is a wise investment in AIDS treatment advocacy. Every donation brings us one step closer to better treatments, a vaccine, and a cure for AIDS. Donate online: www.treatmentactiongroup.org/donate.

Does your company have a matching gifts program? If so, you can double or even triple your donation. Just complete the program's matching gift form and send it in with your donation to TAG.

ABOUT TAG

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS.

TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

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